

NOVEL PHENYLALKYLAMINES AND THEIR USE IN THE TREATMENT OF PSYCHIATRIC DISORDERS

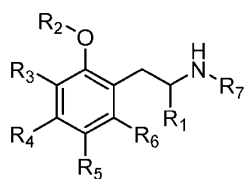
BACKGROUND OF THE DISCLOSURE

Psychiatric illnesses, including depression and anxiety, represent a serious detriment to health and effective human functioning worldwide. Although a number of psychiatric medications are available and extensively prescribed, they fail to deliver relief for many individuals. For those patients who do respond, changes in mood and behavior are often slow to manifest. In recent years, these persistent unmet needs for improved pharmacotherapies to treat psychiatric disorders have led to consideration of previously maligned options. For example, classical serotonergic hallucinogens such as lysergic acid diethylamide (LSD), psilocybin, and dimethyltryptamine (DMT), have been considered as experimental therapeutics for a variety of psychiatric indications.

However, such compounds induce profound hallucinogenic effects, which inhibit normal functioning of individuals so treated. Accordingly, these compounds are currently classified as Schedule I drugs under the Controlled Substances Act due to their high abuse potential, no accepted medical use, and lack of established safety. Such effects are mediated largely through engagement of serotonin receptors. Of particular importance is agonism of the serotonin 2A receptor (5-HT_{2A}), which is responsible for the problematic hallucinogenic activity of these compounds but also thought to be critical for their purported therapeutic effects. Accordingly, compounds of this type that would deliver therapeutic benefits while limiting hallucinogenic activity, and therefore the potential for abuse and adverse events, would be of high therapeutic value.

SUMMARY OF THE DISCLOSURE

The present disclosure relates to a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R₁ is H, methyl, ethyl, -CH₂-OH, -CH₂-O-(methyl), -CH₂F, or -CH₂CH₂F;

R₂ is H, C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R₃ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₆ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₄ is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF₃, NO₂, or SF₅, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, or

R₄ is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), NO₂, or SF₅, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R₄ is not isopropyl;

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S(O)(O)-(C1-C5 alkyl), NH₂, NH(C1-C5 alkyl), or N(C1-C5 alkyl)₂, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, or

R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl is optionally substituted with one or more F;

with the provisos that when R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S(O)(O)-(C1-C5 alkyl), NH₂, NH(C1-C5 alkyl), or N(C1-C5 alkyl)₂, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, then R₄ is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF₃, NO₂, or SF₅, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, or

when R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl is optionally substituted with one or more F, then R₄ is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), NO₂, or SF₅, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R₄ is not isopropyl;

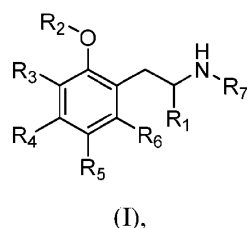
R₇ is H, -CH₂-(aryl), or -CH₂-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the further provisos that:

- (a) when R₂ is methyl, R₃ is methyl, R₄ is Cl or Br, R₅ is methyl, R₆ is H, and R₇ is H, then R₁ is not H or methyl;
- (b) when R₁ is H or methyl, R₂ is H or methyl, R₃ is H, R₅ is methyl, R₆ is H, and R₇ is H, then R₄ is not Cl;
- (c) when R₁ is H, R₂ is methyl, R₃ is H, R₅ is CF₃, R₆ is H, and R₇ is ortho-methoxybenzyl, then R₄ is not Br;

- (d) when R_1 is H, R_2 is H, R_3 is H, R_5 is Cl, R_6 is H, and R_7 is H or benzyl, then R_4 is not cyclohexyl; and
- (e) when R_1 is methyl, R_2 is H, R_3 is H, R_5 is NH_2 , R_6 is H, and R_7 is H, then R_4 is not Cl.

In another embodiment, the present disclosure relates to compounds of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is $-\text{CH}_2\text{-OH}$, $-\text{CH}_2\text{-O-(methyl)}$, $-\text{CH}_2\text{F}$, or $-\text{CH}_2\text{CH}_2\text{F}$;

R_2 is C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R_3 is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R_4 is C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, $-(\text{C1-C5 alkyl})-(\text{C3-C6 cycloalkyl})$, $-\text{S}-(\text{C1-C8 alkyl})$, $-\text{S}-(\text{C3-C8 alkenyl})$, $-\text{S}-(\text{C3-C8 alkynyl})$, $-\text{S}-(\text{C3-C8 cycloalkyl})$, $-\text{S}-(\text{C1-C5 alkyl})-(\text{C3-C6 cycloalkyl})$, F, Cl, Br, I, CN, NO_2 , or SF_5 , wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R_5 is $-\text{O}-(\text{C1-C5 alkyl})$, $-\text{O}-(\text{C3-C5 alkenyl})$, $-\text{O}-(\text{C3-C5 alkynyl})$, $-\text{O}-(\text{C3-C5 cycloalkyl})$, $-\text{O}-(\text{C1-C5 alkyl})-(\text{C3-C5 cycloalkyl})$, CF_3 , CN, Br, or I, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R_6 is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

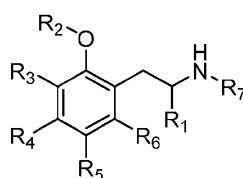
R_7 is H, $-\text{CH}_2-(\text{aryl})$, or $-\text{CH}_2-(\text{heteroaryl})$, wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of

halo, CN, OH, NH₂, NO₂, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the provisos that:

- (a) when R₁ is -CH₂-OH, R₂ is methyl, R₃ is H, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl, -S-(methyl), or n-butyl;
- (b) when R₁ is -CH₂-OH, R₂ is methyl, R₃ is methyl, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl;
- (c) when R₁ is -CH₂CH₂F, R₂ is methyl, R₃ is H, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl; and
- (d) when R₁ is -CH₂-OH, R₂ is methyl, R₃ is methyl, R₅ is Br, R₆ is methyl, and R₇ is H, then R₄ is not methyl.

In a further embodiment, the present disclosure relates to a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R₁ is H, methyl, ethyl, n-propyl, -CH₂-OH, -CH₂-O-(methyl), -CH₂F, or -CH₂CH₂F;

R₂ is C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R₃ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₄ is C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C5 cycloalkyl), -S(O)(O)-(C1-C5 alkyl), -S(O)(O)-(C3-C5 alkenyl), -S(O)(O)-(C3-C5 alkynyl), -S(O)(O)-(C3-C5 cycloalkyl), -S(O)(O)-(C1-C5 alkyl)-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl)-(C3-C5 cycloalkyl), NH₂, NH(C1-C5 alkyl), or N(C1-C5 alkyl)₂, F, Cl, Br, I, CN, or NO₂, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₆ is F;

R₇ is H, -CH₂-(aryl), or -CH₂-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the proviso that when R₁ is H, R₂ is methyl, R₃ is H, R₄ is F, and R₇ is H, then R₅ is not Cl or Br.

The present disclosure also relates to miscellaneous compounds. Further, the present disclosure relates to deuterium analogs of the compounds described hereinabove, i.e., when one or more hydrogens in the alkyl moieties of the various substituents R₁, R₂, R₃, R₄, R₅, R₆, and R₇, is replaced by deuterium.

The present disclosure also relates to the stereoisomers, including enantiomers and diastereomers, of any of the compounds of Formula (I) herein or its deuterium analogs or the miscellaneous compounds.

The present disclosure is also directed to pharmaceutical compositions comprising a therapeutically effective amount of any of the compounds of Formula (I) herein and the deuterium analogs thereof and the miscellaneous compounds and a pharmaceutically acceptable carrier therefor. In addition, the present disclosure relates to a method of treating a psychiatric disorder in a subject, which comprises administering to a subject in need of treatment a therapeutically effective amount of any of the compounds of Formula (I) herein or the deuterium analogs thereof or the miscellaneous compounds.

BRIEF DESCRIPTION OF THE DRAWINGS

The objects, features, and advantages of the present disclosure will become apparent to one of ordinary skill in the art, in view of the following detailed description, taken in combination with the attached drawings.

Figure 1 shows graphically the data collected from a chronic mild stress (CMS) study testing the effects of compound 3DE2. The graph shows the level of sucrose intake in groups of rats administered different weekly treatments across the time course of the study. Large arrows indicate weekly dosing of ketamine (10 mg/kg, IP), while small arrows indicate times compound 3DE2 (0.1-3.2 mg/kg, SC) was dosed. Legends indicate the dose levels tested in parentheses.

Figure 2 shows graphically the data collected from a CMS study testing the effects of compound 1AE2. The graph shows the level of sucrose intake in groups of rats administered different weekly treatments across the time course of the study. Large arrows indicate weekly dosing of ketamine (10 mg/kg, IP), while small arrows indicate times compound 1AE2 (0.1 or 0.32 mg/kg, SC) was dosed. Legends indicate the dose levels tested in parentheses.

Figure 3 shows graphically the data collected from a CMS study testing the effects of compound 6CE2. The graph shows the level of sucrose intake in groups of rats administered different weekly treatments across the time course of the study. Large arrows indicate weekly dosing of ketamine (10 mg/kg, IP), while small arrows indicate times compound 6CE2 (0.1-1 mg/kg, SC) was dosed. Legends indicate the dose levels tested in parentheses.

Figure 4 shows graphically the data collected from a CMS study testing the effects of compound 30E2. The graph shows the level of sucrose intake in groups of rats administered different weekly treatments across the time course of the study. Large arrows indicate weekly dosing of ketamine (10 mg/kg, IP), while small arrows indicate times compound 30E2 (0.32 or 1 mg/kg, SC) was dosed. Legends indicate the dose levels tested in parentheses.

DETAILED DESCRIPTION OF THE PRESENT DISCLOSURE

The present disclosure provides, for example, compounds which are modulators of 5-HT_{2A} receptors (5-HT_{2A}), their use as medicinal agents, processes for their preparation, and pharmaceutical compositions containing them as an active ingredient both alone or in combination with other agents. It further provides for their use as medicaments and/or in the manufacture of medicaments for the activation of 5-HT_{2A} in warm-blooded animals such as humans. In particular, this disclosure relates to compounds useful for the treatment of psychiatric diseases or disorders. Further, this disclosure provides compounds that induce useful therapeutic effects while exhibiting attenuated or no hallucinogenic effects.

Before further description of the present disclosure, certain terms employed in the specification, examples, and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety, unless a particular passage is cited. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The present disclosure relates to various compounds identified as Formula (I), wherein the structures are the same, but the definitions of the substituents identified as R₁, R₂, R₃, R₄, R₅, R₆, and R₇ with respect one set of compounds of Formula (I) may be the same or different from the definition of the corresponding substituent with respect to a different set of compounds of Formula (I). For example, the definitions of R₁ with respect to a compound of Formula (I) may be

the same or different with respect to the corresponding R₁ of another compound of Formula (I). To avoid confusion as to which definition of the substituents refers to which compound of Formula (I), it is to be understood that the various substituents will refer to the previous drawn compound of Formula (I).

Unless indicated to the contrary or clear from the context, notwithstanding the above, reference to Formula (I), in general, will refer to any or all of the compounds of Formula (I).

Unless indicated to the contrary, all percentages are by weight.

The term “active ingredient”, as used herein refers to compounds of Formula I, as defined herein and miscellaneous compounds, as defined herein.

“Treating” includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

The term “alkoxy” as used herein refers to a straight or branched alkyl group attached at oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C₁-C₆ alkoxy, and C₂-C₆ alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

The term “alkyl” as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C₁-C₆ alkyl, C₁-C₄ alkyl, and C₁-C₃ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, and the like.

The term “alkenyl” as used herein refers to a straight or branched hydrocarbon with one or more double bonds. Exemplary alkenyl groups include, but are not limited to, straight or branched hydrocarbons of 2-6, 2-4, or 2-3 carbon atoms with one double bond. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, homoallyl, and the like.

The terms “aryl” and “ar-”, used alone or as part of a larger moiety, e.g., “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, refer to monocyclic and bicyclic ring systems having a total of

five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with the term "aryl ring". In certain embodiments of the present disclosure, "aryl" refers to an aromatic ring system which includes, but is not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl", as used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

The term "cyano" as used herein refers to the radical -CN.

The terms "cycloalkyl" or a "carbocyclic group" as used herein refers to a saturated or partially unsaturated cyclic hydrocarbon group of, for example, 3-6, or 4-6 carbons, referred to herein as C₃-C₆ cycloalkyl or C₄-C₆ cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl, cyclopropyl, and the like.

The term "cycloalkylalkyl" as used herein refers to a saturated straight or branched hydrocarbon substituted with a saturated or partially unsaturated cyclic hydrocarbon group of, for example, 3-6, or 4-6 carbons. Exemplary cycloalkylalkyl groups include, but are not limited to, cyclopropylmethyl, cyclopentylmethyl, 2-cyclopropylethyl, and the like.

The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, e.g., "heteroaralkyl", or "heteroaralkoxy", refer to groups having 5 to 14 ring atoms, for example, 5, 6, 9, or 10 ring atoms, having 6, 10, or 14 π electrons shared in an aromatic cyclic array, and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings. Nonlimiting examples include indolyl, isoindolyl, benzothienyl,

benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4H-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, and pyrido[2,3-b]-1,4-oxazin- 3(4H)-one. A heteroaryl group may be mono- or bicyclic or tricyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and the rings of the heteroaryl moiety (either the heteroaromatic or non-heteroaromatic rings) independently are optionally substituted.

The terms "heterocyclyl" or "heterocyclic group" are art-recognized and refer to saturated or partially unsaturated, 4-10 membered ring structures, including bridged or fused rings, whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran, dihydrofuran, and the like.

The terms "hydroxy" and "hydroxyl" as used herein refer to the radical -OH.

The terms "about" or "approximately" as used herein mean within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, *i.e.*, the limitations of the measurement system. For example, "about" can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, a range of up to 10%, a range of up to 5%, and/or a range of up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, *e.g.*, within 5-fold, or within 2-fold, of a value. "About" and "approximately" are used interchangeably herein.

"Pharmaceutically or pharmacologically acceptable" include molecular entities and compositions that do not produce an adverse, allergic, or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by the relevant governmental regulatory body.

The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein, refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

“Individual,” “patient,” or “subject” are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like), and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like). The mammal treated in the methods of the disclosure is desirably a mammal in which treatment of a psychiatric disease or disorder is desired.

“Modulation” includes antagonism (*e.g.*, inhibition), agonism, partial antagonism, and/or partial agonism.

In the present specification, the term “therapeutically effective amount” means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, or animal, (*e.g.* mammal or human) that is being sought by the researcher, veterinarian, medical doctor, or other clinician. The compounds of the disclosure are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in a decrease in symptoms of a psychiatric disorder, including, but not limited to, reducing the frequency or severity of sadness or lethargy, depressed mood, anxious or sad feelings, diminished interest in all or nearly all activities, significant increased or decreased appetite leading to weight gain or weight loss, insomnia, irritability, fatigue, feelings of worthlessness, feelings of helplessness, inability to concentrate, and recurrent thoughts of death or suicide; or providing a desired pharmacologic and/or

physiologic effect, for example, reducing, inhibiting, or reversing one or more of the underlying pathophysiological mechanisms underlying the neurological dysfunction, modulating dopamine levels or signaling, modulating serotonin levels or signaling, modulating norepinephrine levels or signaling, modulating glutamate or GABA levels or signaling, modulating synaptic connectivity or neurogenesis in certain brain regions, or a combination thereof. The precise dosage will vary according to a variety of factors, such as subject-dependent variables (*e.g.*, age, immune system health, clinical symptoms, and the like), the disease or disorder being treated, as well as the route of administration and the pharmacokinetics of the agent being administered.

Unless indicated to the contrary, the terms “drugs” and “medicament” are synonymous.

As used herein, the terms “comprises,” “comprising,” “includes,” “including,” “has,” “having,” or any other variation thereof, are intended to cover a non-exclusive inclusion. For example, a composition, process, method, article, or apparatus that comprises a list of elements is not necessarily limited to only those elements, but may include other elements not expressly listed or inherent to such composition, process, method, article, or apparatus.

Also, the use of “a” or “an” are employed to describe elements and components described herein. This is done merely for convenience and to give a general sense of the scope of the invention. This description should be read to include one or at least one.

Moreover, the singular also includes the plural and vice versa unless it is obvious that it is meant otherwise.

Further, unless expressly stated to the contrary, “or” refers to an inclusive “or” and not to an exclusive “or.” For example, a condition A or B is satisfied by any one of the following: A is true (or present), and B is false (or not present), A is false (or not present), and B is true (or present), and both A and B are true (or present).

Moreover, the term “and/or” is synonymous with the term “or”, as used herein.

When a range or list of values is expressed, an embodiment includes the endpoint of the ranges and/or list and all the points therebetween. For example, a range of 6 to 9, includes the value 6 and 9 and all values therebetween. Similarly, when values are expressed as approximations, by use of the antecedent “about,” it will be understood that the values range from about the two endpoints, where “about” is defined as herein described. All ranges are inclusive and combinable. Further, reference to values stated in ranges includes each and every value within that range.

The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, including, but not limited to, malate, oxalate, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-*bis*-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming a wide variety of salts with various inorganic and organic bases. The bases that may be used to prepare pharmaceutically acceptable base salts of such acidic compounds are those that form non-toxic base salts, i.e., salts containing pharmaceutically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups, for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term "stereoisomers" when used herein refers to all enantiomers or diastereomers. Specific stereoisomers of such compounds may be designated by the symbols "(+)," "(-)," "R", or "S," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present disclosure encompasses various stereoisomers of these compounds in pure form and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol $\equiv$ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the “Z” or “E” configuration wherein the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the “E” and “Z” isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond.

Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. The arrangement of substituents around a carbocyclic or heterocyclic ring are designated as being in the “Z” or “E” configuration wherein the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both “Z” and “E” isomers. Substituents around a carbocyclic or heterocyclic rings may also be referred to as “cis” or “trans”, where the term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of the plane of the ring are designated “cis/trans.”

Individual enantiomers and diastereomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography, and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns, or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well-known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an

unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations, and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

In some embodiments, a composition prepared herein may be enriched in a specific enantiomer of any compound disclosed herein relative to the corresponding opposite enantiomer of that compound, such that the mixture is not racemic. In such cases, the subject mixture of isomers is understood to have an enantiomeric excess and optical purity >0%. The enantiomeric excess or optical purity of the isomeric mixture may be, for example, >0%, >5%, >25%, >50%, >75%, >90%, >95%, >97%, >98%, or >99%. The enantiomeric excess or optical purity of the isomeric mixture may be, for example, 5-100%, 25-100%, 50-100%, 75-100%, 90-100%, 95-100%, 97-100%, 98-100%, or 99-100%. Thus, for example, contemplated herein is a composition including the S enantiomer of a compound substantially free of the R enantiomer, or the R enantiomer substantially free of the S enantiomer. Further, if the named compound includes more than one chiral center, the scope of the present disclosure also includes compositions containing the various stereoisomers and diastereomers, including mixtures of varying proportions between the various stereoisomers and/or diastereomers or pharmaceutically acceptable salts thereof, as well as compositions including one or more stereoisomers and diastereomers substantially free of one or more of the other stereoisomers and/or diastereomers, respectively. By “substantially free” in this context, it is meant that the composition includes less than, for example, 50%, 25%, 15%, 10%, 8%, 5%, 3%, 2%, or 1% of the minor enantiomer or diastereomer(s). For example, the expression that a compound is enantiomerically pure refers to the compound being substantially free of other stereoisomers, including any other enantiomers or diastereomers.

For clarity, in the context of the present disclosure, chemical structures of a compound depicted with a specific stereochemical orientation at any particular chiral center, as defined by wedge and dash notation, are intended to represent the specified stereoisomer of said compound in substantially pure form, or a mixture enriched in the stereoisomer(s) with the specified stereochemical orientation at the defined chiral center over the stereoisomer(s) with the opposite orientation at said chiral center.

The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

The disclosure also embraces isotopically labeled compounds of the disclosure which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. For example, a compound of the disclosure may have one or more H atoms replaced with deuteriums.

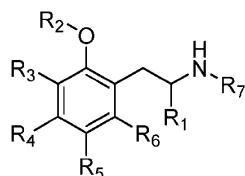
Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Compounds incorporating tritium (*i.e.*, ^3H) or carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, due to the kinetic isotope effect, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life, reduced dosage requirements, or attenuation of the formation of one or more metabolites) and hence may be preferred in some circumstances. Isotopically labeled compounds of the disclosure can generally be prepared by following procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

As used in the chemical structures herein, the symbol "D" indicates a deuterium-enriched H-site wherein the isotopic composition of the site is enriched to a level greater than the natural abundance of deuterium. The level of deuterium enrichment at such a site may thus be, for example, greater than 0.02%, greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, greater than 95%, greater than 97%, greater than 98%, or greater than 99%.

COMPOUNDS

I. FIRST SET OF COMPOUNDS OF FORMULA (I)

The present disclosure, in an embodiment, relates to a compound of Formula (I)



(I),

wherein R₁, R₂, R₃, R₄, R₅, R₆, and R₇ are as defined herein.

In an embodiment, R₁ is H, methyl, ethyl, -CH₂-OH, -CH₂-O-(methyl), -CH₂F, or -CH₂CH₂F. In another embodiment, R₁ is H, methyl, or ethyl. In another embodiment, R₁ is H or methyl. In another embodiment, R₁ is ethyl, -CH₂-OH, or -CH₂-O-(methyl). In another embodiment, R₁ is -CH₂F or -CH₂CH₂F. In another embodiment, R₁ is methyl or ethyl. In another embodiment, R₁ is H. In another embodiment, R₁ is methyl. In another embodiment, R₁ is ethyl. In another embodiment, R₁ is -CH₂-OH. In another embodiment, R₁ is -CH₂-O-(methyl). In another embodiment, R₁ is -CH₂F. In another embodiment, R₁ is -CH₂CH₂F.

R₂, in an embodiment, is hydrogen, C1-C3 alkyl, cyclopropyl, 1 or 2-propenyl, or 1 or 2-propynyl, wherein alkyl, propenyl, propynyl, and cyclopropyl are unsubstituted or substituted with one or more F. In another embodiment, R₂ is H, methyl or ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F. In a further embodiment, R₂ is methyl or ethyl, wherein methyl and ethyl are optionally substituted with one or more F. In an additional embodiment, R₂ is methyl, which is optionally substituted with F. In a further embodiment, R₂ is methyl, which is unsubstituted.

In an embodiment, R₃ is H, methyl or ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F. In a further embodiment, R₃ is H or F. In a further embodiment, R₃ is hydrogen.

In another embodiment, R₆ is H, methyl or ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F. In a further embodiment, R₃ is H or F. In a further embodiment, R₃ is hydrogen. In a further embodiment, both R₃ and R₆ are hydrogen.

In an embodiment, R_7 is H, $-\text{CH}_2$ -(6-membered aryl), or $-\text{CH}_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2 , NO_2 , C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, $-\text{O}$ -(C1-C5 alkyl), $-\text{O}$ -(C3-C5 alkenyl), $-\text{O}$ -(C3-C5 alkynyl), $-\text{O}$ -(C3-C5 cycloalkyl), $-\text{S}$ -(C1-C5 alkyl), $-\text{S}$ -(C3-C5 alkenyl), $-\text{S}$ -(C3-C5 alkynyl), $-\text{S}$ -(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S. In another embodiment, R_7 is H, $-\text{CH}_2$ -(6-membered aryl), or $-\text{CH}_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2 , NO_2 , C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, $-\text{O}$ -(C1-C3 alkyl), $-\text{O}$ -(C3 alkenyl), $-\text{O}$ -(C3 alkynyl), $-\text{O}$ -(cyclopropyl), $-\text{S}$ -(C1-C3 alkyl), $-\text{S}$ -(C3 alkenyl), $-\text{S}$ -(C3 alkynyl), $-\text{S}$ -(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In another embodiment, R_7 is $-\text{CH}_2$ -(6-membered aryl) or $-\text{CH}_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2 , NO_2 , C1-C3 alkyl, cyclopropyl, $-\text{O}$ -(C1-C3 alkyl), $-\text{O}$ -(cyclopropyl), $-\text{S}$ -(C1-C3 alkyl), $-\text{S}$ -(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In still another embodiment, R_7 is $-\text{CH}_2$ -(6-membered aryl) or $-\text{CH}_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, $-\text{O}$ -(C1-C3 alkyl), $-\text{O}$ -(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In an even further embodiment, R_7 is $-\text{CH}_2$ -(6-membered aryl) or $-\text{CH}_2$ -(6-membered heteroaryl), wherein aryl and

heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In another embodiment, R₇ is -CH₂-(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or -O-(methyl), or with a methylenedioxy ring linking the ortho and meta positions. In a further embodiment, R₇ is H, unsubstituted -CH₂-(6-membered aryl), or unsubstituted -CH₂-(6-membered heteroaryl). In an even further embodiment, R₇ is unsubstituted phenyl or H. In a still further embodiment, R₇ is H. In an even further embodiment, R₃, R₆ and R₇ are all hydrogen.

In an embodiment, R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₅ are optionally substituted with one or more F, and R₄ is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF₃, or SF₅, wherein alkyl, alkenyl, alkynyl of R₄ are optionally substituted with one or more F, and wherein cycloalkyl of R₄ is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl or C2-C5 alkynyl. In another embodiment, R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₅ are optionally substituted with one or more F, and R₄ is C2-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF₃, or SF₅, wherein alkyl, alkenyl, and alkynyl of R₄ are optionally substituted with one or more F, and wherein cycloalkyl of R₄ is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl.

In another embodiment, R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl of R₅ is optionally substituted with one or more F, and R₄ is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl of

R₄ is optionally substituted with one or more F, and cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl or C2-C5 alkynyl, and R₄ is not isopropyl. In another embodiment, R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl of R₅ is optionally substituted with one or more F, and R₄ is C2 alkyl substituted with one or more F, C3-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), SF₅, wherein alkyl, alkenyl, and alkynyl of R₄ are optionally substituted with one or more F, wherein cycloalkyl of R₄ is optionally substituted with one or more F, C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R₄ is not isopropyl.

In another embodiment, R₁ is as defined hereinabove, R₂ is H, C1-C3 alkyl, C3 cycloalkyl, C3 alkenyl, or C3 alkynyl, wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₂ are optionally substituted with one or more F; R₃ is H, methyl, ethyl, or F, wherein methyl and ethyl of R₃ are optionally substituted with one or more F; R₆ is H, methyl, ethyl, or F, wherein methyl and ethyl of R₆ are optionally substituted with one or more F; either R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₅ are optionally substituted with one or more F, and R₄ is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF₃, or SF₅, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl; or alternatively R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl of R₅ is optionally substituted with one or more F, and R₄ is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), SF₅, wherein alkyl, alkenyl, and alkynyl of R₄ are optionally substituted with one or more F, and wherein cycloalkyl of R₄ is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R₄ is not isopropyl; and R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3

alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₇ are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

In another embodiment, R₁ is as defined hereinabove, R₂ is H, methyl, or ethyl, wherein methyl and ethyl of R₂ are optionally substituted with one or more F; R₃ is H or F; R₆ is H or F; either R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₅ are optionally substituted with one or more F, and R₄ is C2-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF₃, or SF₅, wherein alkyl, alkenyl, and alkynyl of R₄ are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more F, C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl; or in the alternative, R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl of R₅ is optionally substituted with one or more F and R₄ is C2 alkyl substituted with one or more F, C3-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), SF₅, wherein alkyl, alkenyl, and alkynyl of R₄ are optionally substituted with one or more F, wherein cycloalkyl of R₄ is optionally substituted with one or more F, C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R₄ is not isopropyl; and R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl and cycloalkyl of R₇ are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl of R₇, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

In an embodiment, R₂ is methyl. In an embodiment, R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl,

and cycloalkyl of R₅ are optionally substituted with one or more F, and R₄ is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF₃, or SF₅, wherein alkyl, alkenyl, and alkynyl of R₄ are optionally substituted with one or more F, and wherein cycloalkyl of R₄ is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and R₁ is H, methyl, ethyl, or -CH₂-O- (methyl); R₃ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl of R₃ are optionally substituted with one or more F; R₆ is H, C1-C3 alkyl, cyclopropyl, or F, and R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₇ are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In an embodiment, R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₅ are optionally substituted with one or more F; R₄ is C2-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF₃, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₄ are optionally substituted with one or more F, and wherein cycloalkyl of R₄ is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and R₁, R₃, R₆ and R₇ are as defined herein. In an embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₃ is H or F, and R₁, R₆ and R₇ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₃ is H, and R₁, R₆ and R₇ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₆ is hydrogen or F, and R₁, R₃, and R₇ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₆ is hydrogen, and R₁, R₃, and R₇ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is hydrogen and R₁, R₃, and R₆ are as defined herein. In a further embodiment,

when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S, and R₁, R₃, and R₆ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), wherein alkyl and cyclopropyl of R₇ are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S, and R₁, R₃, and R₆ are as defined herein. In a further embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring, and R₁, R₃, and R₆ are as defined herein. In still another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is -CH₂-(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or -O-(methyl), or with a methylenedioxy ring linking the ortho and meta positions, and R₁, R₅, and R₆ are as defined herein.

In another embodiment, R₂ is methyl, R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl of R₅ is optionally substituted with one or more F, R₄ is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), SF₅, wherein alkyl, alkenyl, and alkynyl of R₄ are optionally substituted with one or more F, wherein cycloalkyl of R₄ is optionally substituted

with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R₄ is not isopropyl; and R₁, R₃, R₆ and R₇ are as defined herein. In another embodiment, R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl of R₅ is optionally substituted with one or more F, R₄ is C2 alkyl substituted with one or more F, C3-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), SF₅, wherein alkyl, alkenyl, and alkynyl of R₄ are optionally substituted with one or more F, wherein cycloalkyl of R₄ is optionally substituted with one or more F, C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R₄ is not isopropyl, and R₁, R₃, R₆ and R₇ are as defined herein. In an embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₃ is H or F, and R₁, R₆ and R₇ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₃ is H, and R₁, R₆ and R₇ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₆ is hydrogen or F, and R₁, R₃, and R₇ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₆ is hydrogen, and R₁, R₃, and R₇ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is hydrogen and R₁, R₃, and R₆ are as defined herein. In a further embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S, and R₁, R₃, and R₆ are as defined herein. In another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O,

N, and S, and R₁, R₃, and R₆ are as defined herein. In a further embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring, and R₁, R₃, and R₆ are as defined herein. In still another embodiment, when R₂, R₄ and R₅ are as defined in this paragraph, R₇ is -CH₂-(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or -O-(methyl), or with a methylenedioxy ring linking the ortho and meta positions, and R₁, R₅, and R₆ are as defined herein.

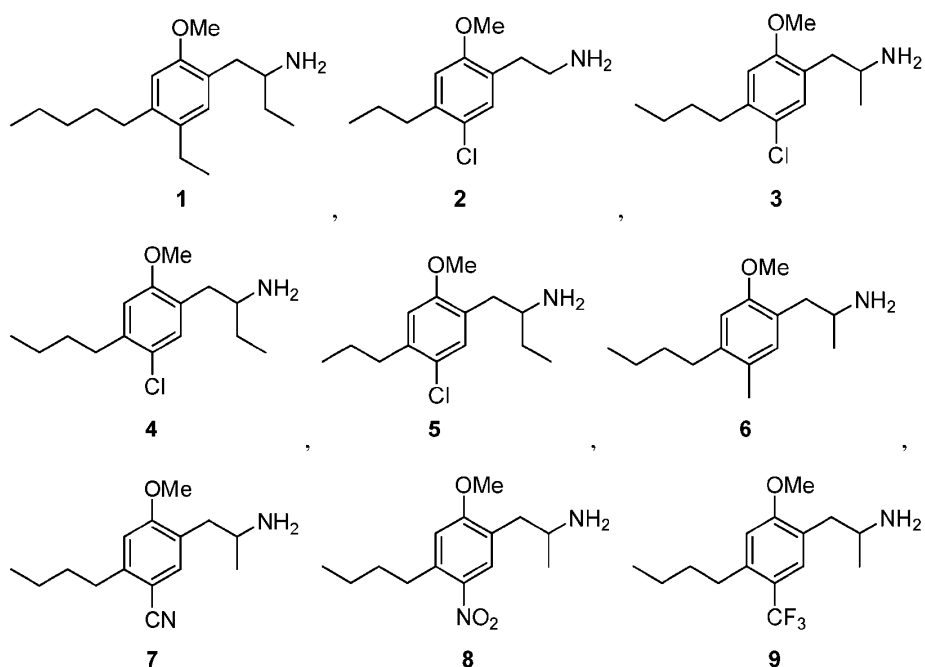
In an embodiment, R₂ is methyl, R₁ is H, methyl, ethyl, or -CH₂-O-(methyl); R₃ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl of R₃ are optionally substituted with one or more F; R₆ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl of R₆ are optionally substituted with one or more F and R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₇ are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; R₄ is C2-C8 alkyl, Br, SF₅, and R₅ is C1-C5 alkyl, Cl, CN, NO₂, CF₃, SMe, -S(O)(O)-(C1-C5 alkyl). In another embodiment, R₂ is methyl, R₁ is H, methyl or ethyl; R₃ is H, C1-C3 alkyl, or F, wherein alkyl of R₃ is optionally substituted with one or more F; R₆ is H, C1-C3 alkyl, or F, wherein alkyl of R₆ is optionally substituted with one or more F; and R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl of R₇ are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3

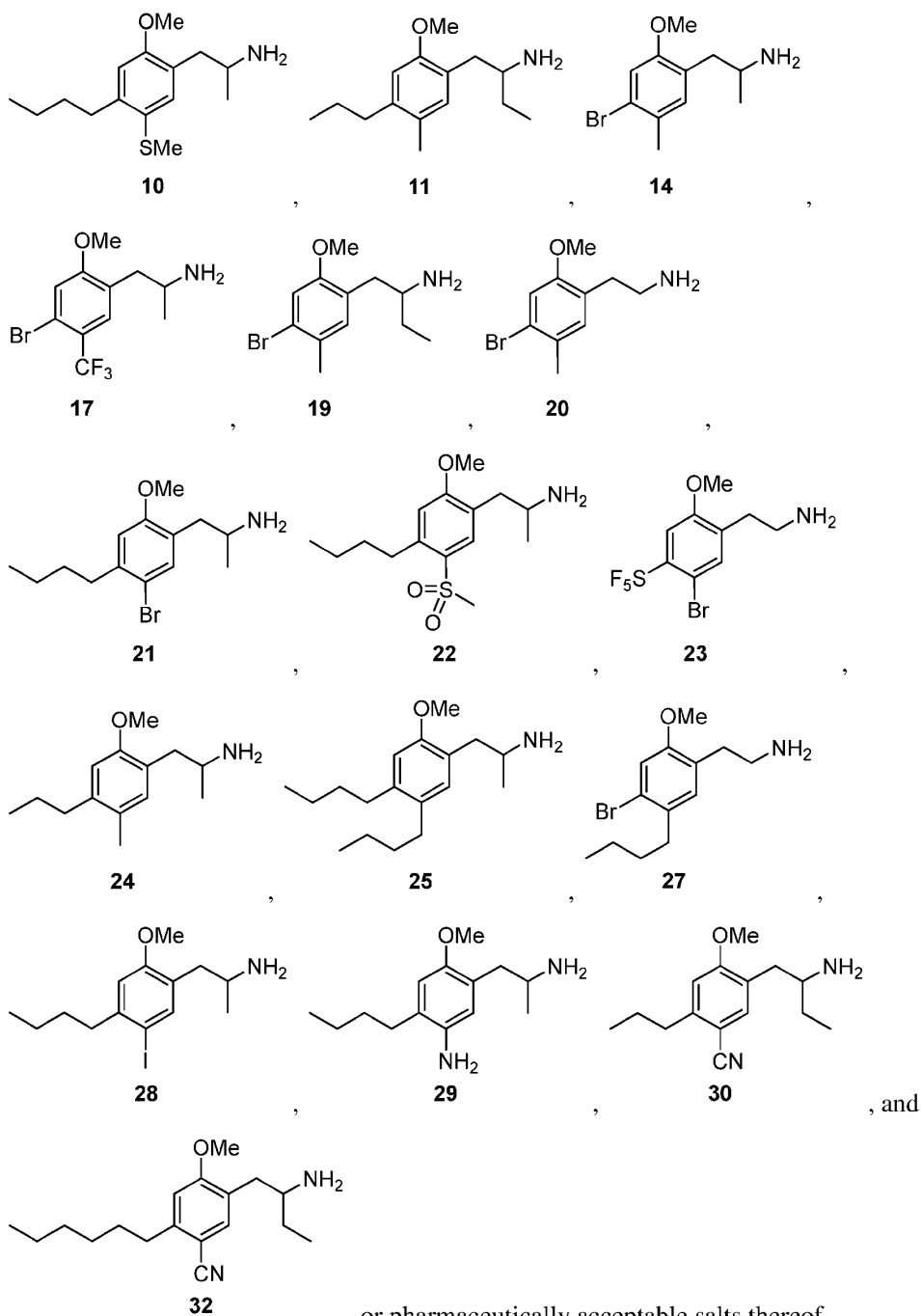
alkynyl), -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl of R₇ are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S; R₄ is C2-C8 alkyl, Br, SF₅, and R₅ is C1-C5 alkyl, Cl, CN, NO₂, CF₃, SMe, -S(O)(O)-(C1-C5 alkyl). In another embodiment, R₂ is methyl, R₁ is H, methyl or ethyl; R₃ is H, C1-C3 alkyl, or F, wherein alkyl of R₃ is optionally substituted with one or more F; R₆ is H, C1-C3 alkyl, or F, wherein alkyl of R₆ is optionally substituted with one or more F; R₇ is H; R₄ is C2-C8 alkyl, Br, SF₅, and R₅ is C1-C5 alkyl, Cl, CN, NO₂, CF₃, SMe, -S(O)(O)-(C1-C5 alkyl).

All of the different combinations and permutations of variables R₁, R₂, R₃, R₄, R₅, R₆, and R₇, as defined herein, are embodiments of the present disclosure and are within the scope of present disclosure.

The present disclosure includes stereoisomers of the first set of compounds of Formula (I).

In an embodiment, the compound of the first set of compounds of Formula (I) is selected from the group consisting of:





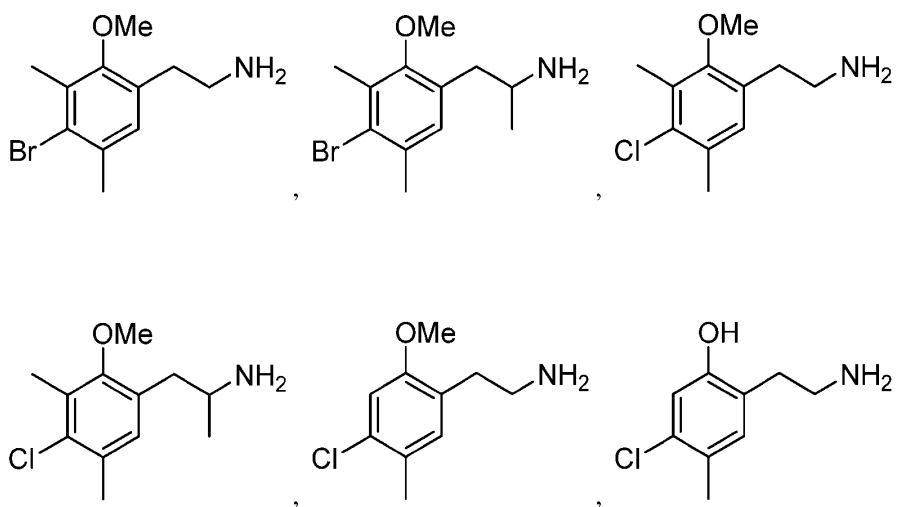
Any of the compounds disclosed above containing one or more chiral centers can be a pure enantiomeric (R or S) or diastereomeric version thereof. In embodiments, the present

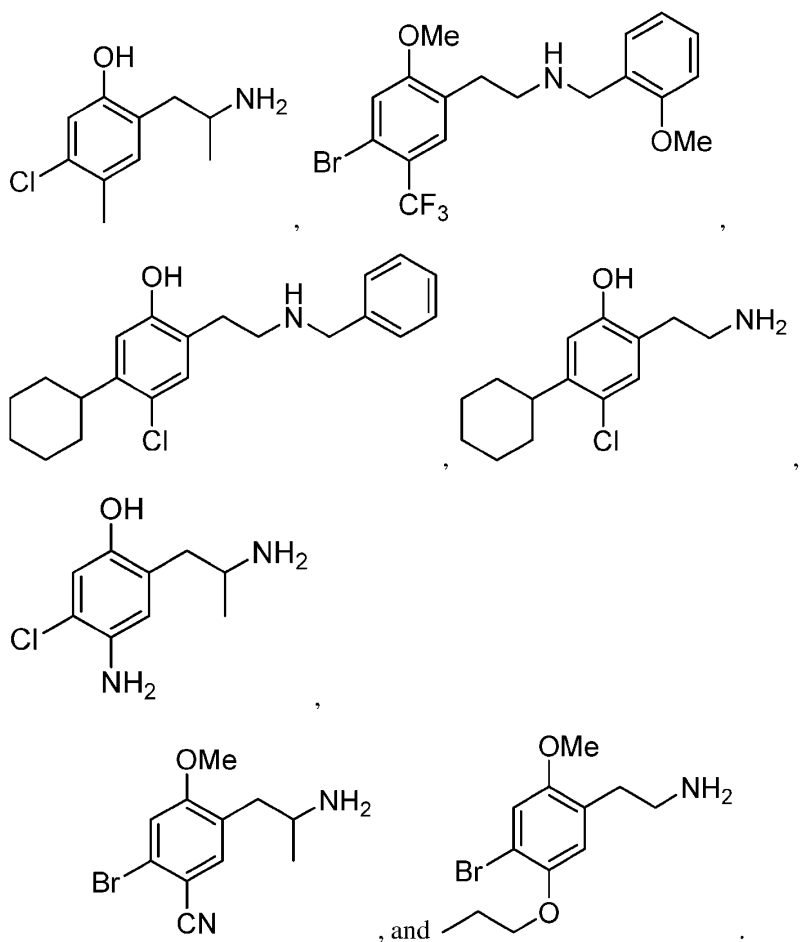
disclosure includes the R and S stereoisomers of the compounds identified as compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 14, 17, 19, 21, 22, 24, 25, 28, 29, 30, and 32, in both substantially pure form as well as mixtures of the same.

In embodiments, the following compounds are excluded:

- (a) when R₂ is methyl, R₃ is methyl, R₄ is Cl or Br, R₅ is methyl, R₆ is H, and R₇ is H, then R₁ is not H or methyl;
- (b) when R₁ is H or methyl, R₂ is H or methyl, R₃ is H, R₅ is methyl, R₆ is H, and R₇ is H, then R₄ is not Cl;
- (c) when R₁ is H, R₂ is methyl, R₃ is H, R₅ is CF₃, R₆ is H, and R₇ is ortho-methoxybenzyl, then R₄ is not Br;
- (d) when R₁ is H, R₂ is H, R₃ is H, R₅ is Cl, R₆ is H, and R₇ is H or benzyl, then R₄ is not cyclohexyl; and
- (e) when R₁ is methyl, R₂ is H, R₃ is H, R₅ is NH₂, R₆ is H, and R₇ is H, then R₄ is not Cl.

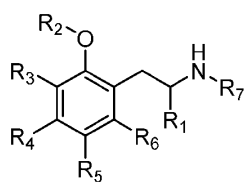
In another embodiment, the following compounds are excluded from the present disclosure:





II. SECOND SET OF COMPOUNDS OF FORMULA (I)

In another embodiment, the present disclosure relates to the following compounds of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof,
wherein:

R₁ is -CH₂-OH, -CH₂-O-(methyl), -CH₂F, or -CH₂CH₂F;

R₂ is C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R₃ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₄ is C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₅ is -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl)-(C3-C5 cycloalkyl), CF₃, CN, Br, or I, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₆ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₇ is H, -CH₂-(aryl), or -CH₂-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the provisos that:

- (a) when R₁ is -CH₂-OH, R₂ is methyl, R₃ is H, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl, -S-(methyl), or n-butyl; and
- (b) when R₁ is -CH₂-OH, R₂ is methyl, R₃ is methyl, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl.

In an embodiment, R₂ is C1-C3 alkyl, cyclopropyl, C3 alkenyl, or C3 alkynyl, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F;

R₃ is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R₅ is -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -O-(C1-C3 alkyl)-(cyclopropyl), CF₃, or CN, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein cyclopropyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R₆ is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S, and

R₁ and R₄ are as defined herein with respect to the second set of compounds of Formula (I).

In a further embodiment of the second set of compounds of Formula (I),

R₂ is methyl or ethyl, wherein methyl and ethyl are optionally substituted with one or more F;

R₃ is H or F;

R₄ is C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R₅ is -O-(methyl), -O-(ethyl), or CN, wherein methyl and ethyl are optionally substituted with one or more F;

R₆ is H or F;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

In an embodiment, R₁ is -CH₂-OH. In another embodiment, R₁ is -CH₂-O-(methyl). In a further embodiment, R₁ is -CH₂F. In still another embodiment, R₁ is -CH₂CH₂F. With respect to each embodiment, R₂, R₃, R₄, R₅, R₆ and R₇ are as defined with respect to the second set of compounds of Formula (I).

In an embodiment, R₂ is methyl. In a further embodiment, R₅ is -O-(C1-C5 alkyl). In another embodiment, R₅ is -O-(methyl). In even a further embodiment, R₂ is methyl and R₅ is -O-(C1-C5 alkyl), for instance, R₅ is -O-(methyl). Regarding each embodiment, R₁, R₃, R₄, R₆ and R₇ are as defined with respect to the second set of compounds of Formula (I).

In an embodiment, R₃ is hydrogen. In another embodiment, R₆ is H. In a further embodiment, R₃ and R₆ are both hydrogen. Regarding each embodiment, R₁, R₂, R₄, R₅ and R₇ are as defined with respect to the second set of compounds of Formula (I).

In an embodiment, R₄ is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl. In another embodiment, R₄ is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and

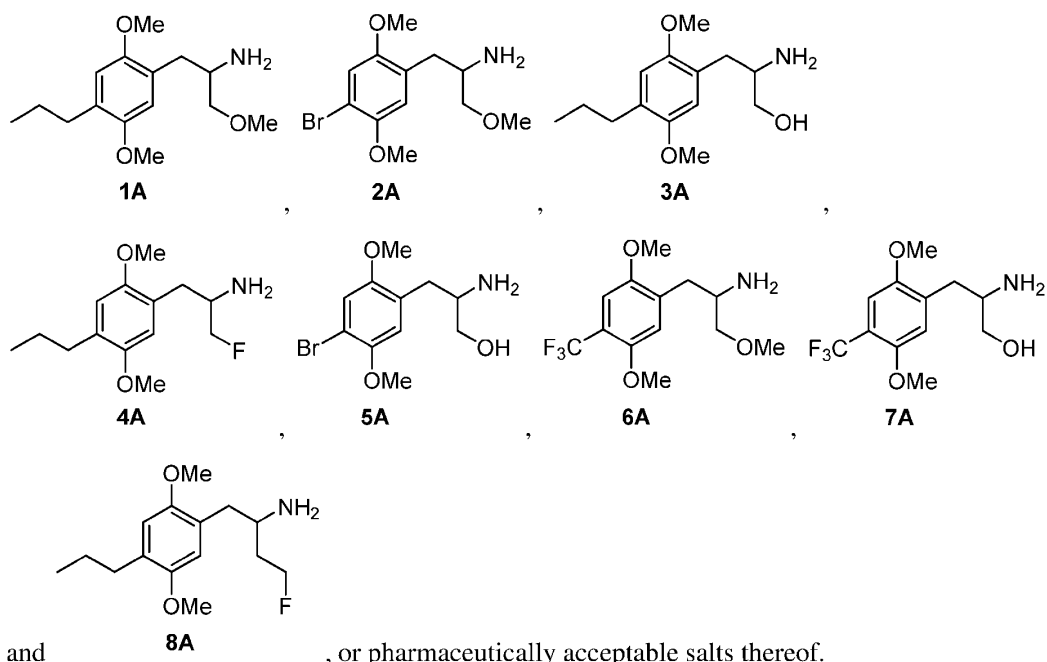
wherein cycloalkyl is optionally substituted with one to three C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl. Regarding each embodiment, R₁, R₂, R₅, R₆ and R₇ are as defined with respect to the second set of compounds of Formula (I).

In an embodiment, R₇ is H. In another embodiment, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In another embodiment, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In a further embodiment, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), and -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In a still further embodiment, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring. In an even another embodiment, wherein R₇ is -CH₂-(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or -O-(methyl), or with a methylenedioxy ring

linking the ortho and meta positions. Regarding each embodiment, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined with respect to the second set of compounds of Formula (I).

The present disclosure includes stereoisomers of the second set of compounds of Formula (I). Any of the compounds disclosed above containing one or more chiral centers can be a pure enantiomeric (R or S) or diastereomeric version thereof.

The following are examples of compounds contemplated within the present disclosure with respect to the second set of compounds of Formula (I):



and , or pharmaceutically acceptable salts thereof.

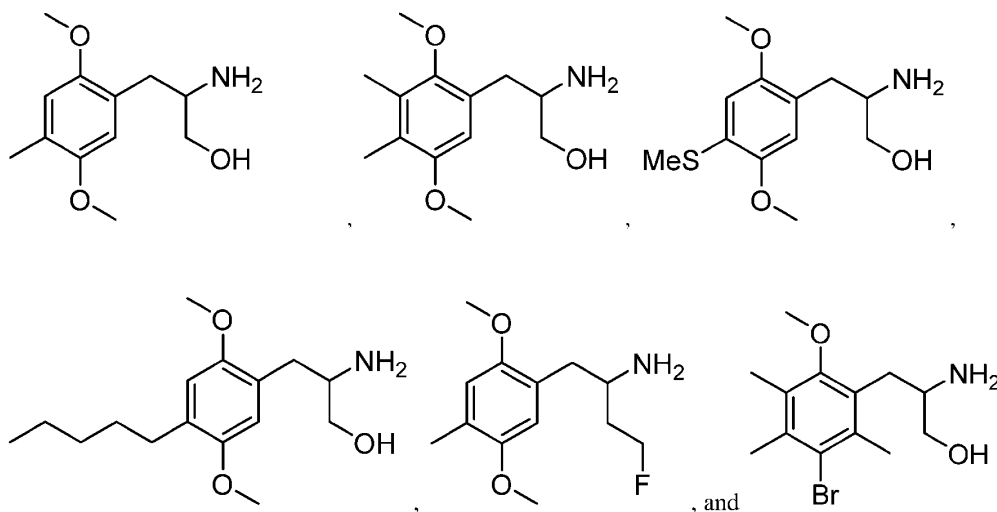
The present disclosure includes the R and S stereoisomers of compounds identified as 1A, 2A, 3A, 4A, 5A, 6A, 7A, and 8A, in both substantially pure form as well as mixtures of the same.

In an embodiment, the following compounds are excluded:

- (a) R₁ is -CH₂-OH, R₂ is methyl, R₃ is H, R₅ is -O-(methyl), R₆ is H, and R₇ is H, and R₄ is not methyl, -S-(methyl), or n-butyl;
- (b) R₁ is -CH₂-OH, R₂ is methyl, R₃ is methyl, R₅ is -O-(methyl), R₆ is H, and R₇ is H, and R₄ is not methyl;
- (c) when R₁ is -CH₂CH₂F, R₂ is methyl, R₃ is H, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl; and

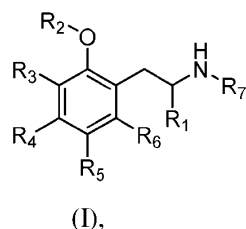
(d) when R_1 is $-\text{CH}_2\text{-OH}$, R_2 is methyl, R_3 is methyl, R_5 is Br, R_6 is methyl, and R_7 is H, then R_4 is not methyl.

In an embodiment, the following compounds are excluded:



III. THIRD SET OF COMPOUNDS OF FORMULA (I)

In an embodiment, this third set of compounds of Formula (I) have the formula:



or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is H, methyl, ethyl, n-propyl, $-\text{CH}_2\text{-OH}$, $-\text{CH}_2\text{-O-(methyl)}$, $-\text{CH}_2\text{F}$, or $-\text{CH}_2\text{CH}_2\text{F}$;

R_2 is C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R_3 is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₄ is C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C5 cycloalkyl), -S(O)(O)-(C1-C5 alkyl), -S(O)(O)-(C3-C5 alkenyl), -S(O)(O)-(C3-C5 alkynyl), -S(O)(O)-(C3-C5 cycloalkyl), -S(O)(O)-(C1-C5 alkyl)-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl)-(C3-C5 cycloalkyl), NH₂, NH(C1-C5 alkyl), or N(C1-C5 alkyl)₂, F, Cl, Br, I, CN, or NO₂, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₆ is F;

R₇ is H, -CH₂-(aryl), or -CH₂-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the proviso that when R₁ is H, R₂ is methyl, R₃ is H, R₄ is F, and R₇ is H, then R₅ is not Cl or Br.

In an embodiment, with respect to the third set of compounds within Formula (I),

R₂ is C1-C3 alkyl, cyclopropyl, C3 alkenyl, or C3 alkynyl, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F;

R₃ is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R₅ is -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -O-(C1-C3 alkyl)-(cyclopropyl), or CN, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein cyclopropyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S, and

R₁, R₄ and R₆ are defined hereinabove with respect to the third set of compounds of Formula (I).

In an embodiment,

R₂ is methyl or ethyl, wherein methyl and ethyl are optionally substituted with one or more F;

R₃ is H or F;

R₄ is C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R₅ is -O-(methyl), -O-(ethyl), or CN, wherein methyl and ethyl are optionally substituted with one or more F;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from

the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S,

and R₁ and R₆ are as defined hereinabove with respect to the third set of compound of Formula (I).

In an embodiment, R₁ is H or Me. In another embodiment, R₁ is ethyl. In a further embodiment, R₁ is n-propyl. In a still further embodiment, R₁ is -CH₂-OH. In an even further embodiment, R₁ is -CH₂-O-(methyl). In addition, R₁ is -CH₂F in another embodiment. In an even still further embodiment, R₁ is -CH₂CH₂F. With respect to each embodiment, R₂, R₃, R₄, R₅, R₆ and R₇ are as defined with respect to the third set of compounds of Formula (I).

In an embodiment, R₂ is C1-C5 alkyl, such as C1-C3 alkyl, for example, methyl. In an embodiment, R₅ is -O-(C1-C5 alkyl), such as -O-(C1-C3 alkyl), for example, -O-(methyl). In a further embodiment, R₂ is C1-C5 alkyl, such as C1-C3 alkyl, for example, methyl and R₅ is -O-(C1-C5 alkyl), such as -O-(C1-C3 alkyl), for example, -O-(methyl). Regarding each embodiment, R₁, R₃, R₄, R₆ and R₇ are as defined with respect to the third set of compounds of Formula (I).

In an embodiment, R₃ is H, C1-C3 alkyl, such as methyl or ethyl, or F. In another embodiment, R₃ is H or F. In a further embodiment, R₃ is H. Regarding each embodiment, R₁, R₂, R₄, R₅, R₆, and R₇ are as defined with respect to the third set of compounds of Formula (I).

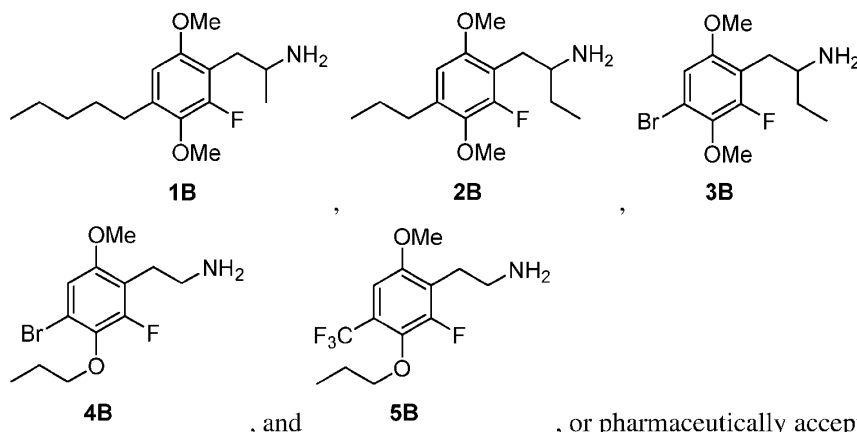
In an embodiment, R₄ is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl. In a further embodiment, R₄ is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and

wherein cycloalkyl is optionally substituted with one to three C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl. Regarding each embodiment, R₁, R₂, R₃, R₅, R₆ and R₇ are as defined with respect to the third set of compounds of Formula (I).

In another embodiment, R₇ is H. In a further embodiment, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In a still further embodiment, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), and -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S. In an even further embodiment, R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring. In another embodiment, R₇ is -CH₂-(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or -O-(methyl), or with a methylenedioxy ring linking the ortho and meta positions. Regarding each embodiment, R₁, R₂, R₃, R₄, R₅ and R₆ are as defined with respect to the third set of compounds of Formula (I).

The present disclosure includes stereoisomers of the third set of compounds of Formula (I). Any of the compounds disclosed above containing one or more chiral centers can be a pure enantiomeric (R or S) or diastereomeric version thereof.

The following are examples of compounds contemplated within the present disclosure with respect to the third set of compounds of Formula (I):

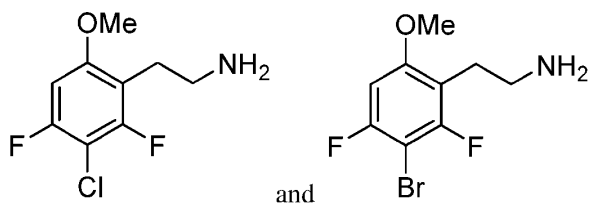


The present disclosure includes the R and S stereoisomers of compounds 1B, 2B and 3B, in both substantially pure form as well as mixtures of the same.

The following compounds are excluded from the present disclosure:

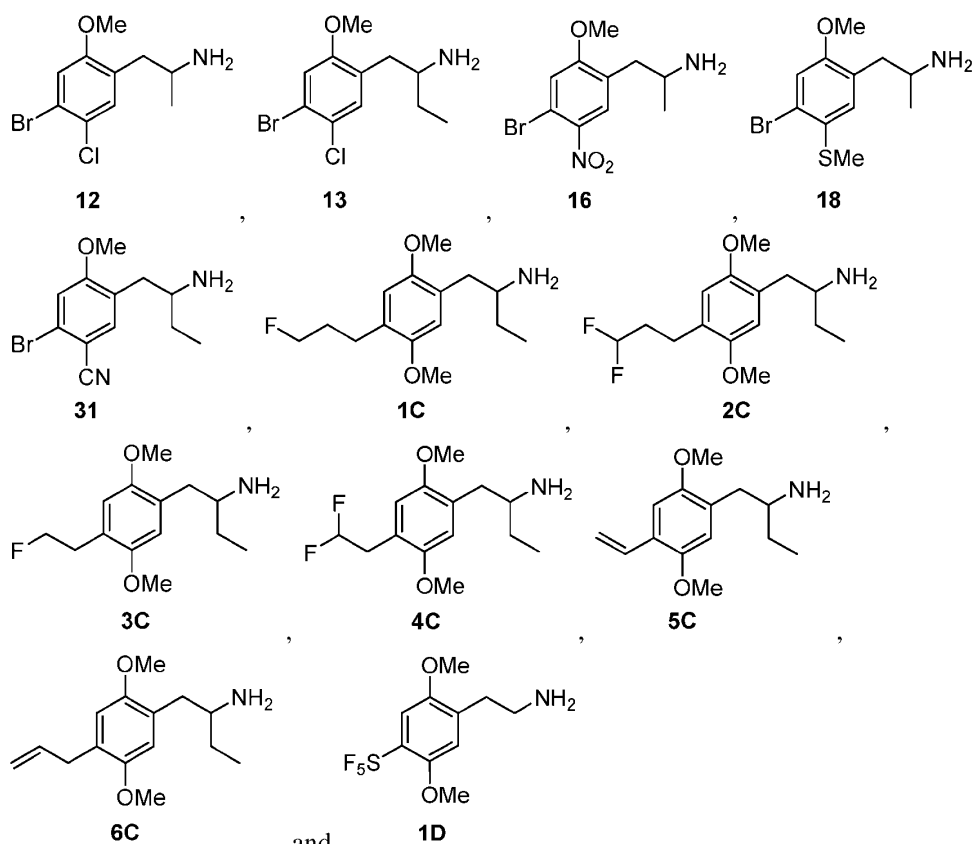
R₁ is H, R₂ is methyl, R₃ is H, R₄ is F, and R₇ is H, and R₅ is not Cl or Br.

In an embodiment, the following compounds are excluded:



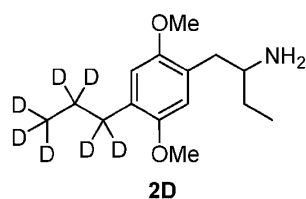
IV. MISCELLANEOUS COMPOUNDS

The following compounds are also contemplated to be within the scope of the present disclosure:



or a pharmaceutically acceptable salt thereof. In addition, the present disclosure includes the R and S stereoisomers of 12, 13, 16, 18, 31, 1C, 2C, 3C, 4C, 5C, and 6C, in both substantially pure form as well as mixtures of the same.

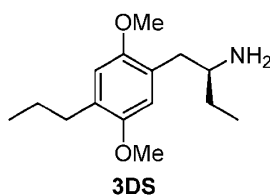
Further, the following deuterated compound is part of the present disclosure:



wherein each deuterium-enriched H-site is greater than 0.02% deuterium, or pharmaceutically acceptable salts thereof. In embodiments, the level of deuterium at each deuterium-enriched H site of the compound ranges from about 0.02% to 100%. In other embodiments, the level of deuterium at each deuterium-enriched H site of the compound is 50%-100%, 70%-100%, 90%-

100%, 95%-100%, 96%-100%, 97%-100%, 98%-100%, or 99%-100%. In an embodiment, each deuterium-enriched H-site is greater than 90% deuterium, and in a further embodiment, each deuterium-enriched H-site is greater than 95% deuterium. Moreover, the present disclosure includes the R and S stereoisomers of 2D.

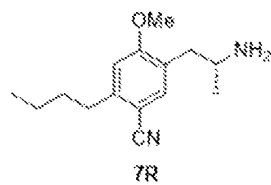
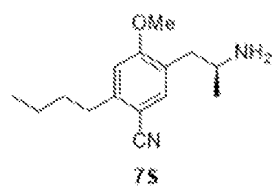
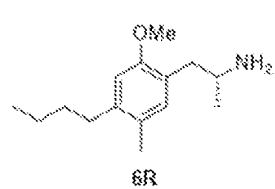
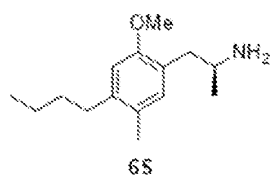
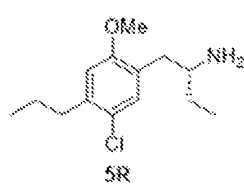
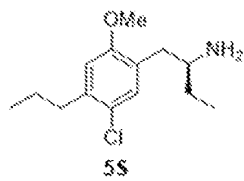
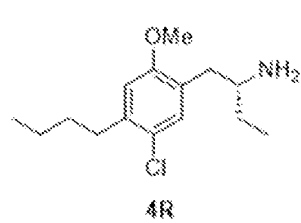
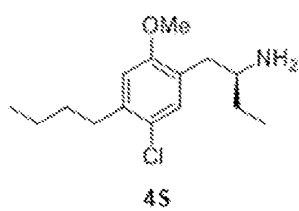
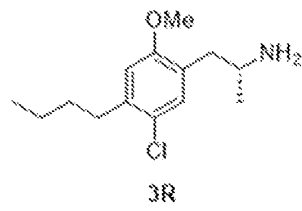
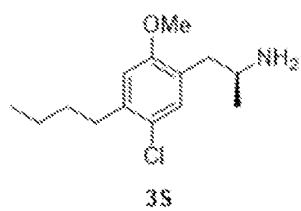
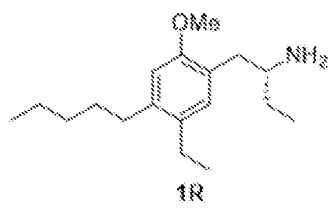
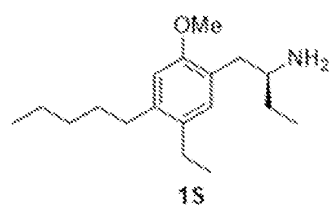
In another embodiment, the following composition comprising the S-enantiomeric form of the following compound is also contemplated to be within the scope of the present disclosure:

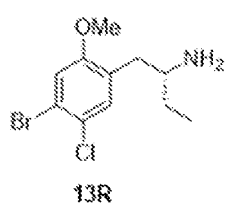
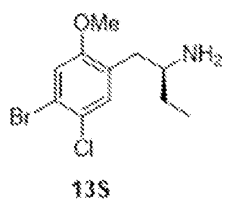
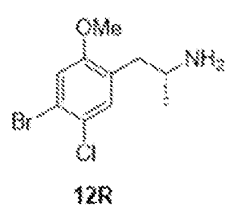
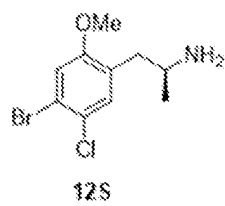
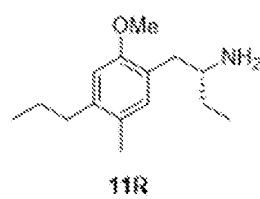
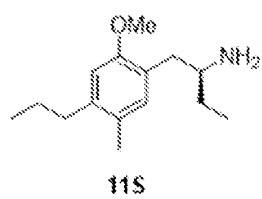
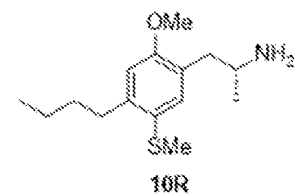
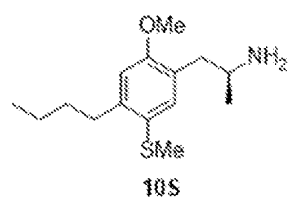
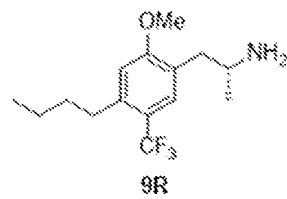
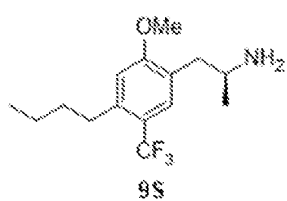
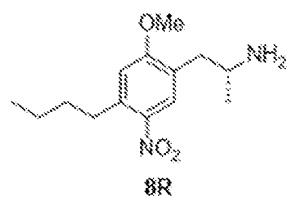
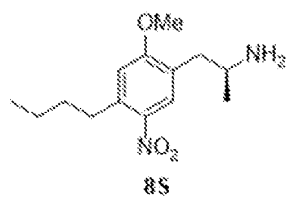


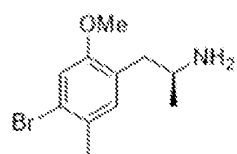
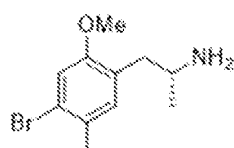
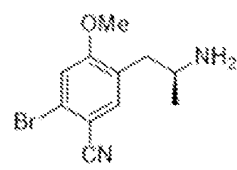
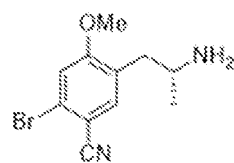
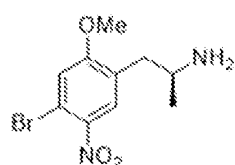
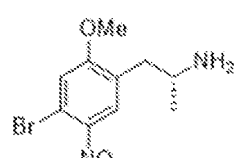
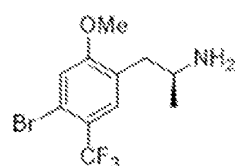
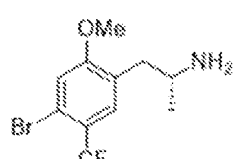
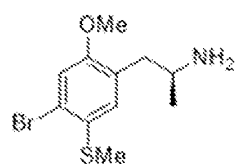
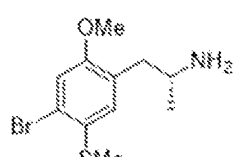
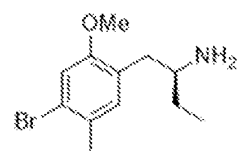
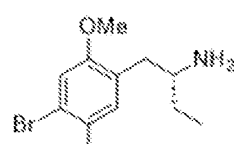
or pharmaceutically acceptable salts thereof, which optionally includes the R-enantiomeric form of the same compound, provided that the composition contains greater than 50% of the S-enantiomeric form. In a further embodiment, the composition contains greater than 90% of the S-enantiomeric form. In a further embodiment, the composition contains greater than 95% of the S-enantiomeric form.

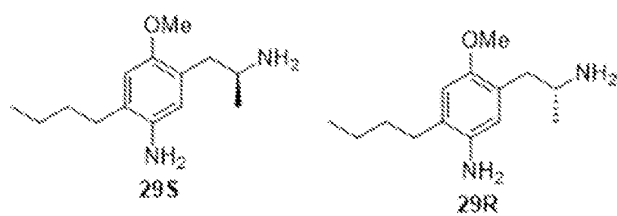
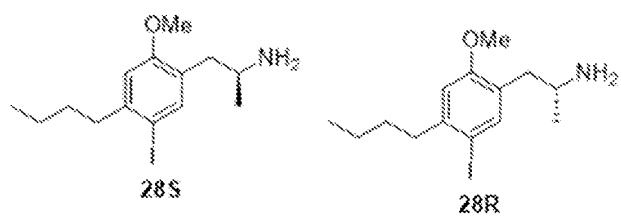
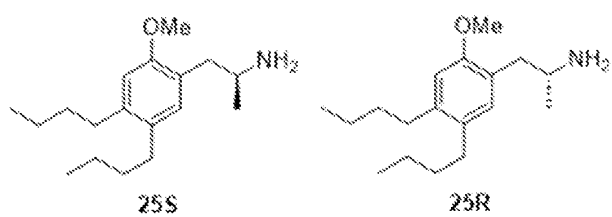
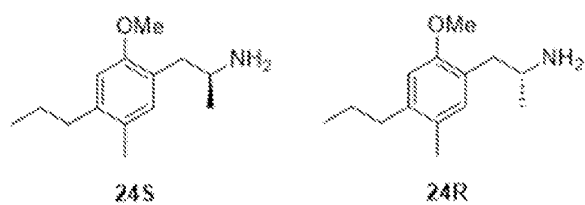
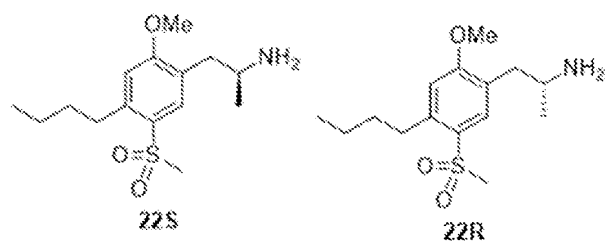
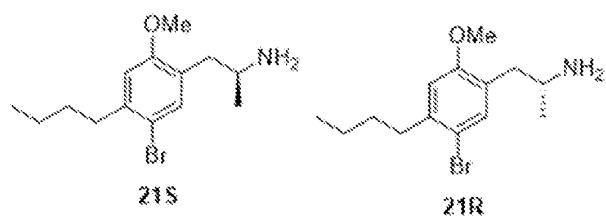
These compounds in this section, including their pharmaceutically acceptable salts thereof, will generally be identified as miscellaneous compounds. As used herein, the term “miscellaneous compounds” will refer to all of the compounds in this section. If reference is made to individual compounds in this section, it will be specifically identified.

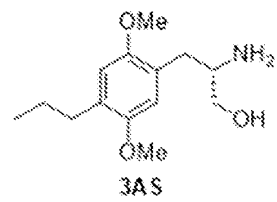
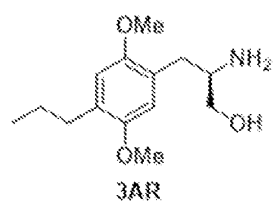
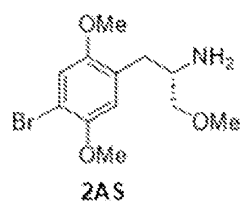
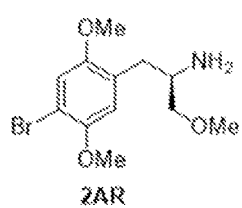
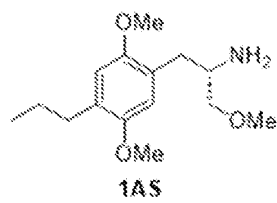
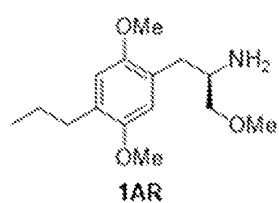
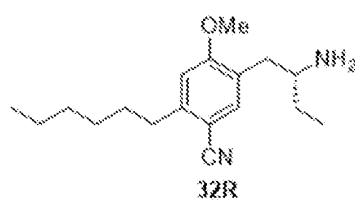
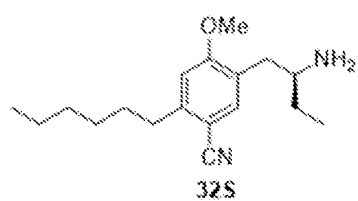
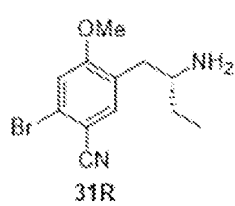
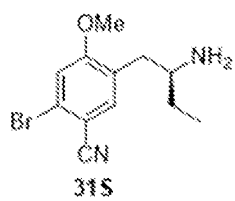
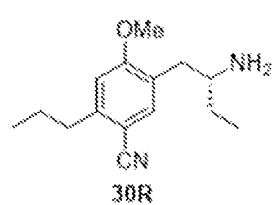
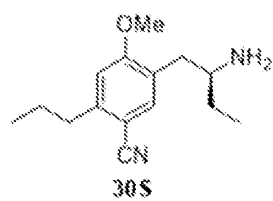
In embodiments, the compounds may be selected from any one or more of the following enantiomeric compounds:

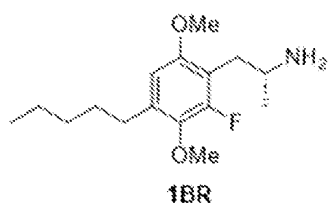
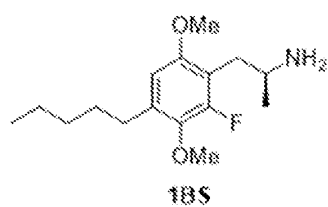
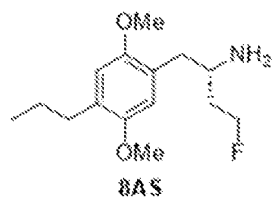
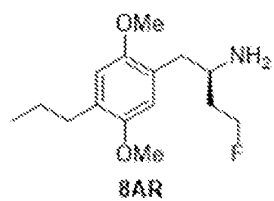
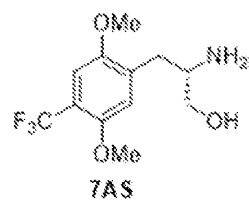
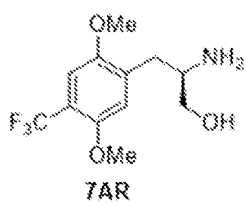
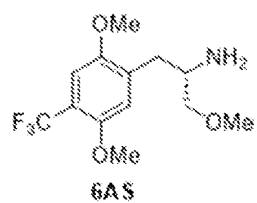
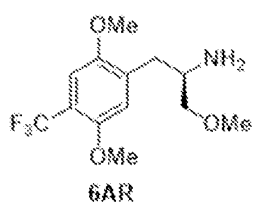
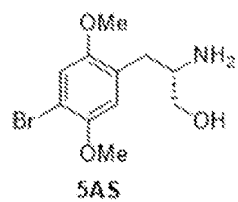
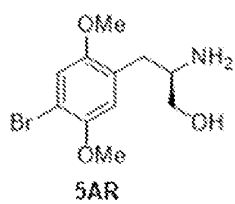
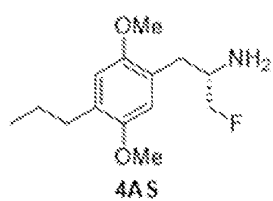
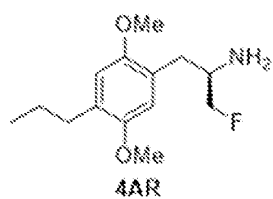


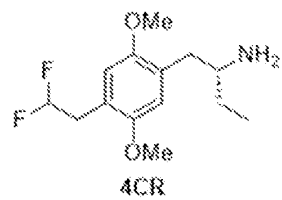
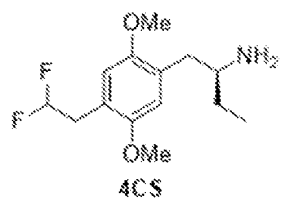
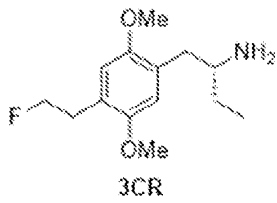
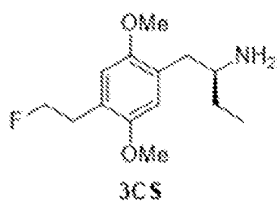
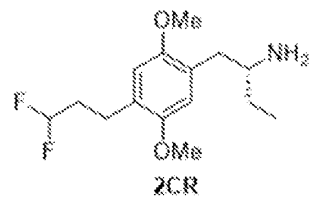
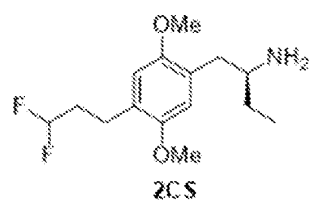
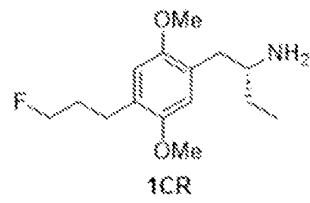
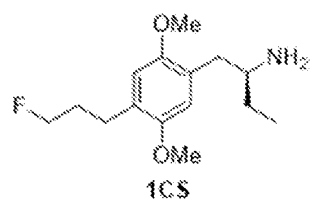
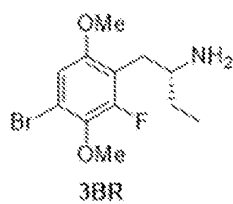
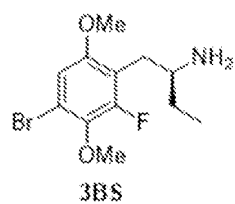
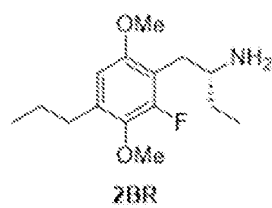
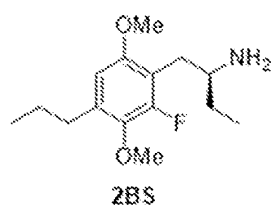


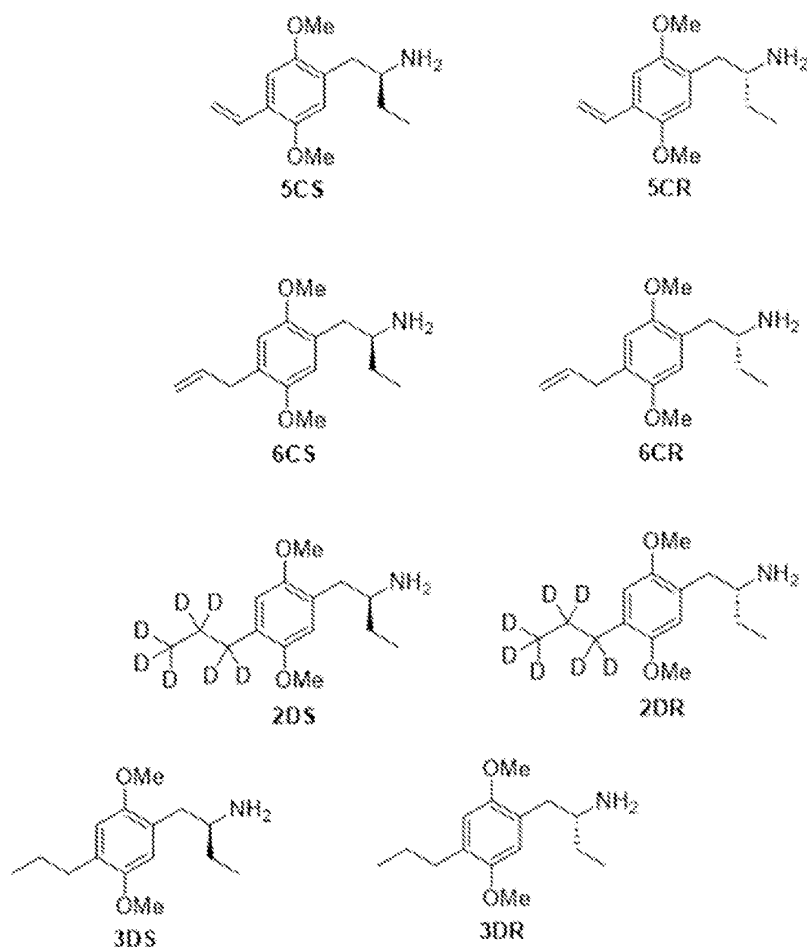
**14S****14R****15S****15R****16S****16R****17S****17R****18S****18R****19S****19R**











V. REMARKS REGARDING COMPOUNDS

The three sets of compounds of Formula (I) contain seven variables, R₁, R₂, R₃, R₄, R₅, R₆, and R₇. The disclosure has not identified all combinations and permutations of these various variables with each set of compounds of Formula (I). Nevertheless, these compounds of all three sets of Formula (I) as well as their pharmaceutically acceptable salts thereof are part of the present disclosure and are contemplated to be within the scope thereof.

Further, the compounds of each of the sets of Formula (I) and their pharmaceutically acceptable salts thereof as well as the miscellaneous compounds and their pharmaceutically acceptable salts thereof contain chiral centers, and thus can exist in various stereoisomeric forms. The various stereoisomers, including enantiomers and diastereomers, in both substantially pure form as well as mixtures thereof, including racemic and scalemic mixtures, are part of the

present disclosure and are contemplated to be within the scope thereof. In embodiments, any of the compounds disclosed herein containing one or more chiral centers can be a pure enantiomeric (R or S) or diastereomeric version thereof.

Salts of compounds of the present disclosure can be prepared by the reaction of a compound of the present disclosure with an appropriate acid or base in a suitable solvent, or mixture of solvents (such as an ether, for example, diethyl ether, or an alcohol, for example ethanol, or an aqueous solvent) using conventional procedures. Salts of compounds of the present disclosure can be exchanged for other salts by treatment using conventional ion-exchange chromatography procedures or reformation of the free base or free acid followed by reaction with an alternative acid or base, respectively.

Where it is desired to obtain a particular enantiomer of a compound of the present disclosure, this may be produced from a corresponding mixture of enantiomers by employing any suitable conventional procedure for resolving enantiomers. For example, diastereomeric derivatives (such as salts) can be produced by reaction of a mixture of enantiomers of a compound of the present disclosure (such as a racemate) and an appropriate chiral compound (such as a chiral acid). The diastereomers can then be separated by any conventional means such as crystallization, and the desired enantiomer recovered (such as by treatment with a base in the instance where the diastereomer is an acid salt). Alternatively, a racemic mixture of esters can be resolved by kinetic hydrolysis using a variety of biocatalysts (for example, see Patel *Stereoselective Biocatalysts*, Marcel Decker; New York 2000).

In another resolution process, a racemate of a compound of the present disclosure can be separated using chiral High Performance Liquid Chromatography. Alternatively, a particular enantiomer can be obtained by using an appropriate chiral intermediate in one of the processes described above. Chromatography, recrystallisation, and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular diastereomer, regioisomer, or geometric isomer of the compounds disclosed herein

PHARMACEUTICAL COMPOSITIONS AND KITS

Another aspect of the disclosure provides pharmaceutical compositions comprising compounds of Formula (I) and the miscellaneous compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier. In particular, the present disclosure provides

pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. Pharmaceutical compositions typically include a pharmaceutically acceptable carrier in which the one or more active compounds are contained (e.g., dissolved, suspended, or admixed). As well known, the pharmaceutically acceptable carrier is composed of one or more substances that are considered safe and effective. The carrier includes all components present in the pharmaceutical formulation other than the active ingredient(s). The term “carrier” includes, but is not limited to, diluents, binders, lubricants, glidants, disintegrants, fillers, and coating compositions. Suitable dosage forms for a compound disclosed herein include, but are not limited to, oral forms, such as tablets, hard or soft gelatin capsules, powders, granules and oral solutions, syrups or suspensions, troches, as well as sublingual, buccal, intratracheal, intraocular, or intranasal forms, forms adapted to inhalation, topical forms, transdermal forms, or parenteral forms, for example, forms adapted for intravenous, intra-arterial, intraperitoneal, intrathecal, intraventricular, intramuscular or subcutaneous administration. In embodiments, for such parenteral administration, it may be in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

The pharmaceutical formulations include those suitable for oral, topical, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), rectal, vaginal, intranasal, aerosol, or vaporization administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

Exemplary pharmaceutical compositions of this disclosure may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the disclosure, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic,

pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the disclosure, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for

example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch,

tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

In another aspect, the disclosure provides enteral pharmaceutical formulations including the compound of Formula (I) or miscellaneous compounds and an enteric material; and a pharmaceutically acceptable carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (e. g. , Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

Pharmaceutical compositions herein may also be provided with immediate release, delayed release, extended release, or modified release profiles. In embodiments, pharmaceutical compositions with different drug release profiles may be combined to create a two-phase or three-phase release profile. For example, pharmaceutical compositions may be provided with an

immediate release and an extended-release profile. In embodiments, pharmaceutical compositions may be provided with an extended release and delayed release profile. Such composition may be provided as pulsatile formulations, multilayer tablets, or capsules containing tablets, beads, granules, or the like.

The pharmaceutical composition may also include one or more auxiliary agents. The auxiliary agent(s), also may also be referred to as accessory ingredient(s), include any of the additional conventional substances of the art, such as fillers, binders, diluents, disintegrants, lubricants, colorants, flavoring agents, anti-oxidants, and wetting agents. Such auxiliary agents are suitably selected with respect to the intended form and route of administration and as consistent with conventional pharmaceutical practices.

The present disclosure also provides kits for use by, e.g., a consumer in need of treatment with the compound of Formula (I) and/or the miscellaneous compounds. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to treat a medical disorder, for example, a psychiatric disease or disorder. The instructions direct the user to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which

the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.*, as follows “First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . etc.”. Other variations of memory aids will be readily apparent. A “daily dose” can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

Also contemplated herein are methods and compositions that include a second active agent or administering a second active agent.

UTILITY AND METHODS OF USE

The compounds of Formula (I) and the miscellaneous compounds of the present disclosure are agonists of the 5-HT_{2A} receptor. In embodiments, the compounds of Formula (I) and/or the miscellaneous compounds selectively bind to and activate the 5-HT_{2A} receptor. Activation of 5-HT_{2A} receptors located in cortical and subcortical structures of the brain are believed to mediate the subjective, behavioral, and psychological effects of psychedelics in both animals and humans. As such, these compounds of Formula (I) and miscellaneous compounds are useful for treating psychiatric disorders. However, unlike other phenylalkylamine psychedelics, the compounds of Formula (I) and miscellaneous compounds have reduced or no hallucinogenic effects.

Another aspect of the disclosure provides methods of treating a disease associated with expression or activity of 5-HT_{2A} in a patient. For example, a contemplated method includes administering the compound of Formula (I) and/or the miscellaneous compounds in an amount sufficient to establish activation of 5-HT_{2A} effective to decrease the symptoms of a psychiatric disease or disorder in the patient. Further, treatment with a compound of Formula (I) and/or miscellaneous compounds may also increase neuroplasticity or neurogenesis in a 5-HT_{2A}-dependent manner.

In some embodiments, the present disclosure provides a method of treating a psychiatric disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula (I) and/or miscellaneous compounds of the present disclosure, such as any one of the compounds of Formula (I) and/or miscellaneous compounds.

In some embodiments, the psychiatric disease or disorder is selected from the group consisting of major depressive disorder, persistent depressive disorder, postpartum depression, premenstrual dysphoric disorder, seasonal affective disorder, psychotic depression, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition.

In some embodiments, the psychiatric disease or disorder is selected from the group consisting of bipolar disorder I, bipolar disorder II, cyclothymic disorder, substance/medication-induced bipolar and related disorder, and bipolar and related disorder due to another medical condition.

In some embodiments, the psychiatric disease or disorder is a substance-related disorder or substance-use disorder.

In some embodiments, the psychiatric disease or disorder is selected from the group consisting of separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder, panic disorder, panic attack, agoraphobia, generalized anxiety disorder, substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition.

In some embodiments, the psychiatric disease or disorder is selected from the group consisting of obsessive-compulsive and related disorders, trauma- and stressor-related disorders, feeding and eating disorders, borderline personality disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder.

In some embodiments, the psychiatric disorder is a neurocognitive disorder.

In some embodiments, the psychiatric disease or disorder is a treatment-resistant disease or disorder, such as treatment-resistant depressive disorder.

The present disclosure further provides a method of enhancing creativity or cognition in a subject, said method comprising administering to said subject a composition comprising an effective amount of a compound of Formula (I) and/or miscellaneous compounds of the present disclosure.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Depressive Disorders, *e.g.*, Major Depressive Disorder, Persistent Depressive Disorder, Postpartum Depression, Premenstrual Dysphoric Disorder, Seasonal Affective Disorder,

Psychotic Depression, Disruptive Mood Dysregulation Disorder, Substance/Medication-Induced Depressive Disorder, and Depressive Disorder Due to Another Medical Condition.

Also provided herein are compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same for treating refractory or treatment-resistant depression, *e.g.*, patients suffering from a depressive disorder that does not, and/or has not, responded to adequate courses of at least one, or at least two, other antidepressant compounds or therapeutics. As used herein "depressive disorder" encompasses refractory depression.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Bipolar and Related Disorders, *e.g.*, Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder, Substance/Medication-Induced Bipolar and Related Disorder, and Bipolar and Related Disorder Due to Another Medical Condition.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Substance-Related Disorders, *e.g.*, preventing a substance use craving, diminishing a substance use craving, and/or facilitating substance use cessation or withdrawal. Substance use disorders involve abuse of psychoactive compounds such as alcohol, caffeine, cannabis, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, nicotine and tobacco. As used herein "substance" or "substances" are psychoactive compounds which can be addictive such as alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, anxiolytics, stimulants, nicotine and tobacco. For example, the methods and compositions may be used to facilitate smoking cessation or cessation of opioid use.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Anxiety Disorders, *e.g.*, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance/Medication-Induced Anxiety Disorder, and Anxiety Disorder Due to Another Medical Condition.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Obsessive-Compulsive and Related Disorders, *e.g.*, Obsessive-Compulsive Disorder, Body

Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder), Excoriation (Skin-Picking) Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, and Obsessive-Compulsive and Related Disorder Due to Another Medical Condition.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Trauma- and Stressor-Related Disorders, *e.g.*, Reactive Attachment Disorder, Disinhibited Social Engagement Disorder, Posttraumatic Stress Disorder, Acute Stress Disorder, and Adjustment Disorders.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Feeding and Eating Disorders, *e.g.*, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Pica, Rumination Disorder, and Avoidant/Restrictive Food Intake Disorder.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Neurocognitive Disorders, *e.g.*, Delirium, Major Neurocognitive Disorder, Mild Neurocognitive Disorder, Major or Mild Neurocognitive Disorder Due to Alzheimer's Disease, Major or Mild Frontotemporal Neurocognitive Disorder, Major or Mild Neurocognitive Disorder With Lewy Bodies, Major or Mild Vascular Neurocognitive Disorder, Major or Mild Neurocognitive Disorder Due to Traumatic Brain Injury, Substance/Medication-Induced Major or Mild Neurocognitive Disorder, Major or Mild Neurocognitive Disorder Due to HIV Infection, Major or Mild Neurocognitive Disorder Due to Prion Disease, Major or Mild Neurocognitive Disorder Due to Parkinson's Disease, Major or Mild Neurocognitive Disorder Due to Huntington's Disease, Major or Mild Neurocognitive Disorder Due to Another Medical Condition, and Major or Mild Neurocognitive Disorder Due to Multiple Etiologies.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Neurodevelopmental Disorders, *e.g.*, Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, Stereotypic Movement Disorder, Tic Disorders, Tourette's Disorder, Persistent (Chronic) Motor or Vocal Tic Disorder, and Provisional Tic Disorder.

In some embodiments, the compounds of Formula (I) and compositions comprising the same may be used to treat a psychiatric disorder including Personality Disorders, *e.g.*, Borderline Personality Disorder.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Sexual Dysfunctions, *e.g.*, Delayed Ejaculation, Erectile Disorder, Female Orgasmic Disorder, Female Sexual Interest/Arousal Disorder, Genito-Pelvic Pain/Penetration Disorder, Male Hypoactive Sexual Desire Disorder, Premature (Early) Ejaculation, and Substance/Medication-Induced Sexual Dysfunction.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a psychiatric disorder including Gender Dysphoria, *e.g.*, Gender Dysphoria.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat a headache or a headache disorder. In some embodiments, a headache disorder is a migraine or cluster headaches.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat an inflammatory disorder. In some embodiments, an inflammatory disorder is inflammatory bowel disease, including ulcerative colitis and Crohn's disease. In some embodiments, an inflammatory disorder is inflammatory bowel syndrome. In some embodiments, an inflammatory disorder is an inflammation-related cardiovascular disorder, such as atherosclerosis and coronary artery disease. In some embodiments, an inflammatory disorder is an inflammatory disorder dependent on TNF- α activity.

In some embodiments, the compounds of Formula (I) and/or miscellaneous compounds and compositions comprising the same may be used to treat high intraocular pressure.

The compounds of Formula (I) and miscellaneous compounds of the present disclosure may be administered to patients (animals and humans) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. It will be appreciated that the dose required for use in any particular application will vary from patient to patient, not only with the particular compound of Formula (I) and/or particular compound of miscellaneous compounds or composition selected, but also with the route of administration, the nature of the condition being

treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. For treating clinical conditions and diseases noted above, a compound of Formula (I) and/or miscellaneous compounds of this disclosure may be administered orally, subcutaneously, topically, parenterally, by inhalation spray, by vaporization, intranasally, or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Parenteral administration may include subcutaneous injections, intravenous injections, intramuscular injections, or infusion techniques.

Treatment can be continued for as long or as short a period as desired. The compositions may be administered on a regimen of, for example, one to four or more times per day. A suitable treatment period can be, for example, at least about one week, at least about two weeks, at least about one month, at least about six months, at least about 1 year, or indefinitely. A treatment period can terminate when a desired result, for example a decrease in symptoms of a psychiatric disorder, is achieved. A treatment regimen can include a corrective phase, during which a dose sufficient to provide symptomatic relief is administered, and can be followed by a maintenance phase, during which a lower dose sufficient to prevent a return of symptoms is administered. A suitable maintenance dose is likely to be found in the lower parts of the dose ranges provided herein, but corrective and maintenance doses can readily be established for individual subjects by those of skill in the art without undue experimentation, based on the disclosure herein. Maintenance doses can be employed to maintain remission in subjects whose symptoms have been previously controlled by other means, including treatments employing other pharmacological agents.

In some embodiments, methods include treating a psychiatric disorder, *e.g.*, a depressive disorder, by administering to a patient in need thereof a pharmaceutical composition including about 0.01 mg to about 400 mg of a compound of Formula (I) and/or miscellaneous compounds of the present disclosure. In some embodiments, doses may be, *e.g.*, in the range of about 0.01 to 400 mg, 0.01 to 300 mg, 0.01 to 250 mg, 0.01 to 200 mg, 0.01 to 150 mg, 0.01 to 100 mg, 0.01 to 75 mg, 0.01 to 50 mg, 0.01 to 25 mg, 0.01 to 20 mg, 0.01 to 15 mg, 0.01 to 10 mg, 0.01 to 5 mg, 0.01 to 1 mg, 0.01 to 0.5 mg, 0.01 to 0.1 mg, 0.1 to 400 mg, 0.1 to 300 mg, 0.1 to 250 mg, 0.1 to 200 mg, 0.1 to 150 mg, 0.1 to 100 mg, 0.1 to 75 mg, 0.1 to 50 mg, 0.1 to 25 mg, 0.1

to 20 mg, 0.1 to 15 mg, 0.1 to 10 mg, 0.1 to 5 mg, 0.1 to 1 mg, 10 to 400 mg, 10 to 300 mg, 10 to 250 mg, 10 to 200 mg, 10 to 150 mg, 10 to 100 mg, 10 to 50 mg, 10 to 25 mg, 10 to 15 mg, 20 to 400 mg, 20 to 300 mg, 20 to 250 mg, 20 to 200 mg, 20 to 150 mg, 20 to 100 mg, 20 to 50 mg, 50 to 400 mg, 50 to 300 mg, 50 to 250 mg, 50 to 200 mg, 50 to 150 mg, 50 to 100 mg, 100 to 400 mg, 100 to 300 mg, 100 to 250 mg, 100 to 200 mg, with doses of, *e.g.*, about 0.01 mg, 0.025 mg, 0.05 mg, 0.1 mg, 0.15 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.25 mg, 1.5 mg, 1.75 mg, 2.0 mg, 2.5 mg, 3.0 mg, 3.5 mg, 4.0 mg, 4.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, and 400 mg being examples.

In some embodiments, dosages may include amounts of a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof in the range of about, *e.g.*, 1 mg to 50 mg, 1 mg to 40 mg, 1 mg to 30 mg, 1 mg to 20 mg, 1 mg to 15 mg, 1 mg to 10 mg, 0.1 mg to 10 mg, 0.1 to 5 mg, or 0.1 to 1 mg, with doses of 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.5 mg, 1.0 mg, 1.75 mg, 2 mg, 2.5 mg, 2.75 mg, 3 mg, 3.5 mg, 3.75 mg, 4 mg, 4.5 mg, 4.75 mg, 5 mg, 5.5 mg, 6 mg, 6.5 mg, 7 mg, 7.5 mg, 8 mg, 8.5 mg, 9 mg, 10 mg, 11 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 22.5 mg, 25 mg, 27.5 mg, 30 mg, 35 mg, 40 mg, 45 mg, and 50 mg being specific examples of doses.

Typically, dosages of a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof, are administered once, twice, three or four times daily, every other day, every three days, twice weekly, once weekly, twice monthly, once monthly, every two months, every 3 months, twice yearly, or once yearly to a patient in need thereof. In some embodiments, the dosage is about, *e.g.*, 0.1-400 mg/administration, 0.1-300 mg/administration, 0.1-250 mg/administration, 0.1-200 mg/administration, 0.1 -100 mg/administration, 0.1-50 mg/administration, or 0.1 to 25 mg/administration, for example 300 mg/administration, 250 mg/administration, 200 mg/administration, 150 mg/administration, 100 mg/administration, 75 mg/administration, 50 mg/administration, 25 mg/administration, 20 mg/administration, 10 mg/administration, 5 mg/administration, 2.5 mg/administration, 1 mg/administration, 0.5 mg/administration, 0.25 mg/administration, or 0.1 mg/administration.

In some embodiments, the disclosure includes pharmaceutical compositions for parenteral or inhalation, *e.g.*, a spray or mist, administration of a compound of Formula (I)

and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof, having a concentration of about 0.005 mg/mL to about 500 mg/mL. In some embodiments, the compositions include a compound of Formula (I) of the present disclosure or a pharmaceutically acceptable salt thereof, at a concentration of, *e.g.*, about 5 mg/mL to about 500 mg/mL, about 5 mg/mL to about 100 mg/mL, about 5 mg/mL to about 50 mg/mL, about 1 mg/mL to about 100 mg/mL, about 1 mg/mL to about 50 mg/mL, about 0.1 mg/mL to about 25 mg/mL, about 0.1 mg/mL to about 10 mg/mL, about 0.05 mg/mL to about 10 mg/mL, about 0.05 mg/mL to about 5 mg/mL, about 0.05 mg/mL to about 1 mg/mL, about 0.005 mg/mL to about 1 mg/mL, about 0.005 mg/mL to about 0.25 mg/mL, or about 0.005 mg/mL to about 0.1 mg/mL.

In some embodiments, the composition includes a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof, at a concentration of, *e.g.*, about 0.05 mg/mL to about 500 mg/mL, about 0.05 mg/mL to about 100 mg/mL, about 0.05 mg/mL to about 50 mg/mL, about 0.05 mg/mL to about 25 mg/mL, about 0.05 mg/mL to about 10 mg/mL, about 0.05 mg/mL to about 5 mg/mL, about 0.005 mg/mL to about 1 mg/mL, about 0.005 mg/mL to about 0.25 mg/mL, about 0.005 mg/mL to about 0.05 mg/mL, or about 0.005 mg/mL to about 0.025 mg/mL. In some embodiments, the pharmaceutical compositions are formulated as a total volume of about, *e.g.*, 0.1 mL, 0.25 mL, 0.5 mL, 1 mL, 2 mL, 5 mL, 10 mL, 20 mL, 25 mL, 50 mL, 100 mL, 200 mL, 250 mL, or 500 mL.

Typically, dosages may be administered to a subject once, twice, three times or four times daily, every other day, every three days, twice weekly, once weekly, twice monthly, once monthly, thrice yearly, twice yearly, or once yearly. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject once in the morning, or once in the evening. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject once in the morning, and once in the evening. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject three times a day (*e.g.*, at breakfast, lunch, and dinner), at a dose, *e.g.*, of 0.5 mg/administration (*e.g.*, 1.5 mg/day).

In some embodiments, any compound of Formula (I) and/or miscellaneous compounds (or pharmaceutical composition thereof) disclosed in this application may be administered one, two, three, or four times per day, wherein the administrations may be the same or different and are independently selected from any of the dosages provided in this application. In some embodiments, any compound of Formula (I) and/or miscellaneous compounds (or pharmaceutical composition thereof) disclosed in this application may be administered one, two, three, four, five, six, seven, eight, nine, or ten times per week (possibly at equally spaced or alternating intervals), wherein the administrations may be the same or different and are independently selected from any of the dosages provided in this application. In some embodiments, any compound of Formula (I) and/or miscellaneous compounds (or pharmaceutical composition thereof) disclosed in this application may be administered one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or fifteen times per month (possibly at equally spaced or alternating intervals, such as every two, three, four, or five days, or alternating between any of these), wherein the administrations may be the same or different and are independently selected from any of the dosages provided in this application. In some embodiments, any compound of Formula (I) and/or miscellaneous compounds (or pharmaceutical composition thereof) disclosed in this application may be administered one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, twenty, twenty-one, twenty-two, twenty-three, twenty-four, or twenty-five times per year (possibly at equally spaced or alternating intervals, such as every two, three, or four weeks, or once or twice a month, or alternating between any of these), wherein the administrations may be the same or different and are independently selected from any of the dosages provided in this application.

In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 0.5 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 1 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 2.5 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or

miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 5 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 10 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 15 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 20 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 25 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 30 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 40 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 50 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 75 mg/day in one or more doses. In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a subject at a dose of 100 mg/day in one or more doses.

In some embodiments, the dosage of a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is 0.0005-5 mg/kg, 0.001-1 mg/kg, 0.01-1 mg/kg or 0.1-5 mg/kg once, twice, three times or four times daily. For example, in some embodiments, the dosage is 0.0005 mg/kg, 0.001 mg/kg, 0.005 mg/kg, 0.01 mg/kg, 0.025 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.15 mg/kg, 0.2 mg/kg, 0.25 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, once, twice, three times, or four

times daily. In some embodiments, a subject is administered a total daily dose of 0.01 mg to 500 mg of a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof once, twice, three times, or four times daily. In some embodiments, the total amount administered to a subject in 24-hour period is, *e.g.*, 0.01 mg, 0.025 mg, 0.05 mg, 0.075 mg, 0.1 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg. In some embodiments, the subject may be started at a low dose and the dosage is escalated. In some embodiments, the subject may be started at a high dose and the dosage is decreased.

In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a patient under the supervision of a healthcare provider.

In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered to a patient under the supervision of a healthcare provider at a clinic specializing in the delivery of psychoactive treatments.

In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure is administered to a patient under the supervision of a healthcare provider at a high dose intended to induce a psychedelic experience in the subject, *e.g.*, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 17.5 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, or 100 mg.

In some embodiments, the administration to a patient of a high dose under the supervision of a healthcare provider occurs periodically in order to maintain a therapeutic effect in the patient, *e.g.*, every three days, twice weekly, once weekly, twice monthly, once monthly, four times yearly, thrice yearly, twice yearly, or once yearly.

In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered by a patient on their own at home or otherwise away from the supervision of a healthcare provider.

In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof is administered by a patient

on their own at home or otherwise away from the supervision of a healthcare provider at a low dose intended to be sub-perceptual or to induce threshold psychoactive effects, *e.g.*, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 2.5 mg, 3 mg, or 4 mg.

In some embodiments, the administration by a patient of a low dose on their own occurs periodically in order to maintain a therapeutic effect in the patient, *e.g.*, daily, every other day, every three days, twice weekly, once weekly, twice monthly, or once monthly,

In some embodiments, a compound of Formula (I) and/or miscellaneous compounds of the present disclosure or a pharmaceutically acceptable salt thereof may be administered, *e.g.*, via inhalation or orally, at specified intervals. For example, during treatment a patient may be administered a compound of the present disclosure at intervals of every, *e.g.*, 1 year, 6 months, 4 months, 90 days, 60 days, 30 days, 14 days, 7 days, 3 days, 24 hours, 12 hours, 8 hours, 6 hours, 5 hours, 4 hours, 3 hours, 2.5 hours, 2.25 hours, 2 hours, 1.75 hours, 1.5 hours, 1.25 hours, 1 hour, 0.75 hour, 0.5 hour, or 0.25 hour.

GENERAL SYNTHESIS

The compounds disclosed herein are prepared by art recognized methods. The compounds of Formula (I) as well as the miscellaneous compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures well known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment, and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

EXAMPLES

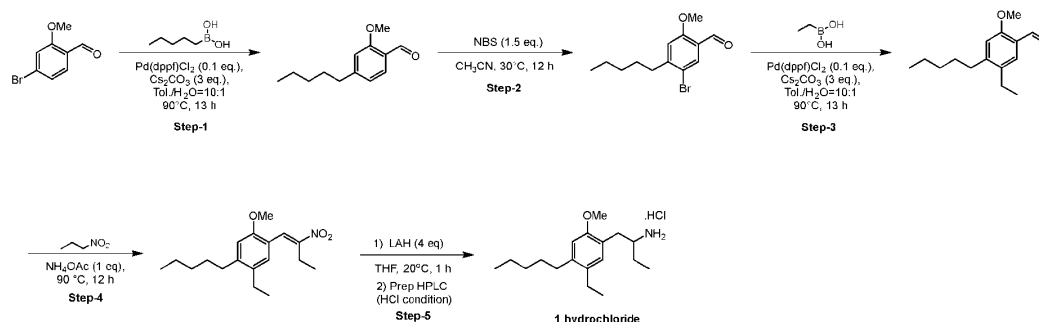
The following non-limiting examples further illustrate the teachings in the present disclosure.

Throughout the following examples, several compounds are prepared in substantially enantiomerically pure form via chiral supercritical fluid chromatography (SFC) separation of a racemic mixture of the compound itself or a synthetic intermediate that is then converted to the compound while maintaining the same absolute stereochemistry at the chiral center.

Enantiomerically pure compounds prepared in this way are assigned as enantiomer 1 (E1) or enantiomer 2 (E2), where these terms denote the first and second eluting enantiomer, respectively, from the indicated chiral SFC method. However, the absolute stereochemistry of these enantiomerically pure compounds was not determined experimentally, so in the context of the examples, the assignment of E1 or E2 to R or S stereochemistry in the drawn schemes should be considered arbitrary.

Example 1: Preparation of 1-(5-ethyl-2-methoxy-4-pentylphenyl)butan-2-amine (1) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 2-methoxy-4-pentylbenzaldehyde

To a solution of 4-bromo-2-methoxybenzaldehyde (1 g, 4.65 mmol) in a toluene (23 mL) and water (2.3 mL) was added pentylboronic acid (808.93 mg, 6.98 mmol), cesium carbonate (4.55 g, 13.95 mmol) and Pd(dppf)Cl_2 (340.26 mg, 465.02 μmol) under N_2 atmosphere. The mixture was stirred at 90°C for 13 h. After completion of reaction, the aqueous phase was extracted with

ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether and ethyl acetate gradient, eluting with 2% ethyl acetate) to afford 2-methoxy-4-pentylbenzaldehyde as an oil (Yield: 770 mg, 80 %). **¹H NMR (400MHz, CDCl₃):** δ = 10.40 (s, 1H), 7.73 (d, J = 7.9 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.78 (s, 1H), 3.91 (s, 3H), 2.63 (t, J = 7.8 Hz, 2H), 1.68 - 1.59 (m, 2H), 1.37 - 1.28 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H).

Step 2:

Preparation of 5-bromo-2-methoxy-4-pentylbenzaldehyde

To a solution of 2-methoxy-4-pentylbenzaldehyde (670 mg, 3.25 mmol) in acetonitrile (7 mL) was added NBS (867.14 mg, 4.87 mmol). The mixture was stirred at 30 °C for 12 h. The reaction mixture was partitioned between ethyl acetate (10 mL x 3) and water (10 mL). The combined organic phase was washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether and ethyl acetate gradient, eluting with 2% ethyl acetate) to afford 5-bromo-2-methoxy-4-pentylbenzaldehyde as an oil (Yield: 740 mg, 76%). **¹H NMR (400MHz, CDCl₃):** δ = 10.33 (s, 1H), 7.94 (s, 1H), 6.84 (s, 1H), 3.92 (s, 3H), 2.79 - 2.70 (m, 2H), 1.69 - 1.60 (m, 2H), 1.45 - 1.36 (m, 4H), 0.97 - 0.89 (m, 3H).

Step 3:

Preparation of 5-ethyl-2-methoxy-4-pentylbenzaldehyde

To a solution of 5-bromo-2-methoxy-4-pentylbenzaldehyde (780 mg, 2.74 mmol) in toluene (18 mL) and water (1.8 mL) was added Pd(dppf)Cl₂ (200.13 mg, 273.52 μ mol), ethylboronic acid (303.14 mg, 4.10 mmol) and cesium carbonate (2.67 g, 8.21 mmol) under N₂ atmosphere. The mixture was stirred at 90 °C for 13 h. The reaction mixture was partitioned between ethyl acetate (10 mL x 3) and water (10 mL). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether and ethyl acetate gradient, eluting with 2% ethyl acetate) to afford 5-ethyl-2-methoxy-4-pentylbenzaldehyde as a yellow oil (Yield: 600 mg, 79.25%; 84.6% purity). **¹H NMR (400MHz,**

CDCl₃): δ = 10.40 (s, 1H), 7.63 (s, 1H), 6.76 (s, 1H), 3.91 (s, 3H), 2.66 - 2.57 (m, 4H), 1.65 - 1.57 (m, 2H), 1.42 - 1.35 (m, 4H), 1.21 (t, J = 7.6 Hz, 3H), 0.96 - 0.90 (m, 3H).

Step 4:

Preparation of (E)-1-ethyl-4-methoxy-5-(2-nitrobut-1-en-1-yl)-2-pentylbenzene

To a solution of 5-ethyl-2-methoxy-4-pentylbenzaldehyde (600 mg, 2.56 mmol) in 1-nitropropane (6 mL) was added ammonium acetate (197.36 mg, 2.56 mmol) under N₂ atmosphere. The mixture was stirred at 90 °C for 12 h. The reaction mixture was partitioned between ethyl acetate (10 mL x 3) and water (10 mL). The combined organic fractions were washed with brine (10 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel (petroleum ether and ethyl acetate gradient, eluting with 2% ethyl acetate) to afford (E)-1-ethyl-4-methoxy-5-(2-nitrobut-1-en-1-yl)-2-pentylbenzene (Yield: 530 mg, 67%) as a yellow oil. **¹H NMR (400MHz, CDCl₃)**: δ = 8.25 (s, 1H), 7.11 (s, 1H), 6.73 (s, 1H), 3.86 (s, 3H), 2.84 (q, J = 7.3 Hz, 2H), 2.67 - 2.59 (m, 4H), 1.66 - 1.57 (m, 2H), 1.42 - 1.36 (m, 4H), 1.29 (t, J = 7.4 Hz, 3H), 1.23 (t, J = 7.6 Hz, 3H), 0.96 - 0.91 (m, 3H).

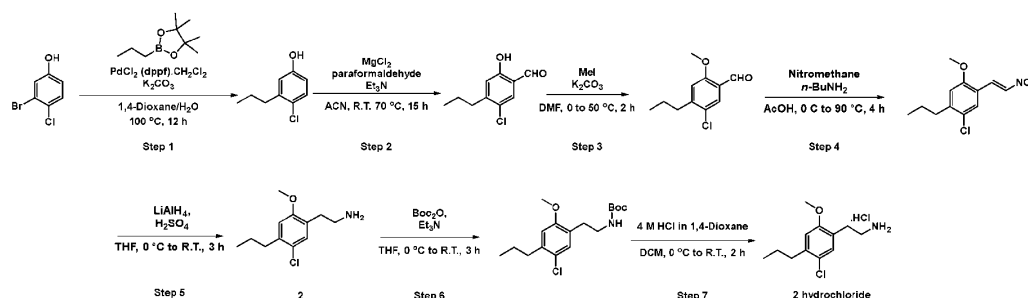
Step 5:

Preparation of 1-(5-ethyl-2-methoxy-4-pentylphenyl)butan-2-amine (1) hydrochloride

To a solution of (E)-1-ethyl-4-methoxy-5-(2-nitrobut-1-en-1-yl)-2-pentylbenzene (530.00 mg, 1.74 mmol) in THF (5 mL) was added LAH (263.43 mg, 6.94 mmol) at 0 °C. The reaction mixture was then stirred at 20 °C for 1 h. Upon completion, the reaction mixture was quenched by addition H₂O (0.3 mL) and 30% of aq. NaOH (0.3 mL) at 0 °C. The resulting suspension was filtered, the filter cake was washed with THF (20 mL x 3), and the filtrate was concentrated. The residue was purified by prep-HPLC [Column: Phenomenex Luna 80 mm x30 mm, 3 μ m; Mobile phase: water (with HCl additive) ACN 15%-40%; 8 min run] to afford 1-(5-ethyl-2-methoxy-4-pentylphenyl)butan-2-amine (**1**) hydrochloride (**1**; Yield 295 mg, 61 %) as a white solid. **LC-MS**: m/z 277.4 [M+H]⁺; **¹H NMR (400MHz, METHANOL-d₄)**: δ = 6.98 (s, 1H), 6.83 - 6.72 (m, 1H), 3.85 (s, 3H), 3.38 (m, 1H), 3.34 - 3.31 (m, 1H), 3.00 - 2.79 (m, 2H), 2.68 - 2.55 (m, 4H), 1.61 (d, J = 7.5 Hz, 4H), 1.45 - 1.34 (m, 4H), 1.20 (t, J = 7.6 Hz, 3H), 1.05 (t, J = 7.5 Hz, 3H), 0.97 - 0.90 (m, 3H); **¹³C NMR (101 MHz, METHANOL-d₄)**: δ = 155.65, 140.87, 133.89, 131.21, 121.05, 54.43, 53.45, 32.87, 32.47, 31.68, 31.01, 25.17, 24.33, 22.25, 14.89, 13.01, 8.57.

Example 2: Preparation of 2-(5-chloro-2-methoxy-4-propylphenyl)ethan-1-amine (2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 4-chloro-3-propylphenol

To a stirred solution of 3-bromo-4-chlorophenol (3.0 g, 14.6 mmol) in 1,4-dioxane/water (3:1, 30 mL) was added dipotassium carbonate (6.0 g, 43.8 mmol), *n*-propyl boronic acid pinacol ester (4.9 g, 29.2 mmol), and Pd(dppf)Cl₂-CH₂Cl₂ (0.6 g, 0.73 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS: and TLC. After completion, the reaction mixture was diluted with ethyl acetate (50 mL) and filtered through a Celite pad. The filtrate was partitioned between ethyl acetate (50 mL) and water (50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get the crude product. This crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford 4-chloro-3-propylphenol as an off-white solid (Yield: 1.4 g, 56%). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.54 (s, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.8 Hz, 1H), 6.60 (dd, *J* = 8.8, 2.8 Hz, 1H), 2.56-2.49 (m, 2H), 1.59-1.49 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H).

Step 2:

Preparation of 5-chloro-2-hydroxy-4-propylbenzaldehyde

To a stirred solution of 4-chloro-3-propylphenol (1.4 g, 8.22 mmol) in anhydrous ACN (14.0 mL) was added triethylamine (2.26 mL, 16.4 mmol) and stirred at room temperature for 15 min. Then, paraformaldehyde (1.4 g, 49.2 mmol) and magnesium chloride (1.2 g, 12.2 mmol) added to the reaction mixture. The reaction mixture was warmed to 70 °C and stirred for 15 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was partitioned between ethyl acetate (20 mL) and water (20 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford 5-chloro-2-hydroxy-4-propylbenzaldehyde as an off-white solid (Yield: 1.0 g, 66%). **LC-MS:** m/z 199 [M+1]⁺.

Step 3:***Preparation of 5-chloro-2-methoxy-4-propylbenzaldehyde***

To a stirred solution of 5-chloro-2-hydroxy-4-propylbenzaldehyde (0.51 g, 2.57 mmol) in dimethylformamide (5.0 mL) was added dipotassium carbonate (1.0 g, 7.72 mmol) followed by dropwise addition of iodomethane (155 µL, 6.42 mmol) at 0 °C. The reaction mixture was warmed to 50 °C and stirred for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with chilled water (20 mL) and extracted with ethyl acetate (25 mL x 2). The combined organic part was washed with brine (10 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by column chromatography (silica gel; eluting with 0-15% EtOAc in heptanes) to afford desired 5-chloro-2-methoxy-4-propylbenzaldehyde as a colorless liquid (Yield: 0.41 g, 75%). **LC-MS:** m/z 213 [M+1]⁺.

Step 4:***Preparation of (E)-1-chloro-4-methoxy-5-(2-nitrovinyl)-2-propylbenzene***

To a stirred solution of 5-chloro-2-methoxy-4-propylbenzaldehyde (0.41 g, 1.93 mmol) in acetic acid (5.0 mL) was added nitromethane (1.17 g, 19.3 mmol) followed by *n*-butylamine (0.7 mL, 9.65 mmol) at 0 °C. Then, the reaction mixture was warmed to 90 °C and stirred for 4 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured in chilled water (20 mL), the precipitate formed was filtered, washed with chilled water

and dried under reduced pressure to afford the desired (*E*)-1-chloro-4-methoxy-5-(2-nitrovinyl)-2-propylbenzene as a yellow solid (Yield: 0.38 g, 77%). ¹H NMR (400 MHz, DMSO-d₆): δ = 8.18–8.10 (m, 2H), 7.92 (s, 1H), 7.15 (s, 1H), 3.93 (s, 3H), 2.69 (t, *J* = 7.6 Hz, 2H), 1.64–1.59 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

Step 5:

Preparation of 2-(5-chloro-2-methoxy-4-propylphenyl)ethan-1-amine (2)

To a stirred solution of LAH solution (2.0 M in THF; 5.96 mL, 11.93 mmol) in anhydrous THF (10 mL) was added H₂SO₄ (0.31 mL, 5.92 mmol) dropwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-chloro-4-methoxy-5-(2-nitrovinyl)-2-propylbenzene (0.38 g, 1.49 mmol) in THF (5 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2.5 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and was added THF/water (1:1, 14 mL) at same temperature until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (10 mL), combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 2-(5-chloro-2-methoxy-4-propylphenyl)ethan-1-amine (**2**) as a yellow gum (Yield: 0.30 g, 88%), which was directly taken for the next step. LC-MS: *m/z* 228 [M+1]⁺.

Step 6:

Preparation of tert-butyl (5-chloro-2-methoxy-4-propylphenethyl)carbamate

To a stirred solution of 2-(5-chloro-2-methoxy-4-propylphenyl)ethan-1-amine (**2**; 0.30 g, 1.32 mmol) in THF (10 mL), triethylamine (0.46 mL, 3.30 mmol) followed by di-*tert*-butyl dicarbonate (0.45 mL, 1.98 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10%

ethyl acetate in heptanes) to afford *tert*-butyl (5-chloro-2-methoxy-4-propylphenethyl)carbamate as an off-white solid (Yield: 100 mg, 23%). **LC-MS:** m/z 228 $[M+H-100]^+$; **1H NMR (400 MHz, DMSO- d_6):** δ = 7.08 (s, 1H), 6.89 (s, 1H), 6.80 (t, J = 5.2 Hz, 1H), 3.77 (s, 3H), 3.06 (q, J = 6.4 Hz, 2H), 2.61 (t, J = 7.2 Hz, 4H), 1.60–1.54 (m, 2H), 1.37 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H).

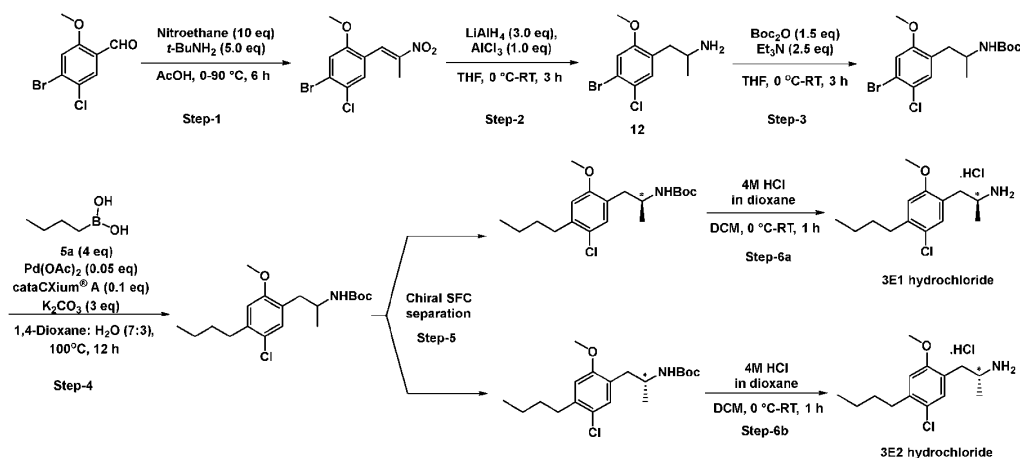
Step 7:

Preparation of 2-(5-chloro-2-methoxy-4-propylphenyl)ethan-1-amine (2) hydrochloride

To a stirred solution of *tert*-butyl (5-chloro-2-methoxy-4-propylphenethyl)carbamate (100 mg, 0.305 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.76 mL, 3.05 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 2-(5-chloro-2-methoxy-4-propylphenyl)ethan-1-amine (2) hydrochloride as an off-white solid (Yield: 31 mg, 38%). **LC-MS:** m/z 228 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6):** δ = 7.85 (s, 3H), 7.20 (s, 1H), 6.96 (s, 1H), 3.80 (s, 3H), 2.97 (m, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 1.63–1.54 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H).

Example 3: Preparation of 1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-amine enantiomer 1 (3E1) hydrochloride and 1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-amine enantiomer 2 (3E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of (E)-1-bromo-2-chloro-5-methoxy-4-(2-nitroprop-1-en-1-yl)benzene

To a stirred solution of 4-bromo-5-chloro-2-methoxybenzaldehyde (see **Example 4**; 700 mg, 2.81 mmol) in acetic acid (10 mL) was added nitroethane (2.0 mL, 28.1 mmol) followed by *tert*-butyl amine (1.47 mL, 14.05 mmol) at 0 °C. Then mixture was warmed to 90 °C and stirred for 6 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water (25 mL), the precipitate that formed was filtered, washed with chilled water (10 mL x 3) and dried under reduced pressure to afford the desired (E)-1-bromo-2-chloro-5-methoxy-4-(2-nitroprop-1-en-1-yl)benzene as a yellow solid (Yield: 780 g, 90%). ¹H NMR (400 MHz, DMSO-d₆): δ = 7.93 (s, 1H), 7.63 (s, 1H), 7.54 (s, 1H), 3.89 (s, 3H), 2.28 (s, 3H).

Step 2:

Preparation of 1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-amine (12)

To a stirred solution of LAH solution (2.0 M in THF; 3.81 mL, 7.62 mmol) in anhydrous THF (30 mL) was added AlCl₃ (96.5 mg, 2.54 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (E)-1-bromo-2-chloro-5-methoxy-4-(2-nitroprop-1-en-1-yl)benzene (780 mg, 2.54 mmol) in THF (5 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2.5 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was

allowed to cool to 0 °C and was added THF/water (1:1, 10 mL) at same temperature until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (40 mL), combined organic part was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-amine (**12**) as a gummy solid (Yield: 700 mg, crude), which was used directly in the next step.

Step 3:

Preparation of tert-butyl (1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate

To a stirred solution of 1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-amine (700 mg, 2.51 mmol) in THF (10 mL), triethylamine (0.9 mL, 6.27 mmol) followed by di-*tert*-butyl dicarbonate (0.78 mL, 3.76 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-15% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 450 mg, 47%). **LC-MS:** m/z 379.05 [M+1]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 7.29 (s, 1H), 7.28 (s, 1H), 6.67 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 3.71-3.69 (s, 1H), 2.67 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.51-2.42 (m, 1H), 1.29 (s, 9H), 1.03 (d, *J* = 6.4 Hz, 3H).

Step 4:

Preparation of tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate (400 mg, 1.05 mmol) in 1,4-dioxane/water (7:3, 8 mL) was added dipotassium carbonate (437 mg, 3.57 mmol), *n*-butylboronic acid (426 mg, 4.75 mmol), 1-[1-adamantanyl(butyl)phosphino]adamantane (38 mg, 0.105 mmol), palladium bis(acetate) (12 mg, 0.053 mmol) under argon at room temperature. The reaction mixture was purged with argon for

10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS: and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (10 mL) and water (10 mL). The combined organic phase was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 100 mg, 27 %). **LC-MS:** m/z 256.15 [M+1-100]⁺.

Step 5:

Preparation of tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate (100 mg) were separated by chiral SFC [Column Name: Phenomenex[®], Lux i-Amylose-3 (30 mm x 250 mm) 5 µm; Mobile Phase: supercritical CO₂/IPA (70:30); Flow Rate: 80 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (Yield: 40 mg, 40%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (Yield: 40 mg, 40%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) as off-white solids.

tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1

LC-MS: m/z 256.05 [M+1-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 7.08 (s, 1H), 6.87 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H), 3.71-3.65 (m, 1H), 2.68-2.60 (m, 3H), 2.57-2.40 (m, 1H), 1.56-1.48 (m, 2H), 1.37-1.20 (m, 2H), 1.32 (s, 9H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (>99%) was determined by chiral SFC analysis (Column Name: Phenomenex Lux i-Amylose-3 (150 mm x 4.6 mm, 3 µm); Mobile Phase: supercritical CO₂ (80%), MeOH/IPA (20%); Flow Rate: 3.0 mL/min; Column Temp: 30 °C, λ = 283 nm); *R*_t = 1.70 min (enantiomer 1), 2.15 min (enantiomer 2).

tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2

LC-MS: m/z 256.05 [M+1-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 7.08 (s, 1H), 6.87 (s, 1H), 6.65 (d, J = 8.4 Hz, 1H), 3.77 (s, 3H), 3.72-3.66 (m, 1H), 2.64-2.62 (m, 2H), 2.57-2.47 (m, 2H), 1.54-1.51 (m, 2H), 1.37-1.16 (m, 2H), 1.30 (s, 9H), 1.01 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). The enantiomeric excess (>99%) was determined by chiral SFC analysis (Column Name: Phenomenex Lux i-Amylose-3 (150 mm x 4.6 mm, 3 μ m); Mobile Phase: supercritical CO₂ (80%), MeOH/IPA (20%); Flow Rate: 3.0 mL/min; Column Temp: 30 °C, λ = 283 nm); R_t = 1.70 min (enantiomer 1), 2.15 min (enantiomer 2).

Step 6a:***Preparation of 1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-amine (3E1) hydrochloride***

To a stirred solution of *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (40 mg, 0.112 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.28 mL, 1.12 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford 1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-amine enantiomer 1 (**3E1**) hydrochloride as an off-white solid (Yield: 15 mg, 46%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 256.20 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.89 (s, 3H), 7.19 (s, 1H), 6.97 (s, 1H), 3.79 (s, 3H), 3.40 (q, J = 6.8 Hz, 1H), 2.85 (dd, J = 13.2, 6.0 Hz, 1H), 2.70-2.63 (m, 3H), 1.58-1.51 (m, 2H), 1.40-1.31 (m, 2H), 1.09 (d, J = 6.4 Hz, 3H), 0.92 (t, J = 7.6 Hz, 3H).

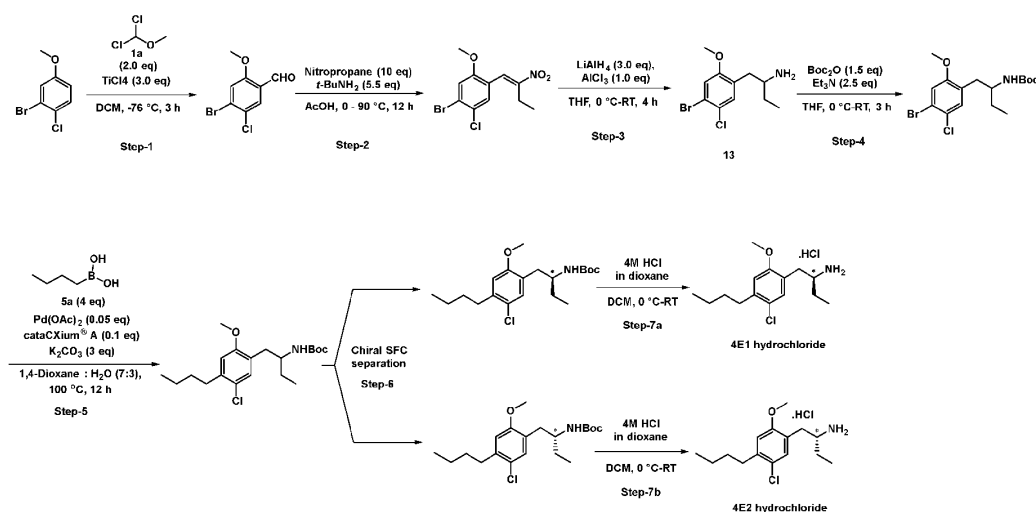
Step 6b:***Preparation of 1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-amine (3E2) hydrochloride***

To a stirred solution of *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (40 mg, 0.112 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.28 mL, 1.12 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed

with diethyl ether (5.0 mL) to afford 1-(4-butyl-5-chloro-2-methoxyphenyl)propan-2-amine enantiomer 2 (**3E2**) hydrochloride as an off-white solid (Yield: 16 mg, 49%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z 256.20 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.84 (s, 3H), 7.19 (s, 1H), 6.97 (s, 1H), 3.79 (s, 3H), 3.40 (q, J = 6.4 Hz, 1H), 2.84 (dd, J = 13.2, 6.0 Hz, 1H), 2.70-2.63 (m, 3H), 1.58-1.51 (m, 2H), 1.40-1.31 (m, 2H), 1.09 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H).

Example 4: Preparation of 1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-amine enantiomer 1 (4E1**) hydrochloride and 1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-amine enantiomer 2 (**4E2**) hydrochloride**

Synthetic Scheme:



Step 1:

Preparation of 4-bromo-5-chloro-2-methoxybenzaldehyde

To a stirred solution of 2-bromo-1-chloro-4-methoxybenzene (5.0 g, 22.8 mmol) in DCM (20 mL) was added titanium tetrachloride (7.4 mL, 68.4 mmol) at -76 °C followed by dropwise addition of dichloro(methoxy)methane (4.2 mL, 45.6 mmol) at the same temperature. The reaction mixture was stirred at -76 °C for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction was diluted with chilled water (50 mL) and extracted with

EtOAc (100 mL x 2). The combined organic fractions were washed with brine (50 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure to get the crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford 4-bromo-5-chloro-2-methoxybenzaldehyde as a liquid (Yield: 2.3 g, 41%). ¹H NMR (400 MHz, CDCl₃): δ = 10.35 (s, 1H), 7.87 (s, 1H), 7.28 (s, 1H), 3.94 (s, 3H).

Step 2:

Preparation of (E)-1-bromo-2-chloro-5-methoxy-4-(2-nitrobut-1-en-1-yl)benzene

To a stirred solution of 4-bromo-5-chloro-2-methoxybenzaldehyde (1.5 g, 6.07 mmol) in acetic acid (15 mL) was added 1-nitropropane (5.4 mL, 60.7 mmol) followed by *tert*-butyl amine (3.55 mL, 33.3 mmol) at 0 °C. Then, the reaction mixture was warmed to 90 °C and stirred for 12 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into chilled water (50 mL), the precipitate that formed was filtered, washed with chilled water (50 mL x 2) and dried under reduced pressure to afford the desired (*E*)-1-bromo-2-chloro-5-methoxy-4-(2-nitrobut-1-en-1-yl)benzene as a yellow solid (Yield: 1.0 g, 51%). ¹H NMR (400 MHz, CDCl₃): δ = 7.99 (s, 1H), 7.32 (s, 1H), 7.18 (s, 1H), 3.87 (s, 3H), 2.79-2.71 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

Step 3:

Preparation of 1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-amine (13)

To a stirred solution of LAH solution (2.0 M in THF; 4.70 mL, 9.40 mmol) in anhydrous THF (30 mL) was added AlCl₃ (625 mg, 3.13 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-bromo-2-chloro-5-methoxy-4-(2-nitrobut-1-en-1-yl)benzene (1.0 g, 3.13 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was cooled to 0 °C and THF/water (1:1, 12 mL) was added at same temperature, until effervescence stopped. The reaction mixture was diluted with THF (10 mL) and stirred at room temperature for 30 min under argon atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (20 mL x 2), dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure to afford 1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-amine (**13**) as a gummy solid (Yield: 0.87 g, 95%). **LC-MS:** m/z 293.9[M+1]⁺.

Step 4:

Preparation of tert-butyl (1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate

To a stirred solution of 1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-amine (0.87 g, 2.97 mmol) in THF (10 mL), triethylamine (1.0 mL, 7.44 mmol) followed by di-*tert*-butyl dicarbonate (1.0 mL, 4.45 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layer was washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound. The crude material was purified by flash column chromatography (eluting with 0-10% EtOAc in heptanes) to afford *tert*-butyl (1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate as an off-white solid (Yield: 500 mg, 42%). **LC-MS:** m/z 293.9 [M+1-100]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.28 (s, 1H), 7.26 (s, 1H), 6.57 (d, *J* = 9.6 Hz, 1H), 3.80 (s, 3H), 3.50 (br, 1H), 2.75-2.67 (m, 1H), 2.40-2.33 (m, 1H), 1.46-1.31 (m, 2H), 1.27 (s, 9H), 0.83 (t, *J* = 7.2 Hz, 3H).

Step 5:

Preparation of tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate (0.45 g, 1.15 mmol) in 1,4-dioxane/water (7:3) (10 mL) was added dipotassium carbonate (476 mg, 3.45 mmol), *n*-butyl boronic acid (466 mg, 4.6 mmol), 1-[1-adamantanyl(butyl)phosphino]adamantane (41 mg, 0.115 mmol), palladium bis(acetate) (13 mg, 0.057 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (20 mL) and water (10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to get the crude material. The crude obtained was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to

afford *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate as an off-white solid (Yield: 140 mg, 33%). **LC-MS:** m/z 256 $[M+1-100]^+$; **1H NMR (400 MHz, $CDCl_3$):** δ = 7.08 (s, 1H), 6.68 (s, 1H), 4.50 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 3.72 (br, 1H), 2.78-2.74 (m, 1H), 2.68 (t, J = 8.0 Hz, 2H), 2.60 (dd, J = 13.6, 8.4 Hz, 1H), 1.63-1.51 (m, 3H), 1.45-1.28 (m, 4H), 1.38 (s, 9H), 0.98-0.87 (m, 6H).

Step 6:

Preparation of tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate (140 mg) were separated by chiral SFC [Column Name: Phenomenex, Lux Amylose-1 (21.2 mm x 250 mm) 5 μ m; Mobile Phase: supercritical CO_2 /IPA (75:25); Flow Rate: 70 mL/min; Column temp: 30 $^{\circ}C$]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 60 mg, 43%; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2 (Yield: 50 mg, 36%; drawn as R enantiomer but absolute stereochemistry not determined experimentally) off-white solids.

tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1

LC-MS: m/z 270 $[M+H-100]^+$; **1H NMR (400 MHz, $DMSO-d_6$):** δ = 7.09 (s, 1H), 6.86 (s, 1H), 6.55 (d, J = 9.2 Hz, 1H), 3.77 (s, 3H), 3.52- 3.50 (m, 1H), 2.73- 2.68 (m, 1H), 2.62 (t, J = 8.0 Hz, 2H), 2.42-2.36 (m, 1H), 1.56-1.48 (m, 2H), 1.44-1.24 (m, 4H), 1.28 (s, 9H), 0.91 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H). The enantiomeric excess (>99%) was determined by chiral SFC analysis [Column Name: Phenomenex, Lux Amylose-1 (250mm x 4.6 mm) 5 μ m; Mobile Phase: supercritical CO_2 /IPA containing 0.2% isopropyl amine (75:25); Flow Rate: 3.0 mL/min; Column Temp: 30 $^{\circ}C$] R_t = 1.55 min (enantiomer 1), 5.27 min (enantiomer 2).

tert-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2

LC-MS: m/z 270 [M+H-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 7.08 (s, 1H), 6.68 (s, 1H), 4.49 (br, 1H), 3.83 (s, 3H), 3.72 (br, 1H), 2.76-2.73 (m, 1H), 2.68 (t, J = 8.0 Hz, 2H) 2.60 (dd, J = 13.6, 8.4 Hz, 1H), 1.62-1.51 (m, 3H), 1.50-1.38 (m, 3H), 1.38 (s, 9H), 0.98-0.88 (m, 6H). The enantiomeric excess (>99%) was determined by chiral SFC [Column Name: Phenomenex, Lux Amylose-1 (250mm x 4.6 mm) 5 μ m; Mobile Phase: supercritical CO₂/IPA containing 0.2% isopropyl amine (75:25); Flow Rate: 3.0 mL/min; Column Temp: 30 °C] R_t = 1.55 min (enantiomer 1), 5.27 min (enantiomer 2).

Step 7a:

Preparation of 1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-amine enantiomer 1 (4E1) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1 (60 mg, 0.16 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.4 mL, 1.6 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-amine enantiomer 1 (**4E1**) hydrochloride (Yield: 50 mg, 99%; drawn as S enantiomer but absolute stereochemistry not determined experimentally) as an off-white solid. **LC-MS:** m/z 270.25 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.87 (s, 3H), 7.22 (s, 1H), 6.96 (s, 1H), 3.79 (s, 3H), 3.26-3.23 (m, 1H), 2.77 (dd, J = 6.4, 1.6 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.58-1.45 (m, 4H), 1.40-1.31 (m, 2H), 0.94-0.86 (m, 6H).

Step 7b:

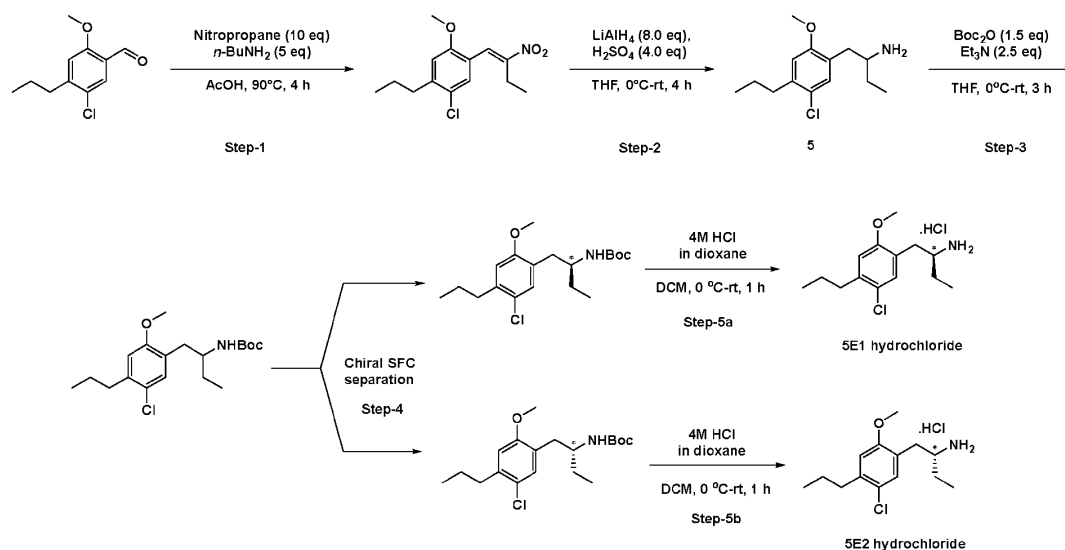
Preparation of 1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-amine enantiomer 2 (4E2) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-butyl-5-chloro-2-methoxyphenyl)butan-2-yl)carbamate (50 mg, 0.14 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane) (0.05 mL, 1.4 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl

ether (5.0 mL) to afford the desired 1-(4-butyl-2-methoxy-5-methylphenyl)butan-2-amine enantiomer 2 (**4E2**) hydrochloride (Yield: 30 mg, 59.5%; drawn as R enantiomer but absolute stereochemistry not determined experimentally) as an off-white solid. **LC-MS**: m/z 270.20 $[M+H]^+$; **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.85 (s, 3H), 7.22 (s, 1H), 6.96 (s, 1H), 3.79 (s, 3H), 3.27-3.22 (m, 1H), 2.79-2.75 (m, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.58-1.45 (m, 4H), 1.40-1.31 (m, 2H), 0.94-0.86 (m, 6H).

Example 5: Preparation of 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine enantiomer 1 (5E1) hydrochloride and 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine enantiomer 2 (5E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of (E)-1-chloro-4-methoxy-5-(2-nitrobut-1-en-1-yl)-2-propylbenzene

To a stirred solution of 5-chloro-2-methoxy-4-propylbenzaldehyde (see **Example 2**; 0.3 g, 1.41 mmol) in acetic acid (3 mL) was added 1-nitropropane (1.25 mL, 14.1 mmol) followed by *n*-butyl amine (0.73 mL, 7.05 mmol) at 0 °C. Then mixture was warmed to 90 °C and stirred for 4

h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water (25 mL), the precipitate that formed was filtered, washed with chilled water (10 mL x 3), and dried under reduced pressure to afford the desired (*E*)-1-chloro-4-methoxy-5-(2-nitrobut-1-en-1-yl)-2-propylbenzene as a yellow solid (Yield: 0.30 g, 75%), which was directly taken for the next step.

Step 2:

Preparation of 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine (5)

To a stirred solution of LAH solution (2.0 M in THF; 1.66 mL, 8.40 mmol) in anhydrous THF (15 mL) was added H₂SO₄ (310 mg, 4.20 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-chloro-4-methoxy-5-(2-nitrobut-1-en-1-yl)-2-propylbenzene (0.30 g, 1.05 mmol) in THF (5 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3.5 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and THF/water (1:1, 7 mL) was added at the same temperature until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad, washed with THF (40 mL), the solvent was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine (**5**) as a pale yellow solid (Yield: 0.20 g, 74%), which was used directly in the next step.

Step 3:

Preparation of tert-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate

To a stirred solution of 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine (0.20 g, 7.81 mmol) in THF (5 mL), triethylamine (0.27 mL, 1.95 mmol) followed by di-*tert*-butyl dicarbonate (0.26 mL, 1.72 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (15 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in

heptanes) to afford *tert*-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate as an off-white solid (Yield: 160 mg, 57%). ¹H NMR (400 MHz, CDCl₃): δ = 7.28 (s, 1H), 7.26 (s, 1H), 6.57 (d, *J* = 9.6 Hz, 1H), 3.80 (s, 3H), 3.53 – 3.48 (m, 1H), 2.75 – 2.67 (m, 2H), 2.40 – 2.33 (m, 2H), 1.45 – 1.30 (m, 3H), 1.27 (s, 9H), 1.17 (s, 2H), 0.83 (t, *J* = 7.2 Hz, 3H).

Step 4:

Preparation of tert-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate (160 mg) were separated by chiral SFC [Column Name: Phenomenex[®], Lux Amylose-1 (21mm x 250 mm) 5 μ m; Mobile Phase: supercritical CO₂/MeOH (75:25); Flow Rate: 70 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 57 mg, 36%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (Yield: 63 mg, 39%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) as off-white solids.

tert-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1

LC-MS: m/z 356.15 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.08 (s, 1H), 6.86 (s, 1H), 6.56 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H), 3.49 (br, 1H), 2.71 – 2.67 (m, 1H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.41 – 2.35 (m, 1H), 1.58 – 1.55 (m, 2H), 1.45 – 1.33 (m, 2H), 1.27 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis (Column Name: Lux Amylose-1 (4.6 mm x 250 mm) 5 μ m; Mobile Phase: CO₂/IPA with 0.2% isopropylamine additive (75:25); Flow Rate : 3.0 mL/min; Column Temp: 30 °C) *R*_t = 1.53 min (enantiomer 1), 5.39 min (enantiomer 2).

tert-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2

LC-MS: m/z 356.15 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.08 (s, 1H), 6.86 (s, 1H), 6.53 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H), 3.51 – 3.49 (m, 1H), 2.72 – 2.63 (m, 1H), 2.61 (t, *J* = 7.2

Hz, 2H), 2.41 – 2.33 (m, 1H), 1.55 – 1.48 (m, 2H), 1.43 – 1.33 (m, 2H), 1.27 (s, 9H), 0.90 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis (Column Name: Lux Amylose-1 (4.6 mm x 250 mm) 5 μ m; Mobile Phase: CO₂/IPA with 0.2% isopropylamine additive (75:25); Flow Rate : 3.0 mL/min; Column Temp: 30 °C) R_t = 1.53 min (enantiomer 1), 5.37 min (enantiomer 2).

Step 5a:

Preparation of 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine enantiomer 1 (5E1) hydrochloride

To a stirred solution of *tert*-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 (57 mg, 0.160 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.37 mL, 1.5 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine enantiomer 1 (**5E1**) hydrochloride as an off-white solid (Yield: 34 mg, 83%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 256.20 $[M+H]^+$; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.79 (s, 3H), 7.22 (s, 1H), 6.97 (s, 1H), 3.79 (s, 3H), 3.28-3.25 (m, 1H), 2.80-2.71 (m, 2H), 2.67-2.61 (m, 2H), 1.64-1.55 (m, 2H), 1.52-1.45 (m, 2H), 0.96-0.89 (m, 6H).

Step 5b:

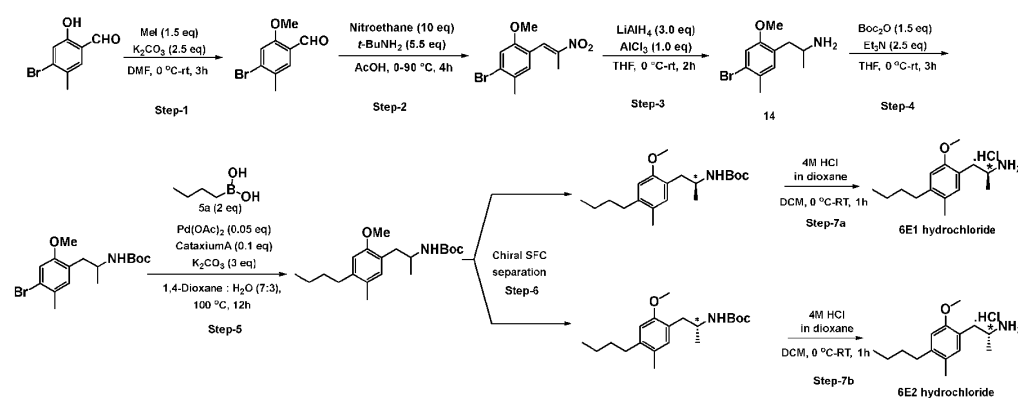
Preparation of 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine enantiomer 2 (5E2) hydrochloride

To a stirred solution of *tert*-butyl (1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (63 mg, 0.177 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.049 mL, 1.49 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(5-chloro-2-methoxy-4-propylphenyl)butan-2-amine enantiomer 2 (**5E2**) hydrochloride as an off-white solid (Yield: 37 mg, 90%; drawn as R

enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z 256.20 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.81 (s, 3H), 7.22 (s, 1H), 6.96 (s, 1H), 3.79 (s, 3H), 3.30-3.22 (m, 1H), 2.81-2.71 (m, 2H), 2.66-2.61 (m, 2H), 1.63-1.54 (m, 2H), 1.52-1.45 (m, 2H), 0.95-0.89 (m, 6H).

Example 6: 1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-amine enantiomer 1 (6E1) hydrochloride and 1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-amine enantiomer 2 (6E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 4-bromo-2-methoxy-5-methylbenzaldehyde

To a stirred solution of 4-bromo-2-hydroxy-5-methylbenzaldehyde (2.0 g, 9.3 mmol) in dimethylformamide (20 mL) was added potassium carbonate (3.2 g, 23.2 mmol) followed by dropwise addition of iodomethane (868 μ L, 14 mmol) at 0 °C. The reaction mixture was warmed to 50 °C and stirred for 3 h. The progress of reaction was monitored by TLC. Upon completion, the reaction was diluted with ice-cold water (20 mL) and extracted with ethyl acetate (25 mL x 3). The combined organic part was washed with brine (20 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by column chromatography by using 40 g of silica gel column eluting with 0-15% ethyl acetate in heptanes to afford desired 4-bromo-2-methoxy-5-methylbenzaldehyde as a colorless liquid (Yield: 2.0 g, 93.9%). **LC-MS**: m/z

230.95 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃): δ = 10.38 (s, 1H), 7.66 (s, 1H), 7.19 (s, 1H), 3.91 (s, 3H), 2.36 (3H).

Step 2:

Preparation of (E)-1-bromo-5-methoxy-2-methyl-4-(2-nitroprop-1-en-1-yl)benzene

To a stirred solution of 4-bromo-2-methoxy-5-methylbenzaldehyde (1.0 g, 4.37 mmol) in acetic acid (10 mL) was added nitroethane (2.3 mL, 43.7 mmol) followed by *tert*-butylamine (2.55 mL, 24 mmol) at 0 °C. Then mixture was warmed to 85 °C and stirred for 4 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water (50 mL), the precipitate that formed was filtered, washed with chilled water (10 mL x 3), and dried under reduced pressure to afford the desired (E)-1-bromo-5-methoxy-2-methyl-4-(2-nitroprop-1-en-1-yl)benzene as a yellow solid (Yield: 1.0 g, 80%). LC-MS: m/z 287.8 [M+1]⁺; ¹H NMR (400 MHz, CDCl₃): δ = 8.14 (s, 1H), 7.12 (s, 2H), 3.81 (s, 3H), 2.36 (s, 6H).

Step 3:

Preparation of 1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-amine (14)

To a stirred solution of LAH solution (2.0 M in THF; 5.23 mL, 10.47 mmol) in anhydrous THF (30 mL) was added AlCl₃ (465 mg, 3.49 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (E)-1-bromo-5-methoxy-2-methyl-4-(2-nitroprop-1-en-1-yl)benzene (1.0 g, 3.49 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and was added THF/water (1:1, 14 mL) at same temperature, until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (40 mL), combined organic part was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-amine (**14**) as a gummy solid (Yield: 0.7 g, 77.6%), which was used directly in the next step.

Step 4:

Preparation of tert-butyl (1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-yl)carbamate

To a stirred solution of 1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-amine (**14**; 0.7 g, 2.71 mmol) in THF (10 mL), triethylamine (0.65 mL, 6.8 mmol) followed by di-*tert*-butyl dicarbonate (0.9 mL, 4.6 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by flash column chromatography (eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 400 mg, 63%). **LC-MS:** m/z 258 [M+1]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 7.02 (s, 1H), 6.98 (s, 1H), 4.59 (brs, 1H), 3.88-3.83 (br s, 1H), 3.81 (s, 3H), 2.69-2.63 (m, 2H), 2.31 (s, 3H), 1.40 (s, 9H), 1.12 (d, *J* = 6.4 Hz, 3H).

Step 5:***Preparation of tert-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate***

To a stirred solution of *tert*-butyl (1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-yl)carbamate (0.3 g, 0.837 mmol) in 1,4-dioxane/water (3:1, 8 mL) was added dipotassium carbonate (347 mg, 2.51 mmol), butylboronic acid (171 mg, 1.67 mmol), 1-[1-adamantanyl(butyl)phosphino]adamantane (30 mg, 0.083 mmol), palladium bis(acetate) (9.4 mg, 0.042 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. Progress of the reaction was monitored by LC-MS: and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (10 mL) and water (10 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (eluting with 0-30% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 180 mg, 64%). **¹H NMR (400 MHz, CDCl₃):** δ = 6.88 (s, 1H), 6.65 (s, 1H), 4.78 (br s, 1H), 3.86 (br s, 1H), 3.82 (s, 3H), 2.75-2.63 (m, 2H), 2.56 (t, *J* = 8.0 Hz, 2H), 2.21 (s, 3H), 1.59-1.52 (m, 2H), 1.46-1.37 (m, 2H), 1.41 (s, 9H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H).

Step 6:***Preparation of tert-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate enantiomer 2***

The enantiomers of *tert*-butyl (1-(4-butyl-2-methoxy-5-methylphenyl) propan-2-yl)carbamate (180 mg) were separated by chiral SFC [Column Name: Lux Amylose-1 (21.2mm x 250 mm) 5 μ m; Mobile Phase: supercritical CO₂/IPA (75:25); Flow Rate: 70 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate enantiomer 1 (Yield: 50 mg, 31%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate enantiomer 2 (Yield: 60 mg, 37%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) as off-white solids.

tert-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate enantiomer 1

LC-MS: m/z 336.1 [M+H]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.86 (s, 1H), 6.62 (s, 1H), 4.75 (br s, 1H), 3.85 (br s, 1H), 3.80 (s, 3H), 2.69-2.61 (m, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 2.19 (s, 3H), 1.57-1.49 (m, 2H), 1.44-1.35 (m, 2H), 1.38 (s, 9H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column name: Lux Amylose-1 (250 mm x 4.6 mm) 5 μ m; Mobile Phase: CO₂/IPA with 0.2% isopropylamine additive (80:20); Flow Rate: 3.0 mL/min; 15 min run time; Column Temp: 30 °C] *R*_t = 1.67 min (enantiomer 1), 3.97 min (enantiomer 2).

tert-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate enantiomer 2

LC-MS: m/z 336.1 [M+H]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.89 (s, 1H), 6.64 (s, 1H), 4.68 (d, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 3.69 (br s, 1H), 2.75-2.65 (m, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 2.21 (s, 3H), 1.65-1.49 (m, 4H), 1.38 (s, 9H), 1.02-0.90 (m, 6H). The enantiomeric excess (99%) was determined by chiral SFC [Column name: Lux Amylose-1 (250 mm x 4.6 mm) 5 μ m; Mobile Phase: CO₂/IPA with 0.2% isopropylamine additive (80:20); Flow Rate: 3.0 mL/min; 8 min run time; Column Temp: 30 °C] *R*_t = 1.79 min (enantiomer 1), 3.23 min (enantiomer 2).

Step 7a:***Preparation of 1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-amine enantiomer 1 (6E1) hydrochloride***

To a stirred solution of *tert*-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate enantiomer 1 (50 mg, 0.149 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.37 mL, 1.5 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-amine enantiomer 1 (**6E1**) hydrochloride as an off-white solid (Yield: 21 mg, 51.7%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 236.3 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.88 (s, 3H), 6.88 (s, 1H), 6.76 (s, 1H), 3.75 (s, 3H), 3.39-3.38 (m, 1H), 2.84 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.60 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.54-2.52 (m, 2H), 2.16 (s, 3H), 1.53-1.45 (m, 2H), 1.40-1.31 (m, 2H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H).

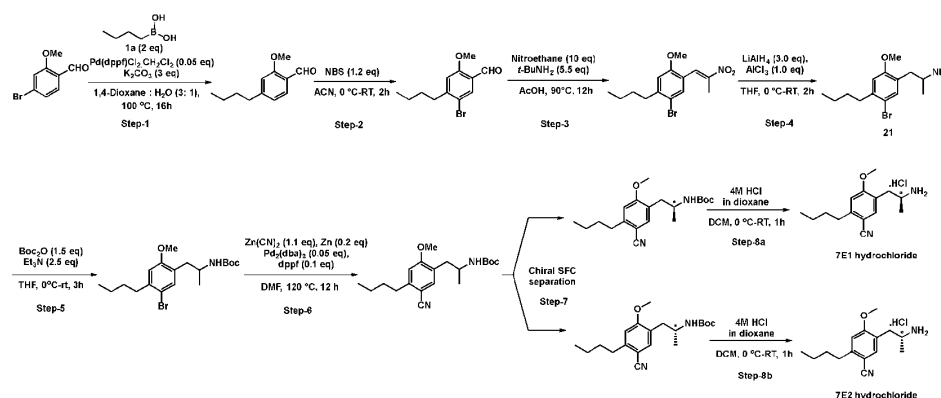
Step 7b:***Preparation of 1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-amine enantiomer 2 (6E2) hydrochloride***

To a stirred solution of *tert*-butyl (1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-yl)carbamate enantiomer 2 (60 mg, 0.179 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.45 mL, 1.79 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-2-methoxy-5-methylphenyl)propan-2-amine enantiomer 2 (**6E2**) hydrochloride as an off-white solid (Yield: 29 mg, 59.5%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 236.3 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.88 (s, 3H), 6.88 (s, 1H), 6.76 (s, 1H), 3.75 (s, 3H), 3.41-3.38 (m, 1H), 2.84 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.60 (dd, *J* = 13.2, 8.8 Hz, 1H), 2.54-

2.50 (m, 2H), 2.16 (s, 3H), 1.53-1.45 (m, 2H), 1.40-1.31 (m, 2H), 1.06 (d, $J = 6.4$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H).

Example 7: 5-(2-aminopropyl)-2-butyl-4-methoxybenzonitrile enantiomer 1 (7E1) hydrochloride and 5-(2-aminopropyl)-2-butyl-4-methoxybenzonitrile enantiomer 2 (7E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 4-butyl-2-methoxybenzaldehyde

To a stirred solution of 4-bromo-2-methoxybenzaldehyde (5 g, 23.2 mmol) in 1,4-dioxane/water (3:1, 50 mL) was added dipotassium carbonate (7.6 g, 69.6 mmol), *n*-butyl boronic acid (4.74 g, 46.4 mmol), and bis(diphenylphosphino)ferrocene)dichloropalladium dichloromethane complex (946 mg, 1.16 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 16 h. The progress of the reaction was monitored by LC-MS: and TLC. After completion, the reaction mixture was diluted with ethyl acetate (100 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (100 mL) and water (70 mL). The combined organic layer was washed with brine (70 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (silica gel; eluting with 0-15% ethyl acetate in heptanes) to afford 4-butyl-2-methoxybenzaldehyde as a yellow liquid (Yield: 2.0 g, 45 %). **LC-MS:** m/z 193.10 $[M+H]^+$; **1H NMR (400 MHz, $CDCl_3$):** δ = 10.41 (s, 1H), 7.765 (d, $J = 8.0$ Hz, 1H), 6.87 (d, $J = 8.0$

Hz, 1H), 6.8079 (s, 1H), 3.94 (s, 3H), 2.6766 (t, $J = 8.0$ Hz, 2H), 1.687-1.60 (m, 2H), 1.4241-1.32 (m, 2H), 0.95 96 (t, $J = 7.2$ Hz, 3H).

Step 2:

Preparation of 5-bromo-4-butyl-2-methoxybenzaldehyde

To a stirred solution of 4-butyl-2-methoxybenzaldehyde (2 g, 10.40 mmol) in acetonitrile (25 mL), *N*-bromosuccinimide (973 mg, 12.48 mmol) was added portionwise at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, then warmed to room temperature, and stirred for 2 h. Progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with chilled water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford 5-bromo-4-butyl-2-methoxybenzaldehyde as an off-white solid (Yield: 1.5 g, 53.2%). **¹H NMR (400 MHz, CDCl₃):** δ = 10.35 (s, 1H), 7.97 (s, 1H), 6.85 (s, 1H), 3.94 (s, 3H), 2.77 (t, $J = 8.0$ Hz, 2H), 1.65-1.59 (m, 2H), 1.48-1.42 (m, 2H), 0.99 (t, $J = 7.6$ Hz, 3H).

Step 3:

Preparation of (E)-1-bromo-2-butyl-4-methoxy-5-(2-nitroprop-1-en-1-yl)benzene

To a stirred solution of 5-bromo-4-butyl-2-methoxybenzaldehyde (1.5 g, 5.53 mmol) in acetic acid (10 mL) was added nitroethane (2.9 mL, 55.3 mmol) followed by *tert*-butylamine (3.23 mL, 30.4 mmol) at 0 °C. Then mixture was warmed to 90 °C and stirred for 12 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford (*E*)-1-bromo-2-butyl-4-methoxy-5-(2-nitroprop-1-en-1-yl)benzene as a yellow solid (Yield: 1.2 g, 66%). **¹H NMR (400 MHz, CDCl₃):** δ = 8.02 (s, 1H), 7.56 (s, 1H), 7.13 (s, 1H), 3.86 (s, 3H), 2.71 (t, $J = 8.0$ Hz, 2H), 2.30 (s, 3H), 1.61-1.53 (m, 2H), 1.42-1.33 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H).

Step 4:***Preparation of 1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-amine (21)***

To a stirred solution of LAH solution (2.0 M in THF; 5.49 mL, 10.98 mmol) in anhydrous THF (30 mL) was added AlCl₃ (487 mg, 3.66 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-bromo-2-butyl-4-methoxy-5-(2-nitroprop-1-en-1-yl)benzene (1.2 g, 3.66 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 1.5 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and was added THF/water (1:1, 14 mL) at same temperature, until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad, washed with THF (40 mL), the combined solvents were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-amine (**21**) as a gummy solid (Yield: 1.0 g), which was used directly for the next step.

Step 5:***Preparation of tert-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate***

To a stirred solution of crude 1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-amine (1.0 g, 3.33 mmol) in THF (10 mL), triethylamine (1.2 mL, 8.32 mmol) followed by di-*tert*-butyl dicarbonate (1.14 mL, 4.99 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 1.0 g, 75%). **LC-MS:** m/z 300.05 [M+1-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 7.23 (s, 1H), 6.68 (s, 1H), 4.56 (br s, 1H), 3.87 (br s, 1H), 3.81 (s, 3H), 2.68-2.65 (m, 4H), 1.42-1.38 (m, 4H), 1.38 (s, 9H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H).

Step 6:***Preparation of tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate***

To a stirred solution of tert-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate (0.3 g, 0.75 mmol) in DMF (10 mL) was added Zn(CN)₂ (96.8 mg, 0.82 mmol), zinc (9.8 mg, 0.15 mmol), 1,1'-ferrocenediyl-bis(diphenylphosphine) (41.5 mg, 0.075 mmol) and tris(dibenzylideneacetone)dipalladium (34 mg, 0.037 mmol). The reaction mixture was purged with argon for 10 min, then heated at 120 °C for 12 h. The progress of the reaction was monitored by LC-MS: and TLC. After completion, the reaction mixture was diluted with ethyl acetate (50 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (500 mL) and water (30 mL). The combined organic layer was washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get the crude compound. This crude material was purified by flash chromatography (silica gel; eluting with 0-20% ethyl acetate in heptanes) to afford tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate as a yellow solid (Yield: 150 mg, 58%). **LC-MS:** m/z 347.25 [M+1]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.39 (s, 1H), 7.00 (s, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 3.72-3.69 (m, 1H), 2.73-2.66 (m, 3H), 2.45-2.21 (m, 1H), 1.61-1.53 (m, 2H), 1.37-1.29 (m, 2H), 1.26 (s, 9H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H).

Step 7:***Preparation of tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate******enantiomer 1 and tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2***

The enantiomers of tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate (150 mg) were separated by chiral SFC [Column Name: Diacel CHIRALPAK IC (21 mm x 250 mm) 5 μm; Mobile Phase: supercritical CO₂: IPA (80:20); Flow Rate: 70 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 as an off-white solid (Yield: 50 mg, 33%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 as an off-white solid (Yield: 50 mg, 33%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1

LC-MS: m/z 347.25 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.39 (s, 1H), 7.00 (s, 1H), 6.66 (d, *J* = 9.2 Hz, 1H), 3.85 (s, 3H), 3.70 (t, *J* = 5.6 Hz, 1H), 2.73-2.67 (m, 3H), 2.45-2.42 (m, 1H), 1.61-1.54 (m, 2H), 1.35-1.9 (m, 1H), 1.26 (s, 9H), 1.20-1.17 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column Name: CHIRALPAK IC (250 mm x 4.6 mm) 5 μ m; Mobile Phase: supercritical CO₂/IPA containing 0.2% isopropylamine (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 °C]. *R*_t = 2.61 min (enantiomer 1), 2.89 min (enantiomer 2).

tert-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2

LC-MS: m/z 347.25 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.39 (s, 1H), 7.00 (s, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 3.70-3.69 (m, 1H), 2.73-2.67 (m, 3H), 2.45-2.42 (m, 1H), 1.61-1.53 (m, 2H), 1.35-1.23 (m, 11H), 1.20-1.17 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.6 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column Name: CHIRALPAK IC (250 mm x 4.6 mm) 5 μ m; Mobile Phase: supercritical CO₂/IPA containing 0.2% isopropylamine (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 °C]. *R*_t = 2.61 min (enantiomer 1), 2.87 min (enantiomer 2).

Step 8a:***Preparation of 5-(2-aminopropyl)-2-butyl-4-methoxybenzonitrile enantiomer 1 (7E1) hydrochloride***

To a stirred solution of *tert*-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (50 mg, 0.144 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.36 mL, 1.44 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 5-(2-aminopropyl)-2-butyl-4-methoxybenzonitrile enantiomer 1 (**7E1**) hydrochloride as a yellow sticky solid (Yield: 28 mg, 68%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 247.25 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.88 (br s, 3H), 7.56 (s, 1H),

7.09 (s, 1H), 3.87 (s, 3H), 3.44-3.42 (m, 1H), 2.87 (dd, $J = 13.6, 6.0$ Hz, 1H), 2.77-2.68 (m, 3H), 1.64-1.57 (m, 2H), 1.40-1.30 (m, 2H), 1.10 (d, $J = 6.8$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H).

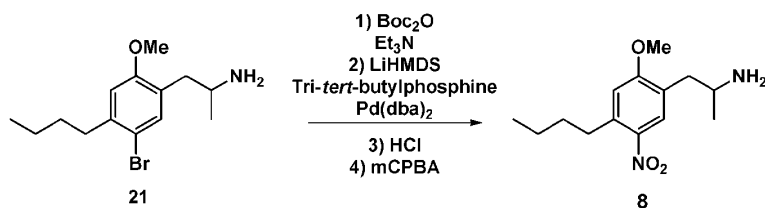
Step 8b:

Preparation of 5-(2-aminopropyl)-2-butyl-4-methoxybenzonitrile enantiomer 2 (7E2) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-butyl-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (50 mg, 0.144 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.36 mL, 1.44 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 5-(2-aminopropyl)-2-butyl-4-methoxybenzonitrile enantiomer 2 (**7E2**) hydrochloride as a yellow sticky solid (Yield: 21 mg, 51%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z 247.20 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.90 (br s, 3H), 7.56 (s, 1H), 7.09 (s, 1H), 3.87 (s, 3H), 3.44-3.42 (m, 1H), 2.87 (dd, $J = 13.6, 6.0$ Hz, 1H), 2.77-2.62 (m, 3H), 1.64-1.57 (m, 2H), 1.40-1.34 (m, 2H), 1.10 (d, $J = 6.4$ Hz, 3H), 0.92 (t, $J = 7.6$ Hz, 3H).

Example 8: Preparation of 1-(4-butyl-2-methoxy-5-nitrophenyl)propan-2-amine (8)

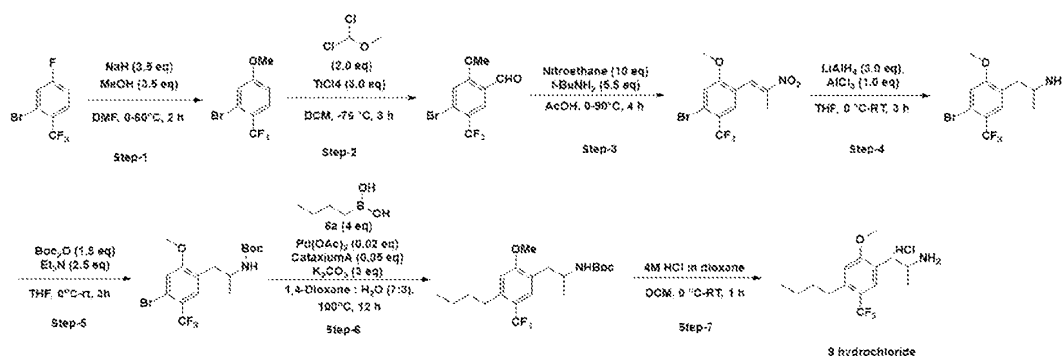
Synthetic Scheme:



This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 9: Preparation of 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine (9) hydrochloride and its enantiomers 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine enantiomer 1 (9E1) hydrochloride and 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine enantiomer 2 (9E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 2-bromo-4-methoxy-1-(trifluoromethyl)benzene

To a stirred suspension of sodium hydride (60% dispersion in mineral oil; 1.15 g, 28.8 mmol) in DMF (15 mL, 90.4 mmol) at 0 °C, was added methanol (1.17 mL, 28.8 mmol) dropwise under nitrogen atmosphere. After gas evolution ceased, the suspension was stirred at 0 °C for 20 min and 2-bromo-4-fluoro-1-(trifluoromethyl)benzene (2.0 g, 8.23 mmol) was added dropwise over 5 min. The reaction mixture was allowed to warm up to room temperature and then heated at 60 °C for 3 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with chilled water (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford 2-bromo-4-methoxy-1-(trifluoromethyl)benzene as an oil (Yield: 1.6 g, 76%). **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.74 (d, *J* = 8.8 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.11 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.85 (s, 3H).

Step 2:***Preparation of 4-bromo-2-methoxy-5-(trifluoromethyl)benzaldehyde***

To a solution of dichloromethoxymethane (1.05 g, 11.76 mmol) in anhydrous DCM (15 mL) was added TiCl_4 (1.96 mL, 17.64 mmol) dropwise at $-76\text{ }^\circ\text{C}$ under argon atmosphere. After complete addition, 2-bromo-4-methoxy-1-(trifluoromethyl)benzene (1.5 g, 5.88 mmol) was added to the reaction mixture and stirred at $-76\text{ }^\circ\text{C}$ for 3 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with DCM (20 mL x 2) and water (10 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford 4-bromo-2-methoxy-5-(trifluoromethyl)benzaldehyde as an oil (Yield: 870 mg, 52%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 10.26$ (s, 1H), 7.97 (s, 1H), 7.79 (s, 1H), 4.04 (s, 3H).

Step 3:***Preparation of (E)-1-bromo-5-methoxy-4-(2-nitroprop-1-en-1-yl)-2-(trifluoromethyl)benzene***

To a stirred solution of 4-bromo-2-methoxy-5-(trifluoromethyl)benzaldehyde (870 mg, 3.07 mmol) in acetic acid (10 mL) was added nitroethane (2.3 mL, 30.7 mmol) followed by *t*-butylamine (1.77 mL, 16.88 mmol) at $0\text{ }^\circ\text{C}$. Then mixture was warmed to $90\text{ }^\circ\text{C}$ and stirred for 4 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with ice-cold water (30 mL) and extracted with DCM (50 mL x 2) and water (30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptanes) to afford (E)-1-bromo-5-methoxy-4-(2-nitroprop-1-en-1-yl)-2-(trifluoromethyl)benzene as a yellow solid (Yield: 850 mg, 80%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 7.96$ (s, 1H), 7.77 (s, 1H), 7.62 (s, 1H), 3.97 (s, 3H), 2.27 (s, 3H).

Step 4:***Preparation of 1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine***

To a stirred solution of LAH solution (2.0 M in THF; 3.75 mL, 7.50 mmol) in anhydrous THF (30 mL) was added AlCl₃ (332.5 mg, 2.5 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-bromo-5-methoxy-4-(2-nitroprop-1-en-1-yl)-2-(trifluoromethyl)benzene (850 mg, 2.50 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 2.5 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and was added THF/water (1:1, 14 mL) at same temperature, until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (40 mL), the combined organic solvent was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine (**17**) as a gummy solid (Yield: 0.7 g, 90%), which was used directly in the next step.

Step 5:***Preparation of tert-butyl (1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate***

To a stirred solution of 1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine (0.7 g, 2.24 mmol) in THF (10 mL), trimethylamine (0.485 mL, 3.36 mmol) followed by di-*tert*-butyl dicarbonate (1.28 mL, 5.6 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate as an off-white solid (Yield: 520 mg, 56%). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.49 (s, 1H), 7.38 (s, 1H), 6.68 (*J* = 4.8 Hz, 1H), 3.88 (s, 3H), 3.74 (br s, 1H), 2.74 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.5-2.49 (m, 1H), 1.24 (s, 9H) 1.05 (d, *J* = 4.8 Hz, 3H).

Step 6:***Preparation of tert-butyl (1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate***

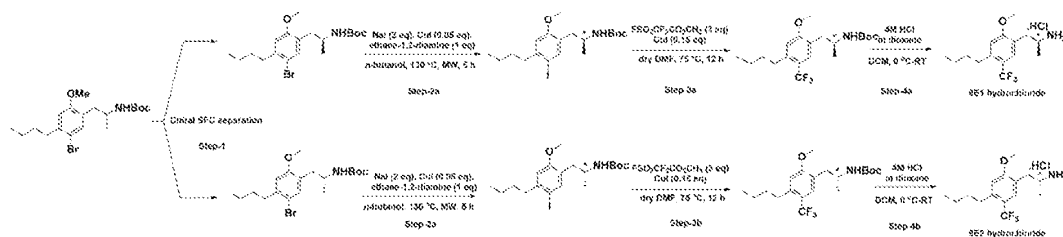
To a stirred solution of *tert*-butyl (1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate (520 mg, 1.26 mmol) in 1,4-dioxane/water (7:3, 10 mL) was added dipotassium carbonate (521 mg, 3.78 mmol), *n*-butylboronic acid (514 mg, 5.05 mmol), 1-[1-adamantanyl(butyl)phosphino]adamantane (22 mg, 0.063 mmol), palladium bis(acetate) (5.64 mg, 0.025 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. Progress of the reaction was monitored by LC-MS: and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was partitioned between ethyl acetate (10 mL) and water (10 mL). The combined organic solvent was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate as an off-white solid (Yield: 230 mg, 47%). **LC-MS:** *m/z* 290 [M+1-100]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.33 (s, 1H), 6.97 (s, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 3.84 (s, 3H), 3.73-3.71 (m, 1H), 2.73-2.64 (m, 3H), 2.52-2.46 (m, 1H), 1.58-1.15 (m, 2H), 1.41-1.33 (m, 2H), 1.25 (s, 9H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H)

Step 7:***Preparation of 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine (9) hydrochloride***

To a stirred solution of *tert*-butyl (1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate (50 mg, 0.128 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.37 mL, 1.28 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine (**9**) hydrochloride as an off-white solid (Yield: 20 mg, 49%). **LC-MS:** *m/z* 290 [M+1]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.92 (s, 3H), 7.43 (s,

1H), 7.08 (s, 1H), 3.87 (s, 3H), 3.42-3.97 (m, 1H), 2.90 (dd, $J = 13.2, 6$ Hz, 1H), 2.77-2.68 (m, 3H), 1.61-1.53 (m, 2H), 1.43-1.34 (m, 2H), 1.10 (d, $J = 6.8, 3$ H), 0.92 (t, $J = 6.8, 3$ H); ^{19}F NMR (376 MHz, DMSO- d_6): $\delta = -56.72$.

Synthetic Scheme:



Step 1:

Preparation of tert-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate (600 mg; see **Example 7**) were separated by chiral SFC [Column Name: Lux Amylose-1 21.2 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂:100% IPA (70:30); Flow Rate: 70 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (off-white solid; Yield: 250 mg, 41.67%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (off-white solid; Yield: 240 mg, 40.00%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

tert-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1

LC-MS: m/z : 300.00 $[\text{M}-100]^+$; ^1H NMR (400 MHz, DMSO- d_6): $\delta = 7.23$ (s, 1H), 6.88 (s, 1H), 6.65 (d, $J = 8.4$ Hz 1H), 3.77 (s, 3H), 3.68-3.62 (m, 1H), 2.64-2.60 (m, 3H), 2.50-2.45 (m, 1H), 1.53-1.48 (m, 2H), 1.37-1.33 (m, 2H), 1.29 (s, 9H), 1.01 (d, $J = 6.4$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H). The enantiomeric excess (99.80%) was determined by chiral SFC analysis [Column Name:

Lux Amylose-1 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂:100% IPA (70:30)); Flow Rate: 3.0 mL/min; Column temp: 30 °C] R_t = 1.39 (enantiomer 1), 2.59 (enantiomer 2).

***tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2**

LC-MS: m/z: 300.05 [M+H-100]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.23 (s, 1H), 6.88 (s, 1H), 6.65 (d, J = 8.4 Hz 1H), 3.77 (s, 3H), 3.70-3.66 (m, 1H), 2.64-2.60 (m, 3H), 2.50-2.45 (m, 1H), 1.53-1.47 (m, 2H), 1.37-1.33 (m, 2H), 1.29 (s, 9H), 1.01 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). The enantiomeric excess (99.52%) was determined by chiral SFC analysis [Column Name: Lux Amylose-1 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂:100% IPA (70:30)); Flow Rate: 3.0 mL/min; Column temp: 30 °C] R_t = 1.42 (enantiomer 1), 2.59 (enantiomer 2).

Step 2a:

Preparation of tert-butyl (1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1

To a stirred solution of *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (0.1 g, 0.251 mmol) in *n*-BuOH (2 mL) was added CuI (0.002 g, 0.013 mmol), ethane-1,2-diamine (0.015 g, 0.251 mmol) and NaI (0.075 g, 0.502 mmol) at room temperature. Then, the reaction mixture was stirred at 130 °C for 12 h. The progress of reaction was monitored by LC-MS. Upon completion, the reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (5 mL). The organic extract was dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound. This crude material was purified by silica flash column chromatography to afford *tert*-butyl (1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 as an off-white solid (80 mg, Yield: 71.60%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z: 392.23 [M+H-56]⁺.

Step 2b:

Preparation of tert-butyl (1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2

To a stirred solution of *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (0.1 g, 0.251 mmol) in *n*-BuOH (2 mL) was added CuI (0.002 g, 0.013 mmol), Ethane-1,2-diamine (0.015 g, 0.251 mmol) and NaI (0.075 g, 0.501 mmol) at room temperature. Then, the reaction mixture was stirred at 130 °C for 12 h. The progress of reaction was monitored by LC-MS. Upon completion, the reaction mixture was allowed to cool to room temperature and then concentrated under reduced pressure. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with water (5 mL). The organic extract was dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound. This crude material was purified by silica flash column chromatography to afford *tert*-butyl (1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 as an off-white solid (85 mg, yield: 76.07%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z: 392.06 [M+H-56]⁺.

Step 3a:

Preparation of tert-butyl (1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate enantiomer 1

tert-butyl (1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-yl)carbamate enantiomer 1 (off-white solid; Yield: 60 mg, 46%; drawn as S enantiomer but absolute stereochemistry not determined experimentally) was synthesized from *tert*-butyl (1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 (80 mg) following general procedure E (see **Example 61**). (10 mg, yield: 14.36%). **LC-MS:** m/z: 290.10 [M+H-100]⁺.

Step 3b:

Preparation of tert-butyl (1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate enantiomer 2

tert-butyl (1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate enantiomer 2 (off white solid; Yield: 10 mg, 14.36%; drawn as R enantiomer but absolute stereochemistry not determined experimentally) was synthesized from *tert*-butyl (1-(4-iodo-2,5-dimethoxyphenyl)-3-

methoxypropan-2-yl)carbamate enantiomer 2 (85 mg) following general procedure E (see **Example 61**). (Yield: 10 mg, 14.36%). **LC-MS**: m/z : 290.10 $[M+H-100]^+$.

Step 4a:

Preparation of 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine enantiomer 1 (9E1) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate enantiomer 1 (10 mg, 0.026 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.02 mL, 0.078 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (2.0 mL) to yield 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine enantiomer 1 (**9E1**) hydrochloride (Yield: 5 mg, 59.77%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z : 290.30 $[M+1]^+$; **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.81 (s, 3H), 7.43 (s, 1H), 7.07 (s, 1H), 3.86 (s, 3H), 3.43-3.38 (m, 1H), 2.90-2.85 (m, 1H), 2.77-2.73 (m, 1H), 2.71-2.67 (m, 2H), 1.61-1.53 (m, 2H), 1.43-1.35 (m, 2H), 1.10 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.32 Hz, 3H). **¹⁹F-NMR (376 MHz, DMSO-*d*₆)**: δ -56.72 (s).

Step 4b:

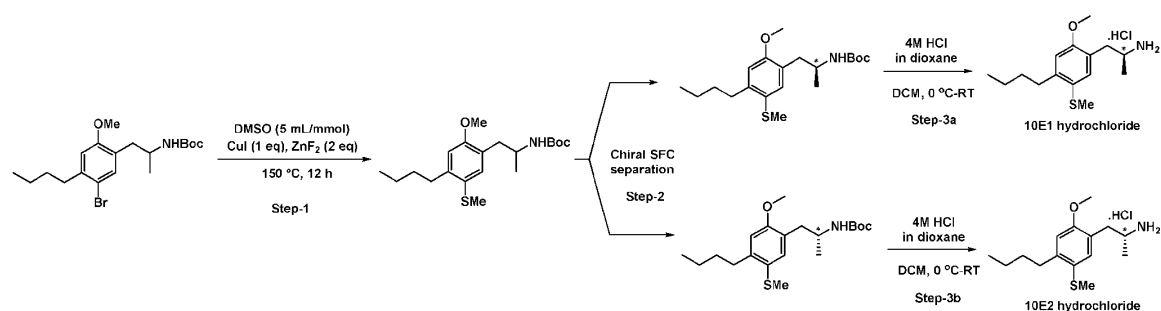
Preparation of 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine enantiomer 2 (9E2) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate enantiomer 2 (10 mg, 0.026 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.02 mL, 0.078mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (2.0 mL) to afford 1-(4-butyl-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine enantiomer 2 (**9E2**) hydrochloride (Yield: 4 mg, 47.82%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z : 290.25 $[M+1]^+$; **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.86 (s, 3H), 7.43 (s, 1H),

7.07 (s, 1H), 3.86 (s, 3H), 3.44-3.38 (m, 1H), 2.91-2.86 (m, 1H), 2.77-2.74 (m, 1H), 2.72-2.67 (m, 2H), 1.61-1.53 (m, 2H), 1.43-1.33 (m, 2H), 1.10 (d, $J = 6.4$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H).
¹⁹F-NMR (376 MHz, DMSO-*d*₆): δ -56.71 (s).

Example 10: Preparation of 1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-amine enantiomer 1 (10E1) hydrochloride and 1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-amine enantiomer 2 (10E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate (see **Example 7**; 600 mg, 1.27 mmol) in DMSO (6 mL) was added zinc difluoride (260 mg, 2.55 mmol) followed by CuI (241 mg, 1.27 mmol) at 0 °C. Then mixture was heated to 150 °C and stirred for 12 h. The progress of reaction was monitored by LC-MS. Upon completion, the reaction mixture was concentrated and purified by flash column chromatography followed by prep HPLC [Column: X-Bridge C8; 19 mm x 250 mm, 5 μ m; Gradient: acetonitrile/0.1% formic acid in water (2% - 98%); Flow rate: 18 ml/min; 22 min run time] to afford the desired *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate as a white solid (Yield: 78 mg, 16.6%). **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.04 (s, 1H), 6.77 (s, 1H), 6.63 (d, $J = 8.4$ Hz, 1H), 3.74 (s, 3H), 3.69 (br s, 1H), 2.66-2.60 (m, 2H), 2.36 (s, 3H), 1.54-1.47 (m, 2H), 1.35-1.34 (m, 2H), 1.32 (s, 9H), 1.23-1.18 (m, 2H), 1.00 (d, $J = 6.4$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H).

Step 2:***Preparation of tert-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate enantiomer 2***

The enantiomers of *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate (78 mg) were separated by chiral SFC [Column Name: Daicel, CHIRALPAK IG (30 mm x 250 mm) 5 μ m; Mobile Phase: supercritical CO₂/IPA (80:20); Flow Rate: 70 mL/min Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate enantiomer 1 (Yield: 15 mg, 38%, >98% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate enantiomer 2 (Yield: 14 mg, 36%, >98% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) as off-white solids.

tert-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate enantiomer

1LC-MS: m/z 368.05 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.04 (s, 1H), 6.77 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 3.76 (s, 3H), 3.70-3.67 (m, 1H), 2.67-2.62 (m, 4H), 2.37 (s, 3H), 1.53-1.47 (m, 2H), 1.36-1.19 (m, 2H), 1.30 (s, 9H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (98.7%) was determined by chiral SFC analysis [Column Name: Chiralpak IG (250 mm x 4.6 mm) 5 μ m; Mobile Phase: supercritical CO₂/100% IPA (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 °C] *R*_t = 2.13 min (enantiomer 1), 3.51 min (enantiomer 2).

tert-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate enantiomer

2LC-MS: m/z 368.10 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.05 (s, 1H), 6.78 (s, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 3.75 (s, 3H), 3.70 (br, 1H), 2.67-2.62 (m, 2H), 2.51-2.50 (m, 2H), 2.37 (s, 3H), 1.51-1.49 (m, 2H), 1.34-1.19 (m, 2H), 1.30 (s, 9H), 1.00 (d, *J* = 5.6 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (98.7%) was determined by chiral SFC analysis [Column Name: Chiralpak IG (250 mm x 4.6 mm) 5 μ m; Mobile Phase: supercritical CO₂/100% IPA (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 °C] *R*_t = 1.99 min (enantiomer 1), 3.57 min (enantiomer 2).

Step 3a:***Preparation of 1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-amine enantiomer 1 (10E1) hydrochloride***

To a stirred solution of *tert*-butyl 1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate enantiomer 1 (0.015 g, 0.004 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.1 mL, 0.40 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-amine enantiomer 1 (**10E1**) hydrochloride as an off-white solid (Yield: 10 mg, 80%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 268.20 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.84 (br s, 3H), 7.08 (s, 1H), 6.86 (s, 1H), 3.77 (s, 3H), 3.72-3.67 (m, 1H), 3.46-3.34 (m, 2H), 2.85 (dd, *J* = 13.2, 6.0 Hz, 1H), 2.71-2.64 (m, 3H), 2.39 (s, 3H), 1.56-1.49 (m, 2H), 1.39-1.30 (m, 2H), 1.1 (d, *J* = 6.4 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

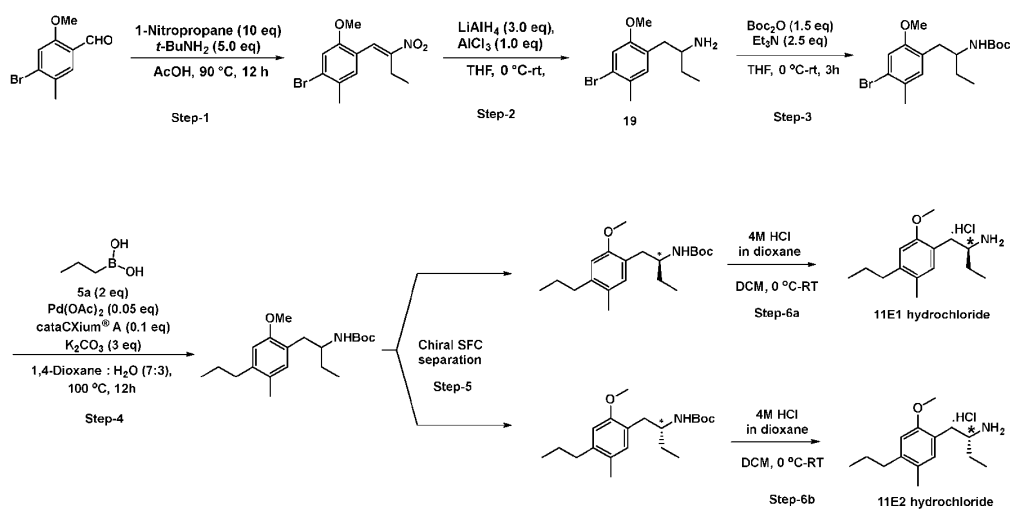
Step 3b:***Synthesis of 1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-amine enantiomer 2 (10E2) hydrochloride***

To a stirred solution of *tert*-butyl 1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate enantiomer 2 (14 mg, 0.003 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.1 mL, 0.381 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-amine enantiomer 2 (**10E2**) hydrochloride as an off-white solid (Yield: 4 mg, 35%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 268.25 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.80 (br s, 2H), 7.08 (s, 1H), 6.86 (s, 1H), 3.77 (s, 3H), 3.41-3.39 (m, 1H), 2.84 (dd, *J* = 13.2, 6 Hz, 1H),

2.71-2.63 (m, 3H), 2.39 (s, 3H), 1.56-1.49 (m, 2H), 1.39-1.32 (m, 2H), 1.10 (d, $J = 6.4$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H).

Example 11: Preparation of 1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-amine enantiomer 1 (11E1) hydrochloride and 1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-amine enantiomer 1 (11E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of (E)-1-bromo-5-methoxy-2-methyl-4-(2-nitrobut-1-en-1-yl)benzene

To a stirred solution of 4-bromo-2-methoxy-5-methylbenzaldehyde (see **Example 6**; 1.0 g, 4.37 mmol) in acetic acid (10 mL) was added 1-nitropropane (4.0 mL, 43.7 mmol) followed by *tert*-butyl amine (2.55 mL, 24 mmol) at 0 °C. Then mixture was warmed to 90 °C and stirred for 4 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water (25 mL), the precipitate that formed was filtered, washed with chilled water (10 mL x 3) and dried under reduced pressure to afford the desired (*E*)-1-bromo-5-methoxy-2-methyl-4-(2-nitrobut-1-en-1-yl)benzene as a yellow solid (Yield: 1.0 g, 76%). **LC-MS**: m/z 301 $[M+1]^+$; **¹H NMR (400 MHz, CDCl₃)**: δ = 8.07 (s, 1H), 7.11 (s, 2H), 3.86 (s, 3H), 2.77 (q, $J = 7.2$ Hz, 2H), 2.36 (s, 3H), 1.25 (t, $J = 7.2$ Hz, 3H).

Step 2:***Preparation of 1-(4-bromo-2-methoxy-5-methylphenyl)butan-2-amine***

To a stirred solution of LAH solution (2.0 M in THF; 4.99 mL, 9.99 mmol) in anhydrous THF (30 mL) was added AlCl₃ (443 mg, 3.33 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-bromo-5-methoxy-2-methyl-4-(2-nitrobut-1-en-1-yl)benzene (1.0 g, 3.33 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and was added THF/water (1:1, 14 mL) at same temperature until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (40 mL), combined organic part was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(4-bromo-2-methoxy-5-methylphenyl)butan-2-amine (**19**) as a gummy solid (Yield: 0.560 g, 61%), which was directly taken for the next step.

Step 3:***Preparation of tert-butyl (1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-yl)carbamate***

To a stirred solution of 1-(4-bromo-2-methoxy-5-methylphenyl)butan-2-amine (**19**; 0.56 g, 2.05 mmol) in THF (10 mL), triethylamine (0.7 mL, 5.14 mmol) followed by di-*tert*-butyl dicarbonate (0.7 mL, 3.04 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by flash column chromatography (eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 500 mg, 71%). **LC-MS:** m/z 273 [M+H-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.99 (s, 1H), 6.98 (s, 2H), 4.46 (s, 1H), 3.79 (s, 3H), 3.68 (s, 1H), 2.73-2.63 (m, 2H), 2.29 (s, 3H), 1.54-1.49 (m, 2H), 1.36 (s, 9H), 0.95-0.91 (t, *J* = 7.2 Hz, 3H).

Step 4:***Preparation of tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate***

To a stirred solution of *tert*-butyl (1-(4-bromo-2-methoxy-5-methylphenyl)butan-2-yl)carbamate (0.50 g, 1.34 mmol) in 1,4-dioxane/water (3:1, 8 mL) was added dipotassium carbonate (552 mg, 4.0 mmol), *n*-propyl boronic acid (235 mg, 2.68 mmol), 1-[1-adamantanyl(butyl)phosphino]adamantane (98 mg, 0.13 mmol), palladium bis(acetate) (15 mg, 0.067 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. Progress of the reaction was monitored by LC-MS: and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through Celite pad. The filtrate was extracted with ethyl acetate (10 mL) and water (10 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (eluting with 0-30% ethyl acetate in heptanes) to afford *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate as an off-white solid (Yield: 150 mg 33 %). **LC-MS:** *m/z* 316.15 [M+1]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.87 (s, 1H), 6.61 (s, 1H), 4.64 (s, 1H), 3.79 (s, 3H), 3.67 (br s, 1H), 2.69-2.63 (m, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 1.62-1.47 (m, 2H), 1.36 (s, 9H), 1.44-1.31 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H).

Step 5:***Preparation of tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate******enantiomer 1 and tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 2***

The enantiomers of *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate (150 mg) were separated by chiral SFC [Column Name: Phenomenex®, Lux Amylose-1 21.2 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂:100% IPA (75:25); Flow Rate : 70 mL/min; Column temp: 30 °C. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 as an off-white solid (Yield: 60 mg, 40%; >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 as an off-white solid

(Yield: 50 mg, 33%; >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 1

LC-MS: m/z 336.1 [M+H]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.89 (s, 1H), 6.64 (s, 1H), 4.64 (br s, 1H), 3.81 (s, 3H), 3.68 (br s, 1H), 2.70-2.69 (m, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 2.21 (s, 3H), 1.64-1.51 (m, 2H), 1.46-1.37 (m, 1H), 1.41 (s, 9H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis. [Column Name: Lux Amylose-1 (4.6 mm x 250 mm) 5 μ m; Mobile Phase: CO₂/IPA with 0.2% isopropylamine additive (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 °C] *R*_t = 2.00 min (enantiomer 1), 2.61 min (enantiomer 2).

tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 2

LC-MS: m/z 336.1 [M+H]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.89 (s, 1H), 6.64 (s, 1H), 4.65 (s, 1H), 3.81 (s, 3H), 3.68 (br s, 1H), 2.70-2.69 (m, 2H), 2.54 (t, *J* = 8.0 Hz, 2H), 2.21 (s, 3H), 1.64-1.51 (m, 2H), 1.44-1.53 (m, 1H), 1.51 (s, 9H), 0.99 (t, *J* = 8 Hz, 3H), 0.95 (m, *J* = 8 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC [Column Name: Lux Amylose-1 (4.6 mm x 250 mm) 5 μ m; Mobile Phase: CO₂/IPA with 0.2% isopropylamine additive (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 °C] *R*_t = 2.00 min (enantiomer 1), 2.61 min (enantiomer 2).

Step 6a:

Preparation of 1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-amine enantiomer 1 (11E1) hydrochloride

To a stirred solution of *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 (50 mg, 0.149 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.37 mL, 1.5 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-amine enantiomer 1 (**11E1**) hydrochloride as an off-white solid (Yield: 25 mg, 61%; drawn as S

enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 236.3 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6):** δ = 7.81 (s, 3H), 6.92 (s, 1H), 6.76 (s, 1H), 3.75 (s, 3H), 3.22-3.21 (m, 1H), 2.78-2.68 (m, 2H), 2.52-2.50 (m, 2H), 2.16 (s, 3H), 1.57-1.42 (m, 4H), 0.94 (t, J = 6.8 Hz, 3H), 0.91 (t, J = 6.8 Hz, 3H).

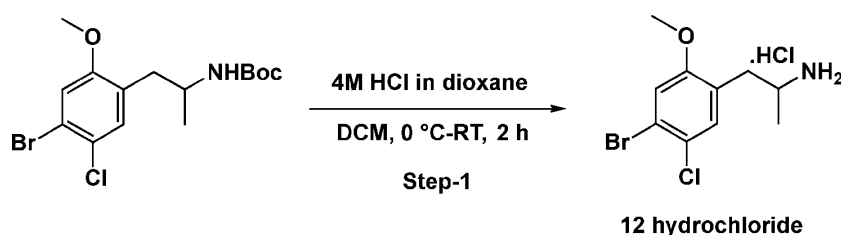
Step 6b:

Preparation of 1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-amine enantiomer 2 (11E2) hydrochloride

To a stirred solution of *tert*-butyl 1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (50 mg, 0.149 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.049 mL, 1.49 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-amine enantiomer 2 (**11E2**) hydrochloride as an off-white solid (Yield: 35 mg, 86%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 236.3 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6):** δ = 7.82 (s, 3H), 6.91 (s, 1H), 6.76 (s, 1H), 3.75 (s, 3H), 3.27-3.20 (m, 1H), 2.78-2.67 (m, 1H), 2.52-2.50 (m, 2H), 2.16 (s, 3H), 1.58-1.40 (m, 4H), 0.94 (t, J = 6.8 Hz, 3H), 0.89 (t, J = 6.8 Hz, 3H).

Example 12: Preparation of 1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-amine (12) hydrochloride

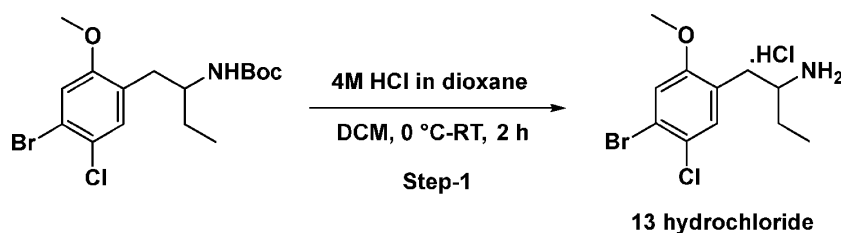
Synthetic Scheme:



Step 1:

Preparation of 1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-amine (12) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-ylcarbamate (see **Example 3**; 50 mg, 0.132 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.33 mL, 1.32 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-amine (**12**) hydrochloride as an off-white solid (Yield: 34 mg, 82%). **LC-MS:** m/z 278.00 $[M+H]^+$; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.90 (s, 3H), 7.45 (s, 1H), 7.38 (s, 1H), 3.82 (s, 3H), 3.42-3.39 (m, 1H), 2.84 (dd, J = 13.6, 6.0 Hz, 1H), 2.71 (dd, J = 13.6, 6.0 Hz, 1H), 1.11 (d, J = 6.8 Hz, 3H).

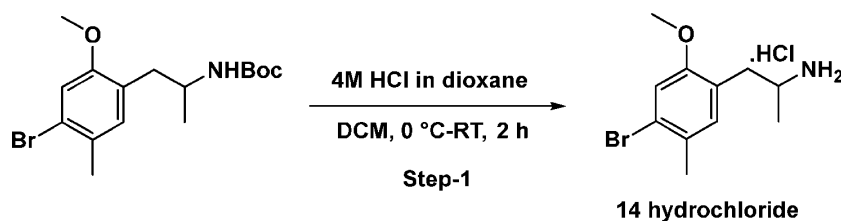
Example 13: 1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-amine (13) hydrochloride**Synthetic Scheme:****Step 1:****Preparation of 1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-amine (13) hydrochloride**

To a stirred solution of *tert*-butyl 1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-ylcarbamate (see **Example 4**; 50 mg, 0.127 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.32 mL, 1.27 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-bromo-5-chloro-2-methoxyphenyl)butan-2-amine (**13**) hydrochloride as an off-white solid (Yield: 40 mg, 95%). **LC-MS:** m/z 292.00

[M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆): δ = 7.90 (s, 3H), 7.48 (s, 1H), 7.37 (s, 1H), 3.82 (s, 3H), 3.28-3.23 (m, 1H), 2.85-2.73 (m, 2H), 1.55-1.47 (m, 2H), 0.92 (d, *J* = 7.6 Hz, 3H).

Example 14: Preparation of 1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-amine (14) hydrochloride

Synthetic Scheme:



Step 1:

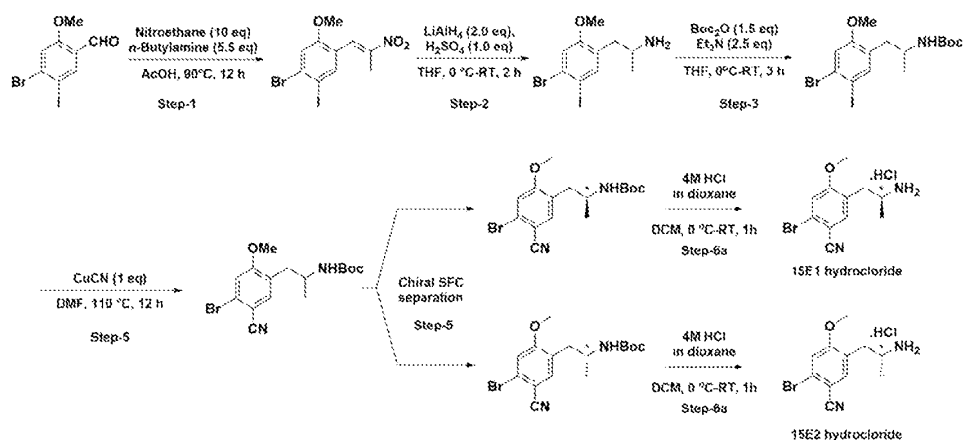
Preparation of 1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-amine (14) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-ylcarbamate (see **Example 6**, 50 mg, 0.139 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.35 mL, 1.39 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-amine (**14**) hydrochloride as an off-white solid (Yield: 35 mg, 85%).

LC-MS: *m/z* 258.15 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆): δ = 7.93 (s, 3H), 7.19 (s, 1H), 7.14 (s, 1H), 3.78 (s, 3H), 3.42-3.35 (m, 1H), 2.85 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.65 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.26 (s, 3H), 1.09 (d, *J* = 6.4 Hz, 3H).

Example 15: Preparation of 5-(2-aminopropyl)-2-bromo-4-methoxybenzonitrile enantiomer 1 (15E1) hydrochloride and 5-(2-aminopropyl)-2-bromo-4-methoxybenzonitrile enantiomer 2 (15E2) hydrochloride

Synthetic Scheme:



Steps 1-3:

Preparation of tert-butyl (1-(4-bromo-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate

tert-butyl (1-(4-bromo-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate was synthesized from 4-bromo-5-iodo-2-methoxybenzaldehyde (3.0 g) over three steps following general procedure A (see **Example 61**). Yield: 800 mg, 19% (over 3 steps). ¹H NMR (400 MHz, CDCl₃): δ = 7.52 (s, 1H), 7.08 (s, 1H), 3.95-3.87 (m, 1H), 3.80 (s, 3H), 2.65-2.58 (m, 2H), 1.38 (s, 9H), 1.10 (d, *J* = 6.64 Hz, 3H).

Step 4:

Preparation of tert-butyl (1-(4-bromo-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate

tert-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate was synthesized from *tert*-butyl (1-(4-bromo-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate following general procedure D (see **Example 61**). White solid; Yield: 100 mg, 25%. LC-MS: *m/z*: 368.90 [M+H]⁺.

Step 5:

Preparation of tert-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate (100 mg) were separated by chiral SFC [Column Name: CHIRALPAK IC 21.0 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂:0.1% ammonium hydroxide in ACN (90:10)), Flow Rate: 70 mL/min; Column temp: Ambient]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (Yield: 40 mg, 40%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (off-white solid; Yield: 45 mg, 45%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

***tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1**

LC-MS: m/z: 368.90 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.54 (s, 1H), 7.41 (s, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 1H), 2.74-2.71 (m, 1H), 2.47-2.41 (m, 1H), 1.26 (s, 9H), 1.05 (d, *J* = 6.4 Hz, 3H). The enantiomeric excess (98.98%) was determined by chiral SFC analysis [Column Name: Chiralpak IC 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂:100% ACN (75:25)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] *R*_t = 2.34 (enantiomer 1), 3.03 (enantiomer 2).

***tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2**

LC-MS: m/z: 368.95 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.54 (s, 1H), 7.41 (s, 1H), 6.68 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 3H), 3.72 (s, 1H), 2.73-2.70 (m, 1H), 2.47-2.42 (m, 1H), 1.26 (s, 9H), 1.05 (d, *J* = 6.4 Hz, 3H). The enantiomeric excess (87.30%) was determined by chiral SFC analysis [Column Name: Chiralpak IC 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂:100% ACN (75:25)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] *R*_t = 2.34 (enantiomer 1), 3.04 (enantiomer 2).

Step 6a:

Preparation of 5-(2-aminopropyl)-2-bromo-4-methoxybenzonitrile enantiomer 1 (15E1) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (40 mg, 0.108 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.135 mL, 0.54 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 5-(2-aminopropyl)-2-bromo-4-methoxybenzonitrile enantiomer 1 (**15E1**) as a hydrochloride salt (Yield: 26 mg, 83%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z: 269.2 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.92 (br s, 3H), 7.75 (s, 1H), 7.50 (s, 1H), 3.91 (s, 3H), 3.43-3.41 (m, 1H), 2.89-2.84 (m, 1H), 2.76-2.71 (m, 1H), 1.12 (d, *J* = 6.5 Hz, 3H).

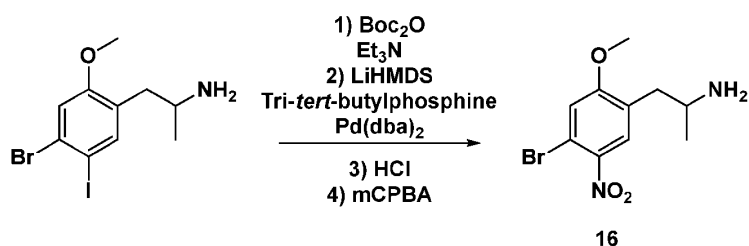
Step 6b:

Preparation of 5-(2-aminopropyl)-2-bromo-4-methoxybenzonitrile enantiomer 2 (15E2) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (45 mg, 0.138 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.17 mL, 0.69 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 5-(2-aminopropyl)-2-bromo-4-methoxybenzonitrile enantiomer 2 (**15E2**) as a hydrochloride salt (Yield: 28 mg, 77%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z: 269.2 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.88 (s, 3H), 7.75 (s, 1H), 7.50 (s, 1H), 3.91 (s, 3H), 3.45-3.40 (m, 1H), 2.89-2.84 (m, 1H), 2.76-2.71 (m, 1H), 1.12 (d, *J* = 6.5 Hz, 3H).

Example 16: Preparation of 1-(4-bromo-2-methoxy-5-nitrophenyl)propan-2-amine (16)

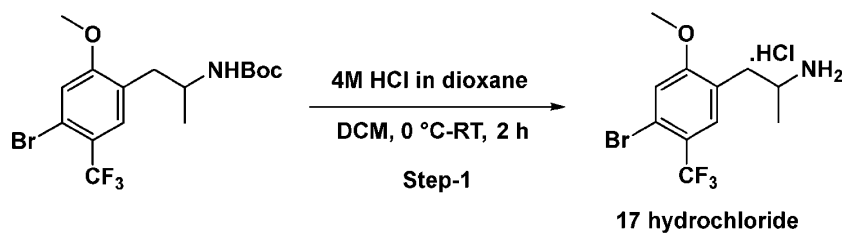
Synthetic Scheme:



This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 17: Preparation of 1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine (17) hydrochloride

Synthetic Scheme:



Step 1:

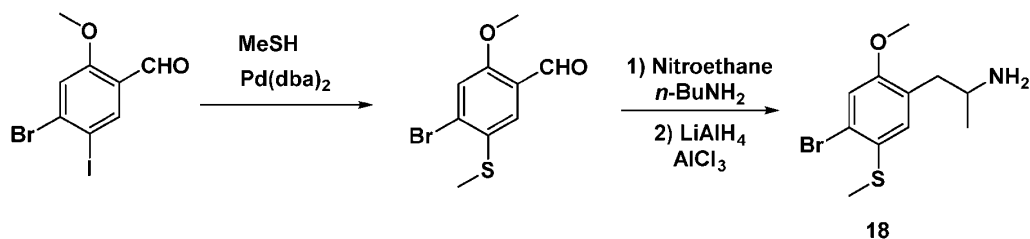
Preparation of 1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine (17) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-yl)carbamate (see **Example 9**; 40 mg, 0.097 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.24 mL, 0.97 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-bromo-2-methoxy-5-(trifluoromethyl)phenyl)propan-2-amine (**17**) hydrochloride as an off-white solid (Yield: 24 mg, 71%). **LC-MS**: m/z 312.10 $[\text{M}+\text{H}]^+$; **^1H NMR (400 MHz, $\text{DMSO}-d_6$)**: δ = 7.90 (s, 3H), 7.64 (s,

1H), 7.47 (s, 1H), 3.90 (s, 3H), 3.46-3.37 (m, 1H), 2.89 (dd, $J = 13.2, 6.8$ Hz, 1H), 2.79 (dd, $J = 13.6, 7.2$ Hz, 1H), 1.13 (d, $J = 6.8$ Hz, 3H); ^{19}F NMR (376 MHz, DMSO- d_6): $\delta = -59.6$.

Example 18: Preparation of 1-(4-bromo-2-methoxy-5-(methylthio)phenyl)propan-2-amine (18)

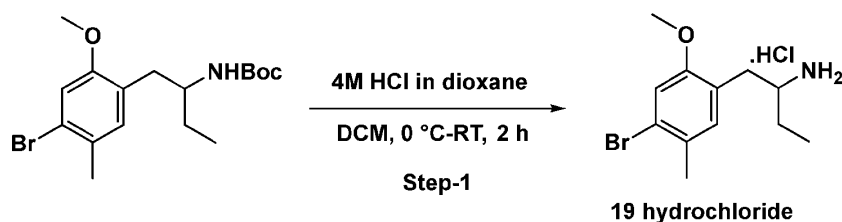
Synthetic Scheme:



This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 19: Preparation of 1-(4-bromo-2-methoxy-5-methylphenyl)butan-2-amine (19) hydrochloride

Synthetic Scheme:



Step 1:

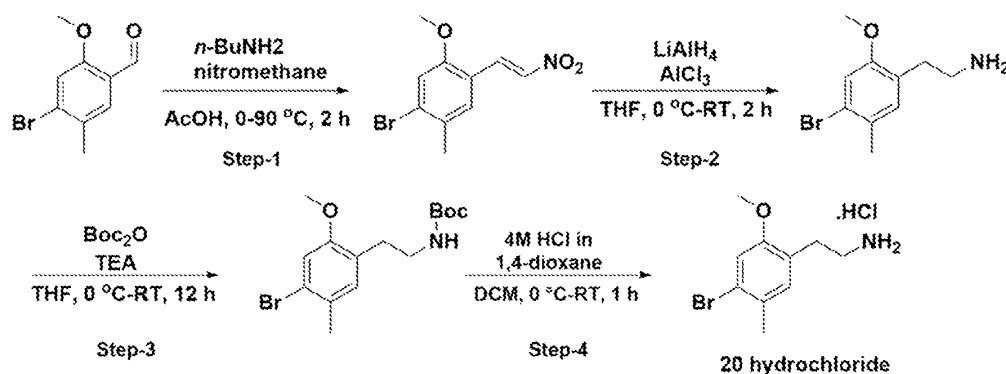
Preparation of 1-(4-bromo-2-methoxy-5-methylphenyl)butan-2-amine (19) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-bromo-2-methoxy-5-methylphenyl)butan-2-yl)carbamate (see **Example 11**; 40 mg, 0.107 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.27 mL, 1.07 mmol) at 0 °C. After complete addition, the reaction mixture was

warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-bromo-2-methoxy-5-methylphenyl)butan-2-amine (**19**) hydrochloride as an off-white solid (Yield: 29 mg, 87%). **LC-MS:** m/z 272.10 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6):** δ = 7.93 (s, 3H), 7.19 (s, 1H), 7.17 (s, 1H), 3.79 (s, 3H), 3.26-3.21 (m, 1H), 2.76 (d, J = 5.6 Hz, 2H), 2.26 (s, 3H), 1.52-1.45 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H).

Example 20: Preparation of 2-(4-bromo-2-methoxy-5-methylphenyl)ethan-1-amine (**20**) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of (E)-1-bromo-5-methoxy-2-methyl-4-(2-nitrovinyl)benzene

To a stirred solution of 4-bromo-2-methoxy-5-methylbenzaldehyde (0.8 g, 3.52 mmol) in acetic acid (10 mL) was added nitromethane (1.3 mL, 35.2 mmol) followed by n -butylamine (1.4 mL, 19.3 mmol) at 0 °C. Then, the reaction mixture was warmed to 90 °C and stirred for 2 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water (15 mL), the precipitate that formed was filtered, washed with chilled water (10 mL x 3), and dried under reduced pressure to afford (E)-1-bromo-5-methoxy-2-methyl-4-(2-nitrovinyl)benzene as yellow solid which was directly used for the next step. (Yield: 0.7 g, 73%).

¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.16-8.08 (s, 2H), 7.83 (s, 1H), 7.04 (s, 1H), 3.93 (s, 3H), 2.30 (s, 3H).

Step 2:

Preparation of 2-(4-bromo-2-methoxy-5-methylphenyl)ethan-1-amine

To a stirred solution of LAH solution (2.0 M in THF; 4 mL, 7.72 mmol) in anhydrous THF (15 mL) was added AlCl₃ (342 mg, 2.57 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-bromo-5-methoxy-2-methyl-4-(2-nitrovinyl)benzene (0.7 g, 2.57 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and was added THF/water (1:1, 6 mL) at same temperature, until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 minutes under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF, combined organic part was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude product, which was used directly for the next step without further characterization.

Step 3:

Preparation of *tert*-butyl (4-bromo-2-methoxy-5-methylphenethyl)carbamate

To a stirred solution of 2-(4-bromo-2-methoxy-5-methylphenyl)ethan-1-amine (0.6 g, 2.45 mmol) in THF (6 mL), triethylamine (0.83 mL, 6.1 mmol) followed by di-*tert*-butyl dicarbonate (0.84 mL, 3.67 mmol) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (18 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic extracts were washed with brine (15 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by silica flash column chromatography (eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (4-bromo-2-methoxy-5-methylphenethyl)carbamate (Yield: 300 mg, 34 %). **LC-MS:** *m/z* 244 [M+H-100]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.11 (s, 1H),

7.05 (s, 1H), 6.82 (t, $J = 5.4$ Hz, 1H), 3.76 (s, 3H), 3.09-3.04 (m, 2H), 2.59 (t, $J = 7.4$ Hz, 2H), 2.23 (s, 3H), 1.35 (s, 9H).

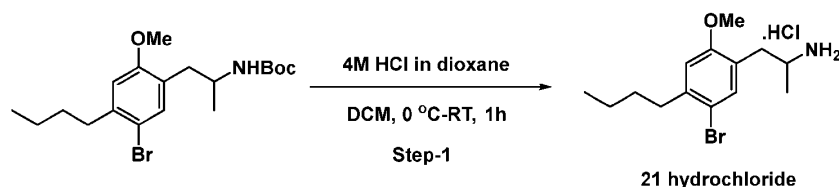
Step 4:

Preparation of 2-(4-bromo-2-methoxy-5-methylphenyl)ethan-1-amine (20) hydrochloride

To a stirred solution of *tert*-butyl (4-bromo-2-methoxy-5-methylphenethyl)carbamate (100 mg, 0.29 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.36 mL, 1.45 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (3.0 mL) to afford the 2-(4-bromo-2-methoxy-5-methylphenyl)ethan-1-amine (20) hydrochloride (Yield: 21 mg, 60%). LC-MS: m/z : 244.2 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6): $\delta = 7.84$ (br s, 3H), 7.18 (s, 1H), 7.15 (s, 1H), 3.79 (s, 3H), 2.94 (t, $J = 8.0$ Hz, 2H), 2.78 (t, $J = 8.0$ Hz, 2H), 2.25 (s, 3H).

Example 21: Preparation of 1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-amine (21) hydrochloride

Synthetic Scheme:



Step 1:

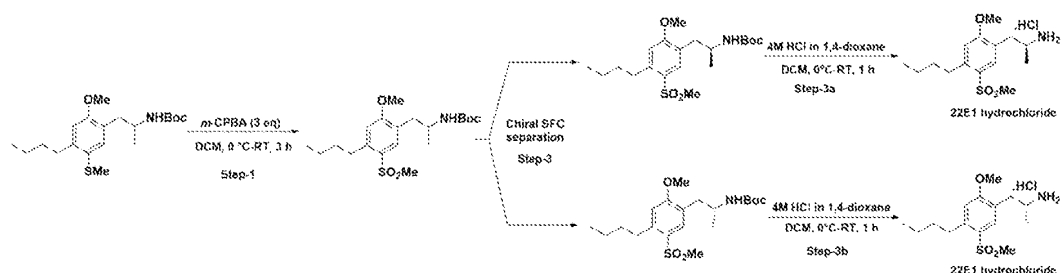
Preparation of 1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-amine (21) hydrochloride

To a stirred solution of *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate (see **Example 7**; 30 mg, 0.074 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.185 mL, 0.74 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed

with diethyl ether (5.0 mL) to afford the desired 1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-amine (**21**) hydrochloride as an off-white solid (Yield: 15 mg, 69%). **LC-MS**: m/z 300.15 $[M+1]^+$; **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.89 (br s, 3H), 7.34 (s, 1H), 6.98 (s, 1H), 3.79 (s, 3H), 3.39 (br s, 1H), 2.84 (dd, J = 13.6, 6.0 Hz, 1H), 2.69-2.63 (m, 3H), 1.57-1.50 (m, 2H), 1.41-1.31 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H).

Example 22: Preparation of 1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-amine enantiomer 1 (22E1) hydrochloride and 1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-amine enantiomer 2 (22E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of tert-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylthio)phenyl)propan-2-yl)carbamate (synthesized as described for **1AE1/1AE2**; 0.15 g, 0.42 mmol) in DCM (5 mL) was added meta-chloroperbenzoic acid ($\leq 77\%$, 0.28 g, 1.26 mmol) at 0 °C. Then the mixture was warmed to room temperature and stirred for 3 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with DCM (10 mL) was washed with sodium carbonate solution (3 x 5 mL), followed by brine wash (10 mL). The organic part was dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound. This crude material was purified by silica flash column chromatography (eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate as an off-white solid (Yield: 120 mg, 74%). **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.69 (s, 1H), 6.98 (s, 1H), 6.70 (d, J = 9.2 Hz 1H), 3.87 (s,

3H), 3.80-3.72 (m, 1H), 3.18 (s, 3H), 2.97-2.89 (m, 2H), 2.70-2.50 (m, 2H), 1.61-1.58 (m, 2H), 1.41-1.36 (m, 2H), 1.27 (s, 9H), 1.00 (d, $J = 6$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H).

Step 2:

Preparation of tert-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate (110 mg) were separated by chiral SFC [Column Name: CHIRALCEL OX-H 30.0 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂:100% IPA (75:25)); Flow Rate: 90 mL/min; Column temp: 35 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate enantiomer 1 (off-white solid; Yield: 45 mg, 40.91%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate enantiomer 2 (off-white solid; Yield: 45 mg, 40.91%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

tert-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate enantiomer 1

LC-MS: m/z: 417.20 [M+18]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.61 (s, 1H), 6.98 (s, 1H), 6.70 (d, $J = 8.4$ Hz 1H), 3.87 (s, 3H), 3.73-3.71 (m, 1H), 3.09 (s, 3H), 2.93-2.88 (m, 2H), 2.70-2.50 (m, 2H), 1.62-1.56 (m, 2H), 1.41-1.33 (m, 2H), 1.27 (s, 9H), 1.00 (d, $J = 6.4$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H). The enantiomeric excess (99.94%) was determined by chiral SFC analysis [Column Name: Chiralcel OX-3 4.6 mm ID x 150 mm, 3 μ m; Mobile Phase: supercritical CO₂ (CO₂:0.1% IPAmine in IPA (80:20)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] R_t = 2.26 (enantiomer 1), 3.78 (enantiomer 2).

tert-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate enantiomer 2

LC-MS: m/z: 417.2 [M+18]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.62 (s, 1H), 6.98 (s, 1H), 6.70 (d, J = 8.4 Hz 1H), 3.87 (s, 3H), 3.75-3.71 (m, 1H), 3.09 (s, 3H), 2.93-2.88 (m, 2H), 2.70-2.56 (m, 2H), 1.64-1.56 (m, 2H), 1.41-1.33 (m, 2H), 1.27 (s, 9H), 1.00 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). The enantiomeric excess (99.91%) was determined by chiral SFC analysis [Column Name: Chiralcel OX-3 4.6 mm ID x 150 mm, 3 μ m; Mobile Phase: supercritical CO₂ (CO₂:0.1% IPAmine in IPA (80:20)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] R_t = 2.26 (enantiomer 1), 3.78 (enantiomer 2).

Step 3a:

Preparation of 1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-amine enantiomer 1 (22E1) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate enantiomer 1 (45 mg, 0.113 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.28 mL, 1.13 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-amine enantiomer 1 (**22E1**) hydrochloride (Yield: 28 mg, 74%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z: 300.25 [M+1]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.87 (s, 3H), 7.67 (s, 1H), 7.08 (s, 1H), 3.89 (s, 3H), 3.41-3.36 (m, 1H), 3.14 (s, 3H), 2.95-2.89 (m, 2H), 2.87-2.73 (m, 2H), 1.66-1.59 (m, 2H), 1.45-1.34 (m, 2H), 1.11 (d, J = 6.52 Hz, 3H), 0.93 (t, J = 7.32 Hz, 3H).

Step 3b:

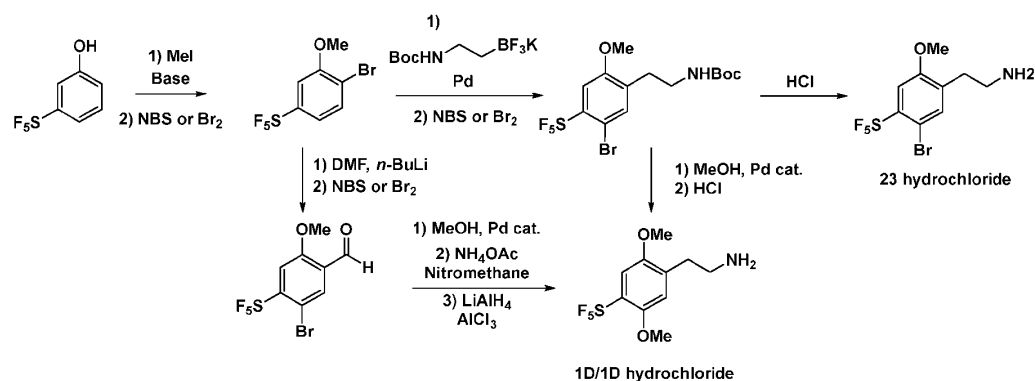
Preparation of 1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-amine enantiomer 2 (22E2) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-yl)carbamate enantiomer 2 (45 mg, 0.113 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.28 mL, 1.13 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and

washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-2-methoxy-5-(methylsulfonyl)phenyl)propan-2-amine enantiomer 2 (**22E2**) hydrochloride (Yield: 28 mg, 74%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z : 300.20 $[M+1]^+$; **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.89 (br s, 3H), 7.67 (s, 1H), 7.08 (s, 1H), 3.89 (s, 3H), 3.41-3.39 (m, 1H), 3.14 (s, 3H), 2.96-2.86 (m, 3H), 2.79-2.73 (m, 1H), 1.66-1.59 (m, 2H), 1.45-1.36 (m, 2H), 1.12 (d, J = 6.52 Hz, 3H), 0.93 (t, J = 7.32 Hz, 3H).

Example 23: Preparation of 2-(5-bromo-2-methoxy-4-(pentafluoro- λ^6 -sulfanyl)phenyl)ethan-1-amine (23)

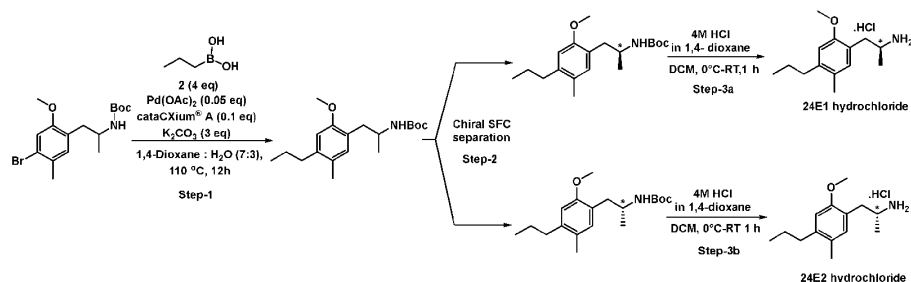
Synthetic Scheme:



This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 24: Preparation of 1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-amine enantiomer 1 (24E1**) hydrochloride and 1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-amine enantiomer 2 (**24E2**) hydrochloride**

Synthetic Scheme:

**Step 1:*****Preparation of tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate***

To a stirred solution of *tert*-butyl (1-(4-bromo-2-methoxy-5-methylphenyl)propan-2-yl)carbamate (see **Example 6**; 0.20 g, 0.56 mmol) in 1,4-dioxane/water (7:3, 6 mL) was added dipotassium carbonate (232 mg, 1.68 mmol), *n*-propylboronic acid (193 mg, 2.2 mmol), 1-[1-adamantany](butyl)phosphino]adamantane (20 mg, 0.056 mmol), palladium bis(acetate) (6.0 mg, 0.028 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (10 mL) and water (10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 100 mg, 56 %). **LC-MS**: *m/z* 322.10 [M+1]⁺.

Step 2:***Preparation of tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate enantiomer 2***

The enantiomers of *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate (100 mg) were separated by chiral SFC [Column Name: Daicel Chiralpak AD-H (21 mm x 250 mm) 5 µm; Mobile Phase: supercritical CO₂/IPA (80:20); Flow Rate: 60mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to

afford *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate enantiomer 1 (Yield: 40 mg, 40%; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate enantiomer 2 (Yield: 40 mg, 40%; drawn as R enantiomer but absolute stereochemistry not determined experimentally) as off-white solids.

tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate enantiomer 1

LC-MS: m/z 322.2 $[M+H]^+$; **1H NMR (400 MHz, $CDCl_3$):** δ = 6.86 (s, 1H), 6.63 (s, 1H), 4.77 (br s, 1H), 3.84 (br s, 1H), 3.79 (s, 3H), 2.70-2.61 (m, 2H), 2.52 (t, J = 8 Hz, 2H), 2.20 (s, 3H), 1.63-1.57 (m, 2H), 1.38 (s, 9H), 1.17 (d, J = 6.4 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H).

The enantiomeric excess (99%) was determined by chiral SFC analysis (Column Name: Chiralpak AD-H (4.6 mm x 250 mm) 5 μ m; Mobile Phase: supercritical CO_2 /IPA containing 0.1% NH_4OH (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 $^{\circ}C$) R_t = 1.55 min (enantiomer 1), 3.23 min (enantiomer 2).

tert-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate enantiomer 2

m/z 322.2 $[M+H-100]^+$; **1H NMR (400 MHz, $CDCl_3$):** δ = 6.86 (s, 1H), 6.63 (s, 1H), 4.77 (br s, 1H), 3.85 (br s, 1H), 3.80 (s, 3H), 2.73-2.61 (m, 2H), 2.52 (t, J = 8 Hz, 2H), 2.19 (s, 3H), 1.63-1.55 (m, 2H), 1.38 (s, 9H), 1.11 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis (Column Name: Chiralpak AD-H (4.6 mm x 250 mm) 5 μ m; Mobile Phase: supercritical CO_2 /IPA containing 0.1% NH_4OH (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 $^{\circ}C$) R_t = 1.57 min (enantiomer 1), 3.29 min (enantiomer 2).

Step 3a:

Preparation of 1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-amine enantiomer 1 (24E1) hydrochloride

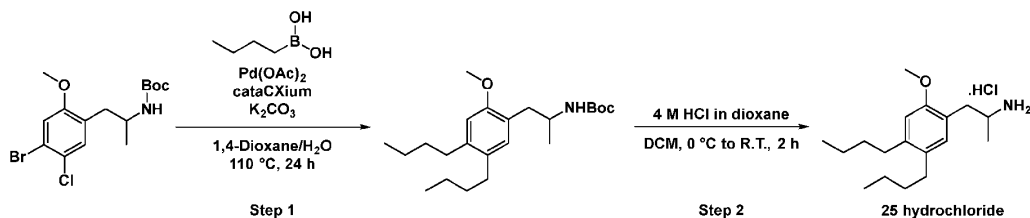
To a stirred solution of *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate enantiomer 1 (40 mg, 0.12 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.30 mL, 1.20 mmol) at 0 $^{\circ}C$. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was concentrated under reduced

pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-amine enantiomer 1 (**24E1**) hydrochloride as an off-white solid (Yield: 24 mg, 75%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z 222.3 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.89 (s, 3H), 6.89 (s, 1H), 6.76 (s, 1H), 3.75 (s, 3H), 3.42-3.33 (m, 1H), 2.85 (dd, J = 13.2, 5.2 Hz, 1H), 2.60 (dd, J = 13.2, 8.8 Hz, 1H), 2.52-2.49 (m, 2H), 2.17 (s, 3H), 1.58-1.49 (m, 2H), 1.06 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H).

Step 3b:

Preparation of 1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-amine enantiomer 2 (24E2) hydrochloride

To a stirred solution of *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-yl)carbamate enantiomer 2 (40 mg, 0.12 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.30 mL, 1.20 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2-methoxy-5-methyl-4-propylphenyl)propan-2-amine enantiomer 2 (**24E2**) hydrochloride as an off-white solid (Yield: 29 mg, 90%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z 222.2 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.87 (s, 3H), 6.89 (s, 1H), 6.76 (s, 1H), 3.75 (s, 3H), 3.42-3.33 (m, 1H), 2.85 (dd, J = 13.2, 5.2 Hz, 1H), 2.61 (dd, J = 13.2, 8.4 Hz, 1H), 2.52-2.49 (m, 2H), 2.17 (s, 3H), 1.58-1.49 (m, 2H), 1.06 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 7.2 Hz, 3H).

Example 25: Preparation of 1-(4,5-dibutyl-2-methoxyphenyl)propan-2-amine (25)**Synthetic Scheme:****Step 1:*****Preparation of tert-butyl (1-(4,5-dibutyl-2-methoxyphenyl)propan-2-yl)carbamate***

To a stirred solution of *tert*-butyl (1-(4-bromo-5-chloro-2-methoxyphenyl)propan-2-yl)carbamate (see **Example 3**; 0.1 g, 0.264 mmol) in 1,4-dioxane/water (7:3, 5 mL) was added dipotassium carbonate (109 mg, 0.792 mmol), *n*-butylboronic acid (135 mg, 1.32 mmol), 1-[1-adamantanyl(butyl)phosphino]adamantane (18.9 mg, 0.0528 mmol), and palladium bis(acetate) (5.93 mg, 0.026 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 24 h. Progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (10 mL) and water (10 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4,5-dibutyl-2-methoxyphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 50 mg, 46.14%). **LC-MS:** *m/z* 330.20 [M+1-56]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.84 (s, 1H), 6.67 (s, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 3.73 (s, 3H), 3.70-3.65 (m, 1H), 2.55-2.44 (m, 6H), 1.53-1.42 (m, 4H), 1.40-1.18 (m, 4H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.93-0.92 (m, 6H)

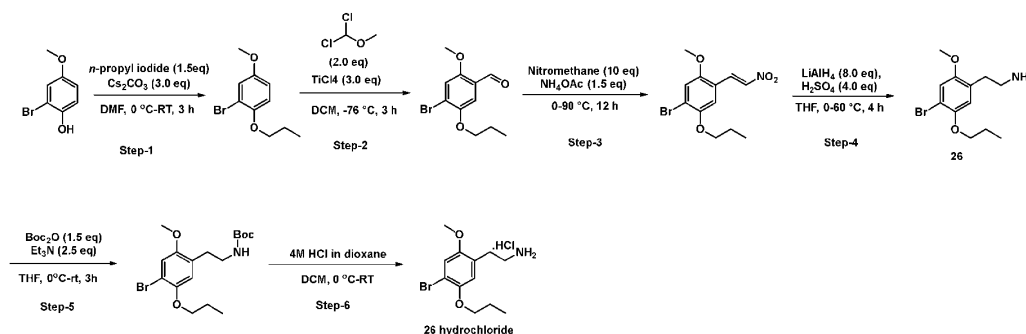
Step 2:***Preparation of 1-(4,5-dibutyl-2-methoxyphenyl)propan-2-amine (25) hydrochloride***

To a stirred solution of *tert*-butyl (1-(4,5-dibutyl-2-methoxyphenyl)propan-2-yl)carbamate (50 mg, 0.132 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.16 mL,

0.66 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4,5-dibutyl-2-methoxyphenyl)propan-2-amine (**25**) hydrochloride as an off-white solid (Yield: 27 mg, 65%). **LC-MS:** m/z 278.25 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 8.0 (s, 3H), 6.88 (s, 1H), 6.76 (s, 1H), 3.76 (s, 3H), 3.40-3.34 (m, 1H), 2.86 (dd, J = 13.2, 5.6 Hz, 1H), 2.68-2.47 (m, 5H), 1.55-1.50 (m, 4H), 1.49-1.28 (m, 4H), 1.07 (d, J = 6.4 Hz, 3H), 0.94-0.87 (m, 6H).

Example 26: Preparation of 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine (**26**) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 2-bromo-4-methoxy-1-propoxybenzene

To a stirred solution of 2-bromo-4-methoxyphenol (2.0 g, 9.85 mmol) in DMF (20 mL) at 0 °C, was added Cs₂CO₃ (9.63 g, 29.6 mmol) under nitrogen atmosphere. After the gas evolution ceased, the suspension was stirred at 0 °C for 10 min, then 1-iodopropane (1.44 mL, 14.8 mmol) was added dropwise over 5 min. The reaction mixture was allowed to warm up to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with chilled water (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude

material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford 2-bromo-4-methoxy-1-propoxybenzene as an off-white solid (Yield: 2.2 g, 91%). **¹H NMR (400 MHz, CDCl₃):** δ = 7.11 (d, J = 2.8 Hz, 1H), 6.85-6.77 (m, 2H), 3.93 (t, J = 6.4 Hz, 2H), 1.87-1.78 (m, 2H), 1.06 (t, J = 7.2 Hz, 3H).

Step 2:

Preparation of 4-bromo-2-methoxy-5-propoxybenzaldehyde

To a solution of dichloromethoxymethane (1.88 g, 16.3 mmol) in anhydrous DCM (20 mL) was added TiCl₄ (2.73 mL, 24.5 mmol) dropwise at -78 °C under argon atmosphere. After complete addition, 2-bromo-4-methoxy-1-propoxybenzene (2.0 g, 8.16 mmol) was added to the reaction mixture and stirred at -78 °C for 3 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was quenched with saturated NH₄Cl solution (10 mL) and extracted with DCM (20 mL x 2) and water (10 mL). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get the crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford 4-bromo-2-methoxy-5-propoxybenzaldehyde as an off-white solid (Yield: 1.5 g, 60%). **¹H NMR (400 MHz, CDCl₃):** δ = 10.38 (s, 1H), 7.32 (s, 1H), 7.23 (s, 1H), 4.00 (t, J = 6.4 Hz, 2H), 3.89 (s, 3H), 1.89-1.80 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H).

Step 3:

Preparation of (E)-1-bromo-5-methoxy-4-(2-nitrovinyl)-2-propoxybenzene

To a stirred solution of 4-bromo-2-methoxy-5-propoxybenzaldehyde (500 mg, 1.83 mmol), was added nitromethane (1.08 mL, 18.3 mmol) followed by ammonium acetate (212 mg, 2.75 mmol) at 0 °C. The reaction mixture was warmed to 90 °C and stirred for 12 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with ice-cold water (10 mL), extracted with DCM (20 mL x 2). The organic solvent was washed with water (10 mL), then brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get the crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptane) to afford (E)-1-bromo-5-methoxy-4-(2-nitrovinyl)-2-propoxybenzene as a yellow solid (Yield: 350 mg, 60%). **¹H NMR**

(400 MHz, CDCl₃): δ = 8.06 (d, J = 13.6 Hz, 1H), 7.85 (d, J = 13.6 Hz, 1H), 3.96 (t, J = 6.4 Hz, 2H), 3.93 (s, 3H), 1.91-1.82 (m, 2H), 1.07 (t, J = 7.6 Hz, 3H).

Step 4:

Preparation of 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine (26)

To a stirred solution of LAH solution (2.0 M in THF; 4.44 mL, 8.88 mmol) in anhydrous THF (30 mL) was added sulfuric acid (443 mg, 4.44 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-bromo-5-methoxy-4-(2-nitrovinyl)-2-propoxybenzene (350 mg, 1.11 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 4 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and THF/water (1:1, 14 mL) was slowly added at same temperature until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad, washed with THF (40 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine (**26**) as a gummy solid (Yield: 0.35 g), which was directly used in the next step.

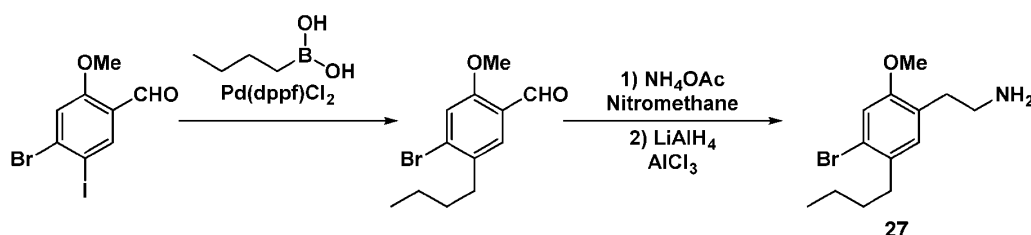
Step 5:

Preparation of tert-butyl (2-(4-bromo-2-methoxy-5-propoxyphenyl)ethyl)carbamate

To a stirred solution of 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine (**26**; 350 mg, 1.21 mmol) in THF (10 mL), trimethylamine (0.427 mL, 3.04 mmol) followed by di-*tert*-butyl dicarbonate (0.442 mL, 1.82 mmol) was added at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (10 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (2-(4-bromo-2-methoxy-5-propoxyphenyl)ethyl)carbamate as an off-white solid (Yield: 370 mg, 78%). **LC-MS**: 331.90 [M+1-56]⁺.

Step 6:**Preparation of 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine (26) hydrochloride**

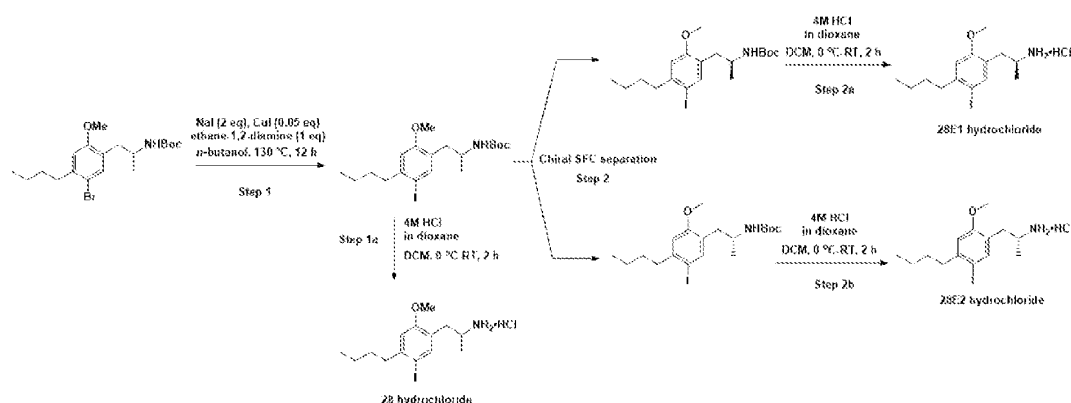
To a stirred solution of *tert*-butyl 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethylcarbamate (70 mg, 0.18 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.45 mL, 1.80 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 2-(4-bromo-2-methoxy-5-propoxyphenyl)ethan-1-amine (26) hydrochloride as an off-white solid (Yield: 35 mg, 60%). **LC-MS:** m/z 288.20 $[M+1]^+$; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.88 (s, 3H), 7.19 (s, 1H), 6.98 (s, 1H), 3.95 (t, J = 6.4 Hz, 2H), 3.77 (s, 3H), 2.97 (br s, 2H), 2.83-2.79 (m, 2H), 1.77-1.68 (m, 2H), 1.0 (t, J = 7.2 Hz, 3H).

Example 27: Preparation of 2-(4-bromo-5-butyl-2-methoxyphenyl)ethan-1-amine (27)**Synthetic Scheme:**

This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 28: Preparation of 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine (28) hydrochloride and its enantiomers 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine enantiomer 1 (28E1) hydrochloride and 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine enantiomer 2 (28E2) hydrochloride

Synthetic Scheme:

**Step 1:****Preparation of tert-butyl (1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate**

To a stirred solution of *tert*-butyl (1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate (see **Example 7**; 0.6 g, 1.50 mmol) in *n*-BuOH (6.0 mL), was added NaI (450 mg, 3.0 mmol) followed by CuI (14.25 mg, 0.075 mmol) at 0 °C and ethane-1,2-diamine (0.01 mL, 1.50 mmol). Then the mixture was warmed to 130 °C and stirred for 12 h. The progress of the reaction was monitored by LC-MS. Upon completion, the reaction mixture was concentrated under reduced pressure and purified by prep-HPLC to afford the desired *tert*-butyl (1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate as a brown solid (Yield: 100 mg, 14%). **LC-MS:** m/z 448 $[M+1]^+$; **1H NMR (400 MHz, $CDCl_3$):** δ = 7.48 (s, 1H), 6.69 (s, 1H), 4.57 (br s, 1H), 3.87 (br s, 1H), 3.80 (s, 3H), 2.66-2.62 (m, 4H), 1.58-1.51 (m, 2H), 1.44-1.38 (m, 2H), 1.38 (s, 9H), 1.10 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.6 Hz, 3H).

Step 1a:**Preparation of 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine (28) hydrochloride**

To a stirred solution of *tert*-butyl (1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate (30 mg, 0.067 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.17 mL, 0.67 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine (**28**) hydrochloride as an off-white solid (Yield: 17 mg, 66%). **LC-MS:** m/z : 348.05 $[M+H]^+$; **1H**

NMR (400 MHz, DMSO- d_6): δ = 7.83 (s, 3H), 7.54 (s, 1H), 6.97 (s, 1H), 3.78 (s, 3H), 3.38-3.36 (br s, 1H), 2.80 (dd, J = 13.2, 6.0 Hz, 1H), 2.67-2.61 (m, 3H), 1.55-1.47 (m, 2H), 1.44-1.34 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H).

Step 2: Preparation of *tert*-butyl 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 and *tert*-butyl 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate (120 mg) were separated by chiral SFC [column name: Lux Amylose-1 (21.2 mm x 250 mm) 5 μ m; mobile phase: supercritical CO₂/ 0.1% NH₄OH in IPA(70:30); flow rate: 60 mL/min; column temp: 30 °C]. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford *tert*-butyl 1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (Yield: 40 mg, 33%, >99% ee; drawn as the *S* enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl 1-(5-bromo-4-butyl-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (Yield: 38 mg, 32%, >99% ee; drawn as the *R* enantiomer but absolute stereochemistry not determined experimentally).

***tert*-butyl 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1. LC-MS:** m/z : 392.05 [M+H-56]⁺; **¹H NMR (400 MHz, DMSO- d_6):** δ = 7.45 (s, 1H), 6.87 (s, 1H), 6.65-6.62 (m, 1H), 3.76 (s, 3H), 3.66-3.65 (m, 1H), 3.16 (d, J = 5.2 Hz, 1H), 2.66-2.57 (m, 3H), 2.50-2.45 (m, 2H), 1.51-1.44 (m, 2H), 1.37-1.29 (m, 9H), 0.99 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). The enantiomeric excess (>99%) was determined by chiral SFC analysis [column name: Lux Amylose-1 (4.6 mm x 250 mm) 5 μ m; mobile phase: supercritical CO₂/0.1% NH₄OH in IPA (70:30); flow rate: 3.0 mL/min; column temp: 35 °C]. R_t = 1.74 min (enantiomer 1), 2.71 min (enantiomer 2).

***tert*-butyl 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2. LC-MS:** m/z : 392.00 [M+H-56]⁺; **¹H NMR (400 MHz, DMSO- d_6):** δ = 7.45 (s, 1H), 6.87 (s, 1H), 6.64-6.62 (m, 1H), 3.76 (s, 3H), 3.66-3.65 (m, 1H), 3.16 (d, J = 5.2 Hz, 1H), 2.66-2.57 (m, 3H), 2.50-2.45 (m, 2H), 1.51-1.44 (m, 2H), 1.37-1.29 (m, 9H), 0.99 (d, J = 6.8 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H). The enantiomeric excess (99.52%) was determined by chiral SFC analysis [column

name: Lux Amylose-1 (4.6 mm x 250 mm) 5 μ m; mobile phase: supercritical CO₂/0.1% NH₄OH in IPA (70:30); flow rate: 3.0 mL/min; column temp: 35 °C]. R_t = 1.81 min (enantiomer 1), 2.67 min (enantiomer 2).

Step 2a:

Preparation of 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine enantiomer 1 (28E1) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 1 (40 mg, 0.089 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.11 mL, 0.445 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (2.0 mL) to afford 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine enantiomer 1 (**28E1**) hydrochloride (18 mg, Yield: 60%; drawn as the *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z: 348.05 [M+H]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.87 (s, 3H), 7.54 (s, 1H), 6.69 (s, 1H), 3.78 (s, 3H), 3.37-3.36 (m, 1H), 2.83-2.79 (m, 1H), 2.67-2.61 (m, 3H), 1.54-1.47 (m, 2H), 1.41-1.32 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H), 0.93 (t, J = 7.28 Hz, 3H).

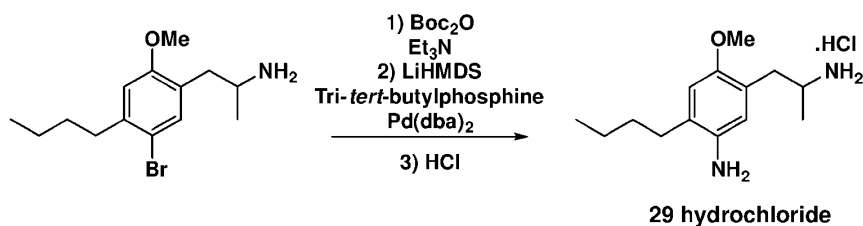
Step 2b:

Preparation of 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine enantiomer 2 (28E2) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-yl)carbamate enantiomer 2 (38 mg, 0.085 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.11 mL, 0.445 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (2.0 mL) to afford 1-(4-butyl-5-iodo-2-methoxyphenyl)propan-2-amine enantiomer 2 (**28E2**) hydrochloride (18 mg, Yield: 60%; drawn as the *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z: 348.05 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.87 (s, 3H), 7.54 (s, 1H), 6.69 (s, 1H),

3.78 (s, 3H), 3.37-3.36 (m, 1H), 2.83-2.79 (m, 1H), 2.67-2.61 (m, 3H), 1.54-1.47 (m, 2H), 1.41-1.32 (m, 2H), 1.08 (d, $J = 6.4$ Hz, 3H), 0.93 (t, $J = 7.28$ Hz, 3H).

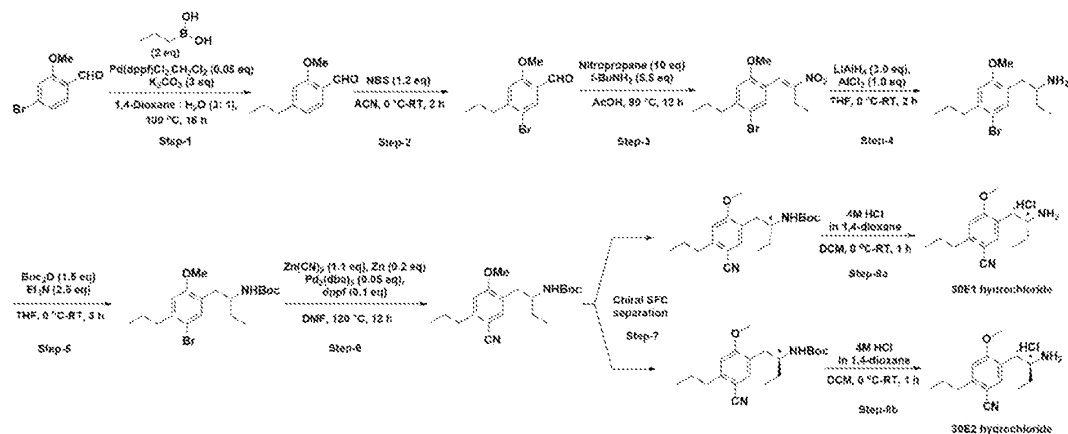
Example 29: Preparation of 5-(2-aminopropyl)-2-butyl-4-methoxyaniline (29)



This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 30: Preparation of 5-(2-aminobutyl)-4-methoxy-2-propylbenzonitrile enantiomer 1 (30E1) hydrochloride and 5-(2-aminobutyl)-4-methoxy-2-propylbenzonitrile enantiomer 2 (30E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 2-methoxy-4-propylbenzaldehyde

2-Methoxy-4-propylbenzaldehyde (off-white solid, Yield: 3.0 g, 72%) was synthesized from 4-bromo-2-methoxybenzaldehyde (5.0 g) following general procedure C (see **Example 61**). **LC-MS**: m/z 176.10 $[M+H]^+$.

Step 2:***Preparation of 5-bromo-2-methoxy-4-propylbenzaldehyde***

To a stirred solution of 2-methoxy-4-propylbenzaldehyde (2.8 g, 15.71 mmol) in acetonitrile (20 mL) was added NBS (3.34 g, 18.8 mmol) in portions at 0 °C. Then reaction mixture was stirred at 0 °C for 5 min then warmed to room temperature and stirred for 2 h. After completion of reaction, the reaction mixture was diluted with cold water (20 mL) and extracted with ethyl acetate (3 x 25 mL). Combined organic layer was washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to get crude 5-bromo-2-methoxy-4-propylbenzaldehyde (Yield: 3.2 g, 79%), which was directly used for next step without further purification. **LC-MS**: m/z 255.95 $[M+H]^+$.

Steps 3-5:***Preparation of tert-butyl (1-(5-bromo-2-methoxy-4-propylphenyl)butan-2-yl)carbamate***

tert-butyl (1-(5-bromo-2-methoxy-4-propylphenyl)butan-2-yl)carbamate (off-white solid Yield: 3.2 g, 64% , over 3 steps) was synthesized from 5-bromo-2-methoxy-4-propylbenzaldehyde (3.2 g) following general procedure A (see **Example 61**). **LC-MS**: m/z 300.10 $[M+H-100]^+$.

Step 6:***Preparation of tert-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)butan-2-yl)carbamate***

A stirred solution of *tert*-butyl (1-(5-bromo-2-methoxy-4-propylphenyl)butan-2-yl)carbamate (500 mg, 1.24 mmol), zinc cyanide (161 mg, 1.37 mmol) and zinc (29.32 mg, 0.24 mmol) in DMF (5 mL) was degassed and purged with nitrogen for 3 times. The 1,1'-ferrocenediyl-bis(diphenylphosphine) (69 mg, 0.12 mmol) and $Pd_2(dba)_3$ (56 mg, 0.06 mmol) was added to the reaction mixture. Then the resulting reaction mixture was allowed stirred at 120 °C for 12 h. Progress of the reaction was monitored by TLC and LC-MS. On completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers was washed with saturated brine solution (20 mL) and dried over

anhydrous sodium sulfate, filtered, concentrated and purified by silica flash column chromatography (eluting with 0-30% ethyl acetate in heptanes) to afford *tert*-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)butan-2-yl)carbamate as a yellow solid (Yield: 150 mg, 35%). **LC-MS:** m/z 347.2 $[M+H]^+$.

Step 7:

Preparation of tert-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)-butan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)-butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)butan-2-yl)carbamate (100 mg) were separated by chiral SFC [Column Name: CHIRALPAK IC 21.2 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 0.1% ammonium hydroxide in methanol (90:10)); Flow Rate: 50 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)-butan-2-yl)carbamate enantiomer 1 (Yield: 33 mg, 33%, 98.96% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) *tert*-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)-butan-2-yl)carbamate enantiomer 2 (Yield: 35 mg, 35%, 98% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally).

tert-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)-butan-2-yl)carbamate enantiomer 1

LC-MS: m/z : 347.2 $[M+H]^+$; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.40 (s, 1H), 7.00 (s, 1H), 6.57 (d, J = 9.20 Hz, 1H), 3.86 (s, 3H), 3.52 (m, 1H), 2.78-2.68 (m, 2H), 2.42-2.34 (m, 2H), 1.65-1.58 (m, 2H), 1.45-1.32 (m, 2H), 1.26 (s, 9H), 1.16-0.93 (m, 6H). The enantiomeric excess (98.9%) was determined by chiral SFC analysis [Column Name: CHIRALPAK IC-3 4.6 mm ID x 150 mm, 3 μ m; Mobile Phase: supercritical CO₂ (CO₂: 0.2% diethylamine in MeOH (80:20)); Flow Rate: 2.5 mL/min; Column temp: 35 °C] R_t = 2.49 min (enantiomer 1), 3.62 min (enantiomer 2).

tert-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)-butan-2-yl)carbamate enantiomer 2

LC-MS: m/z 347.2 $[M+H]^+$; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.40 (s, 1H), 7.00 (s, 1H), 6.57 (d, J = 9.20 Hz, 1H), 3.86 (s, 3H), 3.53-3.51 (m, 1H), 2.78-2.68 (m, 2H), 2.42-2.36 (m, 2H),

1.65-1.60 (m, 2H), 1.45-1.32 (m, 2H), 1.26 (s, 9H), 0.93-0.83 (m, 6H). The enantiomeric excess (98.9%) was determined by chiral SFC analysis [Column Name: CHIRALPAK IC-3 4.6 mm ID x 150 mm, 3 μ m; Mobile Phase: supercritical CO₂ (CO₂: 0.2% diethylamine in MeOH (80:20)); Flow Rate: 2.5 mL/min; Column temp: 35 °C] R_t = 2.49 min (enantiomer 1), 3.23 min (enantiomer 2).

Step 8a:***Preparation of 5-(2-aminobutyl)-4-methoxy-2-propylbenzonitrile (30E1) hydrochloride***

To a stirred solution of *tert*-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)-butan-2-yl)carbamate enantiomer 1 (33 mg, 0.095 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.24 mL, 0.95 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 5-(2-aminobutyl)-4-methoxy-2-propylbenzonitrile enantiomer 1 (**30E1**) hydrochloride (Yield: 19 mg, 71%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 247.2 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.85 (s, 3H), 7.59 (s, 1H), 7.09 (s, 1H), 3.87 (s, 3H), 3.29-3.25 (m, 1H), 2.85-2.71 (m, 4H), 1.70-1.61 (m, 2H), 1.53-1.46 (m, 2H), 0.95-0.89 (m, 6H).

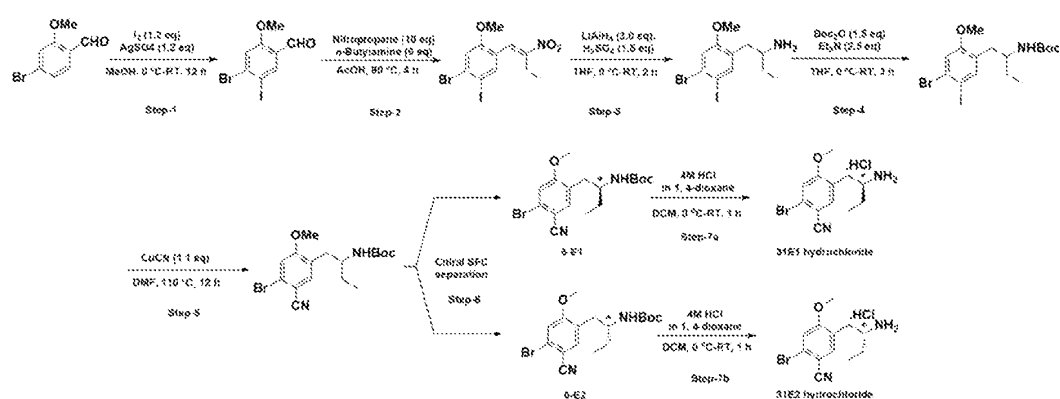
Step 8b:***Preparation of 5-(2-aminobutyl)-4-methoxy-2-propylbenzonitrile (30E2) hydrochloride***

To a stirred solution of *tert*-butyl (1-(5-cyano-2-methoxy-4-propylphenyl)-butan-2-yl)carbamate enantiomer 2 (35 mg, 0.10 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.25 mL, 1.0 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 5-(2-aminobutyl)-4-methoxy-2-propylbenzonitrile enantiomer 2 (**30E2**) hydrochloride (Yield: 21 mg, 74%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 247.2 [M+H]⁺; **¹H NMR (400**

MHz, DMSO-*d*₆: δ = 7.82 (s, 3H), 7.59 (s, 1H), 7.09 (s, 1H), 3.87 (s, 3H), 3.30-3.24 (m, 1H), 2.85-2.75(m, 4H), 1.70-1.61 (m, 2H), 1.53-1.46 (m, 2H), 0.95-0.89 (m, 6H).

Example 31: Preparation of 5-(2-aminobutyl)-2-bromo-4-hydroxybenzonitrile enantiomer 1 (31E1) hydrochloride and 5-(2-aminobutyl)-2-bromo-4-hydroxybenzonitrile enantiomer 2 (31E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 4-bromo-5-iodo-2-methoxybenzaldehyde

To a stirred solution of 4-bromo-2-methoxybenzaldehyde (3g, 13.9 mmol) in methanol (45 mL) was added silver sulfate (5.2g, 16.68 mmol) and iodine (4.2g, 16.68 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. The progress of reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (10 mL). The organic extract was washed with saturated sodium thiosulfate solution (20 mL) dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound. This crude material was purified by silica flash column chromatography (eluting in 0-10% ethyl acetate in heptane) to afford 4-bromo-5-iodo-2-methoxybenzaldehyde as off white solid. (Yield: 4.0 g, 84%). **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 10.17 (s, 1H), 8.035 (s, 1H), 7.65 (s, 1H), 3.93 (s, 3H).

Steps 2-4:***Preparation of tert-butyl (1-(4-bromo-5-iodo-2-methoxyphenyl)butan-2-yl)carbamate***

tert-butyl (1-(4-bromo-5-iodo-2-methoxyphenyl)butan-2-yl)carbamate (Yield: 500 mg, 12% (over 3 steps)) was synthesized from 4-bromo-5-iodo-2-methoxybenzaldehyde (3.0 g) over 3 steps following general procedure A (see **Example 61**). **LCMS:** m/z 383.85 $[M+H-100]^+$; **1H NMR (400 MHz, DMSO- d_6):** δ = 7.56 (s, 1H), 7.23 (s, 1H), 6.57 (d, J = 9 Hz, 1H), 3.78 (s, 3H), 3.47-3.43 (m, 1H), 2.70-2.66 (m, 1H), 2.36-2.31 (m, 1H), 1.44-1.39 (m, 2H), 1.37 (s, 9H), 0.82 (t, J = 7.4 Hz, 3H).

Step 5:***Preparation of tert-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)butan-2-yl)carbamate***

To a stirred solution of *tert*-butyl (1-(4-bromo-5-iodo-2-methoxyphenyl)butan-2-yl)carbamate (0.5g, 1.03 mmol) in dry DMF (8mL) was added CuCN (130 mg, 1.13 mmol) at room temperature. The reaction mixture was heated at 110 °C for 12 h. The progress of reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was allowed to cool to room temperature and then extracted with ethyl acetate (30 mL) and water (15 mL). The organic extract was dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound. This crude material was purified either by silica flash column chromatography (eluting in 0-30% ethyl acetate in heptane) to afford *tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)butan-2-yl)carbamate (Yield: 150 mg, 38 %). **LCMS:** m/z 383.00 $[M+H-100]^+$; **1H NMR (400 MHz, DMSO- d_6):** δ = 7.5 (s, 1H), 7.40 (s, 1H), 6.57 (d, J = 9.2 Hz, 1H), 3.90 (s, 3H), 3.54-3.49 (m, 1H), 2.77-2.75 (m, 1H), 2.41-2.35 (m, 1H), 1.46-1.36 (m, 2H), 1.25 (s, 9H), 0.84 (t, J = 7.3 Hz, 3H).

Step 6:***Preparation of tert-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)butan-2-yl)carbamate******enantiomer 1 and tert-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2***

The enantiomers of *tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)butan-2-yl)carbamate (150 mg) were separated by chiral SFC [Column Name: CHIRALPAK IC 21.0 mm ID x 250 mm,

5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 0.1% ammonium hydroxide in ACN (90:10)); Flow Rate: 70 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 30 mg, 40%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (Yield: 28 mg, 37%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

***tert*-Butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1**

LC-MS: m/z: 383.0 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.53 (s, 1H), 7.40 (s, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.50-3.49 (m, 1H), 2.80-2.70 (m, 2H), 2.40-2.37 (m, 4H), 1.43-1.35 (m, 2H), 1.24 (s, 9H), 0.84 (t, *J* = 7.6 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column Name: Chiralpak IC 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 100% ACN (75:25)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] *R*_t = 2.38 min (enantiomer 1), 2.97 min (enantiomer 2).

***tert*-Butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2**

LC-MS: m/z: 383.0 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.53 (s, 1H), 7.40 (s, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.50-3.49 (m, 1H), 2.80-2.70 (m, 2H), 2.40-2.37 (m, 4H), 1.43-1.35 (m, 2H), 1.24 (s, 9H), 0.84 (t, *J* = 7.6 Hz, 3H). The enantiomeric excess (98.02%) was determined by chiral SFC analysis [Column Name: Chiralpak IC 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 100% ACN (75:25)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] *R*_t = 2.36 min (enantiomer 1), 2.99 min (enantiomer 2).

Step 7a:

Preparation of 5-(2-aminobutyl)-2-bromo-4-methoxybenzonitrile enantiomer 1 (31E1) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-bromo-5-cyano-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1 (30 mg, 0.078 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane) (0.1 mL, 0.39 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC

and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (3.0 mL) to afford the desired 5-(2-aminobutyl)-2-bromo-4-methoxybenzonitrile enantiomer 1 (**31E1**) hydrochloride (Yield: 12 mg, 48%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z: 283.05 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆)**: δ = 7.85 (s, 3H), 7.77 (s, 1H), 7.51 (s, 1H), 3.91 (s, 3H), 3.28-3.25 (m, 1H), 2.87-2.75 (m, 2H), 1.56-1.48 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).

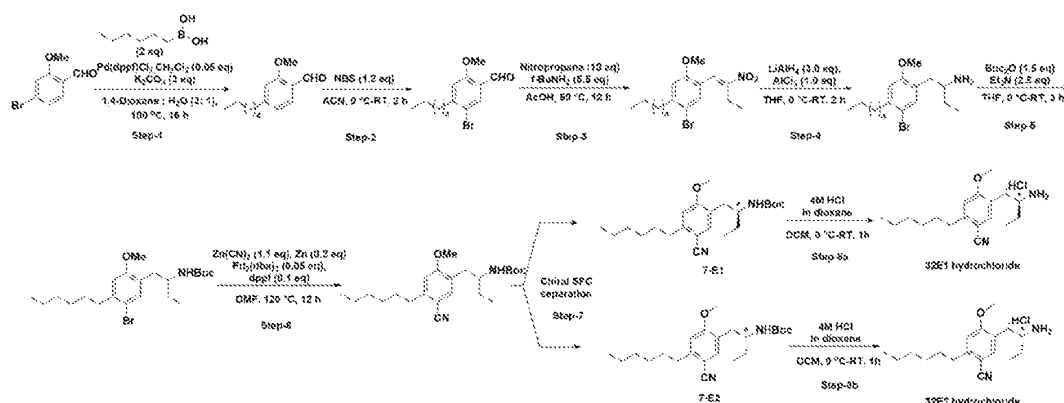
Step 7b:

Preparation of 5-(2-aminobutyl)-2-bromo-4-methoxybenzonitrile enantiomer 2 (31E2) hydrochloride

To a stirred solution of *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (28 mg, 0.073 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.1 mL, 0.1 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (3.0 mL) to afford the desired 5-(2-aminobutyl)-2-bromo-4-methoxybenzonitrile enantiomer 2 (**31E2**) hydrochloride (Yield: 11 mg, 47%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z: 283.05 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆)**: δ = 7.85 (s, 3H), 7.78 (s, 1H), 7.51 (s, 1H), 3.92 (s, 3H), 3.29-3.26 (m, 1H), 2.88-2.77 (m, 2H), 1.54-1.50 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H).

Example 32: Preparation 5-(2-aminobutyl)-2-hexyl-4-methoxybenzonitrile enantiomer 1 (32E1) hydrochloride and 5-(2-aminobutyl)-2-hexyl-4-methoxybenzonitrile enantiomer 2 (32E2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 4-hexyl-2-methoxybenzaldehyde

4-Hexyl-2-methoxybenzaldehyde (white solid; Yield: 1.3 g, 63%) was synthesized from 4-bromo-2-methoxybenzaldehyde (2.0 g) following general procedure C (see **Example 61**). **LC-MS**: m/z 221.21 [M+H]⁺.

Step 2:

Preparation of 5-bromo-4-hexyl-2-methoxybenzaldehyde

To a stirred solution of 4-hexyl-2-methoxybenzaldehyde (1.3 g, 5.45 mmol) in acetonitrile (15 mL), NBS (0.92 g, 5.23 mmol) was added portion-wise at 0 °C and stirred for 5 min. The reaction mixture was warmed to room temperature and stirred for 2 h. After completion of reaction (monitored by TLC). The reaction mixture was diluted with cold water (20 ml) and extracted with ethyl acetate (2 x 25 mL). Combined organic layers was washed with brine (20 mL) and concentrated under reduced pressure to get crude 5-bromo-4-hexyl-2-anisaldehyde as colorless liquid (Yield: 1.2 g, 68%), which was directly used for next step without further purification or characterization.

Steps 3-5:

Preparation of tert-butyl (1-(5-bromo-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate

tert-butyl (1-(5-bromo-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate (white solid; Yield: 600 g, 33% , over 3 steps) was synthesized from 5-bromo-4-hexyl-2-methoxybenzaldehyde following general procedure A (see **Example 61**). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.23 (s, 1H), 6.86

(s, 1H), 6.52 (d, $J = 8.8$ Hz, 1H), 3.77 (s, 3H), 3.51-3.47 (m, 1H), 2.71-2.58 (m, 4H), 2.40-2.32 (m, 1H), 1.60-1.52 (m, 2H), 1.51-1.45 (m, 5H), 1.27 (s, 9H), 1.21-1.13 (m, 2H) 0.87-0.80 (m, 6H).

Step 6:***Preparation of tert-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate***

To a stirred solution of *tert*-butyl (1-(5-bromo-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate (600 g, 1.36 mmol) in DMF (10 mL) was added zinc bis(cyanide) (189 g, 1.62 mmol), zinc (17 mg, 0.27 mmol) and 1,1'-ferrocenediyl-bis(diphenylphosphine) (72 mg, 0.13 mmol) and Pd₂dba₃ (62 mg, 0.07 mmol). Nitrogen gas was purged for 30 minutes through reaction mixture and was stirred at 120 °C for 12 h. The progress of reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 25 mL) The combined organic layer was washed with saturated brine solution (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated and purified by silica flash column chromatography (eluted with 0-20% ethyl acetate in heptane) to afford *tert*-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate (300 mg, 57%). **LC-MS:** m/z 389.30 [M+H]⁺.

Step 7:***Preparation of tert-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2***

The enantiomers of *tert*-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate (300 mg) were separated by chiral SFC. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1 (off-white solid; Yield: 130 mg, 43%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2 (off-white solid; Yield: 140 mg, 46%, 97.5% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

tert-Butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1

LC-MS: m/z 389.30 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.38 (s, 1H), 6.99 (s, 1H), 6.56 (d, *J* = 9.6 Hz, 1H), 3.85 (s, 3H), 3.52-3.48 (m, 1H), 2.76-2.68 (m, 3H), 2.40-2.32 (m, 1H), 1.57-1.50 (m, 2H), 1.44-1.39 (m, 2H), 1.38-1.28 (m, 6H), 1.24 (s, 9H), 0.87-0.81 (m, 6H). The enantiomeric excess (>99%) was determined by chiral SFC analysis [Column Name: Chiralart SC 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 0.1% ammonium hydroxide in IPA (80:20)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] *R*_t = 2.09 min (enantiomer 1), 2.99 min (enantiomer 2).

tert-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2

LC-MS: m/z 389.25 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.38 (s, 1H), 6.99 (s, 1H), 6.56 (d, *J* = 9.6 Hz, 1H), 3.85 (s, 3H), 3.52-3.49 (m, 1H), 2.76-2.68 (m, 3H), 2.40-2.32 (m, 1H), 1.57-1.50 (m, 2H), 1.44-1.39 (m, 2H), 1.38-1.28 (m, 6H), 1.24 (s, 9H), 0.87-0.81 (m, 6H). The enantiomeric excess (97.5%) was determined by chiral SFC analysis [Column Name: Chiralart SC 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 0.1% ammonium hydroxide in IPA (80:20)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] *R*_t = 2.10 min (enantiomer 1), 2.99 min (enantiomer 2).

Step 8a:***Preparation of 5-(2-aminobutyl)-2-hexyl-4-methoxybenzonitrile enantiomer 1 (32E1) hydrochloride***

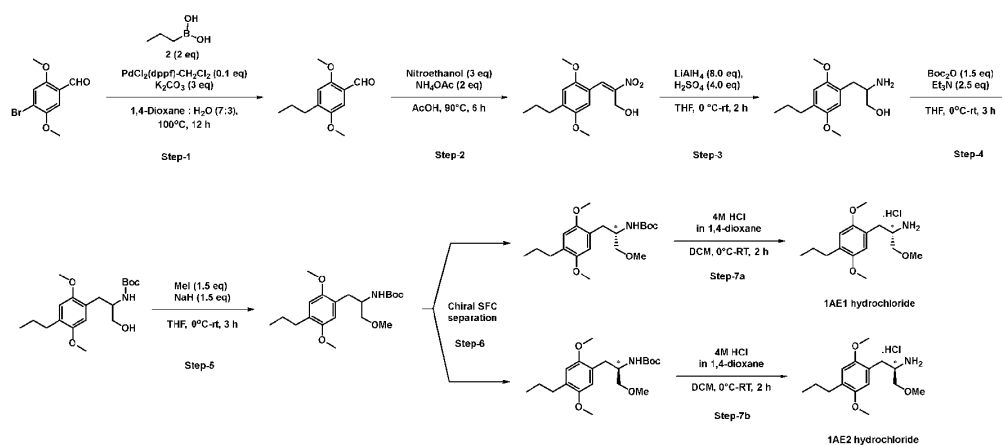
To a stirred solution of *tert*-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 1 (130 mg, 0.335 mmol) in DCM (5.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.41 mL, 1.675 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 5-(2-aminobutyl)-2-hexyl-4-methoxybenzonitrile enantiomer 1 (**32E1**) hydrochloride (Yield: 96 mg, 88%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 289.25 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.89 (s, 3H), 7.58 (s, 1H), 7.09 (s, 1H), 3.87 (s,

3H), 3.28-3.25 (m, 1H), 2.81-2.79 (m, 2H), 2.76-2.72 (m, 2H), 1.63-1.57 (m, 2H), 1.53-1.46 (m, 2H), 1.31-1.27 (m, 6H), 0.93-0.91 (m, 3H), 0.89-0.86 (m, 3H).

Step 8b:***Preparation of 5-(2-aminobutyl)-2-hexyl-4-methoxybenzonitrile enantiomer 2 (32E2) hydrochloride***

To a stirred solution of *tert*-butyl (1-(5-cyano-4-hexyl-2-methoxyphenyl)butan-2-yl)carbamate enantiomer 2 (140 mg, 0.36 mmol) in DCM (5.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.45 mL, 1.80 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 5-(2-aminobutyl)-2-hexyl-4-methoxybenzonitrile enantiomer 2 (**32E2**) hydrochloride (Yield: 108 mg, 92%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z: 289.30 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.90 (s, 3H), 7.58 (s, 1H), 7.09 (s, 1H), 3.87 (s, 3H), 3.27-3.26 (m, 1H), 2.81-2.77 (m, 2H), 2.76-2.72 (m, 2H), 1.63-1.58 (m, 2H), 1.53-1.46 (m, 2H), 1.31-1.23 (m, 6H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.88-0.84 (m, 3H).

Example 33: Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-amine (1AE1) hydrochloride and 1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-amine (1AE2) hydrochloride**Synthetic Scheme:**



Step 1:

Preparation of 2,5-dimethoxy-4-propylbenzaldehyde

To a stirred solution of 4-bromo-2,5-dimethoxybenzaldehyde (2.0 g, 8.16 mmol) in 1,4-dioxane/water (7:3, 10 mL) was added dipotassium carbonate (3.38 g, 24.48 mmol), *n*-propyl boronic acid (1.43 g, 16.32 mmol), Pd(dppf)Cl₂-CH₂Cl₂ (66 mg, 0.816 mmol), under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through Celite pad. The filtrate was extracted with ethyl acetate (10 mL) and water (10 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford 2,5-dimethoxy-4-propylbenzaldehyde as a yellow solid (Yield: 950 mg, 56 %). **LC-MS:** *m/z* 209.15 [M+1]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 10.30 (s, 1H), 7.16 (s, 1H), 7.07 (s, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 1.60-1.53 (m, 2H), 0.92 (t, *J* = 4 Hz, 3H).

Step 2:

Preparation of Synthesis of (E)-3-(2,5-dimethoxy-4-propylphenyl)-2-nitroprop-2-en-1-ol

To a stirred solution of 2,5-dimethoxy-4-propylbenzaldehyde (950 mg, 4.56 mmol) in acetic acid (10 mL) was added nitroethanol (1.18 mL, 13.68 mmol) followed by ammonium acetate (703 mg, 9.12 mmol) at 0 °C. Then mixture was warmed to 90 °C and stirred for 6 h. The progress of

the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water (25 mL), the precipitate that formed was filtered, washed with chilled water (10 mL x 3), and dried under reduced pressure to afford the desired (*E*)-3-(2,5-dimethoxy-4-propylphenyl)-2-nitroprop-2-en-1-ol as a yellow solid (Yield: 650 mg, 51%), which was used directly in the next step.

Step 3:

Preparation of 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol

To a stirred solution of LAH solution (2.0 M in THF; 9.24 mL, 18.48 mmol) in anhydrous THF (30 mL) was added H₂SO₄ (906 mg, 9.24 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-3-(2,5-dimethoxy-4-propylphenyl)-2-nitroprop-2-en-1-ol (650 mg, 2.31 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and was added THF/water (1:1, 14 mL) at same temperature until effervescence ceased. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (40 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol as a gummy liquid (Yield: 450 mg, 77%), which was used directly in the next step.

Step 4:

Preparation of tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate

To a stirred solution of 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol (450 mg, 1.776 mmol) in THF (10 mL), triethylamine (0.61 mL, 4.44 mmol) followed by di-*tert*-butyl dicarbonate (0.61 mL, 2.66 mmol) was added at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was

purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate as an off-white solid (Yield: 370 mg, 69%). **LC-MS:** m/z 254.15 $[M+H-100]^+$; **1H NMR (400 MHz, $CDCl_3$):** δ = 6.76 (s, 1H), 6.69 (s, 1H), 6.42 (d, J = 12 Hz, 1H), 4.62 (t, J = 5.2 Hz, 1H), 3.72 (s, 6H), 3.70-3.64 (m, 1H), 3.33-3.25 (m, 2H), 2.80 (dd, J = 4, 12 Hz, 1H), 2.50-2.38 (m, 4H), 1.53-1.47 (m, 2H), 1.28 (s, 9H), 0.87 (t, J = 8 Hz, 3H).

Step 5:

Preparation of tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate (370 mg, 1.046 mmol) in THF (10 mL), sodium hydride (37 mg, 1.57 mmol) was added at 0 °C and stirred for 30 min, followed by iodomethane (0.1 mL, 1.57 mmol). The reaction mixture was then warmed to room temperature and stirred for 2.5 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate as a white solid (Yield: 100 mg, 26%). **LC-MS:** m/z 268.15 $[M+H-100]^+$; **1H NMR (400 MHz, $CDCl_3$):** δ = 6.73 (d, J = 12 Hz, 1H), 6.59 (d, J = 12 Hz, 1H), 3.81-3.73 (m, 1H), 3.70 (d, J = 4 Hz, 6H), 3.27-3.19 (m, 5H), 2.78 (dd, J = 4, 12 Hz, 1H), 2.50-2.43 (m, 4H), 1.53-1.48 (m, 2H), 1.28 (s, 9H), 0.88 (t, J = 4 Hz, 3H).

Step 6:

Preparation of tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate (100 mg) were separated by chiral SFC [Column Name: Phenomenex Lux i-Amylose-3 (30 mm x 250 mm) 5 μ m; Mobile Phase: supercritical CO_2 /IPA (70:30); Flow Rate: 80 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced

pressure and lyophilized to afford *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 (Yield: 20 mg, 20%; drawn as S enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2 (Yield: 20 mg, 20%; drawn as R enantiomer but absolute stereochemistry not determined experimentally) as off-white solids.

***tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1**

LC-MS: m/z 268.15 [M+H-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.71 (d, *J* = 12 Hz, 1H), 6.58 (d, *J* = 4 Hz, 1H), 3.79-3.70 (m, 1H), 3.70 (s, 6H), 3.23 (m, 3H), 2.77 (dd, *J* = 8, 16 Hz, 2H), 1.53-1.47 (m, 2H), 1.28 (s, 9H), 0.88 (t, *J* = 8 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column Name: Phenomenex Lux i-Amylose-3 (4.6 mm x 250 mm) 5 μm; Mobile Phase: CO₂/IPA (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 °C] *R*_t = 1.94 min (enantiomer 1), 2.98 min (enantiomer 2).

***tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2**

LC-MS: m/z 268.15 [M+H-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.72 (d, *J* = 9 Hz, 1H), 6.58 (d, *J* = 8 Hz, 1H), 3.80-3.74 (m, 1H), 3.70-3.64 (m, 5H), 3.32-3.21 (m, 5H), 2.77 (dd, *J* = 8, 16 Hz, 1H), 2.50-2.43 (m, 3H), 1.55-1.47 (m, 2H), 1.36 (s, 9H), 0.83 (t, *J* = 8 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column Name: Phenomenex Lux i-Amylose-3 (4.6 mm x 250 mm) 5 μm; Mobile Phase: CO₂/IPA (80:20); Flow Rate: 3.0 mL/min; Column Temp: 30 °C] *R*_t = 1.94 min (enantiomer 1), 2.98 min (enantiomer 2).

Step 7a:

Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-amine enantiomer 1 (1AE1) hydrochloride

To a stirred solution of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 (20 mg, 0.054 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.37 mL, 1.5 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2,5-dimethoxy-4-propylphenyl)-3-

methoxypropan-2-amine enantiomer 1 (**1AE1**) hydrochloride as an off-white solid (Yield: 16 mg, 96%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 268.15 [M+H]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 7.99 (s, 3H), 6.80 (s, 1H), 6.77 (s, 1H), 3.75-3.72 (m, 6H), 3.45-3.40 (m, 1H), 3.39-3.36 (m, 1H), 3.33-3.28 (m, 4H), 2.86-2.79 (m, 1H), 2.51-2.48 (m, 2H), 1.57-1.48 (m, 2H), 0.89 (t, *J* = 8 Hz, 3H).

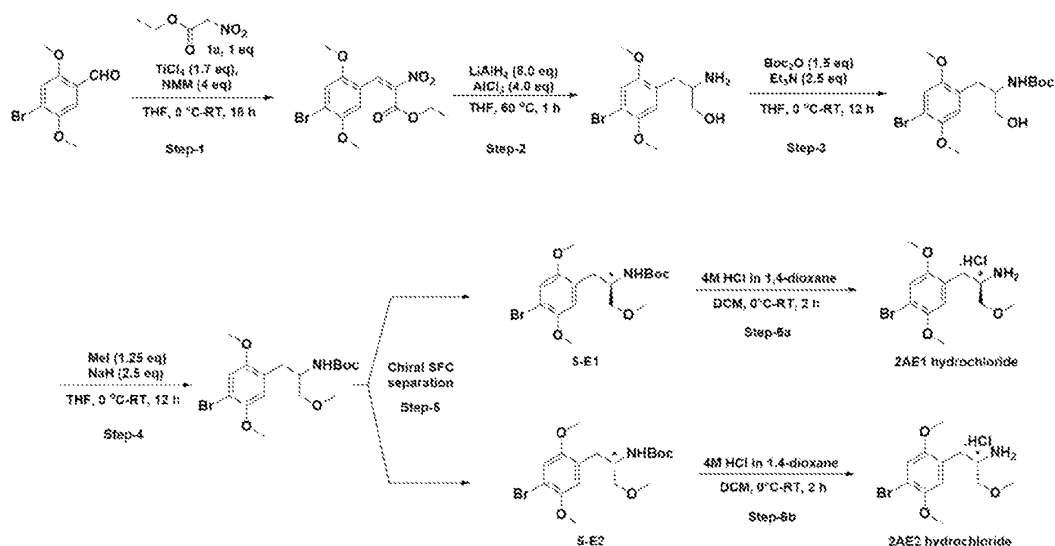
Step 7b:

Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-amine enantiomer 2 (1AE2) hydrochloride

To a stirred solution of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-yl)carbamate (20 mg, 0.054 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.37 mL, 1.5 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2,5-dimethoxy-4-propylphenyl)-3-methoxypropan-2-amine enantiomer 2 (**1AE2**) hydrochloride as a yellow solid (Yield: 10 mg, 69%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 268.15 [M+H]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 7.97 (s, 3H), 6.80 (s, 1H), 6.77 (s, 1H), 3.75-3.72 (m, 6H), 3.45-3.40 (m, 1H), 3.39-3.36 (m, 1H), 3.33-3.28 (m, 4H), 2.86-2.79 (m, 1H), 2.51-2.48 (m, 2H), 1.57-1.48 (m, 2H), 0.89 (t, *J* = 8 Hz, 3H).

Example 34: Preparation of 1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-amine enantiomer 1 (2AE1) hydrochloride and 1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-amine enantiomer 2 (2AE2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of ethyl 3-(4-bromo-2,5-dimethoxyphenyl)-2-nitroacrylate

To a stirred solution of 4-bromo-2,5-dimethoxybenzaldehyde (2 g, 15 mmol) and ethyl nitroacetate (1.68 mL, 15 mmol) in anhydrous THF (20 mL, 184 mmol) was added titanium tetrachloride (2.85 mL, 25.5 mmol) at 0 °C. Resultant reaction mixture was stirred for 20 mins at same temperature. After that, 4-methylmorpholine (6.61 mL, 60.1 mmol) was added and stirred at room temperature for 18 h. The progress of reaction was monitored by TLC and LCMS. Upon completion, reaction mixture was diluted with chilled water (50 ml) and extracted with ethyl acetate (3 x 30 ml). Combined organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure to get yellow colored crude compound. The crude was purified by flash column chromatography eluting with 0-25% EtOAc in heptanes to afford ethyl (E)-3-(4-bromo-2,5-dimethoxyphenyl)-2-nitroacrylate as a yellow solid. (Yield: 2.0 g, 24%). LC-MS: m/z 361 $[\text{M}+\text{H}]^+$.

Step 2:

Preparation of 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)-1-propanol

To a stirred solution of LiAlH_4 solution (2.0 M in THF; 13.32 mL, 26.64 mmol) in anhydrous THF (30 mL) was added H_2SO_4 (0.7 mL, 13.32 mmol) portionwise at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. Then, ethyl (E)-3-(4-bromo-2,5-dimethoxyphenyl)-2-nitroacrylate

(2.0 g, 3.33 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was heated at 60 °C for 4 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and THF/water (1:1, 5 mL) was added at same temperature, until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (30 mL), combined organic part was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)-1-propanol. (Yield: 1.2 g, 74%), which was directly used for the next step without further characterization or purification.

Step 3:***Preparation of tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate***

To a stirred solution of 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propan-1-ol (2.0 g, 6.92 mmol) in THF (20 mL) was added triethylamine (2.4 mL, 17.3 mmol) at 0 °C. Then di-*tert*-butyl dicarbonate (2.5 mL, 10.38 mmol) was added dropwise. The resultant reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with chilled water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by silica flash column chromatography (eluting with 0-30% ethyl acetate in heptane) to afford *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate (600 mg, Yield: 22%). **LC-MS:** m/z 390 [M+H]⁺.

Step 4:***Preparation of tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate***

To a stirred solution of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate (0.6 g, 1.54 mmol) in anhydrous THF (6.0 mL) was added NaH (60% dispersion in mineral oil; 147 mg, 3.85 mmol) at 0 °C. The reaction mixture was stirred at same temperature for 10 minutes and methyl iodide (0.12 mL, 1.92 mmol) was added dropwise. The resultant reaction mixture was stirred at room temperature for 1 h. Progress of the reaction was monitored by LCMS and TLC. Upon completion, the reaction mixture allowed to cool at 0 °C and

quenched with saturated aqueous solution of NH_4Cl (10 mL) and then extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude material was purified by silica flash column chromatography (eluting with 0-30% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate as an off-white solid (260 mg, 42%). **LC-MS:** m/z 404 $[\text{M}+1]^+$.

Step 5:

Preparation of tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate (260 mg) were separated by chiral SFC [Column Name: Lux Amylose-3 30.0 mm ID x 250 mm, 5 μm ; Mobile Phase: supercritical CO_2 (CO_2 : 100% IPA (85:15)); Flow Rate: 80 mL/min; Column temp: 30 $^\circ\text{C}$]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 (off-white solid; Yield: 120 mg, 46%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2 (off-white solid; Yield: 120 mg, 46%, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally).

(1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1

LC-MS: m/z : 405.90 $[\text{M}+\text{H}]^+$; **^1H NMR (400 MHz, $\text{DMSO}-d_6$):** δ = 7.12 (s, 1H), 6.92 (s, 1H), 6.64 (d, J = 8.8 Hz, 1H), 3.84 (s, 1H), 3.83-3.77 (m, 6H), 3.26-3.20 (m, 5H), 2.83-2.79 (m, 1H), 2.45-2.39 (m, 1H), 1.27 (s, 9H). The enantiomeric excess (99 %) was determined by chiral SFC analysis [Column Name: i Amylose-3 4.6 mm ID x 250 mm, 5 μm ; Mobile Phase: supercritical CO_2 (CO_2 : 0.1% ammonium hydroxide in IPA (80:20)); Flow Rate: 3.0 mL/min; Column temp: 35 $^\circ\text{C}$] R_t = 2.94 (enantiomer 1), 3.76 (enantiomer 2).

(1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2

LC-MS: m/z: 405.95 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.12 (s, 1H), 6.92 (s, 1H), 6.64 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 1H), 3.82-3.79 (m, 6H), 3.26-3.20 (m, 5H), 2.83-2.79 (m, 1H), 2.45-2.42 (m, 1H), 1.27 (s, 9H). The enantiomeric excess (99 %) was determined by chiral SFC analysis [Column Name: i Amylose-3 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 0.1% ammonium hydroxide in IPA (80:20)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] *R*_t = 2.97 (enantiomer 1), 3.91 (enantiomer 2).

Step 6a:

Preparation of 1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-amine enantiomer 1 (2AE1) hydrochloride

To a stirred solution of *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 (120 mg, 0.30 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.37 mL, 1.5 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford 1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-amine enantiomer 1 (**2AE1**) hydrochloride (Yield: 77 mg, 76%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z: 304.2 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.97 (s, 3H), 7.22 (s, 1H), 6.99 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.51-3.43 (br s, 1H), 3.42-3.39 (m, 1H), 3.37-3.29 (m, 4H), 2.83-2.82 (m, 2H).

Step 6b:

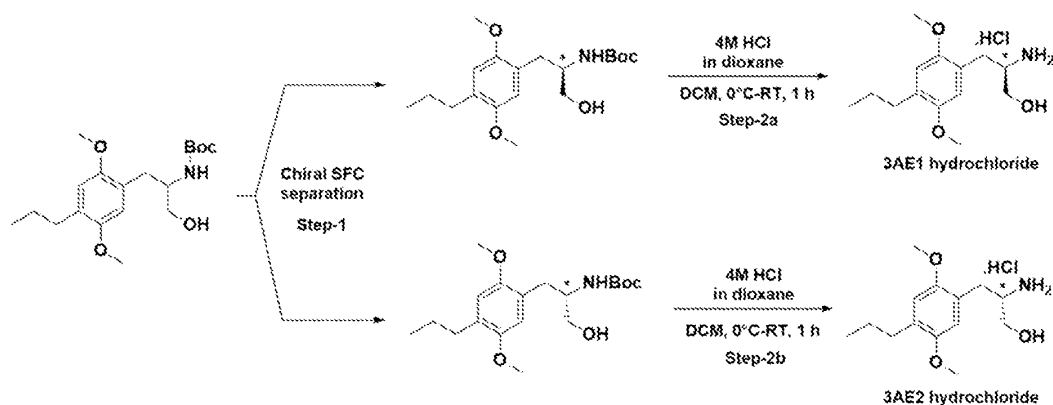
Preparation of 1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-amine enantiomer 2 (2AE2) hydrochloride

To a stirred solution of *tert*-butyl (1-(2-methoxy-5-methyl-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (50 mg, 0.149 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.049 mL, 1.49 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford 1-(4-bromo-2,5-dimethoxyphenyl)-3-methoxypropan-2-amine enantiomer 2 (**2AE2**) hydrochloride (Yield: 75 mg, 74%; drawn as S enantiomer but

absolute stereochemistry not determined experimentally). **LC-MS:** m/z : 304.2 $[M+H]^+$; **1H NMR (400 MHz, DMSO- d_6):** δ = 7.94 (s, 3H), 7.22 (s, 1H), 6.98 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.52-3.44 (br s, 1H), 3.42-3.39 (m, 1H), 3.35-3.29 (m, 4H), 2.83-2.81 (m, 2H).

Example 35: Preparation of 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol enantiomer 1 (3AE1) hydrochloride and 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol enantiomer 2 (3AE2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 1 and *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate (150 mg, 95%; synthesized as described for 1AE1/1AE2) were separated by chiral SFC [Column Name: LUX I AMYLOSE-3 30.0 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 100% IPA (85:15)); Flow Rate: 80 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate **enantiomer 1** (Yield: 60 mg, 40%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-

yl)carbamate (off-white solid; Yield: 60 mg, 40%, 97% ee; ; drawn as S enantiomer but absolute stereochemistry not determined experimentally).

tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 1

LC-MS: m/z 354.25 [M+H]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.76 (s, 1H), 6.70 (s, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.67-4.60 (m, 1H), 3.70 (s, 6H), 3.70-3.60 (1H), 2.82-2.78 (m, 1H), 2.54-2.34 (m, 5H), 1.53-1.48 (m, 2H), 1.28 (s, 9H), 0.88 (t, J = 6.4 Hz, 3H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column Name: Amylose-3 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 100% ACN (80:20)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] R_t = 3.22 (enantiomer 1), 4.20 (enantiomer 2).

tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 2

LC-MS: m/z 354.25 [M+H]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.76 (s, 1H), 6.70 (s, 1H), 6.43 (d, J = 8.4 Hz, 1H), 4.67-4.60 (m, 1H), 3.70 (s, 6H), 3.70-3.60 (1H), 2.82-2.78 (m, 1H), 2.54-2.33 (m, 5H), 1.53-1.48 (m, 2H), 1.28 (s, 9H), 0.88 (t, J = 6.4 Hz, 3H). The enantiomeric excess (97%) was determined by chiral SFC analysis [Column Name: Amylose-3 4.6 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: 100% ACN (80:20)); Flow Rate: 3.0 mL/min; Column temp: 35 °C] R_t = 3.29 (enantiomer 1), 4.07 (enantiomer 2).

Step 2a:

Preparation of 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol enantiomer 1 (3AE1) hydrochloride

To a stirred solution of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 1 (60 mg, 0.17 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.21 mL, 0.85 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-

1-ol enantiomer 1 (**3AE1**) hydrochloride (Yield: 36 mg, 73%; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

LC-MS: m/z: 254.2 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.87 (s, 3H), 6.79 (d, J = 4.4 Hz, 2H), 5.27 (t, J = 4.8 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.50-3.45 (m, 1H), 3.39-3.36 (m, 1H), 3.29 (s, 1H), 2.82-2.73 (m, 2H), 2.50-2.47 (m, 2H), 1.57-1.48 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H).

Step 2b:

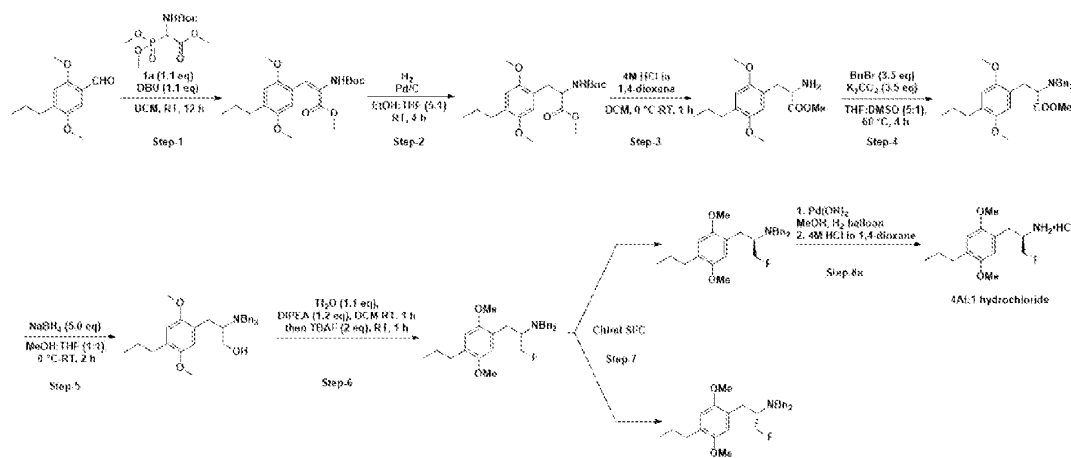
Preparation of 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol enantiomer 2 (3AE2) hydrochloride

To a stirred solution of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 2 (60 mg, 0.17 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.21 mL, 0.85 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol enantiomer 2 (**3AE2**) hydrochloride (Yield: 33 mg, 67%; drawn as S enantiomer but absolute stereochemistry not determined experimentally).

LC-MS: m/z: 254.2 [M+H]⁺; **¹H NMR (400 MHz, DMSO-d₆):** δ = 7.87 (s, 3H), 6.79 (d, J = 4.4 Hz, 2H), 5.27 (t, J = 4.8 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.50-3.47 (m, 1H), 3.39-3.33 (m, 1H), 3.29 (s, 1H), 2.82-2.73 (m, 2H), 2.50-2.47 (m, 2H), 1.57-1.48 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H).

Example 36: Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 1 (4AE1) hydrochloride and racemic 1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine (4A) hydrochloride

Synthetic Scheme:

**Steps 1-2:****Preparation of methyl 2-((tert-butoxycarbonyl)amino)-3-(2,5-dimethoxy-4-propylphenyl)propanoate**

Methyl 2-((tert-butoxycarbonyl)amino)-3-(2,5-dimethoxy-4-propylphenyl)propanoate (white solid; Yield: 5.0 g, 55%) was synthesized from 2,5-dimethoxy-4-propylbenzaldehyde (5.0 g) over two steps following general procedure B (see **Example 61**). **LC-MS**: m/z : 382.20 $[M+H-100]^+$.

Step 3:**Preparation of methyl 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propanoate hydrochloride**

To a stirred solution of methyl 2-((tert-butoxycarbonyl)amino)-3-(2,5-dimethoxy-4-propylphenyl)propanoate (5.0 g, 13.12 mmol) in DCM (50 mL) was added HCl solution (4.0 M in 1,4-dioxane; 16.4 mL, 65.6 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford methyl 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propanoate as a crude hydrochloride material (Yield: 5.5 g, crude yield). **LC-MS**: m/z : 282 $[M+H]^+$.

Step 4:

Preparation of methyl 2-(dibenzylamino)-3-(2,5-dimethoxy-4-propylphenyl)propanoate

To a stirred solution of methyl 2-amino-3-(2,5-dimethoxy-4-propylphenyl)propanoate hydrochloride (5.5 g, 19.6 mmol) in THF/DMSO (5: 1, 55 mL) was added potassium carbonate (9.46 g, 68.5 mmol) at 0 °C followed by dropwise addition of benzyl bromide (8.1 mL, 68.5 mmol). The reaction mixture was stirred at 60 °C for 4 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with chilled water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to yield the crude compound. This crude material was purified by silica flash column chromatography (eluting with 0-30% ethyl acetate in heptane) to afford methyl 2-(dibenzylamino)-3-(2,5-dimethoxy-4-propylphenyl)propanoate (4.5 g, Yield: 56%). **LC-MS:** m/z 462 [M+H]⁺.

Step 5:***Preparation of 2-(dibenzylamino)-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol***

To a stirred solution of methyl 2-(dibenzylamino)-3-(2,5-dimethoxy-4-propylphenyl)propanoate (4.5 g, 9.76 mmol) in THF/MeOH (1:1, 45 mL) was added sodium borohydride (1.85 g, 48.8 mmol) under argon at 0° C. This reaction mixture was stirred at room temperature for 2 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was quenched with saturated solution of NH₄Cl (20 mL) and extracted with ethyl acetate (20 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound 2-(dibenzylamino)-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol (Yield: 3.5 g, 83%). Crude compound was directly used for next step without any further purification. **LC-MS:** m/z 434 [M+H]⁺.

Step 6:***Preparation of N,N-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine***

To a stirred solution of 2-(dibenzylamino)-3-(2,5-dimethoxy-4-propylphenyl)propan-1-ol (500 mg, 1.15 mmol) in anhydrous DCM (5.0 mL) was added a solution of trifluoromethanesulfonic anhydride (1 M in DCM; 1.27 mL, 1.27 mmol). The reaction mixture was stirred at room temperature for 1 h. DIPEA (0.24 mL, 1.38 mmol) was then added and after 1 min stirring, then

a solution of TBAF (1 M in THF, 2.30 mL, 2.30 mmol) was added. The reaction mixture stirred further at room temperature for 2 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was quenched with NaOH (aq. 15%, 520 mL) and extracted with DCM (50 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude compound was purified by prep-HPLC to afford *N,N*-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine (Yield: 100 mg, 20%). **LC-MS:** m/z 436 [M+H]⁺.

Step 7:

Preparation of N,N-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 1 and N,N-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 2

The enantiomers of *N,N*-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine (100 mg) were separated by chiral SFC [Column Name: Lux Amylose-4 30.0 mm ID x 250 mm, 5µm; Mobile Phase: supercritical CO₂ (CO₂: 0.2% DEA in MeOH (90:10); Flow Rate: 50 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *N,N*-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 1 (off-white solid; Yield: 40 mg, 40%, >99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) and *N,N*-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 2 (off-white solid; Yield: 25 mg, >99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally).

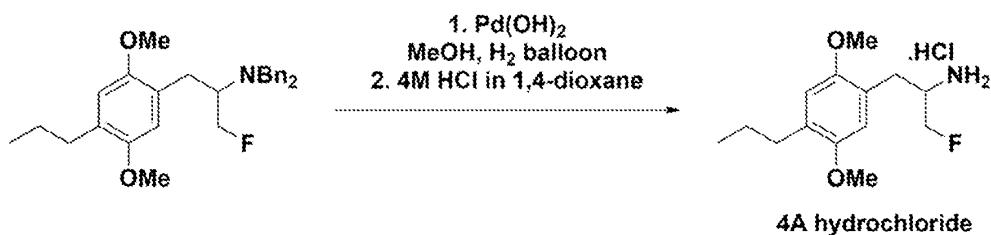
N,N-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 1

LC-MS: m/z: 336.2 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.23-7.18 (m, 10H), 6.68 (d, *J* = 7.4 Hz, 2H), 4.68-4.44 (m, 2H), 3.78-3.63 (m, 7H), 3.52 (s, 3H), 3.16-3.12 (m, 1H), 2.96-2.91 (m, 1H), 2.67-2.54 (m, 1H), 2.53-2.51 (m, 2H), 1.61-1.52 (m, 2H), 1.24-1.15 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H). The enantiomeric excess (90.16%) was determined by chiral SFC analysis [Column Name: CHIRALCEL OX-3 4.6 mm ID x 150 mm, 3µm; Mobile Phase: CO₂/0.2% DEA in MeOH (90:10) (v/v); Flow rate: 3.0 mL/min; Flow mode: Isocratic; Column temp: 35 °C; ABPR pressure: 1500 psi] *R*_t = 2.49 (enantiomer 1), 3.62 (enantiomer 2).

Step 8a:**Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 1 (4AE1) hydrochloride**

To a stirred solution of *N,N*-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 1 (40 mg, 0.091 mmol) in MeOH (2.0 mL) was added 10% Pd/C (29 mg, 0.27 mmol) at room temperature. The reaction mixture was allowed to stir under hydrogen atmosphere at room temperature for 4 h. The progress of reaction was monitored by TLC & LC-MS. After completion, the reaction mixture was filtered through a Celite pad. Filtrate was concentrated under reduced pressure to afford the crude compound. This crude material was dissolved in DCM (2.0 mL) and added HCl solution (4.0 M in 1,4-dioxane; 0.37 mL, 1.5 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 10 mins. Upon completion, the reaction mixture was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine enantiomer 1 (**4AE1**) hydrochloride (white solid; Yield: 7.0 mg, 26% over 2 steps; drawn as R enantiomer but absolute stereochemistry not determined experimentally).

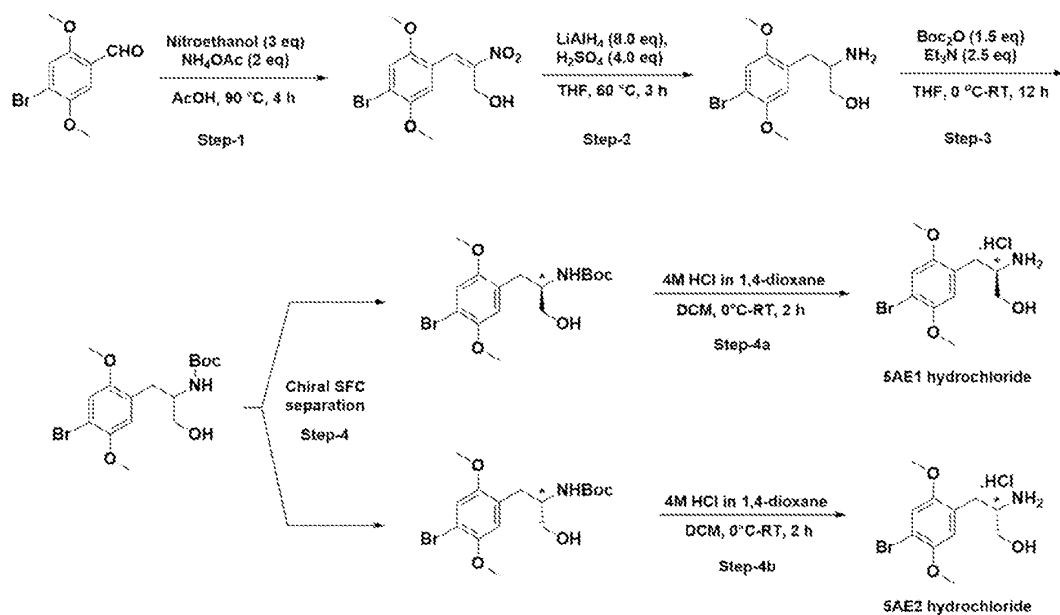
LC-MS: m/z: 256.4 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 8.24 (s, 3H), 6.82 (s, 1H), 6.80 (s, 1H), 4.61-4.33 (m, 2H), 3.73 (s, 3H), 3.68 (s, 3H), 3.63-3.60 (m, 1H), 2.90-2.80 (m, 2H), 2.50-2.45 (m, 2H), 1.58-1.49 (m, 2H), 0.90 (t, *J* = 8.3 Hz, 2H).

Synthetic Scheme:**Step 1:****Preparation of racemic 1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine (4A) hydrochloride**

To a stirred solution of *N,N*-dibenzyl-1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine (80 mg, 0.18 mmol) in MeOH (2.0 mL) was added 10% Pd/C (57 mg, 0.54 mmol) at room temperature. The reaction mixture was allowed to stir under hydrogen at room temperature for 4 h. The progress of reaction was monitored by TLC & LC-MS. After completion, the reaction mixture was filtered through Celite pad. Filtrate was concentrated under reduced pressure to afford crude compound. This crude was then stirred in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.5 mL, 1.5 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 10 mins. Upon completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2,5-dimethoxy-4-propylphenyl)-3-fluoropropan-2-amine (**4A**) as a hydrochloride salt (22 mg, yield: 41%). **LC-MS: m/z: 256.4 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆):** δ = 8.24 (br s, 3H), 6.81 (s, 1H), 6.80 (s, 1H), 4.61-4.33 (m, 2H), 3.74 (s, 3H), 3.72 (s, 3H), 3.66-3.54 (m, 1H), 2.90-2.80 (m, 2H), 2.50-2.45 (m, 2H), 1.58-1.49 (m, 2H), 0.90 (t, *J* = 8.3 Hz, 3H). **¹⁹F-NMR (376 MHz, DMSO-*d*₆):** δ -229 (s).

Example 37: Preparation of 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propan-1-ol enantiomer 1 (5AE1) hydrochloride and 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propan-1-ol enantiomer 2 (5AE2) hydrochloride

Synthetic Scheme:

**Step 1:****Preparation of 2-bromo-6-fluoro-4-methoxyphenol**

To a stirred solution of 4-bromo-2,5-dimethoxybenzaldehyde (1.5 g, 6.14 mmol) in acetic acid (15 mL) was added ammonium acetate (2.85 g, 12.3 mmol) and nitroethanol (6.46 mL, 18.42 mmol) at 0°C . Resultant reaction mixture was stirred at 90°C for 4 h. Progress of the reaction was monitored by TLC and LC-MS. Upon completion, reaction mixture was diluted with chilled water (50 mL) and extracted with ethyl acetate (3 x 30 mL). Combined organic layers was washed with brine (30 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford (E)-3-(4-bromo-2,5-dimethoxyphenyl)-2-nitroprop-2-en-1-ol (Yield: 0.6 g, 31%) as crude compound, which was directly used for the next step.

Steps 2-3:

Preparation of tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate
 tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate (off-white solid, Yield: 80 mg, 10% (over 2 steps)) was synthesized from (E)-3-(4-bromo-2,5-dimethoxyphenyl)-2-nitroprop-2-en-1-ol (0.6 g) over two steps following step 2-3 of the general procedure A (see Example 61). LC-MS: m/z 390 $[\text{M}+\text{H}]^+$.

Step 4:***Preparation of tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 2***

The enantiomers of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate (80 mg) were separated by chiral SFC [Column Name: Lux I Amylose-3 IA 30.0 mm ID x 250 mm, 5 μ m; Mobile Phase: supercritical CO₂ (CO₂: ACN (70:30); Flow Rate: 70 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 1 (off-white solid; Yield: 30 mg, 38%, 99% ee; drawn as R enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 2 (off-white solid; Yield: 30 mg, 38%, 99% ee; drawn as S enantiomer but absolute stereochemistry not determined experimentally).

tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 1

LC-MS: m/z 391 [M+2]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.10 (s, 1H), 6.94 (s, 1H), 6.46-6.44 (m, 1H), 4.70-4.66 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.70-3.67 (m, 1H), 3.34-3.30 (m, 1H), 2.86-2.81 (m, 1H), 1.30-1.23 (m, 9H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column Name: I Amylose-3 4.6 mm ID x 250 mm, 3 μ m; Mobile Phase: supercritical CO₂ (CO₂: ACN (70:20) (v/v)); Flow rate: 3.0 mL/min; Flow mode: Isocratic; Column temp: 35 °C] *R*_t = 2.89 min (enantiomer 1), 3.68 min (enantiomer 2).

tert-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 2

LC-MS: m/z 391 [M+2]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.10 (s, 1H), 6.94 (s, 1H), 6.46-6.44 (m, 1H), 4.70-4.66 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.70-3.67 (m, 1H), 3.34-3.30 (m, 1H), 2.86-2.81 (m, 1H), 1.30-1.23 (m, 9H). The enantiomeric excess (99%) was determined by chiral SFC analysis [Column Name: I Amylose-3 4.6 mm ID x 250 mm, 3 μ m; Mobile Phase:

supercritical CO₂ (CO₂: ACN (70:20) (v/v)); Flow rate: 3.0 mL/min; Flow mode: Isocratic; Column temp: 35 °C] *R*_t = 2.86 min (enantiomer 1), 3.73 min (enantiomer 2).

Step 4a:

Preparation of 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propan-1-ol enantiomer 1 (5AE1) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 1 (30 mg, 0.077 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.19 mL, 0.77 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propan-1-ol enantiomer 1 (**5AE1**) hydrochloride (Yield: 23 mg, 92%; drawn as R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: *m/z* 290.10 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.88 (s, 3H), 7.20 (s, 1H), 7.02 (s, 1H), 5.32 (s, 1H), 3.79-3.76 (m, 6H), 3.68-3.66 (m, 1H), 3.52-3.49 (m, 1H), 3.38-3.33 (m, 1H), 2.80-2.78 (m, 2H).

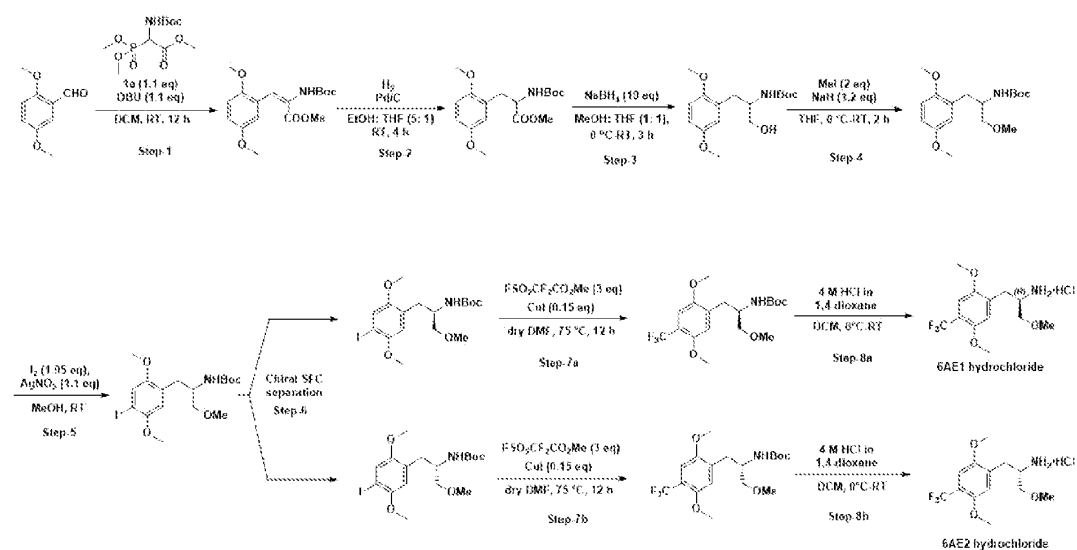
Step 4b:

Preparation of 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propan-1-ol enantiomer 2 (5AE2) hydrochloride

To a stirred solution of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate enantiomer 2 (30 mg, 0.077 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.19 mL, 0.77 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford 2-amino-3-(4-bromo-2,5-dimethoxyphenyl)propan-1-ol enantiomer 2 (**5AE2**) hydrochloride (Yield: 25 mg, 99%; drawn as S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: *m/z* 290.10 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.87 (br s, 3H), 7.20 (s, 1H), 7.02 (s, 1H), 5.32 (s, 1H), 3.79-3.76 (m, 6H), 3.71-3.70 (m, 1H), 3.47-3.46 (m, 1H), 3.39-3.38 (m, 1H), 2.80-2.78 (m, 2H).

Example 38: Preparation of 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-2-amine enantiomer 1 (6AE1) hydrochloride and 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-2-amine enantiomer 2 (6AE2) hydrochloride

Synthetic Scheme:



Steps 1-2:

Preparation of methyl 2-((tert-butoxycarbonyl)amino)-3-(2,5-dimethoxyphenyl)propanoate

To a solution of 2,5-dimethoxybenzaldehyde (2.0 g, 12 mmol) in DCM (120 mL), DBU (2.1 g, 13.2 mmol) was added at 0 °C. Then reaction mixture was allowed to stir at 0 °C for 10 min. Methyl 2-((tert-butoxycarbonyl)amino)-2-(dimethoxyphosphoryl)acetate (3.92 g, 13.2 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptane) to afford methyl (*E*)-2-((tert-butoxycarbonyl)amino)-3-(2,5-dimethoxyphenyl)-acrylate, which was used without further characterization. To a stirred solution of methyl (*E*)-2-((tert-

butoxycarbonyl)amino)-3-(2,5-dimethoxyphenyl)-acrylate in EtOH/THF (5:1, 120 mL) was added 10% Pd/C (0.36 g) at room temperature. The reaction flask was evacuated of atmosphere under vacuum, and backfilled with hydrogen gas (H₂ gas) and stirred for 4 h. The progress of reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was filtered through Celite pad and washed with ethyl acetate (20 mL). The organic fractions were combined, concentrated under reduced pressure to afford methyl 2-((*tert*-butoxycarbonyl)amino)-3-(2,5-dimethoxyphenyl)propanoate (Yield: 1.6 g, 36%). **LC-MS:** m/z 240.20 [M+H-100]⁺.

Step 3:***Preparation of tert-butyl (1-(2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate***

To a stirred solution of methyl 2-((*tert*-butoxycarbonyl)amino)-3-(2,5-dimethoxyphenyl)-propanoate (1.6 g, 4.42 mmol) in THF/MeOH (1:1, 16 mL) was added sodium borohydride (1.6g, 44.2 mmol) under argon at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with saturated NH₄Cl solution (10 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford *tert*-butyl (1-(2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate (1.1 g), which used without further purification. **LC-MS:** m/z: 312.15 [M+H]⁺.

Step 4:***Preparation of tert-butyl (1-(2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate***

To a solution of *tert*-butyl (1-(2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate (1.1 g, 3.53 mmol) in THF (15 mL) was added sodium hydride (60% dispersion in mineral oil; 162 mg, 4.23 mmol) under argon at 0 °C. The reaction mixture was stirred for 15 min. Iodomethane (0.43 mL, 7.06 mmol) was added at 0 °C, and the reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford *tert*-butyl (1-(2,5-

dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate (0.9 g), which was used without further purification and characterization. **LC-MS**: m/z : 326 $[M+H]^+$.

Step 5:

Preparation of tert-butyl (1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate

To a solution of *tert*-butyl (1-(2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate (0.8 g, 2.46 mmol) in methanol (40 mL) was added silver nitrate (0.5 g, 2.95 mmol) and I₂ (0.37 g, 2.95 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The progress of reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude residue was diluted with ethyl acetate (40 mL) and washed with water (10 mL). The organic fraction was washed with saturated sodium thiosulfate solution (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting in 0-10% ethyl acetate in heptane) to afford *tert*-butyl (1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate (Yield: 550 mg, 51%). **LC-MS**: m/z : 452.00 $[M+H]^+$. **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.24 (s, 1H), 6.81 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.89-3.81 (m, 1H), 3.28-3.20 (m, 5H), 2.82-2.77 (m, 1H), 2.45-2.39 (m, 1H), 1.27 (s, 9H).

Step 6:

Preparation of tert-butyl 1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 and tert-butyl 1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate (350 mg) were separated by chiral SFC [column name: Lux i-Amylose-3 (30 mm x 250 mm; 5 μ m) mobile phase: supercritical CO₂/100% IPA (80: 20); flow rate: 90 mL/min; column temp : 30 °C]. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford *tert*-butyl 1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 (Yield: 150 mg, 43%, >99% ee; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl 1-(4-iodo-2,5-

dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2 (Yield: 150 mg, 43%, >99% ee; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally).

***tert*-Butyl 1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1.**

LC-MS: m/z: 351.90 [M+H-100]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.25 (s, 1H), 6.82 (s, 1H), 6.63 (d, *J* = 9 Hz, 1H), 3.85-3.80 (m, 1H), 3.74 (s, 3H) 3.73 (s, 3H) 3.29-3.23 (m, 6H), 2.83-2.78 (m, 1H), 2.45-2.38 (m, 1H), 1.24 (s, 9H). The enantiomeric excess (99%) was determined by chiral SFC analysis [column name: ChiralPak IG (4.6 mm x 250 mm), 5 μ m; mobile phase: supercritical CO₂/0.1% NH₄OH in IPA (80:020); flow rate: 3.0 mL/min; column temp: 35°C). *R*_t = 3.41 min (enantiomer 1), 5.47 min (enantiomer 2).

***tert*-Butyl 1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2.**

LC-MS: m/z: 351.95 [M+H-100]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.25 (s, 1H), 6.82 (s, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 3.85-3.80 (m, 1H), 3.74 (s, 3H) 3.73 (s, 3H) 3.29-3.20 (m, 6H), 2.83-2.78 (m, 1H), 2.45-2.39 (m, 1H), 1.27 (s, 9H). The enantiomeric excess (99%) was determined by chiral SFC [column name: ChiralPak IG (4.6 mm x 250 mm), 5 μ m; mobile phase: supercritical CO₂/0.1% NH₄OH in IPA (80:020); flow rate: 3.0 mL/min; column temp: 35°C). *R*_t = 3.41 min (enantiomer 1), 5.44 min (enantiomer 2).

Step 7a:

Preparation of tert-butyl 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1

To a solution of *tert-butyl* 1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 1 (150 mg, 0.33 mmol) in dry DMF (10 mL) was added CuI (9.5 mg, 0.05 mmol) followed by methyl fluorosulfonyldifluoroacetate (190 mg, 1.0 mmol) at room temperature. The reaction was heated to 80 °C and stirred for 12 h. Progress of the reaction was monitored by LC-MS. Upon completion, the reaction mixture was allowed to cool to room temperature and then extracted with ethyl acetate (2 x 50 mL) and water (10 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting in 0-10% ethyl acetate in heptane) to afford *tert-butyl* 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-

yl)carbamate enantiomer 1 (Yield: 40 mg, 35%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: *m/z*: 294.10 [M+H-100]⁺.

Step 7b:

Preparation of tert-butyl 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2

To a solution of *tert-butyl* 1-(4-iodo-2,5-dimethoxyphenyl)-3-methoxypropan-2-yl)carbamate enantiomer 2 (150 mg, 0.33 mmol) in dry DMF (10 mL) was added CuI (9.5 mg, 0.05 mmol) followed by methyl fluorosulfonyldifluoroacetate (190 mg, 1.0 mmol) at room temperature. The reaction was heated to 80 °C and stirred for 12 h. Progress of the reaction was monitored by LC-MS. Upon completion, the reaction mixture was allowed to cool to room temperature and then extracted with ethyl acetate (2 x 50 mL) and water (10 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting in 0-10% ethyl acetate in heptane) to afford *tert-butyl* 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-yl)carbamate enantiomer 2 (Yield: 60 mg, 46%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: *m/z*: 294.10 [M+H-100]⁺.

Step 8a:

Preparation of 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-2-amine enantiomer 1 (6AE1) hydrochloride

To a stirred solution of *tert-butyl* 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-yl)carbamate enantiomer 1 (40 mg, 0.0102 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.2 mL, 0.05 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-2-amine enantiomer 1 (**6AE1**) hydrochloride (Yield: 18 mg, 54%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: *m/z*: 294.15 [M+H]⁺. **¹H NMR (400 MHz, DMSO-*d*₆)**: δ

= 8.05 (br s, 3H), 7.15 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.56-3.53 (m, 1H), 3.49-3.41 (m, 1H), 3.38-3.28 (m, 4H), 2.91 (d, $J = 8$ Hz, 2H). ^{19}F NMR (376 MHz, DMSO- d_6): $\delta = 60.26$ (s).

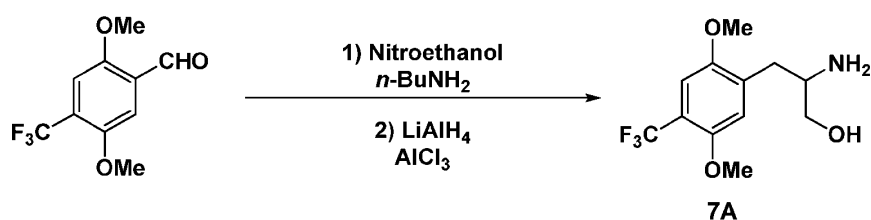
Step 8b:

Preparation of 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-2-amine enantiomer 2 (6AE2) hydrochloride

To a stirred solution of *tert*-butyl 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-yl)carbamate enantiomer 2 (60 mg, 0.015 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.3 mL, 0.07 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)-3-methoxypropan-2-amine enantiomer 2 (**6AE2**) hydrochloride (Yield: 41 mg, 81%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). LC-MS: m/z 294.15 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, DMSO- d_6): $\delta =$ 7.98 (br s, 3H), 7.16 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.56-3.55 (m, 1H), 3.45-3.35 (m, 2H), 3.29 (s, 3H), 3.0-2.8(m, 2H). ^{19}F NMR (376 MHz, DMSO- d_6): $\delta = 60.26$ (s).

Example 39: Preparation of 2-amino-3-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)propan-1-ol (7A)

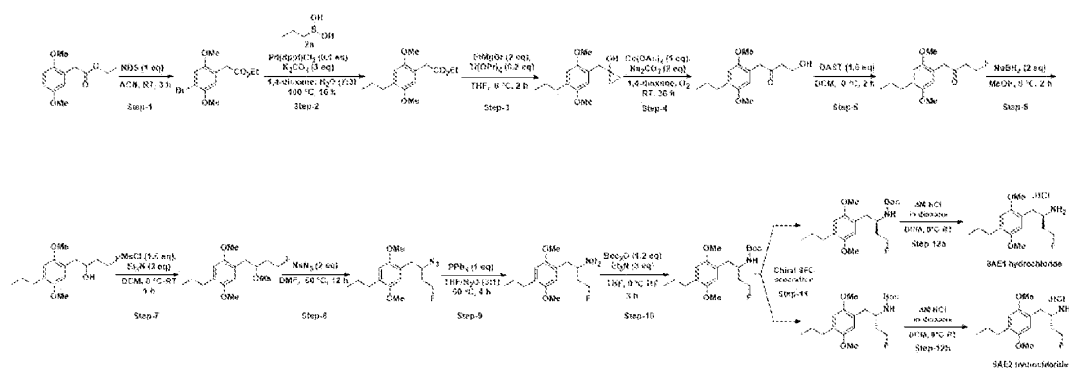
Synthetic Scheme:



This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 40: Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-amine enantiomer 1 (8AE1) hydrochloride and 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-amine enantiomer 2 (8AE2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of ethyl 2-(4-bromo-2,5-dimethoxyphenyl)acetate

To a solution of ethyl 2-(2,5-dimethoxyphenyl)acetate (3.0 g, 13.83 mmol) in ACN (20 mL) was added *N*-bromosuccinimide (2.46 g, 13.83 mmol) at room temperature and stirred for 3 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with chilled water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The organic fractions were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford ethyl 2-(4-bromo-2,5-dimethoxyphenyl)acetate (3.1 g, Yield: 76%). **LC-MS:** m/z 304 [M+H]⁺.

Step 2:

Preparation of ethyl 2-(2,5-dimethoxy-4-propylphenyl)acetate

To a solution of ethyl 2-(4-bromo-2,5-dimethoxyphenyl)acetate (3.1 g, 10.22 mmol) in 1,4-dioxane/water (7:3, 30 mL) was added dipotassium carbonate (0.41 g, 30.7 mmol) and *n*-propylboronic acid (1.8 g, 20.4 mmol) followed by Pd(dppf)Cl₂•CH₂Cl₂ (0.42 g, 0.51 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS and TLC. After

completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (60 mL) and water (20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford ethyl 2-(2,5-dimethoxy-4-propylphenyl)acetate (Yield: 1.4 g, 51%) which was used without further characterization.

Step 3:***Preparation of 1-(2,5-dimethoxy-4-propylbenzyl)cyclopropan-1-ol***

To a solution of ethyl 2-(2,5-dimethoxy-4-propylphenyl)acetate (1.4 g, 5.25 mmol) in THF (50 mL) was added titanium isopropoxide (0.3 g, 1.05 mmol) at 0 °C under argon atmosphere. Ethyl magnesium bromide (3M solution in THF; 10.5 mmol) was added to the reaction mixture dropwise over period of 20 min. The reaction mixture was stirred at 0 °C for 2 h. The progress of reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was quenched by the addition of saturated NH₄Cl solution (25 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting in 0-30% ethyl acetate in heptane) to afford 1-(2,5-dimethoxy-4-propylbenzyl)cyclopropan-1-ol (Yield: 0.9 g, 68%), which was used without further characterization.

Step 4:***Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-4-hydroxybutan-2-one***

To a solution of 1-(2,5-dimethoxy-4-propylbenzyl)cyclopropan-1-ol (900 mg, 3.59 mmol) in 1,4-dioxane (40 mL) was added cobalt (II) acetate (895 mg, 3.59 mmol) and sodium carbonate (712 mg, 6.72 mmol) at room temperature. The reaction mixture was stirred at room temperature under oxygen atmosphere for 24 h. Progress of the reaction was monitored by TLC and LCMS. Upon completion, reaction mixture was diluted with chilled water (10 mL) and extracted with ethyl acetate (2 x 25 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting in 0-30% ethyl acetate in heptane) to afford 1-(2,5-

dimethoxy-4-propylphenyl)-4-hydroxybutan-2-one (Yield: 350 mg, 88%), which was used without further characterization.

Steps 5-6:

Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-ol

To a solution of 1-(2,5-dimethoxy-4-propylphenyl)-4-hydroxybutan-2-one (350 mg, 1.31 mmol) in DCM (15 mL) was added DAST (318 mg, 1.97 mmol) at 0 °C. The reaction mixture was stirred for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with chilled water (20 mL) and extracted with DCM (2 X 20 mL). The organic fractions were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-one which was used without further purification. To a stirred solution of 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-one (350 mg, 1.31 mmol) in THF/MeOH (1:1, 20 mL) was added sodium borohydride (99 mg, 2.62 mmol) under argon at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was quenched with saturated NH₄Cl solution (50 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-ol (Yield: 190 mg, 53% over two steps) which was used without further purification or characterization.

Steps 7-8:

Preparation of 1-(2-azido-4-fluorobutyl)-2,5-dimethoxy-4-propylbenzene

To a solution of 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-ol (190 mg, 0.703 mmol) in DCM (10 mL) was added triethylamine (213 mg, 2.11 mmol) under argon at 0 °C followed by dropwise addition of methanesulfonyl chloride (120 mg, 1.05 mmol). After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with chilled water (10 mL) and extracted with DCM (2 x 20 mL). The organic fractions were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude material which was used without further purification or

characterization. To a stirred solution of 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl methanesulfonate (220 mg, 0.63 mmol) in DMF (5 mL) was added sodium azide (82 mg, 1.26 mmol) at room temperature. The reaction mixture was heated at 60 °C and stirred for 12 h. The progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with chilled water (50 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-60% ethyl acetate in heptane) to afford 1-(2-azido-4-fluorobutyl)-2,5-dimethoxy-4-propylbenzene (Yield: 140 mg, 67% over two steps), which was used without further characterization.

Steps 9-10:***Preparation of tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate***

To a stirred solution of 1-(2-azido-4-fluorobutyl)-2,5-dimethoxy-4-propylbenzene (140 mg, 0.52 mmol) in THF/H₂O (4:1; 10 mL) was added triphenyl phosphine (136 mg, 0.52 mmol) at room temperature. The reaction mixture was heated to 60 °C for 4 h. The progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was concentrated under reduced pressure to afford 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-amine, which was used without further purification or characterization. To a solution of 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-amine (140 mg, 0.52 mmol) in THF (50 mL) was added triethylamine (158 mg, 1.56 mmol) at 0 °C, followed by addition of di-*tert*-butyl dicarbonate (136 mg, 0.624 mmol). The reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with chilled water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-40% ethyl acetate in heptane) to afford *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate (Yield: 100 mg, 57% over two steps), which was used without further characterization.

Step 11:

Preparation of tert-butyl 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate enantiomer 1 and tert-butyl 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate (100 mg) were separated by chiral SFC [column name : ChiralPak IG (21 mm x 250 mm; 5 μ m); mobile phase: supercritical CO₂/0.1% NH₄OH in IPA (85:15); flow rate: 90 mL/min]. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford *tert*-butyl 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate enantiomer 1 (Yield: 35 mg, 35%, 97% ee; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl 1-(4-bromo-2,5-dimethoxyphenyl)-4-fluorobutan-2-yl)carbamate enantiomer 2 (Yield: 38 mg, 38%, 97% ee; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally).

tert-butyl 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate enantiomer 1. LC-MS: m/z: 270.25 [M+1-100]⁺. **¹H NMR (400 MHZ, DMSO-d₆):** δ = 6.65 (s, 1H), 6.63 (s, 1H), 4.72 (s, 1H), 4.63-4.44 (m, 2H), 3.98-3.92 (m, 1H), 3.78 (s, 3H), 3.76(s, 3H), 2.78-2.71 (m, 2H), 2.56-2.52 (m, 2H), 1.98-1.91 (m, 1H), 1.62-1.54 (m, 2H), 1.49-1.43 (m, 1H), 1.33 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H). The enantiomeric excess (97.28%) was determined by chiral SFC analysis [column name: ChiralPak IG-3 (4.6 mm x 150 mm, 3 μ m,); mobile phase: CO₂/0.2 % isopropylamine in IPA (80:20); flow rate: 3.0 mL/min; column temp: 35 °C]. *R_t* = 0.98 min (enantiomer 1), 1.618 min (enantiomer 2).

tert-butyl 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate enantiomer 2. LC-MS: m/z 270.20 [M+1-100]⁺. **¹H NMR (400 MHZ, DMSO-d₆):** δ = 6.65 (s, 1H), 6.63 (s, 1H), 4.72 (s, 1H), 4.63-4.47 (m, 2H), 3.98-3.92 (m, 1H), 3.78 (s, 3H), 3.76(s, 3H), 2.75-2.72 (m, 2H), 2.56-2.52 (m, 2H), 1.98-1.94 (m, 1H), 1.62-1.53 (m, 2H), 1.49-1.43 (m, 1H), 1.36 (s, 9H), 0.94 (t, *J* = 7.3 Hz, 3H). The enantiomeric excess (97%) was determined by chiral SFC analysis [column name: ChiralPak IG-3 (4.6 mm x 150 mm, 3 μ m,); mobile phase: CO₂/0.2 % isopropylamine in IPA (80:20); flow rate: 3.0 mL/min; column temp: 35 °C]. *R_t* = 0.970 min (enantiomer 1), 1.542 min (enantiomer 2).

Step 12a:***Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-amine enantiomer 1 (8AE1) hydrochloride***

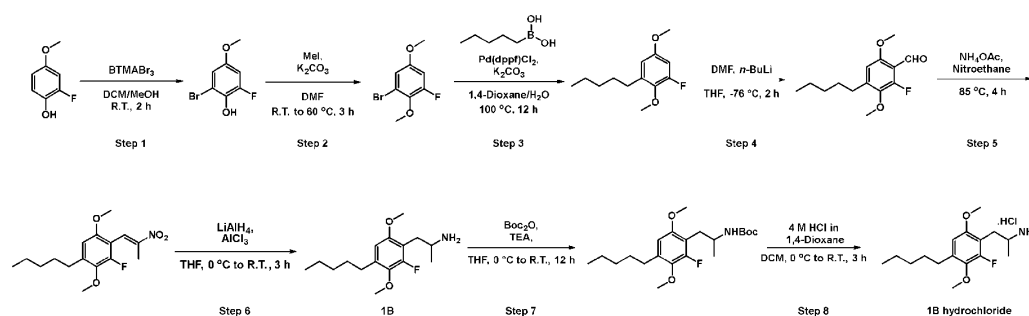
To a solution of *tert*-butyl 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate enantiomer 1 (35 mg, 0.095 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.24 mL, 0.95 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-amine enantiomer 1 (**8AE1**) hydrochloride (Yield: 16 mg, 55%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 270.40 [M+H]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.98 (s, 3H), 6.817 (s, 1H), 6.810 (s, 1H), 4.68-4.46 (m, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.46-3.42 (m, 1H), 2.87-2.81 (m, 2H), 2.51-2.48 (m, 2H), 1.97-1.80 (m, 2H), 1.58-1.48 (m, 2H), 0.90 (t, *J* = 8.0 Hz, 3H). **¹⁹F NMR (376 MHz, DMSO-*d*₆):** δ = -218.25 (s).

Step 12b:***Preparation of 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-amine enantiomer 2 (8AE2) hydrochloride***

To a solution of *tert*-butyl 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-yl)carbamate enantiomer 2 (38 mg, 0.102 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.25 mL, 1.02 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(2,5-dimethoxy-4-propylphenyl)-4-fluorobutan-2-amine enantiomer 2 (**8AE2**) hydrochloride (Yield: 12 mg, 38%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z: 270.40 [M+H]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.96 (br s, 3H), 6.818 (s, 1H), 6.810 (s, 1H), 4.65-4.44 (m, 2H), 3.733 (s, 3H), 3.730 (s, 3H), 3.47-3.44 (m, 1H), 2.87-2.81 (m, 2H), 2.51-2.48 (m, 2H), 1.92-1.84 (m, 2H), 1.56-1.50 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). **¹⁹F NMR (376 MHz, DMSO-*d*₆):** δ = -218.25 (s).

Example 41: Preparation of 1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)propan-2-amine (1B) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 2-bromo-6-fluoro-4-methoxyphenol

To a stirred solution of 2-fluoro-4-methoxyphenol (2.5 g, 17.6 mmol) in MeOH/DCM (5:2, 300 mL) at -76 °C under nitrogen atmosphere, was added (benzyl)trimethylammonium tribromide (6.86 g, 17.6 mmol) over 15 min. The reaction mixture was slowly warmed up room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was concentrated under reduced pressure and extracted with diethyl ether (100 mL x 2) and water (50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get the crude compound. This crude material was purified by flash column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptanes) to afford 2-bromo-6-fluoro-4-methoxyphenol as a brown solid (Yield: 1.6 g, 76%). ¹H NMR (400 MHz, DMSO-d₆): δ = 9.69 (d, *J* = 0.8 Hz, 1H), 6.94-6.93 (m, 1H), 6.89 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.70 (s, 3H).

Step 2:

Preparation of 1-bromo-3-fluoro-2,5-dimethoxybenzene

To a stirred solution of 2-bromo-6-fluoro-4-methoxyphenol (1.4 g, 5.43 mmol) in anhydrous DMF (12 mL) was added dipotassium carbonate (2.25 g, 16.3 mmol) under argon atmosphere. After complete addition, iodomethane (1.93 g, 13.6 mmol) was added to the reaction mixture and

stirred at 60 °C for 3 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was diluted with ice-cold water (30 mL) and extracted with ethyl acetate (40 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford 1-bromo-3-fluoro-2,5-dimethoxybenzene as a colorless oil (Yield: 1.2 g, 80%). **¹H NMR (400 MHz, CDCl₃):** δ = 6.87-6.86 (m, 1H), 6.64 (dd, J = 12, 3.2 Hz, 1H), 3.87 (s, 3H), 3.76 (s, 3H).

Step 3:

Preparation of 1-fluoro-2,5-dimethoxy-3-pentylbenzene

To a stirred solution of 1-bromo-3-fluoro-2,5-dimethoxybenzene (1.2 g, 5.11 mmol) in 1,4-dioxane/water (7:3, 10 mL) was added dipotassium carbonate (2.12 g, 15.3 mmol), pentylboronic acid (2.96 g, 25.5 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (417 mg, 5.11 mmol), under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (20 mL) and water (10 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford 1-fluoro-2,5-dimethoxy-3-pentylbenzene as a colorless oil (Yield: 700 mg, 60.6%). **¹H NMR (400 MHz, CDCl₃):** δ = 6.54-6.48 (m, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 2.63-2.59 (m, 2H), 1.63-1.55 (m, 2H), 1.37-1.30 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H).

Step 4:

Preparation of 2-fluoro-3,6-dimethoxy-4-pentylbenzaldehyde

To a solution of 1-fluoro-2,5-dimethoxy-3-pentylbenzene (700 mg, 3.09 mmol) in anhydrous THF (15 mL) was added *n*-BuLi solution (1.6 M in *n*-hexane; 2.12 mL, 3.40 mmol) dropwise at -76 °C under argon atmosphere. After complete addition, the reaction mixture was stirred at -76 °C for 30 min. After an hour, DMF (281 mg, 3.86 mmol) was added to the reaction mixture and

continued to stir at -76 °C for 1.5 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was quenched with saturated NH₄Cl solution (15 mL) and extracted with ethyl acetate (30 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced. This crude material was purified by flash column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptanes) to afford 2-fluoro-3,6-dimethoxy-4-pentylbenzaldehyde as a colorless oil (Yield: 550 mg, 70%). **¹H NMR (400 MHz, CDCl₃):** δ = 10.38 (s, 1H), 6.55 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.67 (d, J = 8.0 Hz, 2H), 1.63-1.58 (m, 2H), 1.39-1.35 (m, 4H), 0.93(t, J = 6.8 Hz, 3H).

Step 5:

Preparation of (E)-1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)-2-nitropropene

To a stirred solution of 2-fluoro-3,6-dimethoxy-4-pentylbenzaldehyde (550 mg, 2.16 mmol) in nitroethane (1.55 mL, 21.6 mmol) was added ammonium acetate (250 mg, 3.24 mmol) at 0 °C. Then mixture was warmed to 85 °C and stirred for 4 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with ice-cold water (10 mL) and extracted with ethyl acetate (20 mL x 2) and water (10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptanes) to afford (E)-1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)-2-nitropropene as a yellow solid (Yield: 500 mg, 74%). **¹H NMR (400 MHz, CDCl₃):** δ = 7.88 (s, 1H), 6.50 (s, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.65 (d, J = 8.0 Hz, 2H), 2.22 (s, 3H), 1.64-1.56 (m, 2H), 1.42-1.31 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H).

Step 6:

Preparation of 1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)propan-2-amine (1B)

To a stirred solution of LAH solution (2.0 M in THF; 2.41 mL, 4.83 mmol) in anhydrous THF (10 mL) was added AlCl₃ (214 mg, 1.61 mmol) portionwise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (E)-1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)-2-nitropropene (500 mg, 1.61 mmol) in THF (10 mL) was added dropwise over a period of 10 min at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 3 h. The reaction progress was monitored by TLC. Upon completion, the reaction

mixture was allowed to cool to 0 °C and was added THF/water (1:1, 14 mL) at same temperature, until effervescence stopped. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (40 mL), combined organic part was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)propan-2-amine (**1B**) as a gummy solid (Yield: 500 mg, 90%), which was used directly in the next step.

Step 7:***Preparation of tert-butyl (1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)propan-2-yl)carbamate*** To

a stirred solution of 1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)propan-2-amine (**1B**; 500 mg, 1.76 mmol) in THF (10 mL), trimethylamine (0.783 mL, 5.29 mmol) followed by di-*tert*-butyl dicarbonate (0.811 mL, 5.53 mmol) was added at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with cold water (10 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)propan-2-yl)carbamate as an off-white solid (Yield: 300 mg, 48%). **¹H NMR (400 MHz, CDCl₃):** δ = 6.40 (s, 1H), 3.89 (br s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.73-2.67 (m, 2H), 2.58-2.54 (m, 2H), 1.43-1.32 (m, 13H), 1.28-1.22 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 6.8 Hz, 3H).

Step 8:***Preparation of 1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)propan-2-amine (1B) hydrochloride***

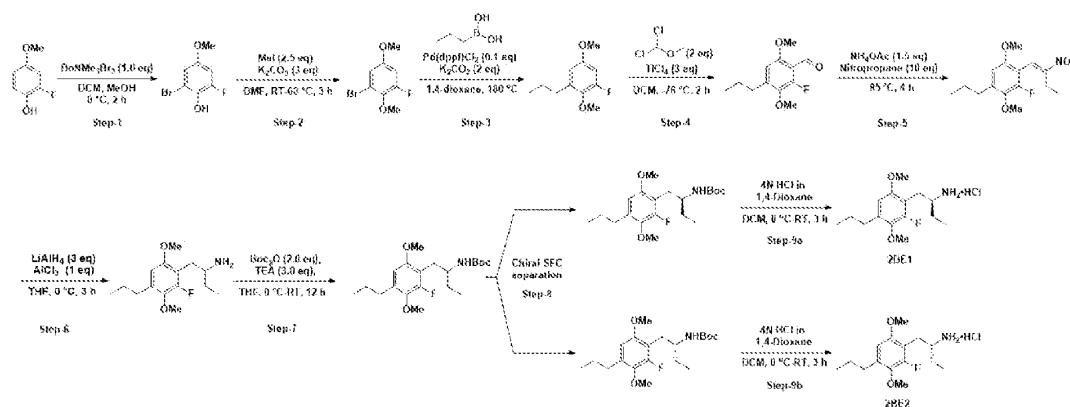
To a stirred solution of *tert*-butyl (1-(2-fluoro-3,6-dimethoxy-4-pentylphenyl)propan-2-yl)carbamate (70 mg, 0.183 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.45 mL, 1.83 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was concentrated under reduced pressure and washed with diethyl ether (5.0 mL) to afford the desired 1-(2-fluoro-3,6-dimethoxy-

4-pentylphenyl)propan-2-amine (**1B**) hydrochloride as an off-white solid (Yield: 41 mg, 49%).

LC-MS: m/z 284.20 $[M+1]^+$; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 8.00 (br s, 3H), 6.67 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.31 (br s, 1H), 2.87 (dd, J = 13.2, 4.4 Hz, 1H), 2.75 (dd, J = 13.2, 8.8 Hz, 1H), 2.58-2.54 (m, 2H), 1.58-1.50 (m, 2H), 1.35-1.30 (m, 4H) 1.08 (d, J = 6.8 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H); **¹⁹F NMR (376 MHz, DMSO-*d*₆):** δ = -133.11.

Example 42: Preparation of 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 1 (2BE1) hydrochloride and 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 2 (2BE2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of 2-bromo-6-fluoro-4-methoxyphenol

To a stirred solution of 2,5-dimethoxy-4-propylbenzaldehyde (5.0 g, 35 mmol) in DCM/MeOH (1:1; 250 mL) was added $\text{BnNMe}_3\text{Br}_3$ (1.0 eq, 35 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford 2-bromo-6-fluoro-4-methoxyphenol (Yield: 3.0 g, 39%). **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 9.70 (s, 1H), 6.93-6.76 (s, 2H), 3.66 (s, 3H).

Step 2:***Preparation of 1-bromo-3-fluoro-2,5-dimethoxybenzene***

To a stirred solution of 2-bromo-6-fluoro-4-methoxyphenol (3.0 g, 13.63 mmol) in DMF (30 mL) was added potassium carbonate (5.64 g, 40.9 mmol) at room temperature followed by dropwise addition of methyl iodide (2.12 mL, 34.07 mmol). After complete addition, the reaction mixture was warmed to 60 °C and stirred for 3 h. The reaction was monitored for completion by TLC and LC-MS. Upon completion, the reaction was diluted with chilled water (30 mL) and extracted with ethyl acetate (2 x 50 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford 1-bromo-3-fluoro-2,5-dimethoxybenzene (1.5 g, Yield: 63%). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 6.86 (m, 1H), 6.63 (dd, *J* = 12.1, 3.2 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H).

Step 3:***Preparation of 1-fluoro-2,5-dimethoxy-3-propylbenzene***

To a stirred solution of 1-bromo-3-fluoro-2,5-dimethoxybenzene (1.5 g, 6.38 mmol) in 1,4-dioxane/water (7:3, 20 mL) was added dipotassium carbonate (2.6 g, 19.4 mmol) and *n*-propylboronic acid (1.12 g, 12.8 mmol) followed by Pd(dppf)Cl₂•CH₂Cl₂ (0.261 g, 0.05 eq) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (3 x 20 mL) and water (20 mL). The organic fractions were combined, washed with brine (2 vol), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford 1-fluoro-2,5-dimethoxy-3-propylbenzene (Yield: 1.0 g, 59%). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 6.52-6.46 (m, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 2.57 (t, *J* = 7.56 Hz, 2H), 1.65-1.55 (m, 2H), 0.95 (t, *J* = 7.32 Hz, 3H).

Step 4:***Preparation of 2-fluoro-3,6-dimethoxy-4-propylbenzaldehyde***

To a solution of anhydrous dichloromethoxymethane (0.9 mL, 10.1 mmol) in DCM (10 mL) was added TiCl_4 (1.6 mL, 15.15 mmol) dropwise at $-78\text{ }^\circ\text{C}$ under argon atmosphere. After complete addition, 1-fluoro-2,5-dimethoxy-3-propylbenzene (1.0 g, 5.05 mmol) was added to the reaction mixture and stirred at $-78\text{ }^\circ\text{C}$ for 2 h. The progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with DCM (2 x 20 mL) and water (10 mL). The organic fractions were combined, washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford 4-bromo-2-methoxy-5-propoxybenzaldehyde (Yield: 0.8 g, 70%). **LC-MS:** m/z 227 $[\text{M}+\text{H}]^+$.

Step 5:***Preparation of (E)-3-fluoro-1,4-dimethoxy-2-(2-nitrobut-1-en-1-yl)-5-propylbenzene***

To a stirred solution of 2-fluoro-3,6-dimethoxy-4-propylbenzaldehyde (0.8 g, 3.54 mmol) in nitropropane (8.0 mL) was added ammonium acetate (2.85 mL, 5.31 mmol) at $0\text{ }^\circ\text{C}$. The reaction mixture was heated to $80\text{ }^\circ\text{C}$ and stirred for 4 h. The progress of reaction was monitored by TLC and LCMS. Upon completion, reaction mixture was diluted with chilled water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The organic fractions were combined, washed with brine (30 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude material was used without further purification.

Step 6:***Preparation of 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine:***

To a stirred solution of LiAlH_4 solution (2.0 M in THF; 3.53 mL, 7.07 mmol) in anhydrous THF (30 mL) was added AlCl_3 (312 mg, 3.33 mmol) portion wise at $0\text{ }^\circ\text{C}$. The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 20 min. Then, (E)-3-fluoro-1,4-dimethoxy-2-(2-nitrobut-1-en-1-yl)-5-propylbenzene (0.7 g, 2.35 mmol) in THF (10 mL) was added dropwise over a period of 10 min at $0\text{ }^\circ\text{C}$. The reaction mixture was warmed to room temperature and stirred for 4 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to $0\text{ }^\circ\text{C}$

and THF/water (1:1, 5 mL) was slowly added. The reaction mixture was then diluted with THF (10 mL) and stirred at room temperature for 30 min under inert atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (30 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine (Yield: 0.75 g), which was used without further purification.

Step 7:

Preparation of tert-butyl (1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate

To a stirred solution of 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine (0.75 g, 2.78 mmol) in THF (7.5 mL) was added triethylamine (1.16 mL, 8.34 mmol) at 0 °C, followed by dropwise addition of di-*tert*-butyl dicarbonate (1.31 mL, 5.56 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction progress was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with chilled water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford *tert*-butyl (1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate (100 mg, Yield: 10%). **LC-MS:** m/z 269 [M+H-100]⁺.

Step 8:

Preparation of tert-butyl 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxypropan-2-yl)carbamate (100 mg) were separated by chiral SFC [column name: ChiralPak IA (21.2 mm x 250 mm) 5µm; mobile phase: supercritical CO₂/0.1% NH₄OH in acetonitrile (90:10); flow rate: 50mL/min; column temp: 30 °C]. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford *tert*-butyl 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 40 mg, 40%, >97% ee; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl 1-(2-

fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (Yield: 40 mg, 40%, >90% ee; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally).

***tert*-Butyl 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1:**

LC-MS: m/z: 270 [M+H-100]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 6.58 (s, 1H), 6.46 (d, *J* = 7.4 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.53-3.51 (m, 2H), 2.64-2.60 (s, 2H), 2.54-2.50 (m, 2H), 1.57-1.50 (m, 2H), 1.37-1.24 (m, 9H), 0.90 (t, *J* = 8 Hz, 3H), 0.83 (t, *J* = 8 Hz, 3H). The enantiomeric excess (93%) was determined by chiral SFC analysis (column name: ChiralPak IA (250 mm x 4.6 mm), 3 μ m; mobile phase: supercritical CO₂/acetonitrile (80:20); flow rate: 3.0 mL/min; column temp: 35 °C) *R*_t = 1.55 min (enantiomer 1), 2.20 min (enantiomer 2).

***tert*-Butyl 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2:**

LC-MS: m/z: 270 [M+H-100]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 6.58 (s, 1H), 6.46 (d, *J* = 7.4 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.53-3.51 (m, 2H), 2.64-2.60 (s, 2H), 2.54-2.50 (m, 2H), 1.57-1.50 (m, 2H), 1.37-1.24 (m, 9H), 0.90 (t, *J* = 8 Hz, 3H), 0.83 (t, *J* = 8 Hz, 3H). The enantiomeric excess (95%) was determined by chiral SFC (column name: ChiralPak IA (250 mm x 4.6 mm), 3 μ m; mobile phase: supercritical CO₂/acetonitrile (80:20); flow rate: 3.0 mL/min; column temp: 35 °C) *R*_t = 1.55 min (enantiomer 1), 2.20 min (enantiomer 2).

Step 9a:

Preparation of 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 1 (2BE1) hydrochloride

To a stirred solution of *tert*-butyl 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 (40 mg, 0.310 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.13 mL, 54 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction progress was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 1 (**2BE1**) hydrochloride (Yield: 22 mg, 76%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS: m/z:** 270 [M+H]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.93 (s, 3H), 6.68 (s, 1H), 3.78 (s, 3H), 3.73 (s,

3H), 3.20-3.15 (m, 1H), 2.8-2.78 (m, 2H), 2.57- 2.53 (m, 2H), 1.60-1.52 (m, 2H), 1.51-1.44 (m, 2H), 0.94-0.85 (m, 6H); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): $\delta = -132.99$ (s).

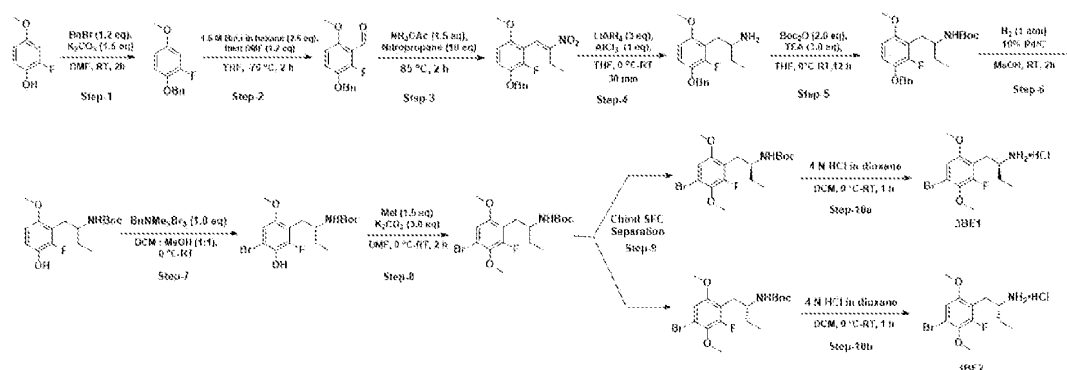
Step 9b:

Preparation of 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 2 (2BE2) hydrochloride

To a stirred solution of *tert*-butyl 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (40 mg, 0.310 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.13 mL, 54 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction progress was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(2-fluoro-3,6-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 2 (2BE2) hydrochloride (Yield: 28 mg, 76%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z : 270 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): $\delta = 7.87$ (s, 3H), 6.67 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.20-3.16 (m, 1H), 2.82-2.79 (m, 2H), 2.58-2.49 (m, 2H), 1.61-1.52 (m, 2H), 1.52-1.43 (m, 2H), 0.94-0.88 (m, 6H); ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): $\delta = -132.00$ (s).

Example 43: Preparation of 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-amine enantiomer 1 (3BE1) hydrochloride and 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-amine enantiomer 2 (3BE2) hydrochloride

Synthetic Scheme:



Step 1:***Preparation of 1-(benzyloxy)-2-fluoro-4-methoxybenzene***

To a stirred solution of 2-fluoro-4-methoxyphenol (3.0 g, 21.12 mmol) in DMF (30 mL) was added dipotassium carbonate (4.37 g, 31.7 mmol) followed by benzyl bromide (3.0 mL, 25.3 mmol) was added at 0 °C. The reaction was warmed to room temperature and stirred for 2 h. Progress of the reaction progress was monitored by TLC. Upon completion, the reaction mixture was diluted with chilled water (70 mL) and extracted with ethyl acetate (2 x 100 mL). The organic fractions were combined, washed with the brine (70 mL), dried over Na₂SO₄, filtered, concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptane) to afford 1-(benzyloxy)-2-fluoro-4-methoxybenzene (3.0 g, Yield: 61%). LC-MS: 231.05 [M-H]⁻.

Step 2:***Preparation of 3-(benzyloxy)-2-fluoro-6-methoxybenzaldehyde***

To a stirred solution of 1-(benzyloxy)-2-fluoro-4-methoxybenzene (3.0 g, 12.9 mmol) in THF (30 mL) was added n-BuLi dropwise (1.6 M in n-hexane; 20 mL, 32.32 mmol) at -78 °C. The reaction mixture was stirred for 1 h. DMF (1.2 mL, 15.5 mmol) was added to the reaction mixture and stirred for 1 h at -78 °C. Progress of the reaction progress was monitored by TLC and LC-MS. Upon completion, the reaction mixture was diluted with saturated NH₄Cl solution (20 mL) and extracted with ethyl acetate (2 x 30 mL) and water (20 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptane) to afford 3-(benzyloxy)-2-fluoro-6-methoxybenzaldehyde (2.6 g, Yield: 70%).

Steps 3-5:***Preparation of tert-butyl (1-(3-(benzyloxy)-2-fluoro-6-methoxyphenyl)butan-2-yl)carbamate***

To a stirred solution of 3-(benzyloxy)-2-fluoro-6-methoxybenzaldehyde (3.2 g, 12.3 mmol) in acetic acid (120 mL) was added nitropropane (120 mL) followed by 2-methylpropan-2-amine (4.9 g, 67.6 mmol) at 0 °C. Then reaction mixture was warmed to 85 °C and stirred for 6 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was poured into cold water (60 mL). The precipitate was filtered, washed with cold water (15 mL), and dried

under reduced pressure to afford (*E*)-1-(benzyloxy)-2-fluoro-4-methoxy-3-(2-nitrobut-1-en-1-yl)benzene and was used without further purification. To a solution of LAH (2.0 M in THF; 36.9 mmol) in anhydrous THF (40 mL) was added AlCl₃ (1.64 g, 12.3 mmol) portion wise at 0 °C under argon atmosphere. The reaction mixture was stirred at 0 °C for 30 min and (*E*)-1-(benzyloxy)-2-fluoro-4-methoxy-3-(2-nitrobut-1-en-1-yl)benzene (4.1 g, 12.3 mmol) in THF (120 mL) was added dropwise over a period of 10 min at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to 0 °C and THF/water (1:1, 14 mL) was slowly added. The reaction mixture was diluted with THF (50 mL) and stirred at room temperature for 30 min under inert atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (120 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford a crude product, which was used without further purification. To a solution of 1-(3-(benzyloxy)-2-fluoro-6-methoxyphenyl)butan-2-amine (3.7 g, 12.3 mmol) in THF (50 mL), triethylamine (3.1 g, 31 mmol) and di-*tert*-butyl dicarbonate (4.02 g, 18 mmol) were added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (100 mL) and extracted with ethyl acetate (2 x 50 mL). The organic fractions were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptane) to afford *tert*-butyl (1-(3-(benzyloxy)-2-fluoro-6-methoxyphenyl)butan-2-yl)carbamate (Yield: 0.7 g, 17%, over 3 steps). **LC-MS:** m/z 303.9 [M+H-100]⁺.

Step 6:

Preparation of tert-butyl (1-(2-fluoro-3-hydroxy-6-methoxyphenyl)butan-2-yl)carbamate

To a solution of *tert*-butyl (1-(3-(benzyloxy)-2-fluoro-6-methoxyphenyl)butan-2-yl) carbamate (0.70 g, 1.73 mmol) in MeOH (10 mL) was added 10% Pd/C (0.7 g) at room temperature. The reaction flask was evacuated of atmosphere under vacuum, and backfilled with hydrogen gas (H₂ gas) and stirred for 4 h. The progress of reaction was monitored by TLC and LC-MS. Upon completion, the reaction mixture was filtered through Celite pad, and washed with ethyl acetate (20 mL). The organic fractions were combined, concentrated under reduced pressure to afford

tert-butyl (1-(2-fluoro-3-hydroxy-6-methoxyphenyl)butan-2-yl)carbamate (Yield: 500 mg, 92%), which was used directly in the next step.

Step 7:

Preparation of tert-butyl (1-(4-bromo-2-fluoro-3-hydroxy-6-methoxyphenyl)butan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(2-fluoro-3-hydroxy-6-methoxyphenyl)butan-2-yl)carbamate (0.5 g, 1.6 mmol) in DCM/MeOH (1:1, 11 mL) was added BnNMe₃Br₃ (0.624 g, 1.6 mmol) at 0 °C. The reaction mixture was stirred at 1 h. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was warmed to room temperature, diluted with water (15 mL), and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrate under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-10% ethyl acetate in heptane) to afford *tert*-Butyl (1-(4-bromo-2-fluoro-3-hydroxy-6-methoxyphenyl)butan-2-yl)carbamate (Yield: 150 mg, 24%), which was used without further purification directly in the next step.

Step 8:

Preparation of tert-butyl (1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(4-bromo-2-fluoro-3-hydroxy-6-methoxyphenyl)butan-2-yl)carbamate (100 mg, 0.256 mmol) in DMF (15 mL) was added potassium carbonate (105.9 mg, 0.77 mmol) under argon at 0 °C and stirred for 15 min. Then, iodomethane (55 mg, 0.387 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. Progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel; eluting with 0-20% ethyl acetate in heptane) to afford *tert*-butyl (1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 80 mg, 77%). **LC-MS:** m/z: 326 [M+H]⁺.

Step 9:

Preparation of tert-butyl 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl-1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate (80 mg) were separated by chiral SFC. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford *tert*-butyl-1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 10 mg, 12.5%, 70% ee; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 13 mg, 16.2%, 99% ee; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally).

***tert*-Butyl-1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1.**

¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.00 (s, 1H), 6.52 (d, *J* = 9.28 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.52-3.51 (m, 1H), 2.62-2.58 (m, 2H), 1.40-1.34 (m, 2H), 1.27 (s, 9H), 0.81 (t, *J* = 7.3 Hz, 3H). The enantiomeric excess (70%) was determined by chiral SFC analysis [column name: Lux-Cellulose-4 (4.6 mm x 250mm), 5 μ m; mobile phase: 0.1% triethylamine in n-hexane/EtOH (98:2); flow rate: 0.5 mL/min; column temp: 25 °C)]. *R*_t = 10.51 min (enantiomer 1), 11.20 min (enantiomer 2).

***tert*-Butyl-1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2.**

¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.00 (s, 1H), 6.52 (d, *J* = 9.3 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.52-3.51 (m, 1H), 2.62-2.58 (m, 2H), 1.40-1.34 (m, 2H), 1.27 (s, 9H), 0.83 (t, *J* = 7.3 Hz, 3H). The enantiomeric excess (70%) was determined by chiral SFC analysis analysis [column name: Lux-Cellulose-4 (4.6 mm x 250mm), 5 μ m; mobile phase: 0.1% triethylamine in n-hexane/EtOH (98:2); flow rate: 0.5 mL/min; column temp: 25 °C)]. *R*_t = 10.67 min (enantiomer 1), 11.36 min (enantiomer 2).

Step 10a:

Preparation of 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-amine enantiomer 1 (3BE1) hydrochloride

To a stirred solution of *tert*-butyl-1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 (10 mg, 0.024 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.06 mL, 0.24 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-amine enantiomer 1 (**3BE1**) hydrochloride (Yield: 6 mg, 80%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z: 306.10 [M+H]⁺. **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.90 (br s, 3H), 7.11 (d, *J* = 1.88 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.21 – 3.17 (m, 1H), 2.87 – 2.77 (m, 2H), 1.54 – 1.47 (m, 2H), 0.92 (t, *J* = 8.0 Hz, 3H). **¹⁹F NMR (376 MHz, DMSO-*d*₆)**: δ = -129.20 (s).

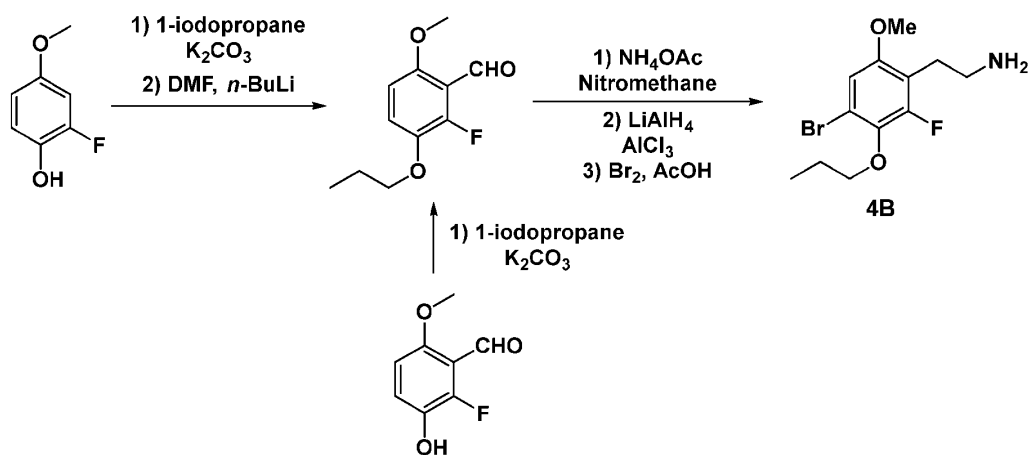
Step 10b:

Preparation of 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-amine enantiomer 2 (3BE2) hydrochloride

To a stirred solution of *tert*-butyl-1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2 (13 mg, 0.032 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.08 mL, 0.32 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(4-bromo-2-fluoro-3,6-dimethoxyphenyl)butan-2-amine enantiomer 2 (**3BE2**) hydrochloride (Yield: 7.5 mg, 76%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z: 306.15 [M+H]⁺. **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.87 (s, 3H), 7.12 (d, *J* = 1.9 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.22-3.18 (m, 1H), 2.87-2.76 (m, 2H), 1.54-1.47 (m, 2H), 0.92 (t, *J* = 8.0 Hz, 3H). **¹⁹F NMR (376 MHz, DMSO-*d*₆)**: δ = -129.20 (s).

Example 44: Preparation of 2-(4-bromo-2-fluoro-6-methoxy-3-propoxyphenyl)ethan-1-amine (4B)

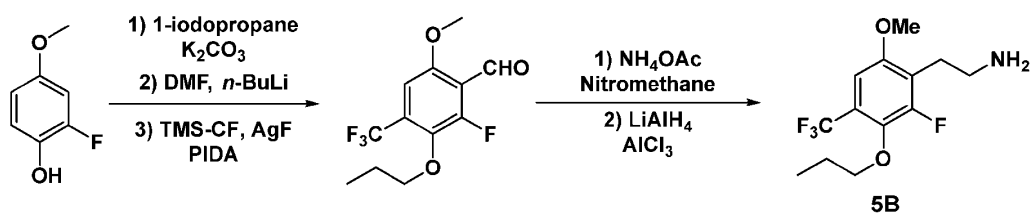
Synthetic Scheme:



This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 45: Preparation of 2-(2-fluoro-6-methoxy-3-propoxy-4-(trifluoromethyl)phenyl)ethan-1-amine (5B)

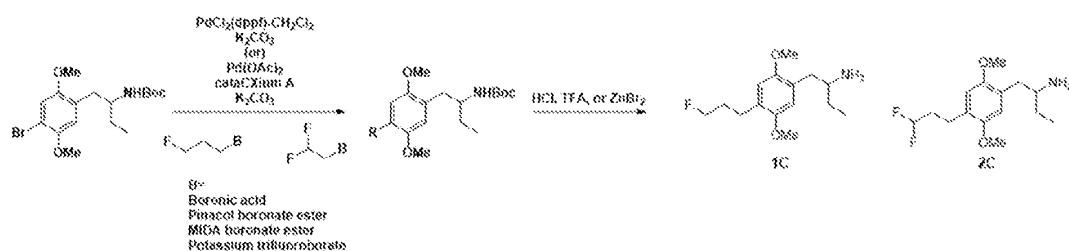
Synthetic Scheme:



This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 46: Preparation of 1-(4-(3-fluoropropyl)-2,5-dimethoxyphenyl)butan-2-amine (1C)

Synthetic Scheme:



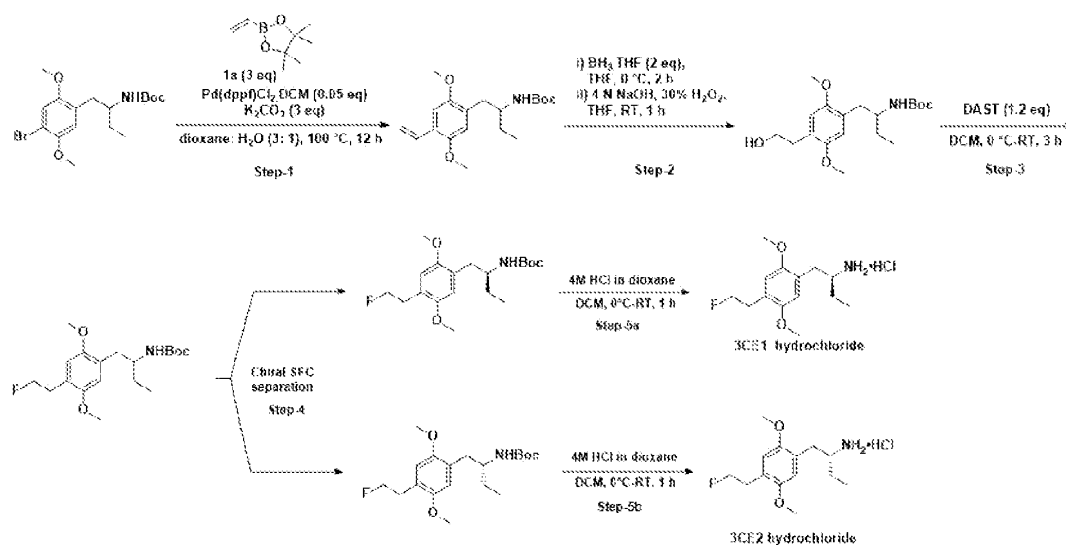
This compound is synthesized according to the general procedures described above and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 47: Preparation of 1-(4-(3,3-difluoropropyl)-2,5-dimethoxyphenyl)butan-2-amine (2C)

This compound is synthesized according to the general procedures described above in **Example 46** and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 48: Preparation of 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 1 (3CE1) hydrochloride and 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (3CE2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of tert-butyl (1-(2,5-dimethoxy-4-vinylphenyl)butan-2-yl)carbamate

To a stirred solution of *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate (1.5 g, 3.86 mmol) in 1,4-dioxane/water (3:1, 10 mL) was added vinylboronic acid pinacol ester (890 mg, 11.58 mmol), dipotassium carbonate (1.6 g, 11.58 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)•CH₂Cl₂ complex (156 mg, 0.192 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The reaction was monitored for completion by LC-MS and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through Celite pad. The filtrate was extracted with ethyl acetate (2 x 20mL) and water (20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel; eluting with 0-10% ethyl acetate in heptane) to afford *tert*-butyl (1-(2,5-dimethoxy-4-vinylphenyl)butan-2-yl)carbamate (Yield: 900 mg, 69%). ¹H NMR (400 MHz, CDCl₃): δ = 7.04 (s, 1H), 6.91 (dd, *J* = 18, 11.2 Hz, 1H), 6.81 (s, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 5.79 (d, *J* = 17.6 Hz, 1H), 5.20 (d, *J* = 12 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.58-3.55 (m, 1H), 2.73-2.69 (m, 1H), 2.51-2.49 (m, 1H), 1.44-1.34 (m, 2H), 1.30 (s, 9H), 0.84 (t, *J* = 7.2 Hz, 3H).

Step 2:***Preparation of tert-butyl (1-(4-(2-hydroxyethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate***

To a stirred solution of *tert*-butyl (1-(2,5-dimethoxy-4-vinylphenyl)butan-2-yl)carbamate (900 mg, 2.68 mmol) in THF (10 mL) was added $\text{BH}_3 \cdot \text{THF}$ (1M solution in THF; 5.36 mL, 5.36 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC. After complete consumption of starting material, the reaction mixture was cooled to 0 °C and aqueous H_2O_2 (30%; 2 mL) followed by 4N NaOH (4 mL) was added to it. The reaction mixture was warmed to room temperature and stirred for 1 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was extracted with ethyl acetate (2 x 30 mL) and water (20 mL). the organic fractions were combined, washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel; eluting with 0-20% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-(2-hydroxyethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 560 mg, 53%). **^1H NMR (400 MHz, DMSO-d_6):** δ = 6.73 (s, 2H), 6.53 (d, J = 8.8 Hz, 1H), 4.55 (t, J = 5.2 Hz, 1H), 3.70 (s, 6H), 3.52-3.45 (m, 3H), 2.68-2.64 (m, 4H), 1.47-1.33 (m, 2H), 1.30 (s, 9H), 0.82 (t, J = 7.6 Hz, 3H).

Step 3:

Preparation of tert-butyl (1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate To a stirred solution of *tert*-butyl (1-(4-(2-hydroxyethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (280 mg, 0.70 mmol) in DCM (10 mL) was added DAST (135 mg, 0.84 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was diluted with chilled water (10 mL) and extracted with DCM (2 x 20 mL). The organic layers were combined, washed with brine (15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 100 mg, 32%). **LC-MS:** m/z 256.10 [$\text{M}+1-100$] $^+$; **^1H NMR (400 MHz, DMSO-d_6):** δ = 6.80 (s, 1H), 6.77 (s, 1H), 6.55 (d, J = 9.2 Hz, 1H), 4.53 (dt, J = 47.2, 2.8 Hz, 2H), 3.72 (s, 3H), 3.71 (s, 3H), 3.55-3.53 (m, 1H), 2.91 (dt, J = 20.8,

2.8 Hz, 2H), 2.71-2.66 (m, 1H), 2.51-2.45 (m, 1H), 1.41-1.32 (m, 2H) 1.29 (s, 9H), 0.82 (t, $J = 7.2$ Hz, 3H).

Step 4:

Preparation of tert-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (100 mg) were separated by chiral SFC [Column Name: Phenomenex, Lux i Amylose-3 (30 mm x 250 mm) 5 μ m, Mobile Phase: supercritical CO₂/IPA (80:20); Flow Rate: 80mL/min Column temp: 30°C]. The desired fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 40 mg, 40%, >99% ee; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 40 mg, 40%, >98% ee; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally).

***tert*-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1.**

LC-MS: m/z 256.10 [M+1-100]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 6.81 (s, 1H), 6.78 (s, 1H), 6.57 (d, $J = 8.8$ Hz, 1H), 4.54 (dt, $J = 47.6, 6.8$ Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.55-3.54 (m, 1H), 2.91 (dt, $J = 21.2, 6.8$ Hz, 2H), 2.71-2.67 (m, 1H), 2.50-2.41 (m, 1H), 1.43-1.32 (m, 2H) 1.30 (s, 9H), 0.83 (t, $J = 7.2$ Hz, 3H). The enantiomeric excess (98.7%) was determined by chiral SFC analysis (Column name: i-Amylose-3 (4.6 mm x 250 mm), 5 μ m; Mobile Phase: supercritical CO₂/0.1% AH in IPA (70:30); Flow Rate: 3.0 mL/min; Column Temp : 30°C) R_t = 1.47 min (enantiomer 1), 2.27 min (enantiomer 2).

***tert*-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2.**

LC-MS: m/z 256.10 [M+1-100]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 6.81 (s, 1H), 6.78 (s, 1H), 6.57 (d, $J = 8.8$ Hz, 1H), 4.54 (dt, $J = 47.2, 6.8$ Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.55-3.54 (m, 1H), 2.91 (dt, $J = 21.2, 6.8$ Hz, 2H), 2.71-2.67 (m, 1H), 2.50-2.41 (m, 1H), 1.43-1.32 (m, 2H) 1.30 (s, 9H), 0.83 (t, $J = 7.2$ Hz, 3H). The enantiomeric excess (98.7%) was determined

by chiral SFC analysis (Column Name: i-Amylose-3 (4.6 mm x 250 mm), 5 μ m; Mobile Phase: supercritical CO₂/0.1% AH in IPA (70:30); Flow Rate: 3.0 mL/min; Column Temp : 30°C) R_t = 1.50 min (enantiomer 1), 2.11 min (enantiomer 2).

Step 5a:

Preparation of 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 1 (3CE1) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 (40 mg, 0.112 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.28 mL, 1.12 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 1 (**3CE1**) hydrochloride (Yield: 29 mg, 88%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 256.20 $[M+1]^+$. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.81 (s, 3H), 6.90 (s, 1H), 6.84 (s, 1H), 4.58 (dt, J = 47.2, 6.4 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.28-3.25 (m, 1H), 2.91 (dt, J = 22, 6.4 Hz, 2H), 2.80-2.74 (m, 2H), 1.52-1.47 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H).

Step 5b:

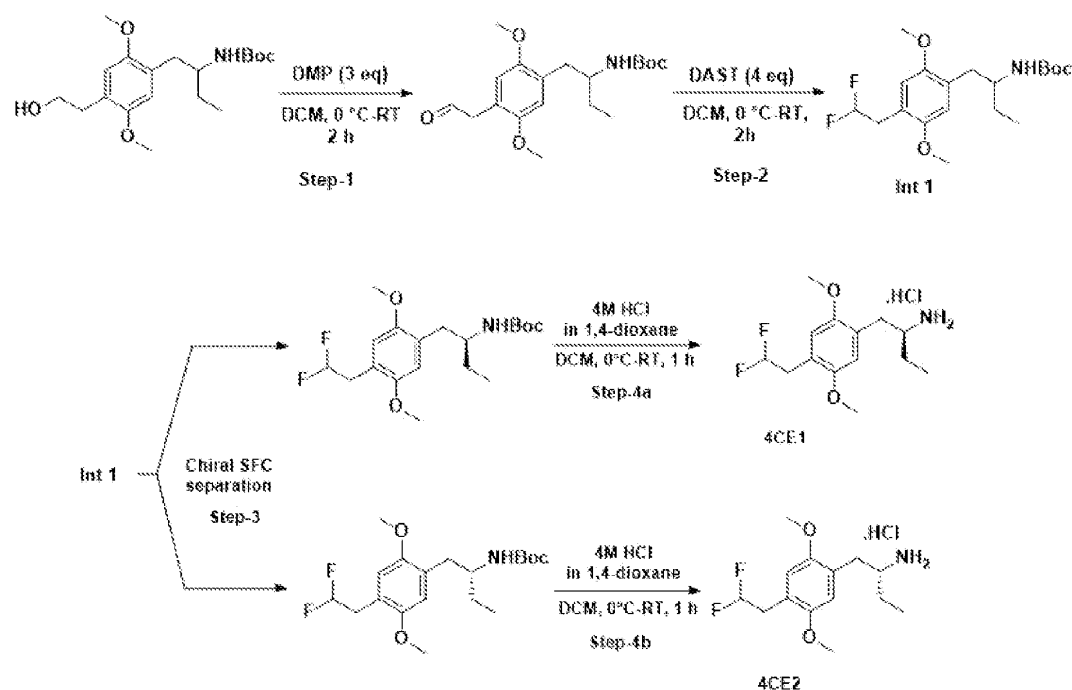
Preparation of 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (3CE2) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2 (40 mg, 0.112 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.28 mL, 1.12 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(4-(2-fluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (**3CE2**) hydrochloride (Yield: 29 mg, 88%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 256.25 $[M+1]^+$. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.84 (s, 3H), 6.90 (s, 1H), 6.85 (s,

1H), 4.58 (dt, $J = 47.2, 6.4$ Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.28-3.25 (m, 1H), 2.91 (dt, $J = 22, 6.4$ Hz, 2H), 2.80-2.78 (m, 2H), 1.51-1.46 (m, 2H), 0.91 (t, $J = 7.2$ Hz, 3H).

Example 49: Preparation of 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 1 (4CE1) hydrochloride and 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (4CE2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of tert-butyl (1-(2,5-dimethoxy-4-(2-oxoethyl)phenyl)butan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(4-(2-hydroxyethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (300 mg, 0.84 mmol) in DCM (10 mL) was added DMP (1.07 g, 2.52 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was diluted with saturated NaHCO_3 solution (5 mL) and extracted with ethyl acetate (2 x 20 mL).

The organic fractions were combined, washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford *tert*-butyl (1-(2,5-dimethoxy-4-(2-oxoethyl)phenyl)butan-2-yl)carbamate (150 mg). The crude material was used without further purification.

Step 2:

Preparation of tert-butyl (1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(2,5-dimethoxy-4-(2-oxoethyl)phenyl)butan-2-yl)carbamate (150 mg, 0.427 mmol) in DCM (10 mL) was added DAST (0.22 mL, 1.71 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was diluted with chilled water (10 mL) and extracted with DCM (2 x 20 mL). The organic fractions were combined, washed with brine (15 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel; eluting with 0-10% ethyl acetate in heptanes) to afford *tert*-butyl (1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 110 mg, 69%). **LC-MS:** m/z 274.15 [M+1-100]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 6.84 (s, 1H), 6.81 (s, 1H), 6.57 (d, *J* = 9.2 Hz, 1H), 6.29-6.00 (m, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.56-3.54 (m, 1H), 3.08 (td, *J* = 17.2, 2.4 Hz, 2H), 2.72-2.45 (m, 2H), 1.29 (s, 9H), 1.43-1.24 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H).

Step 3

Preparation of tert-butyl 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate (**Int 1**, 110 mg) were separated by chiral SFC [Column Name: Phenomenex, Lux i Amylose-3 (30 mm x 250 mm), 5 μ m; Mobile Phase: supercritical CO₂/IPA (85:15); Flow Rate: 85 mL/min; Column temp: 35°C]. The desired fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 30 mg, 27%, 98.8% ee; drawn as *S*

enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2 (Yield: 30 mg, 27%, >99.9% ee; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally).

***tert*-butyl 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer**

1. LC-MS: m/z 274.15 $[M+1-100]^+$. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 6.84 (s, 1H), 6.81 (s, 1H), 6.57 (d, J = 8.8 Hz, 1H), 6.30-6.00 (m, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.58-3.53 (m, 1H), 3.14-3.04 (m, 2H), 2.71-2.50 (m, 2H), 1.50-1.24 (m, 2H), 1.29 (s, 9H), 1.24-1.19 (m, 2H), 0.83 (t, J = 11.6 Hz, 3H). The enantiomeric excess (98.8%) was determined by chiral SFC analysis (Column Name: i-Amylose-3 (4.6 mm x 250 mm), 5 μ m; Mobile Phase: supercritical CO₂/1% isopropylamine in IPA (80:20); Flow Rate: 3.0 mL/min; Column Temp: 35°C) R_t = 1.62 min (enantiomer 1), 2.44 min (enantiomer 2).

***tert*-butyl 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer**

2. LC-MS: m/z 274.19 $[M+1-100]^+$. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 6.84 (s, 1H), 6.81 (s, 1H), 6.57 (d, J = 8.4 Hz, 1H), 6.29-6.00 (m, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.58-3.53 (m, 1H), 3.09 (td, J = 17.2, 4.4 Hz, 2H), 2.71-2.50 (m, 2H), 1.50-1.18 (m, 2H), 1.29 (s, 9H), 0.83 (t, J = 7.2 Hz, 3H). The enantiomeric excess (98.8%) was determined by chiral SFC analysis (Column Name: i-Amylose-3 (4.6 mm x 250 mm), 5 μ m; Mobile Phase: supercritical CO₂/1% isopropylamine in IPA (80:20); Flow Rate: 3.0 mL/min; Column Temp: 35°C) R_t = 1.62 min (enantiomer 1), 2.21 min (enantiomer 2).

Step 4a:

Preparation of 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 1 (4CE1) hydrochloride

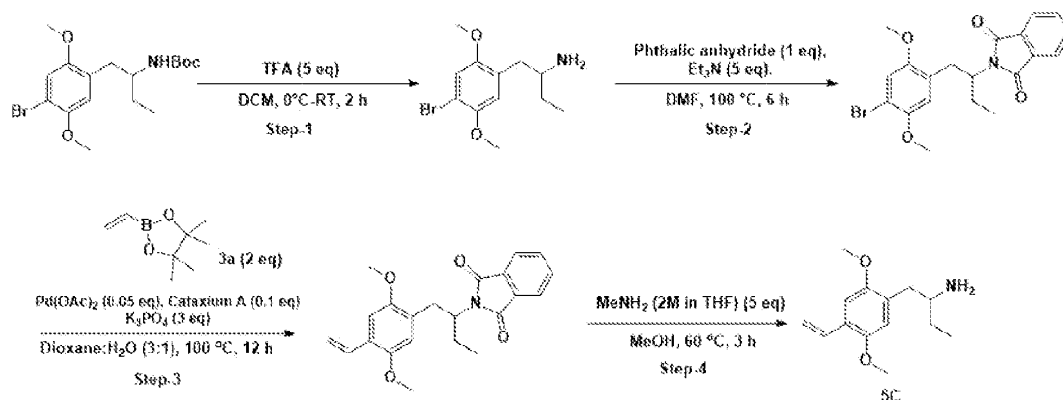
To a stirred solution of *tert*-butyl 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 (30 mg, 0.08 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.2 mL, 0.8 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(4-(2,2-difluoroethyl)-2,5-

dimethoxyphenyl)butan-2-amine enantiomer 1 (**4CE1**) hydrochloride (Yield: 16 mg, 66%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** *m/z* 274.20 [M+1]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.84 (s, 3H), 6.95 (s, 1H), 6.89 (s, 1H), 6.20 (tt, *J* = 56.88, 8.8 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.28-3.22 (m, 1H), 3.13 (dt, *J* = 13.2, 4.8 Hz, 2H), 2.80 (d, *J* = 6.4 Hz, 2H), 1.52-1.48 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H).

Step 4b:***Preparation of 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (4CE2) hydrochloride***

To a stirred solution of *tert*-butyl 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2 (30 mg, 0.08 mmol) in DCM (1.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.2 mL, 0.8 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(4-(2,2-difluoroethyl)-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (**4CE2**) hydrochloride (Yield: 14 mg, 56%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** *m/z* 274.25 [M+1]⁺. **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.82 (s, 3H), 6.95 (s, 1H), 6.89 (s, 1H), 6.20 (tt, *J* = 56.7, 8.4 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.28-3.22 (m, 1H), 3.13 (dt, *J* = 13.2, 4.8 Hz, 2H), 2.80 (d, *J* = 6.4 Hz, 2H), 1.53-1.42 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H).

Example 50: Preparation of 1-(2,5-dimethoxy-4-vinylphenyl)butan-2-amine (5C)**Synthetic Scheme:**

**Step 1:****Preparation of 1-(4-bromo-2,5-dimethoxyphenyl)butan-2-amine**

To a stirred solution of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)butan-2-yl)carbamate (see ACS Chemical Neuroscience (2023), 14(1), 119-135) (1.0 g, 2.58 mmol) in DCM (10.0 mL) was added trifluoroacetic acid (0.98 mL, 12.9 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 2 h. The progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction mixture was concentrated under reduced pressure and the solids were washed with diethyl ether (10.0 mL) to afford the desired compound 1-(4-bromo-2,5-dimethoxyphenyl)butan-2-amine (Yield: 0.7 g), which was used without further purification.

Step 2:**Preparation of 2-(1-(4-bromo-2,5-dimethoxyphenyl)butan-2-yl)isoindoline-1,3-dione**

To a stirred solution of 1-(4-bromo-2,5-dimethoxyphenyl)butan-2-amine (0.7 g, 2.43 mmol) in DMF (5.0 mL) was added phthalic anhydride (359 mg, 2.43 mmol) and triethylamine (1.7 mL, 12.1 mmol) under argon atmosphere at room temperature. The reaction mixture was then heated at 100 °C for 6 h. Progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with cold water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, washed with brine (30 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptanes) to afford 2-(1-(4-bromo-2,5-dimethoxyphenyl)butan-2-yl)isoindoline-1,3-dione (Yield: 0.3 g, 29%). **LC-MS:**

m/z 418.05 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ = 7.75-7.72 (m, 2H), 6.8-7.65 (m, 2H), 6.92 (s, 1H), 6.59 (s, 1H), 4.50-4.45 (m, 1H), 3.72 (s, 3H), 3.58 (s, 3H), 3.24 (dd, J = 13.5, 10.4 Hz, 1H), 3.08 (dd, J = 18.6, 5.0 Hz, 1H), 2.22-2.14 (m, 1H), 1.89-1.82 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H).

Step 3:

Preparation of 2-(1-(2,5-dimethoxy-4-vinylphenyl)butan-2-yl)isoindoline-1,3-dione

To a stirred solution of 2-(1-(4-bromo-2,5-dimethoxyphenyl)butan-2-yl)isoindoline-1,3-dione (0.15 g, 0.35 mmol) in 1,4-dioxane/water (3:1, 6 mL) was added potassium phosphate (222 mg, 1.05 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (107 mg, 0.7 mmol), 1-[1-adamantanylbis(butyl)phosphino]adamantane (12 mg, 0.035 mmol), palladium bis(acetate) (4 mg, 0.0175 mmol) under argon atmosphere at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. Progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through Celite pad. The filtrate was extracted with ethyl acetate (20 mL) and water (10 mL). The organic fraction was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford 2-(1-(2,5-dimethoxy-4-vinylphenyl)butan-2-yl)isoindoline-1,3-dione (Yield: 70 mg, 53%). **LC-MS:** m/z 366.10 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃): δ = 7.75-7.72 (m, 2H), 7.67-7.64 (m, 2H), 6.91 (dd, J = 17.7, 11.1 Hz, 1H), 6.86 (s, 1H), 6.55 (s, 1H), 5.62 (d, J = 17.6 Hz, 1H), 5.17 (d, J = 11.6 Hz, 1H), 4.54-4.46 (m, 1H), 3.75 (s, 3H), 3.55 (s, 3H), 3.25 (dd, J = 13.4, 10.2 Hz, 1H), 3.11 (dd, J = 13.5, 5.2 Hz, 1H), 2.23-2.15 (m, 1H), 1.91-1.81 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H).

Step 4:

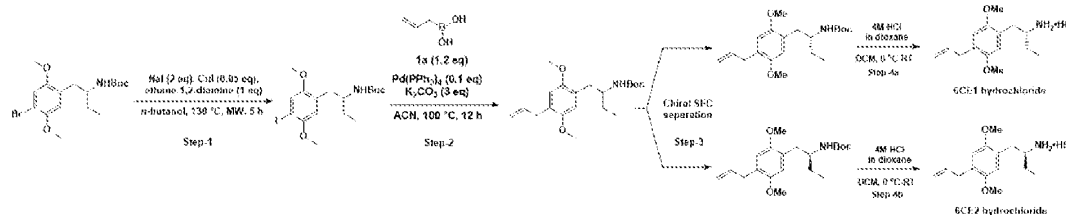
Synthesis of 1-(2,5-dimethoxy-4-vinylphenyl)butan-2-amine (5C):

To a stirred solution of 2-(1-(2,5-dimethoxy-4-vinylphenyl)butan-2-yl)isoindoline-1,3-dione (70 mg, 0.19 mmol) in MeOH was added methylamine (2M in THF, 0.47 mL, 0.95 mmol) at room temperature. The reaction mixture was then heated at 60 °C for 3 h. Progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by reverse phase Prep HPLC [Column Name:

X Select CSH C18 (19 mm x 250 mm) 5 μ m; Mobile Phase: A: 0.1% formic acid in water, B: Acetonitrile; Flow Rate: 18 mL/min]. The desired fractions were combined, concentrated under reduced pressure, and lyophilized to afford 1-(2,5-dimethoxy-4-vinylphenyl)butan-2-amine (Yield: 18 mg, 33%). **LC-MS**: m/z 236.2 [M+H]⁺. **¹H NMR (400 MHz, DMSO-d₆)**: δ = 7.09 (s, 1H) 6.92 (dd, J = 17.7, 11.2 Hz, 1H), 6.85 (s, 1H), 5.82 (d, J = 17.7 Hz, 1H), 5.23 (d, J = 11.2 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.10-3.04 (m, 1H), 2.75 (dd, J = 13.2, 6.6 Hz, 1H), 2.65 (dd, J = 13.2, 6.8 Hz, 1H), 1.48-1.34 (m, 2H), 0.89 (t, J = 7.4 Hz, 3H).

Example 51: Preparation of 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-amine enantiomer 1 (6CE1) hydrochloride and 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (6CE2) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of tert-butyl (1-(4-iodo-2,5-dimethoxyphenyl)butan-2-yl)carbamate

To a solution of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)butan-2-yl)carbamate (see ACS Chemical Neuroscience (2023), 14(1), 119-135) (300 mg, 0.772 mmol) in *n*-BuOH (10 mL) was added CuI (7.3 mg, 0.038 mmol), ethane-1,2-diamine (46.4 mg, 0.772 mmol) and NaI (231 mg, 1.54 mmol) at room temperature. Then, the mixture was heated to 120 °C under microwave irradiation for 5 h. The progress of reaction was monitored by LC-MS. Upon completion, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford *tert*-butyl (1-(4-iodo-2,5-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 130 mg, 46%), **LC-MS**: m/z: 336.12 [M+H-

100]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.24 (s, 1H), 6.81 (s, 1H), 6.57 (d, *J* = 8.0 Hz 1H), 3.75 (s, 3H), 3.73 (s, 3H), 2.72-2.51 (m, 1H), 2.50-2.43 (m, 1H), 1.84-1.82 (m, 1H), 1.44-1.14 (m, 11H), 0.83 (t, *J* = 7.2 Hz, 3H).

Step 2:

Preparation of tert-butyl (1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(4-iodo-2,5-dimethoxyphenyl)butan-2-yl)carbamate (0.130 g, 0.298 mmol) in acetonitrile (4 mL) was added dipotassium carbonate (0.124 g, 0.896 mmol), allylboronic acid (0.031g, 0.358 mmol) and tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.298 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. Progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (10 mL) and water (05 mL). The organic fractions were combined, washed with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel; eluting with 0-30% ethyl acetate in heptane) to afford *tert*-butyl (1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate (Yield: 100 mg, 95.82%). LC-MS: *m/z*: 250.20 [M+H-100]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.62-7.50 (m, 1H), 6.76-6.69 (m, 2H), 6.55-6.53 (m, 1H), 5.94-5.85 (m, 1H), 5.03-4.96 (m, 2H), 3.71 (s, 3H), 3.66 (s, 3H), 3.54-3.53 (m, 1H), 3.26-3.25 (m, 2H), 2.70-2.65 (m, 1H), 2.45-2.39 (m, 1H), 1.46-1.37 (m, 1H), 1.33 (m, 9H), 0.82 (t, *J* = 8.0 Hz, 3H).

Step 3:

Preparation of tert-butyl 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate (100 mg) were separated by chiral SFC [column name: Lux i Amylose-3 (30 mm x 250 mm) 5 μ m; mobile phase: supercritical CO₂/0.1% NH₄OH in IPA (80:20); flow rate: 70mL/min; column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 40 mg, 40%, >99% ee; drawn as *R* enantiomer but absolute stereochemistry not determined

experimentally) and *tert*-butyl 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2 (Yield: 35 mg, 35%, >99% ee; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally).

***tert*-butyl 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1.** LC-MS: *m/z*: 250.20 [M+H-100]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 6.76 (s, 1H), 6.73 (s, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 5.97-5.87 (m, 1H), 5.03-4.97 (m, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.57-3.52 (m, 1H), 3.27 (d, *J* = 8.0 Hz, 2H), 2.71-2.66 (m, 1H), 2.50-2.33 (m, 1H), 1.45-1.32 (m, 2H), 1.32 (s, 9H), 0.83 (t, *J* = 8.0 Hz, 3H). The enantiomeric excess (>99%) was determined by chiral SFC analysis [column name: Lux i Amylose-3 (4.6 mm x 250 mm), 5 μ m; mobile phase: supercritical CO₂/0.3% isopropylamine in IPA (70:30); flow rate: 3.0 ml/min; column temp: 35 °C] *R*_t = 1.49 min (enantiomer 1), 2.24 min (enantiomer 2).

***tert*-butyl 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2.** LC-MS: *m/z*: 250.20 [M+H-100]⁺; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 6.76 (s, 1H), 6.70 (s, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 5.97-5.87 (m, 1H), 5.03-4.97 (m, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.57-3.52 (m, 1H), 3.27 (d, *J* = 8.0 Hz, 2H), 2.71-2.66 (m, 1H), 2.51-2.33 (m, 1H), 1.45-1.32 (m, 2H), 1.30 (s, 9H), 0.83 (t, *J* = 8.0 Hz, 3H). The enantiomeric excess (>99%) was determined by chiral SFC analysis [column name: Lux i Amylose-3 (4.6 mm x 250 mm), 5 μ m; mobile phase: supercritical CO₂/0.3% isopropylamine in IPA (70:30); flow rate: 3.0 ml/min; column temp: 35 °C] *R*_t = 1.51 min (enantiomer 1), 2.26 min (enantiomer 2).

Step 4a:

Preparation of 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-amine enantiomer 1 (6CEI) hydrochloride

To a stirred solution of *tert*-butyl 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 1 (40 mg, 0.114 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.14 mL, 0.57 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(4-allyl-2,5-dimethoxyphenyl)butan-

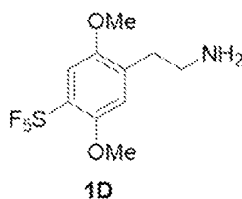
2-amine enantiomer 1 (**6CE1**) hydrochloride (Yield: 21 mg, 74%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z : 250.35 $[M+H]^+$. **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.85 (s, 3H), 6.83 (s, 1H), 6.78 (s, 1H), 5.99-5.89 (m, 1H), 5.07-5.00 (m, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.29 (d, J = 6.6 Hz, 2H), 3.27-3.24 (m, 1H), 2.79 (d, J = 6.8 Hz, 2H), 1.54-1.47 (m, 2H), 0.91 (t, J = 8 Hz, 3H).

Step 4b:

Preparation of 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (6CE2) hydrochloride

To a stirred solution of tert-butyl 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-yl)carbamate enantiomer 2 (35 mg, 0.10 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.125 mL, 0.50 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (5.0 mL) to afford 1-(4-allyl-2,5-dimethoxyphenyl)butan-2-amine enantiomer 2 (**6CE2**) hydrochloride (Yield: 14 mg, 56%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: m/z : 250.35 $[M+H]^+$. **1H NMR (400 MHz, DMSO- d_6)**: δ = 7.88 (s, 3H), 6.84 (s, 1H), 6.79 (s, 1H), 5.99-5.89 (m, 1H), 5.07-5.00 (m, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.29 (d, J = 6.6 Hz, 2H), 3.27-3.24 (m, 1H), 2.79 (d, J = 6.8 Hz, 2H), 1.54-1.47 (m, 2H), 0.91 (t, J = 8 Hz, 3H).

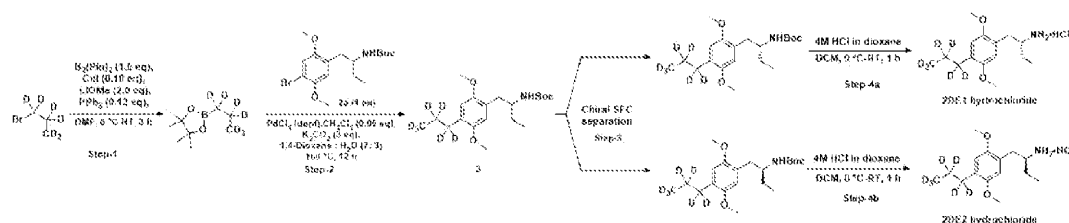
Example 52: Preparation of 2-(2,5-dimethoxy-4-(pentafluoro- λ^6 -sulfaneyl)phenyl)ethan-1-amine (**1D**)



This compound is synthesized according to the general procedures described above in **Example 23** and by modifications of the specific procedures provided in the other examples and other transformations well known in the art.

Example 53: Preparation of 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-amine enantiomer 1 (2DE1) hydrochloride and 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-amine enantiomer 2 (2DE2) hydrochloride

Synthetic Scheme:



Step 1:

*Preparation of 4,4,5,5-tetramethyl-2-(propyl-*d*₇)-1,3,2-dioxaborolane*

To a solution of copper(I) iodide (294 mg, 1.54 mmol), triphenylphosphine (526 mg, 2.0 mmol), lithium methoxide (1.17 g, 30.8 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.86 g, 23.1 mmol) in degassed dimethylformamide (12 mL) was added 1-bromopropane-1,1,2,2,3,3,3-*d*₇ (2.0 g, 15.4 mmol) in dimethylformamide (0.5 mL). The reaction mixture was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with diethyl ether (50 mL) and filtered through Celite pad. The filtrate was diluted with water (50 mL) and extracted with diethyl ether (2x50mL). The organic fractions were combined, washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel; 0-10% diethyl ether in pentane) to afford 4,4,5,5-tetramethyl-2-(propyl-*d*₇)-1,3,2-dioxaborolane (Yield: 1.0 g, 37%).

Step 2:

*Preparation of tert-butyl (1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate*

To a stirred solution of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)butan-2-yl)carbamate (see ACS Chemical Neuroscience (2023), 14(1), 119-135) (1.0 g, 2.58 mmol) in 1,4-dioxane/water (7:3, 10 mL) was added dipotassium carbonate (1.07 g, 7.74 mmol), 4,4,5,5-tetramethyl-2-(propyl-*d*₇)-1,3,2-dioxaborolane (1.0 g, 5.6 mmol), Pd(dppf)Cl₂•DCM (105 mg, 0.129 mmol)

under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with ethyl acetate (25 mL) and filtered through a Celite pad. The filtrate was diluted with water (20 mL) and extracted with ethyl acetate (20 mL). The organic fractions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel; 0-20% ethyl acetate in heptane) to afford *tert*-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate (Yield: 100 mg, 11%). ¹H NMR (400 MHz, CDCl₃): δ = 6.64 (s, 2H), 4.63 (d, *J* = 8.7 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.82-3.70 (m, 1H), 2.72-2.71 (m, 2H), 1.60-1.25 (m, 2H), 1.35 (s, 9H), 0.94 (t, *J* = 7.4 Hz, 3H).

Step 3:

Preparation of tert-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate (450 mg) were separated by chiral SFC [Phenomenex®, Lux i-Amylose-3 (30.0 mm x 250 mm) 5μm; mobile phase: supercritical CO₂/IPA (70:30); flow rate: 70 mL/min; column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 35 mg, 35%, 99% ee; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate enantiomer 2 (Yield: 35 mg, 35%, 97% ee; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally).

***tert*-Butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate enantiomer 1.** LC-MS: *m/z*: 359.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 6.66 (s, 2H), 4.64 (s, 1H), 3.79-3.71 (m, 7H), 2.74-2.72 (m, 2H), 1.37-1.27 (m, 11H), 0.96 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (98.20%) was determined by chiral SFC analysis [column name: I Amylose-3 (4.6 mm x 250 mm) 5μm; mobile phase: supercritical CO₂/0.1% isopropylamine in IPA (80:20) flow rate: 3.0 mL/min; column temp: 35 °C] *R*_t = 1.81 min (enantiomer 1), 3.92 min (enantiomer 2).

***tert*-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate enantiomer 2.** LC-MS: *m/z*: 359.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 6.66 (s, 2H), 4.65 (s, 1H), 3.80-3.72 (m, 7H), 2.74-2.73 (m, 2H), 1.43-1.27 (m, 11H), 0.96 (t, *J* = 7.2 Hz, 3H). The enantiomeric excess (98.98%) was determined by chiral SFC analysis [column name: I Amylose-3 (4.6 mm x 250 mm) 5μm; mobile phase: supercritical CO₂/0.1% isopropylamine in IPA (80:20) flow rate: 3.0 mL/min; column temp: 35 °C] *R*_t = 1.82 (enantiomer 1), 3.88 (enantiomer 2).

Step 4a:

Preparation of 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-amine enantiomer 1 (2DE1) hydrochloride

To a stirred solution of *tert*-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate enantiomer 1 (35 mg, 0.098 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.24 mL, 0.98 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the solids were washed with diethyl ether (10.0 mL) to afford 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-amine enantiomer 1 (**2DE1**) hydrochloride (Yield: 24 mg, 95%; drawn as *R* enantiomer but absolute stereochemistry not determined experimentally). LC-MS: *m/z*: 259 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 7.84 (s, 3H), 6.78 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.27-3.24 (m, 1H), 2.81-2.75 (m, 2H), 1.52-1.46 (m, 2H), 0.91 (t, *J* = 8.0 Hz, 3H).

Step 4b:

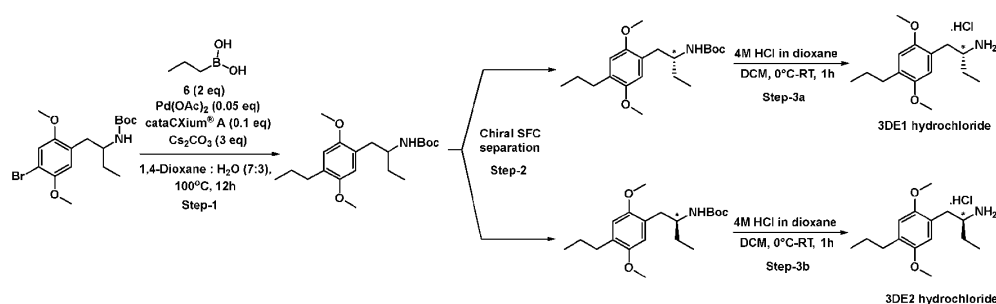
Preparation of 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-amine enantiomer 2 (2DE2) hydrochloride

To a stirred solution of *tert*-butyl 1-(2,5-dimethoxy-4-(propyl-*d*₇)phenyl)butan-2-yl)carbamate enantiomer 2 (35 mg, 0.098 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.24 mL, 0.98 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. After completion, the reaction was concentrated under reduced pressure and the residue was washed with diethyl ether (10.0 mL) to afford 1-(2,5-dimethoxy-4-(propyl-

*d*7)phenyl)butan-2-amine enantiomer 2 (**2DE2**) hydrochloride (Yield: 24 mg, 95%; drawn as *S* enantiomer but absolute stereochemistry not determined experimentally). **LC-MS**: *m/z*: 259 [M+H]⁺. **¹H NMR (400 MHz, DMSO-*d*₆)**: δ = 7.84 (s, 3H), 6.78 (s, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 3.27-3.24 (m, 1H), 2.81-2.75 (m, 2H), 1.52-1.46 (m, 2H), 0.91 (t, *J* = 8.0 Hz, 3H).

Example 54: Preparation of 1-(2,5-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 1 (3DE1; 3DR) hydrochloride and 1-(2,5-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 2 (3DE2; 3DS) hydrochloride

Synthetic Scheme:



Step 1:

Preparation of tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate

To a stirred solution of *tert*-butyl (1-(4-bromo-2,5-dimethoxyphenyl)butan-2-yl)carbamate (see ACS Chemical Neuroscience (2023), 14(1), 119-135; 600 mg, 1.55 mmol) in 1,4-dioxane/water (7:3, 10 mL) was added dipotassium carbonate (642 mg, 4.65 mmol), *n*-propylboronic acid (543 mg, 6.18 mmol), 1-[1-adamantanyl(butyl)phosphino]adamantane (55.5 mg, 0.155 mmol), palladium bis(acetate) (17.4 mg, 0.077 mmol) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was diluted with ethyl acetate (25 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (20 mL) and water (20 mL). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. This crude material was purified by flash chromatography (eluting with 0-20% ethyl acetate in heptanes) to afford *tert*-

butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate as an off-white solid (Yield: 450 mg, 82 %). **LC-MS:** m/z 252.15 [M+1-100]⁺.

Step 2:

Preparation of tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 and tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2

The enantiomers of *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate (450 mg) were separated by chiral SFC [Column Name: Phenomenex[®] Lux i-Amylose-3 (30 mm x 250 mm) 5 μ m; Mobile Phase: supercritical CO₂/IPA/MeOH (80:10:10); Flow Rate: 60 mL/min; Column temp: 30 °C]. The separated fractions were concentrated under reduced pressure and lyophilized to afford *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1 (Yield: 180 mg, 40%; drawn as R enantiomer but absolute stereochemistry not determined experimentally) and *tert*-butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2 (Yield: 180 mg, 40%; drawn as S enantiomer but absolute stereochemistry not determined experimentally) as off-white solids.

tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 1

LC-MS: m/z 252.25 [M+1-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.65 (s, 2H), 4.63 (d, *J* = 5.6 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.79-3.72 (m, 1H), 2.71 (d, *J* = 6.4 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 1.61-1.36 (m, 4H), 1.36 (s, 9H), 0.97-0.92 (m, 6H). The enantiomeric excess (>99%) was determined by chiral SFC analysis [Column Name: Phenomenex Lux i-Amylose-3 (4.6 mm x 150 mm), 3 μ m; Mobile Phase: supercritical CO₂/IPA/MeOH (80:10:10); Flow Rate: 3.0 ml/min; Column Temp: 35 °C, λ = 291 nm] *R*_t = 1.67 min (enantiomer 1), 2.29 min (enantiomer 2).

tert-butyl (1-(2,5-dimethoxy-4-propylphenyl)butan-2-yl)carbamate enantiomer 2

LC-MS: m/z 252.00 [M+1-100]⁺; **¹H NMR (400 MHz, CDCl₃):** δ = 6.65 (s, 2H), 4.63 (br s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.84-3.72 (m, 1H), 2.71 (d, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 7.6 Hz, 2H), 1.67-1.43 (m, 4H), 1.36 (s, 9H), 0.97-0.94 (m, 6H). The enantiomeric excess (>99%) was determined by chiral SFC analysis [Column Name: Phenomenex Lux i-Amylose-3 (4.6 mm x

150 mm), 3 μ m; Mobile Phase: supercritical CO₂/IPA/MeOH (80:10:10); Flow Rate: 3.0 ml/min; Column Temp: 35 °C, λ = 291 nm] R_t = 1.68 min (enantiomer 1), 2.25 min (enantiomer 2).

Step 3a:

Preparation of 1-(2,5-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 1 (3DE1) hydrochloride

To a stirred solution of *tert*-butyl 1-(2,5-dimethoxy-4-propylphenyl)butan-2-ylcarbamate enantiomer 1 (180 mg, 0.51 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.64 mL, 2.55 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (10.0 mL) to afford the desired 1-(2,5-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 1 (**3DE1**) hydrochloride as an off-white solid (Yield: 131 mg, 46%; drawn as the R enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 252.4 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.87 (s, 3H), 6.80 (s, 1H), 6.80 (s, 1H), 3.73(s, 3H), 3.73 (s, 3H), 3.25 (br s, 1H), 2.78 (d, J = 6.8 Hz, 2H), 2.50-2.48 (m, 2H), 1.56-1.48 (m, 4H), 0.93-0.88 (m, 6H).

Step 3b:

Preparation of 1-(2,5-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 2 (3DE2) hydrochloride

To a stirred solution of *tert*-butyl 1-(2,5-dimethoxy-4-propylphenyl)butan-2-ylcarbamate enantiomer 2 (180 mg, 0.51 mmol) in DCM (2.0 mL) was added HCl solution (4.0 M in 1,4-dioxane; 0.64 mL, 2.55 mmol) at 0 °C. After complete addition, the reaction mixture was warmed to room temperature and stirred for 1 h. Progress of the reaction was monitored by TLC and LC-MS. Upon completion, the reaction was concentrated under reduced pressure and washed with diethyl ether (10.0 mL) to afford the desired 1-(2,5-dimethoxy-4-propylphenyl)butan-2-amine enantiomer 2 (**3DE2**) hydrochloride as an off-white solid (Yield: 134 mg, 47%; drawn as the S enantiomer but absolute stereochemistry not determined experimentally). **LC-MS:** m/z 252.4 [M+H]⁺; **¹H NMR (400 MHz, DMSO-*d*₆):** δ = 7.87 (s,

3H), 6.80 (s, 2H), 3.73 (s, 3H), 3.73 (s, 3H), 3.25 (3.35-3.23, 1H), 2.78 (d, $J = 6.8$ Hz, 2H), 2.50-2.49 (m, 2H), 1.56-1.48 (m, 4H), 0.93-0.88 (m, 6H).

Example 55: Metabolic Stability in Human Liver Microsomes

Disclosed compounds were tested for stability in human liver microsomes (HLM), with the results summarized in **Table 1**. Microsomal stability varied widely across tested compounds, suggesting a range of oral bioavailability and half-life depending on the specific compound.

Test Compounds. Disclosed compounds were prepared as described above. All other compounds were commercially obtained or prepared according to literature procedures.

HLM Stability. Pooled HLM from adult male and female donors (Corning 452117) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation medium consisted of PBS (100 mM, pH 7.4), $MgCl_2$ (1 mM), and NADPH (1 mM), with 0.50 mg of liver microsomal protein per mL. Control incubations were performed by replacing the NADPH-cofactor system with PBS. Test compounds (1 μ M, final solvent concentration 1.0%) were incubated with microsomes at 37 °C with constant shaking. Six time points over 60 minutes were analyzed, with 60 μ L aliquots of the reaction mixture being drawn at each time point. The reaction aliquots were stopped by adding 180 μ L of cold (4 °C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4,000 rpm for 20 minutes at 4 °C. Supernatant samples (80 μ L) were diluted with water (240 μ L) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Data Analysis. The elimination constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (CL_{int}) were determined in a plot of $\ln(AUC)$ versus time, using linear regression analysis.

Table 1. Intrinsic clearance (CL_{int}) and half-life ($t_{1/2}$) of compounds in the presence of HLM.

Compound	Cl _{int} (μL/min/mg)	t _{1/2} (min)
1	83.3	16.6
2	1018.4	1.4
3E1	140.8	9.8
3E2	126.3	11.0
4E1	189.2	7.3
4E2	206.6	6.7
5E1	362.7	3.8
5E2	298.9	4.6
6E1	46.4	29.9
6E2	72.9	19.0
7E1	51.2	27.1
7E2	40.3	34.4
9	42.7	32.5
9E1	32.4	42.7
9E2	78.4	17.7
10E1	13.8	100.7
10E2	18.6	74.4
11E1	64.2	21.6
11E2	152.0	9.1
12	<9.6	>145
13	<9.6	>145

17	<9.6	>145
21	87.2	15.9
1AE1	26.4	52.5
1AE2	16.4	84.5
1B	10.6	131.3
3DE1	25.5	54.3
3DE2	23.5	59
20	578.3	2.4
24E1	97.8	14.2
24E2	55.7	24.9
26	12.4	112.2
28	39.5	35.1
28E1	39.4	35.2
28E2	50.3	27.6
30E1	176.4	7.9
30E2	85.8	16.2
31E1	<9.6	>145
31E2	<9.6	>145
32E1	22	63.1
32E2	14.5	95.7
2AE1	<9.6	>145
2AE2	<9.6	>145

4A	<9.6	>145
6AE1	<9.6	>145
6AE2	<9.6	>145
8AE1	16	86.4
8AE2	15.4	90.2
2BE1	90.3	15.4
2BE2	30.8	45.0
3BE1	13.2	104.9
3BE2	27.1	51.1
4CE1	12.4	111.4
4CE2	<9.6	>145
6CE1	33.7	41.1
6CE2	21.3	65.1
2DE1	15	92.5
2DE2	<9.6	>145

Example 56: 5-HT_{2A} Receptor Binding

The binding affinities of disclosed compounds at the ketanserin binding site of the 5-HT_{2A} receptor were determined in radioligand binding experiments.

Test Compounds. Disclosed compounds were prepared as described above. All other compounds were commercially obtained or prepared according to literature procedures.

Method. Affinity of the test compounds for the 5-HT_{2A} receptor was determined in radioligand binding experiments with [³H]ketanserin by WuXi AppTec (Hong Kong) Limited, using methods adapted from the literature and under conditions described in **Table 2**.

Results. Results of the radioligand binding assays are shown in **Table 3**. The tested compounds showed high binding affinity for the 5-HT_{2A} receptor.

Table 2. Assay conditions for 5-HT_{2A} receptor radioligand binding assay.

Receptor Source	HEK293 stable cell line
Vehicle	1.0% DMSO
Incubation Time	1 h
Incubation Temperature	25 °C
Incubation Buffer	50 mM Tris-HCl, pH 7.4
Ligand	1 nM [³ H]ketanserin
Non-Specific Ligand	1 μM ketanserin

Table 3. Results of 5-HT_{2A} receptor binding affinity experiments.

Compound	5-HT_{2A} K_i (nM) ([³H]Ketanserin)
1-(4-iodo-2,5-dimethoxyphenyl)propan-2-amine (DOI)	14.51
2-(4-bromo-2,5-dimethoxyphenyl)ethan-1-amine (2C-B)	8.25
2-(4-ethyl-2,5-dimethoxyphenyl)ethan-1-amine (2C-E)	16.68
1-(2,5-dimethoxy-4-propylphenyl)propan-2-amine (DOPR)	17.56
1-(2,5-dimethoxy-4-pentylphenyl)propan-2-amine (DOAM)	5.41
1-(2,5-dimethoxy-4-pentylphenyl)butan-2-amine (4C-PENT)	26.29

1-(4-hexyl-2,5-dimethoxyphenyl)butan-2-amine (4C-HEX)	9.06
2-(2,5-dimethoxy-4-(trifluoromethyl)phenyl)ethan-1-amine (2C-TFM)	15.84
1	42.93
2	35.84
3E1	28.39
3E2	34.21
4E1	58.28
4E2	73.99
5E1	66.39
5E2	81.28
6E1	42.81
6E2	97.29
7E1	29.08
7E2	21.37
9	18.11
9E1	28.19
9E2	56.46
10E1	24.93
10E2	21.91
11E1	268.65
11E2	286.49
12	26.79
13	49.48
14	157.75
17	67.28
19	204.83
21	18.05
25	138.36
26	62.24
1AE1	56.81
1AE2	111.53

1B	21.36
3DE1	83.8
3DE2	90.16
15E1	379.87
15E2	384.41
20	32.80
22E1	381.89
22E2	181.29
24E1	42.85
24E2	70.77
28	19.70
28E1	10.80
28E2	21.48
30E1	210.53
30E2	315.50
31E1	236.66
31E2	346.02
32E1	3.05
32E2	3.33
2AE1	89.77
2AE2	618.51
3AE1	726.31
3AE2	479.19
4A	52.35
4AE1	87.00
5AE1	>1225
5AE2	831.79
6AE1	19.38
6AE2	39.48
8AE1	134.21
8AE2	102.49
2BE1	184.04
2BE2	507.22

3BE1	506.05
3BE2	260.55
3CE1	50.2.56
3CE2	669.70
4CE1	862.42
4CE2	798.83
5C	1,128.44
6CE1	157.32
6CE2	108.35

Example 57: Functional Activity at Serotonin Receptors

Disclosed compounds were tested for agonist activity at several serotonin receptor subtypes (5-HT2A, 5-HT2B, and 5-HT2C) using Ca^{2+} flux functional assays, with the results summarized in **Table 4**. Agonist activity at 5-HT2B was additionally assessed using a secondary method to measure accumulation of IP1. All compounds tested exhibited potent agonist activity at 5-HT2A, suggestive of potential hallucinogenic activity as well as possible therapeutic effects. However, the potency and signaling efficacy at 5-HT2A, as well as the selectivity for this target over other serotonin receptors, varied dramatically with even small changes to the chemical structure.

Test Compounds. Disclosed compounds were prepared as described above. All other compounds were commercially obtained or prepared according to literature procedures.

FLIPR Functional Assays at 5-HT2A, 5-HT2B, and 5-HT2C. Agonist activity at 5-HT2A, 5-HT2B, 5-HT2C, and 5-HT1A receptors was determined using a FLIPR Ca^{2+} flux assay at WuXi AppTec (Hong Kong) Limited according to their standard protocols. Briefly, stably transfected cells expressing the receptor of interest (HEK293 for 5-HT2A, 5-HT2B, and 5-HT2C, CHO-K1 with $\text{G}\alpha_{15}$ for 5-HT1A) were grown and plated in a 384 well plate and incubated at 37 °C and 5% CO_2 overnight. A solution of 250 mM probenecid in 1mL FLIPR assay buffer was prepared fresh. This was combined with a fluorescent dye (Fluo-4 Direct™) to make a final assay

concentration of 2.5 mM. Compounds were diluted 1:3.16 for 10 points and 750 nL was added to a 384 well compound plate using ECHO along with 30 μ L assay buffer. The fluorescent dye was then added to the assay plate along with assay buffer to a final volume of 40 μ L. The cell plate was incubated for 50 min at 37 °C and 5% CO₂ and placed into the FLIPR Tetra along with the compound plate. 10 μ L of references and compounds were then transferred from the compound plate into the cell plate and the fluorescent signal was read. Alternatively, the agonist activity of some compounds at 5-HT_{2C} was determined using a FLIPR Ca²⁺ flux assay at Eurofins DiscoverX (Fremont, CA), as described below. The two 5-HT_{2C} agonist functional assays provided comparable results for potency and efficacy when the same reference compounds were tested.

FLIPR Functional Assays at 5-HT_{2C}. Agonist activity at 5-HT_{2C} was determined using a FLIPR Ca²⁺ flux assay at Eurofins DiscoverX (Fremont, CA) according to their standard protocols. Briefly, stably transfected U2OS cells expressing the human 5-HT_{2C} receptor were grown and plated in a 384 well plate and incubated at 37 °C and 5% CO₂ overnight. Assays were performed in 1x Dye Loading Buffer consisting of 1x Dye, 1x Additive A, and 2.5 mM Probenecid in HBSS / 20 mM Hepes. Probenecid was prepared fresh. Cells were loaded with dye prior to testing and incubated at 37 °C for 30-60 minutes. After dye loading, cells were removed from the incubator and 10 μ L HBSS / 20 mM Hepes was added. 3x vehicle was included in the assay buffer. Cells were incubated for 30 mins at room temperature in the dark to equilibrate plate temperature. Intermediate dilution of sample stocks was performed to generate 4x sample in assay buffer. Compound agonist activity was measured on a FLIPR Tetra (MDS). Calcium mobilization was monitored for 2 minutes and 10 μ L 4X sample in HBSS / 20 mM Hepes was added to the cells 5 seconds into the assay.

5-HT_{2B} IP1 accumulation assay. Agonist activity at 5-HT_{2B} was determined using a IP1 accumulation assay at Eurofins Cerep (France) according to their standard protocols. Briefly, stably transfected CHO cells expressing the human 5-HT_{2B} receptor were grown and plated in a 384 well plate and incubated at 37 °C and 5% CO₂ overnight. Test compounds were applied to the cells and incubated at 37 °C for 30 mins in the presence of 50 mM LiCl. IP1 accumulation was detected using HTRF.

Table 4. Agonist activity of compounds at select serotonin receptors in Ca²⁺ flux functional assays and 5-HT2B IP1 accumulation.

Compound	5-HT2A EC ₅₀ (nM)	5-HT2A %Act @ Max Dose	5-HT2B EC ₅₀ (nM)	5-HT2B %Act @ Max Dose	5-HT2C EC ₅₀ (nM)	5-HT2C %Act @ Max Dose	5-HT2B IP1 EC ₅₀ (nM)	5-HT2B IP1 %Act @ Max Dose
DOI	0.1897	105.9	4.875	86.3	0.82 ^a	92.6	NT	NT
2C-B	0.478	99.7	20	73.29	1.14 ^a	89.38	NT	NT
2C-E	0.7471	105	29.73	66.22	1.818 ^a	89.464	NT	NT
DOPR	0.12	102.9	13.74	94.5	0.271 ^a	94.4	16	80
DOAM	1.953	100.2	42.02	20	3.75 ^a	90.1	200	36
4C-PENT	36.62	71.5	NS	0.2	1,821.89 ^a	115	ND	1.6
4C-HEX	38.87	71.09	>10,000	34.2	3,341.33 ^a	77.92	ND	-4.9
2C-TFM	1.05	81.5	16.26	82	0.59 ^a	88.2	NT	NT
1	598.2	36.02	>10,000	0.82	2,892.551 ^a	104.57	NT	NT
2	9.057	85.36	19.21	88.66	NT	NT	NT	NT
3E1	5.012	90.23	894.8	24.24	NT	NT	NT	NT
3E2	9.27	93.6	927.1	13.84	NT	NT	NT	NT
4E1	99.53	47.63	>10,000	0.62	NT	NT	NT	NT
4E2	102.4	66.53	>10,000	0.77	NT	NT	NT	NT
5E1	74.44	64.95	1,367	35.8	NT	NT	NT	NT
5E2	40.04	77.51	315.5	22.13	NT	NT	NT	NT
6E1	11.1	75.26	312.1	61.95	NT	NT	NT	NT
6E2	25.4	93.72	163.6	19.56	NT	NT	NT	NT
7E1	1.18	90.96	218	26.92	NT	NT	NT	NT
7E2	0.58	89.44	27.51	14.52	NT	NT	NT	NT
9	14.7	91.34	205.8	12.9	NT	NT	NT	NT
9E1	22.32	96.6	>10000	7.96	NT	NT	NT	NT
9E2	28.02	103.96	>10000	14.49	NT	NT	NT	NT
10E1	1.57	86.43	153	57.13	NT	NT	NT	NT

10E2	1.65	92.62	31.2	3.709	NT	NT	NT	NT
11E1	89.83	54.93	1,277	25.38	NT	NT	NT	NT
11E2	92.48	70.06	763	32.91	NT	NT	NT	NT
12	4.515	102	8.119	84.51	NT	NT	NT	NT
13	117	56.81	340.2	60.14	NT	NT	NT	NT
14	7.152	93.12	NT	NT	NT	NT	NT	NT
17	4.832	95.87	6.774	116	NT	NT	NT	NT
19	90.79	44.4	NT	NT	NT	NT	NT	NT
21	2.472	94.67	273.15	32.14	NT	NT	NT	NT
26	5.702	92.63	140.3	47.33	NT	NT	NT	NT
1AE1	17.59	60.66	786.6	30.53	NT	NT	NT	NT
1AE2	34.12	69.98	>10,000	0.17	>10000 ^b	0.55	NC	2.80
1B	2.96	95.05	>10,000	8.68	NT	NT	NT	NT
3DE1	8.044	99.59	756.3	43.47	54.73 ^b	88.81	1,268	76
3DE2	13.03	92.76	>10,000	0.71	49.42 ^b	81.49	NC	11.4
15E1	3.149	88.72	NT	NT	NT	NT	NT	NT
15E2	6.575	93.09	NT	NT	NT	NT	NT	NT
20	4.852	75.75	10.85	91.5	NT	NT	NT	NT
24E1	3.271	92.74	63.64	94.42	NT	NT	NT	NT
24E2	8.332	88.61	15.03	92.46	NT	NT	NT	NT
28	5.516	93.69	207	25.5	NT	NT	NT	NT
28E1	5.182	81.13	1231	28.47	NT	NT	NT	NT
28E2	7.308	81.69	347.7	17.82	NT	NT	NT	NT
30E1	13.2	64.59	948.8	35	NT	NT	NT	NT
30E2	9.82	67.05	>10000	2.36	448.1 ^b	83.86	NC	25
31E1	72.95	32.55	1129	68.49	NT	NT	NT	NT
31E2	99.56	42.65	516.8	66.66	NT	NT	NT	NT
32E1	41.48	42.55	>10000	30.98	NT	NT	NT	NT
32E2	42.92	50.68	>10000	1.75	NT	NT	NT	NT
2AE1	21.25	61.39	726.5	32.49	NT	NT	NT	NT
2AE2	61.45	66.07	>10000	1.26	NT	NT	NT	NT
3AE1	NT	NT	1306	55.12	NT	NT	NT	NT
3AE2	NT	NT	1419	12.67	NT	NT	NT	NT

4A	3.976	102.61	65.58	71.14	NT	NT	NT	NT
4AE1	1.603	95.26	39.52	80.67	NT	NT	NT	NT
6AE1	15.63	41.13	538.4	54.69	NT	NT	NT	NT
6AE2	68.34	45.52	1975	16.73	NT	NT	NT	NT
8AE1	202.8	28.07	>10000	9.13	NT	NT	NT	NT
8AE2	99.9	42.99	>10000	-1.4	NT	NT	NT	NT
2BE1	29.57	75.32	>10000	3.17	NT	NT	NT	NT
2BE2	66.71	85.49	>10000	0.41	NT	NT	NT	NT
3BE1	99.41	79.47	473.7	43.66	NT	NT	NT	NT
3BE2	31.08	74.35	473.7	43.66	NT	NT	NT	NT
6CE1	18.6	64.82	>10000	20.02	660.6 ^b	47.52	NC	31.6
6CE2	28.66	59.45	>10000	2.25	746.3 ^b	25.65	NC	8.4

NT = not tested; ND = not determined due to lack of measurable agonism, NC = not calculated due to insufficient data and/or lack of measurable agonism, ^a Eurofins 5-HT_{2C} assay, ^b WuXi 5-HT_{2C} assay.

Example 58: Effects on the Head Twitch Response (HTR) in Mice

Disclosed compounds were tested for their ability to induce a head twitch response (HTR) in mice, with the results summarized in **Table 5**. Disclosed compounds varied in the maximal magnitude of HTR that they induced, suggesting a range of potential hallucinogenic effects or lack thereof in humans.

Animals. Adult male C57BL/6 mice, aged 8 weeks (body weight 20-25g) were used in these experiments. Animals were housed under controlled temperatures and 12-hour light/dark cycles (lights on between 07:00–19:00 h), with *ad libitum* food and water. The protocol was approved by relevant Institutional Animal Care and Use Committee. This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. All efforts were made to minimize suffering.

Drugs and Drug Administration. Disclosed compounds were prepared as described above. All other compounds were commercially obtained or prepared according to literature procedures.

Test compounds were used as their hydrochloride salts and were dissolved in a vehicle consisting of normal saline and administered subcutaneously (SC) in a volume of 10 mL/kg. Test compounds were administered at 5 doses per compound (calculated based on the free base) using N = 8 animals/group.

Procedure. Mice were administered one dose of a test drug (or vehicle) SC and immediately placed into a small open field for behavioral observation. Animals were video recorded continuously for 20 mins and the number of HTRs were automatically detected and counted using DeepLabCut.

Statistical analysis. The data points shown in **Table 5** are the mean $\pm$ standard error of the mean (SEM).

Table 5. HTR of compounds in mice.

Compound	Dose (mg/kg)	Average Total HTR Over 20-min Test (SEM)
DOI	0.1	18.8 (1.6)
DOI	0.32	34.2 (3.4)
DOI	1	62.6 (3.8)
DOI	3.2	89.3 (4.2)
DOI	10	92.6 (5.1)
DOI	32	37.5 (3.8)
DOPR	0.1	19.0 (1.2)
DOPR	0.32	36.2 (5.2)
DOPR	1	69.2 (7.5)
DOPR	3.2	80.2 (9.0)
DOPR	10	44.6 (6.7)

DOAM	0.32	7.1 (1.7)
DOAM	1	7.5 (0.9)
DOAM	3.2	10.5 (1.3)
DOAM	10	16.8 (1.6)
DOAM	32	33.6 (2.6)
DOAM	64	29.1 (6.0)
3DE1	0.32	15.625 (4.0)
3DE1	1	10.583 (0.8)
3DE1	3.2	23.125 (1.4)
3DE1	10	47.125 (3.0)
3DE1	32	34.14 (4.9)
3DE2	0.32	10.625 (2.1)
3DE2	1	29.25 (2.3)
3DE2	3.2	23.375 (2.1)
3DE2	10	30.375 (2.3)
3DE2	32	20.375 (3.7)
1AE2	0.1	5.0 (1.9)
1AE2	0.32	2.0 (0.6)
1AE2	1	4.2 (1.3)
1AE2	3.2	7.0 (1.5)
1AE2	10	16.2 (1.5)
1AE2	32	8.0 (1.8)
7E1	0.1	5.0 (0.7)
7E1	0.32	5.0 (1.8)

7E1	1	9.2 (0.8)
7E1	3.2	19.0 (2.0)
7E1	10	36.2 (1.9)
7E1	32	19.5 (4.3)
7E2	0.1	3.2 (0.5)
7E2	0.32	8.5 (0.6)
7E2	1	9.5 (2.4)
7E2	3.2	28.0 (5.0)
7E2	10	50.5 (6.4)
7E2	32	10.5 (1.7)
21	0.1	6.2 (1.4)
21	0.32	5.2 (0.9)
21	1	8.8 (0.8)
21	3.2	21.8 (1.4)
21	10	19.7 (4.2)
21	32	27.0 (2.4)
9	0.1	4.8 (1.1)
9	0.32	4.8 (0.2)
9	1	9.8 (3.2)
9	3.2	9.2 (2.2)
9	10	8.2 (0.8)
9	32	7.2 (1.3)
30E2	0.1	7.2 (1.8)
30E2	0.32	7.2 (2.3)

30E2	1	10.2 (1.1)
30E2	3.2	23.0 (0.6)
30E2	10	24.5 (3.2)
6CE2	0.1	3.3 (0.6)
6CE2	0.32	9.2 (0.9)
6CE2	1	12.4 (0.8)
6CE2	3.2	21.9 (1.0)
6CE2	10	27.2 (1.7)
6CE2	32	18.4 (1.7)

Example 59: Metabolic Stability in Rat Liver Microsomes

Disclosed compounds were tested for stability in rat liver microsomes (RLM), with the results summarized in **Table 6**. Microsomal stability varied widely across tested compounds, suggesting a range of oral bioavailability and half-life depending on the specific compound.

Test Compounds. Disclosed compounds were prepared as described above. All other compounds were commercially obtained or prepared according to literature procedures.

RLM Stability. Pooled RLM from male Sprague-Dawley rats (Xenotech R1000) were used. Microsomal incubations were carried out in multi-well plates. Liver microsomal incubation medium consisted of PBS (100 mM, pH 7.4), MgCl₂ (1 mM), and NADPH (1 mM), with 0.50 mg of liver microsomal protein per mL. Control incubations were performed by replacing the NADPH-cofactor system with PBS. Test compounds (1 μM, final solvent concentration 1.0%) were incubated with microsomes at 37 °C with constant shaking. Six time points over 60 minutes were analyzed, with 60 μL aliquots of the reaction mixture being drawn at each time point. The reaction aliquots were stopped by adding 180 μL of cold (4 °C) acetonitrile containing 200 ng/mL tolbutamide and 200 ng/mL labetalol as internal standards (IS), followed by shaking for 10 minutes, and then protein sedimentation by centrifugation at 4,000 rpm for 20 minutes at

4 °C. Supernatant samples (80 µL) were diluted with water (240 µL) and analyzed for parent compound remaining using a fit-for-purpose liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Data Analysis. The elimination constant (k_{el}), half-life ($t_{1/2}$), and intrinsic clearance (CL_{int}) were determined in a plot of $\ln(AUC)$ versus time, using linear regression analysis.

Table 6. Intrinsic clearance (CL_{int}) and half-life ($t_{1/2}$) of compounds in the presence of RLM.

Compound	CL_{int} (µL/min/mg)	$t_{1/2}$ (min)
1	175.7	7.9
2	1419	1
3E1	691	2
3E2	679	2
4E1	1946.6	0.7
4E2	705.8	2.0
5E1	1524.1	0.9
5E2	2251.8	0.6
6E1	222.3	6.2
6E2	626.0	2.2
7E1	204.1	6.8
7E2	631.5	2.2
9	62.3	22.2
9E1	128.4	10.8
9E2	395.7	3.5

10E1	103.9	13.3
10E2	426.6	3.2
11E1	1573.7	0.9
11E2	1985.9	0.7
12	17.2	80.5
13	31.1	44.5
14	<9.6	>145
17	<9.6	>145
21	357.3	3.9
1AE1	891.9	1.6
1AE2	1932.8	0.7
1B	107.4	12.9
3DE1	698	2
3DE2	1481.2	0.9
20	523.8	2.6
24E1	768.2	1.8
24E2	1743.3	0.8
26	67.5	20.5
28	205.2	6.8
28E1	409.4	3.4
28E2	447.5	3.1
30E1	1478.4	0.9

30E2	2081.2	0.7
31E1	<9.6	>145
31E2	<9.6	>145
32E1	206.6	6.7
32E2	164.3	8.4
2AE1	127.8	10.8
2AE2	304.4	4.6
4A	400.5	3.5
6AE1	67.6	20.5
6AE2	120.3	11.5
8AE1	759.1	1.8
8AE2	1832.6	0.8
2BE1	1717.6	0.8
2BE2	2026.9	0.7
3BE1	839.8	1.7
3BE2	437.3	3.2
4CE1	125.1	11.1
4CE2	238.4	5.8
6CE1	55.8	24.9
6CE2	54.7	25.3
2DE1	748.6	1.9
2DE2	1737.7	0.8

Example 60: Activity in Chronic Mild Stress Assay

A chronic mild stress (CMS) study was carried out in male Wistar-Kyoto rats (Charles River, Sulzfeld, Germany) following the protocol described in articles by Papp in Eur. J. Pharmacol., 1996, 1996; Papp in Curr. Protoc. Pharmacol., 2012, 57; Wilner et al. in Neurosci Biobehav Rev. 1992, 16, 525-534; Papp et al. in J Psychopharmacol, 2020, 34, 1418-1430; and Papp et al. Curr Protoc. 2023, 3, the contents for conducting this protocol being incorporated herein by reference. Briefly, the CMS paradigm began after establishing baseline sucrose intake in Week 0. In week 1 and 2, subjection of animals to CMS was started and sucrose intake was measured to determine the onset of anhedonia. Dosing was initiated on Monday of the following week and continued once weekly until full reversal of the effects of CMS was achieved. During the dosing phase, exposure to CMS was continued. After that, CMS continued but rats were not dosed. For each treatment group, n=8 rats were exposed to CMS stressors, and n=8 rats were unstressed controls.

Figure 1 shows the effects of compound 3DE2 (0.1-3.2 mg/kg, SC) and (*rac*)-ketamine (10 mg/kg, IP) on sucrose intake. Weeks 1 and 2 show the effect of CMS on sucrose intake prior to the initiation of drug treatment; the lower level of sucrose intake in rats exposed to CMS ('Str') compared to control ('Ctrl') rats demonstrates the extent of anhedonia. Stressed rats dosed once weekly with vehicle maintained lower levels of sucrose intake compared to unstressed control rats dosed with vehicle once weekly for the duration of the study. Administration of compound 3DE2 (0.1 or 1 mg/kg) 24 h prior to testing in Week 3 did not increase sucrose intake. The positive control (*rac*)-ketamine (10 mg/kg), increased sucrose intake to almost the same level as control (unstressed) rats dosed with vehicle. In Week 4, the doses of compound 3DE2 were increased to 1 and 3.2 mg/kg. While the lower dose showed only a minor effect, compound 3DE2 at 3.2 mg/kg increased sucrose intake to the level of unstressed vehicle treated rats, indicating full efficacy. In Weeks 5 and 6 compound 3DE2 was not re-dosed, so the effect on sucrose intake reflects residual efficacy from prior doses. The effect of ketamine was maintained with once weekly dosing through the end of the study.

After the effects of compound 3DE2 had washed out and sucrose intake had decreased, the effects of compound 1AE2 (0.1 and 0.32 mg/kg, SC) were evaluated in Weeks 7 and 8

(Figure 2). The lower dose of compound 1AE2 (0.1 mg/kg) did not increase sucrose intake, while the higher dose of compound 1AE2 (0.32 mg/kg) increased sucrose intake to the same level as unstressed control rats dosed with vehicle. In Week 8, rats were dosed again and this second administration of compound 1AE2 (0.1 mg/kg) resulted in full reversal of the effect of CMS, with sucrose intake being the same as unstressed controls dosed with vehicle. Sucrose intake in rats dosed with compound 1AE2 (0.32 mg/kg) in Week 8 was higher, and similar to rats that had received 6 weekly doses of ketamine (10 mg/kg). In Weeks 9 and 10, CMS continued and ketamine treatment continued; however, rats were not dosed with compound 1AE2. Rats previously dosed with compound 1AE2 (0.32 mg/kg) showed only partial residual efficacy in Week 9, which returned to the level of vehicle treated CMS rats by Week 10.

In a separate CMS study, the effects of compound 6CE2 and compound 30E2 were evaluated. Figure 3 shows the effects of once weekly dosing with compound 6CE2 (0.1-1 mg/kg, SC) and (*rac*)-ketamine (10 mg/kg, IP) on sucrose intake. Weeks 1 through 3 show the effect of CMS on sucrose intake prior to the initiation of drug treatment; the lower level of sucrose intake in rats exposed to CMS ('Str') compared to control ('Ctrl') rats demonstrates the extent of anhedonia. Stressed rats dosed once weekly with vehicle maintained lower levels of sucrose intake compared to unstressed control rats dosed with vehicle once weekly for the duration of the study. Administration of the lower dose of compound 6CE2 (0.1 mg/kg) 24 h prior to testing in Week 4 did not increase sucrose intake whereas the higher dose of compound 6CE2 (0.32 mg/kg) was partially effective. The positive control (*rac*)-ketamine (10 mg/kg), increased sucrose intake to the same level as control (unstressed) rats dosed with vehicle. In Week 5 the lower dose of compound 6CE2 was increased to 1 mg/kg, while the higher dose of 0.32 mg/kg was continued for a second week. Both dose groups showed a partial increase in sucrose intake. In Week 6, administration of compound 6CE2 at either 0.32 or 1 mg/kg resulted in sucrose intake equivalent to unstressed control rats dosed with vehicle. In Week 7, CMS continued, but rats were not dosed with compound 6CE2. Residual efficacy of compound 6CE2 was evident in both groups last dosed in Week 6. The effect of ketamine was maintained with once weekly dosing through the end of the study.

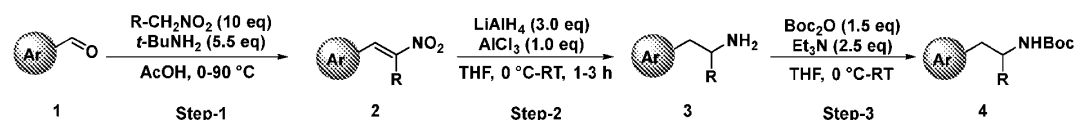
In a different groups of rats within the same study, after re-establishing a stable level of sucrose intake in Weeks 7 and 8, rats were dosed in Week 9 with compound 30E2 (0.32 mg/kg,

SC) and sucrose intake was assessed (Figure 4). Compound 30E2 produced a partial reversal of the effect of CMS, with sucrose intake being intermediate between vehicle-treated CMS rats and vehicle-treated unstressed control rats. When this dose level of compound 30E2 (0.32 mg/kg) was administered again in Week 10, sucrose intake was increased slightly. In Week 11, when the dose was increased to 1 mg/kg, the level of sucrose intake was slightly higher than unstressed control rats dosed with vehicle, indicating full efficacy.

Example 61: General Synthetic Procedures

General procedure A: Preparation of tert-butyl (1-arylpropan-2-yl)carbamate and tert-butyl (1-arylbutan-2-yl)carbamate

Synthetic Scheme:



Step 1:

Preparation of nitrostyrene derivative (2)

To a stirred solution of aldehyde (1 eq) in acetic acid (10 vol) was added nitroethane/nitropropane (10 eq) followed by 2-methylpropan-2-amine (5.5 eq) at 0 °C. Then reaction mixture was warmed to 85 °C and stirred for 2-6 h until starting material is fully consumed. The progress of reaction was monitored by TLC. Upon completion, the reaction mixture was poured into ice-cold water (5 vol), the precipitate that formed was filtered, washed with chilled water (1 vol x 3), and dried under reduced pressure to afford the desired nitrostyrene derivative. Note: the symbol “Ar” denotes an aryl group.

Step 2:

Preparation of 1-arylpropan-2-amine or 1-arylbutan-2-amine (3)

To a stirred solution of LAH solution (2.0 M in THF; 3 eq) in anhydrous THF (3 vol) was added AlCl_3 (1.0 eq) portion wise at 0 °C under argon atmosphere. When H_2SO_4 is used in place of

AlCl₃, the ratio of LAH/H₂SO₄ is 2:1 instead of 3:1. The reaction mixture was stirred at 0 °C for 30 min and nitroalkene (1.0 eq) in THF (10 vol) was added dropwise over a period of 10 min at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 1-3 h. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was allowed to cool to 0 °C and was added THF/water (1:1, 14 mL) at same temperature, until effervescence stopped. The reaction mixture was then diluted with THF (10 vol) and stirred at room temperature for 30 minutes under N₂ atmosphere. The reaction mixture was filtered through a Celite pad and washed with THF (30 vol), combined organic fractions were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude product, which was used directly for the next step.

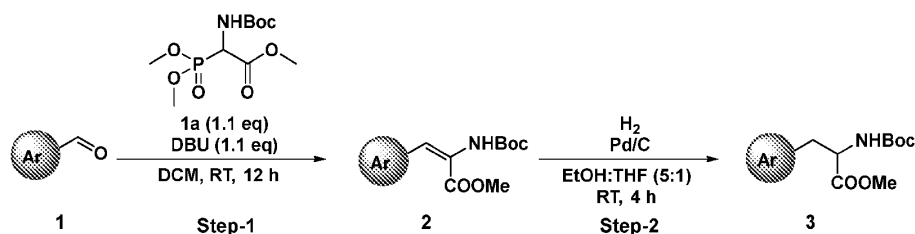
Step 3:

Preparation of tert-butyl (1-arylpropan-2-yl)carbamate and tert-butyl (1-arylbutan-2-yl)carbamate (4)

To a stirred solution of crude 1-arylpropan-2-amine or 1-arylbutan-2-amine (1 eq) in THF (1 vol), triethylamine (2.5 eq) followed by di-*tert*-butyl dicarbonate (1.5 eq) was added at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with cold water (3 vol) and extracted with ethyl acetate (5 vol x 2). The combined organic extracts were washed with brine (3 vol), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by silica flash column chromatography (eluting with ethyl acetate in heptanes) to afford *tert*-butyl (1-arylpropan-2-yl)carbamate or *tert*-butyl (1-arylbutan-2-yl)carbamate.

General procedure B: *Preparation of methyl (tert-butoxycarbonyl)arylalaninate*

Synthetic Scheme:

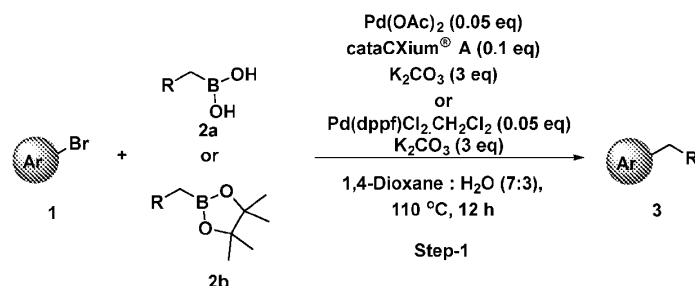
**Step 1:*****Preparation of methyl (E)-2-((tert-butoxycarbonyl)amino)-3-arylacrylate***

To a stirred solution of aldehyde (1 eq) in DCM (10 vol), DBU (1.1 eq) was added at 0 °C. Then reaction mixture was allowed to stir at 0 °C for 10 min. Then, methyl [(tert-butyl)(oxycarbonylamino)](dimethoxyphosphoryl)acetate (1.1 eq) was added to the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred for 12 h. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was diluted with water (3 vol) and extracted with ethyl acetate (4 vol x 2). The combined organic extracts were washed with brine (2 vol), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get crude compound. This crude material was purified by silica flash column chromatography (eluting with ethyl acetate in heptanes) to afford methyl (E)-2-((tert-butoxycarbonyl)amino)-3-arylacrylate.

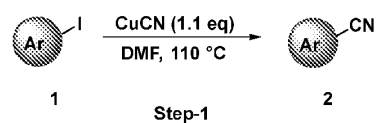
Step 2:***Preparation of methyl (tert-butoxycarbonyl)arylalaninate***

To a stirred solution of methyl (E)-2-((tert-butoxycarbonyl)amino)-3-arylacrylate (1 vol) in EtOH/THF (5:1, 10 vol) was added 10% Pd/C (3 eq) at room temperature. The reaction mixture was allow to stir under hydrogen at room temperature for 4 h. The progress of reaction was monitored by TLC & LC-MS. After completion, the reaction mixture was filtered through Celite pad. The filtrate was extracted with ethyl acetate (3 vol) and water (1 vol). Collected organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford crude compound. Crude compound was directly used for next step.

General procedure C: Suzuki coupling of aryl bromides with n-alkylboronic acid/n-alkylboronates

Synthetic Scheme:

To a stirred solution of aryl bromide (1 eq) in 1,4-dioxane/water (7:3, 3 vol) was added potassium carbonate (3 eq) and *n*-alkylboronic acid/ *n*-alkylboronate ester (2-4 eq) followed by 1-[1-adamantyl(butyl)phosphino]adamantane (0.1 eq) /palladium bis(acetate) (0.05 eq) or Pd(dppf)Cl₂·CH₂Cl₂ (0.05 eq) under argon at room temperature. The reaction mixture was purged with argon for 10 min, then heated at 100 °C for 12 h. The progress of the reaction was monitored by LC-MS and TLC. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was extracted with ethyl acetate (3 vol) and water (1 vol). The combined organic layers were washed with brine (2 vol), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to get the crude compound. This crude material was purified by silica flash chromatography (eluting with ethyl acetate in heptanes) to afford desired coupled product.

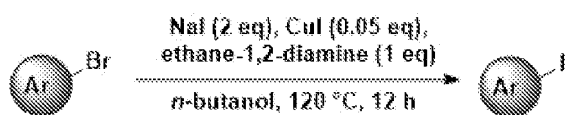
General procedure D: Cynation of aryl iodide**Synthetic Scheme:**

To a stirred solution of aryl iodide (1 eq) in dry DMF (7 vol) was added CuCN (1.1 eq) at room temperature. Then, the reaction mixture was stirred at 110 °C for 12 h. The progress of reaction was monitored by LC-MS and TLC. Upon completion, the reaction mixture was allowed to cool

to room temperature and diluted with chilled water (10 vol) and extracted with ethyl acetate (2x20 vol). The combined organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to get crude compound. This crude material was purified either by flash column chromatography (eluting with ethyl acetate in heptane) to afford desired aryl nitrile.

General procedure E: Trifluoromethylation of aryl iodide

Synthetic Scheme:

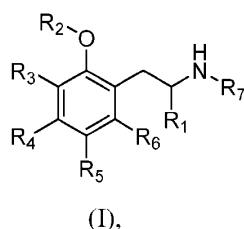


To a stirred solution of aryl iodide (1.0 eq) in dry DMF (10 vol) was added CuI (0.15 eq) followed by methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (3.0 eq) at room temperature. Then the mixture was stirred at 80 °C for 12 h. Progress of the reaction was monitored by LC-MS. Upon completion, the reaction mixture was allowed to cool to room temperature and then extracted with ethyl acetate (3 vol x 2) and water (1 vol). The organic extracts were dried over sodium sulfate, filtered and concentrated under reduced pressure to get the crude compound. This crude material was purified either by flash column chromatography or prep HPLC to afford the desired aryl-CF₃.

While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

R₁ is H, methyl, ethyl, -CH₂-OH, -CH₂-O-(methyl), -CH₂F, or -CH₂CH₂F;

R₂ is H, C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R₃ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₆ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₄ is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF₃, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, or

R₄ is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), NO₂, or SF₅, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R₄ is not isopropyl;

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S(O)(O)-(C1-C5 alkyl), NH₂, NH(C1-C5 alkyl), or N(C1-C5 alkyl)₂, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, or

R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl is optionally substituted with one or more F;

with the provisos that when R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S(O)(O)-(C1-C5 alkyl), NH₂, NH(C1-C5 alkyl), or N(C1-C5 alkyl)₂, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, then R₄ is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF₃, NO₂, or SF₅, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, or

when R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl is optionally substituted with one or more F, then R₄ is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), NO₂, or SF₅, wherein alkyl, alkenyl, and alkynyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more F, C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R₄ is not isopropyl;

R₇ is H, -CH₂-(aryl), or -CH₂-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the further provisos that:

- (a) when R₂ is methyl, R₃ is methyl, R₄ is Cl or Br, R₅ is methyl, R₆ is H, and R₇ is H, then R₁ is not H or methyl;
- (b) when R₁ is H or methyl, R₂ is H or methyl, R₃ is H, R₅ is methyl, R₆ is H, and R₇ is H, then R₄ is not Cl;
- (c) when R₁ is H, R₂ is methyl, R₃ is H, R₅ is CF₃, R₆ is H, and R₇ is ortho-methoxybenzyl, then R₄ is not Br;
- (d) when R₁ is H, R₂ is H, R₃ is H, R₅ is Cl, R₆ is H, and R₇ is H or benzyl, then R₄ is not cyclohexyl; and
- (e) when R₁ is methyl, R₂ is H, R₃ is H, R₅ is NH₂, R₆ is H, and R₇ is H, then R₄ is not Cl.

2. The compound of claim 1, wherein:

R₂ is H, C1-C3 alkyl, cyclopropyl, C3 alkenyl, or C3 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F;

R₃ is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R₆ is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F,

and then R₄ is C2-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), Cl, Br, I, CF₃, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

or R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl is optionally substituted with one or more F,

and then R₄ is C2 alkyl substituted with one or more F, C3-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), NO₂,

or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl, and wherein R₄ is not isopropyl;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

3. The compound of claim 1, wherein:

R₂ is H, methyl, or ethyl, wherein methyl and ethyl are optionally substituted with one or more F;

R₃ is H or F;

R₆ is H or F;

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, or -S(O)(O)-(C1-C5 alkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F,

and then R₄ is C2-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF₃, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

or R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), CN, or NO₂, wherein alkyl is optionally substituted with one or more F,

and then R₄ is C2 alkyl substituted with one or more F, C3-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6

alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R₄ is not isopropyl;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

4. The compound of any one of claims 1-3, wherein R₂ is methyl.

5. The compound of any one of claims 1-4, wherein R₃ and R₆ are both H.

6. The compound of any one of claims 1-5, wherein:

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, or C3-C5 cycloalkyl, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F,

and then R₄ is C2-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF₃, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

or R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), or CN, wherein alkyl is optionally substituted with one or more F,

and then R₄ is C2 alkyl substituted with one or more F, C3-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), NO₂,

or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R₄ is not isopropyl.

7. The compound of any one of claims 1-5, wherein:

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, or C3-C5 cycloalkyl, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F,

and then R₄ is C2-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, CF₃, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

or R₅ is F, Cl, Br, I, -S-(C1-C5 alkyl), or CN, wherein alkyl is optionally substituted with one or more F,

and then R₄ is C2 alkyl substituted with one or more F, C3-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl, and wherein R₄ is not isopropyl.

8. The compound of any one of claims 1-7, wherein R₇ is H.

9. The compound of any one of claims 1-7, wherein R₇ is -CH₂-(6-membered aryl) or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which

they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

10. The compound of any one of claims 1-7, wherein R_7 is $-\text{CH}_2-(6\text{-membered aryl})$ or $-\text{CH}_2-(6\text{-membered heteroaryl})$, wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, $-\text{O}-(\text{C1-C3 alkyl})$, and $-\text{O}-(\text{cyclopropyl})$, wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

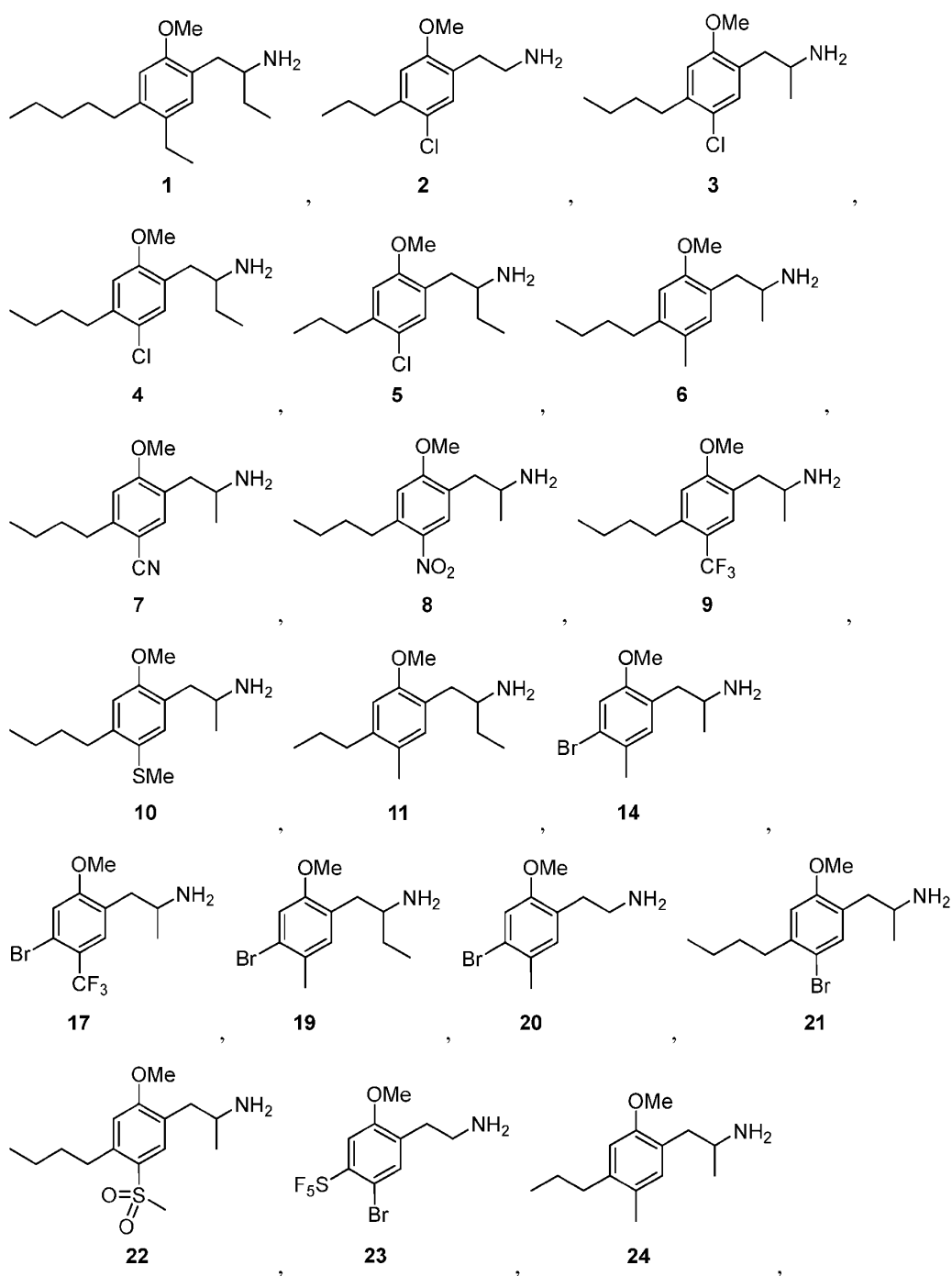
11. The compound of any one of claims 1-7, wherein R_7 is $-\text{CH}_2-(6\text{-membered aryl})$ or $-\text{CH}_2-(6\text{-membered heteroaryl})$, wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and $-\text{O}-(\text{methyl})$, wherein methyl is optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring.

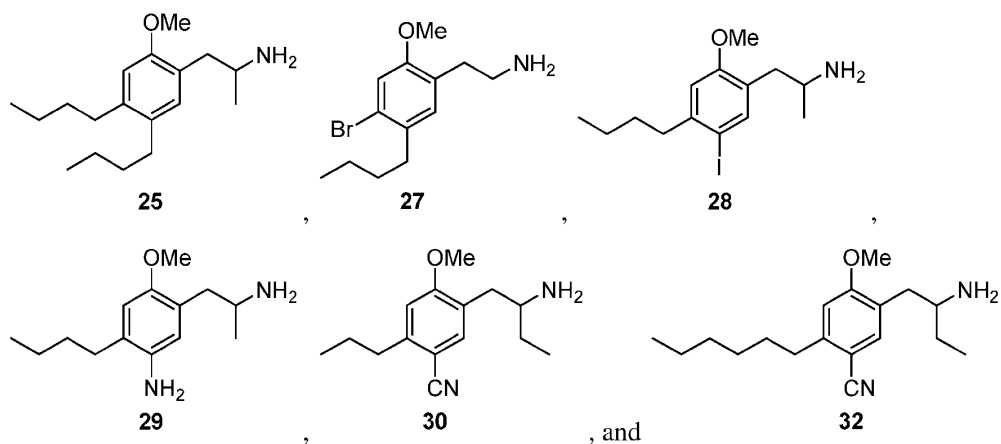
12. The compound of any one of claims 1-7, wherein R_7 is $-\text{CH}_2-(6\text{-membered aryl})$, wherein aryl is optionally substituted at the ortho position with one F, OH, or $-\text{O}-(\text{methyl})$, or with a methylenedioxy ring linking the ortho and meta positions.

13. The compound of any one of claims 1-12, wherein R_1 is H or methyl.

14. The compound of any one of claims 1-12, wherein R_1 is ethyl, $-\text{CH}_2\text{-OH}$, or $-\text{CH}_2\text{-O}-(\text{methyl})$.

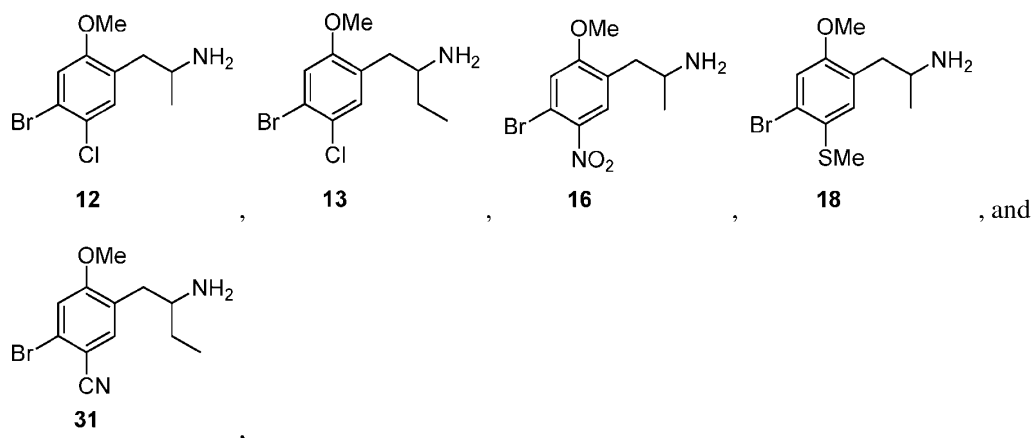
15. The compound of claim 1, selected from the group consisting of:





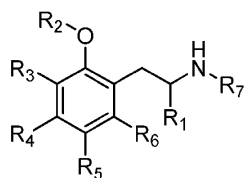
or a pharmaceutically acceptable salt thereof.

16. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

17. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R₁ is -CH₂-OH, -CH₂-O-(methyl), -CH₂F, or -CH₂CH₂F;

R₂ is C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R₃ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₄ is C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₅ is -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl)-(C3-C5 cycloalkyl), CF₃, CN, Br, or I, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₆ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₇ is H, -CH₂-(aryl), or -CH₂-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the provisos that:

- (a) when R₁ is -CH₂-OH, R₂ is methyl, R₃ is H, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl, -S-(methyl), or n-butyl;

- (b) when R₁ is -CH₂-OH, R₂ is methyl, R₃ is methyl, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl;
- (c) when R₁ is -CH₂CH₂F, R₂ is methyl, R₃ is H, R₅ is -O-(methyl), R₆ is H, and R₇ is H, then R₄ is not methyl; and
- (d) when R₁ is -CH₂-OH, R₂ is methyl, R₃ is methyl, R₅ is Br, R₆ is methyl, and R₇ is H, then R₄ is not methyl.

18. The compound of claim 17, wherein:

R₂ is C1-C3 alkyl, cyclopropyl, C3 alkenyl, or C3 alkynyl, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F;

R₃ is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R₅ is -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -O-(C1-C3 alkyl)-(cyclopropyl), CF₃, or CN, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein cyclopropyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R₆ is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

19. The compound of claim 17, wherein:

R₂ is methyl or ethyl, wherein methyl and ethyl are optionally substituted with one or more F;

R₃ is H or F;

R₄ is C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R₅ is -O-(methyl), -O-(ethyl), or CN, wherein methyl and ethyl are optionally substituted with one or more F;

R₆ is H or F;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

20. The compound of any one of claims 17-19, wherein R₂ is methyl and R₅ is -O-(methyl).

21. The compound of any one of claims 17-20, wherein R₃ and R₆ are both H.

22. The compound of any one of claims 17-21, wherein R₄ is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl.

23. The compound of any one of claims 17-21, wherein R_4 is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, or SF_5 , wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and wherein cycloalkyl is optionally substituted with one to three C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl.
24. The compound of any one of claims 17-23, wherein R_7 is H.
25. The compound of any one of claims 17-23, wherein R_7 is $-CH_2$ -(6-membered aryl) or $-CH_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2 , NO_2 , C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.
26. The compound of any one of claims 17-23, wherein R_7 is $-CH_2$ -(6-membered aryl) or $-CH_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), and -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.
27. The compound of any one of claims 17-23, wherein R_7 is $-CH_2$ -(6-membered aryl) or $-CH_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any

two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring.

28. The compound of any one of claims 17-23, wherein R_7 is $-\text{CH}_2-(6\text{-membered aryl})$, wherein aryl is optionally substituted at the ortho position with one F, OH, or $-\text{O}-(\text{methyl})$, or with a methylenedioxy ring linking the ortho and meta positions.

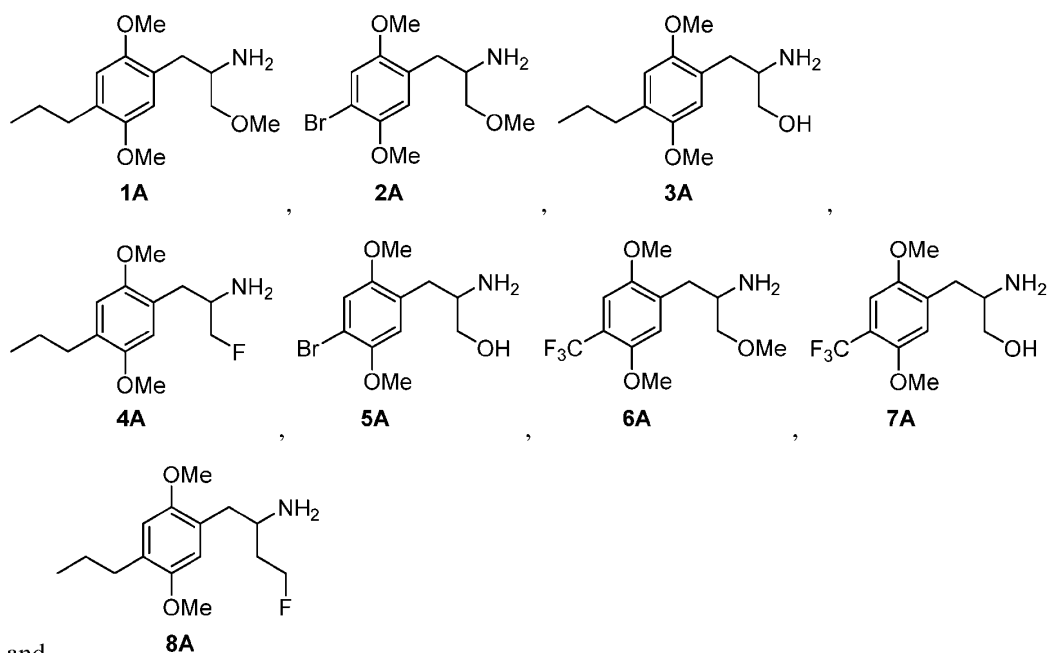
29. The compound of any one of claims 17-28, wherein R_1 is $-\text{CH}_2\text{-OH}$.

30. The compound of any one of claims 17-28, wherein R_1 is $-\text{CH}_2\text{-O}-(\text{methyl})$.

31. The compound of any one of claims 17-28, wherein R_1 is $-\text{CH}_2\text{F}$.

32. The compound of any one of claims 17-28, wherein R_1 is $-\text{CH}_2\text{CH}_2\text{F}$.

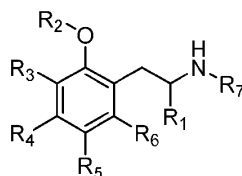
33. The compound of claim 17, selected from the group consisting of:



and

or a pharmaceutically acceptable salt thereof.

34. A compound of Formula (I)



(I),

or a pharmaceutically acceptable salt thereof,

wherein:

R₁ is H, methyl, ethyl, n-propyl, -CH₂-OH, -CH₂-O-(methyl), -CH₂F, or -CH₂CH₂F;

R₂ is C1-C5 alkyl, C3-C5 cycloalkyl, C3-C5 alkenyl, or C3-C5 alkynyl,

wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F;

R₃ is H, C1-C3 alkyl, cyclopropyl, or F, wherein alkyl and cyclopropyl are optionally substituted with one or more F;

R₄ is C1-C8 alkyl, C2-C8 alkenyl, C2-C8 alkynyl, C3-C8 cycloalkyl, -(C1-C5 alkyl)-(C3-C6 cycloalkyl), -S-(C1-C8 alkyl), -S-(C3-C8 alkenyl), -S-(C3-C8 alkynyl), -S-(C3-C8 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C6 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₅ is C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl)-(C3-C5 cycloalkyl), -S(O)(O)-(C1-C5 alkyl), -S(O)(O)-(C3-C5 alkenyl), -S(O)(O)-(C3-C5 alkynyl), -S(O)(O)-(C3-C5 cycloalkyl), -S(O)(O)-(C1-C5 alkyl)-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -O-(C1-C5 alkyl)-(C3-C5 cycloalkyl), NH₂, NH(C1-C5 alkyl), or N(C1-C5 alkyl)₂, F, Cl, Br, I, CN, or NO₂, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C5 alkyl, C2-C5 alkenyl, or C2-C5 alkynyl;

R₆ is F;

R₇ is H, -CH₂-(aryl), or -CH₂-(heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C5 alkyl, C2-C5 alkenyl, C2-C5 alkynyl, C3-C5 cycloalkyl, -O-(C1-C5 alkyl), -O-(C3-C5 alkenyl), -O-(C3-C5 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C5 alkyl), -S-(C3-C5 alkenyl), -S-(C3-C5 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 4-6-membered ring optionally interrupted by 1-3 heteroatoms selected from O, N, and S;

with the proviso that when R₁ is H, R₂ is methyl, R₃ is H, R₄ is F, and R₇ is H, then R₅ is not Cl or Br.

35. The compound of claim 34, wherein:

R₂ is C1-C3 alkyl, cyclopropyl, C3 alkenyl, or C3 alkynyl, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F;

R₃ is H, methyl, ethyl, or F, wherein methyl and ethyl are optionally substituted with one or more F;

R₅ is -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -O-(C1-C3 alkyl)-(cyclopropyl), or CN, wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein cyclopropyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, C3-C5 cycloalkyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(C3-C5 cycloalkyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(C3-C5 cycloalkyl), wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

36. The compound of claim 34, wherein:

R₂ is methyl or ethyl, wherein methyl and ethyl are optionally substituted with one or more F;

R₃ is H or F;

R₄ is C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C6 cycloalkyl, -(C1-C3 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C6 alkyl), -S-(C3-C6 alkenyl), -S-(C3-C6 alkynyl), -S-(C3-C6 cycloalkyl), -S-(C1-C3 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl;

R₅ is -O-(methyl), -O-(ethyl), or CN, wherein methyl and ethyl are optionally substituted with one or more F;

R₇ is H, -CH₂-(6-membered aryl), or -CH₂-(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH₂, NO₂, C1-C3 alkyl, C2-C3 alkenyl, C2-C3 alkynyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(C3 alkenyl), -O-(C3 alkynyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), -S-(C3 alkenyl), -S-(C3 alkynyl), and -S-(cyclopropyl), wherein alkyl, alkenyl, alkynyl, and cyclopropyl are optionally substituted with one or more F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.

37. The compound of any one of claims 34-36, wherein R₂ is methyl and R₅ is -O-(methyl).

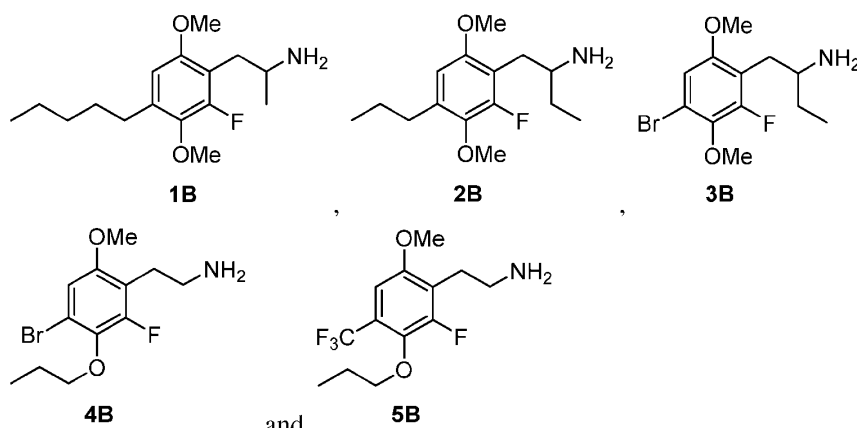
38. The compound of any one of claims 34-37, wherein R₃ is H.

39. The compound of any one of claims 34-38, wherein R₄ is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), F, Cl, Br, I, CN, NO₂, or SF₅, wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one or more F, and wherein cycloalkyl is optionally substituted with one or more C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl.

40. The compound of any one of claims 34-38, wherein R_4 is C1-C4 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C3-C5 cycloalkyl, -(C1-C2 alkyl)-(C3-C5 cycloalkyl), -S-(C1-C4 alkyl), -S-(C3-C4 alkenyl), -S-(C3-C4 alkynyl), -S-(C3-C5 cycloalkyl), -S-(C1-C2 alkyl)-(C3-C5 cycloalkyl), Cl, Br, I, or SF_5 , wherein alkyl, alkenyl, alkynyl, and cycloalkyl are optionally substituted with one to three F, and wherein cycloalkyl is optionally substituted with one to three C1-C3 alkyl, C2-C3 alkenyl, or C2-C3 alkynyl.
41. The compound of any one of claims 34-40, wherein R_7 is H.
42. The compound of any one of claims 34-40, wherein R_7 is $-CH_2$ -(6-membered aryl) or $-CH_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, NH_2 , NO_2 , C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), -O-(cyclopropyl), -S-(C1-C3 alkyl), and -S-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-6-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.
43. The compound of any one of claims 34-40, wherein R_7 is $-CH_2$ -(6-membered aryl) or $-CH_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, C1-C3 alkyl, cyclopropyl, -O-(C1-C3 alkyl), and -O-(cyclopropyl), wherein alkyl and cyclopropyl are optionally substituted with one to three F, and wherein any two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a 5-membered ring optionally interrupted by 1-2 heteroatoms selected from O, N, and S.
44. The compound of any one of claims 34-40, wherein R_7 is $-CH_2$ -(6-membered aryl) or $-CH_2$ -(6-membered heteroaryl), wherein aryl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of halo, CN, OH, methyl, and -O-(methyl), wherein methyl is optionally substituted with one to three F, and wherein any

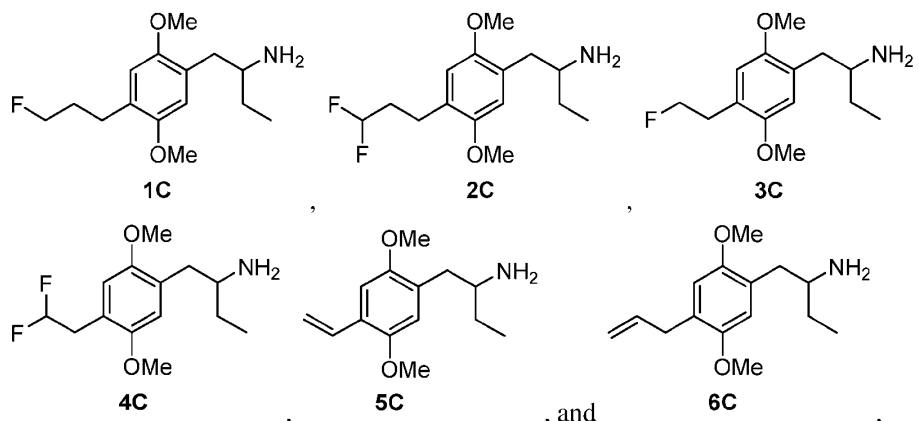
two adjacent substituents on aryl or heteroaryl, together with the atoms to which they are connected, form a methylenedioxy ring.

45. The compound of any one of claims 34-40, wherein R_7 is $-\text{CH}_2$ -(6-membered aryl), wherein aryl is optionally substituted at the ortho position with one F, OH, or $-\text{O}$ -(methyl), or with a methylenedioxy ring linking the ortho and meta positions.
46. The compound of any one of claims 34-45, wherein R_1 is H or Me.
47. The compound of any one of claims 34-45, wherein R_1 is ethyl.
48. The compound of any one of claims 34-45, wherein R_1 is n-propyl.
49. The compound of any one of claims 34-45, wherein R_1 is $-\text{CH}_2\text{-OH}$.
50. The compound of any one of claims 34-45, wherein R_1 is $-\text{CH}_2\text{-O}$ -(methyl).
51. The compound of any one of claims 34-45, wherein R_1 is $-\text{CH}_2\text{F}$.
52. The compound of any one of claims 34-45, wherein R_1 is $-\text{CH}_2\text{CH}_2\text{F}$.
53. The compound of claim 34, selected from the group consisting of:



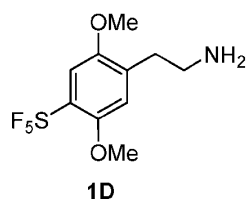
or a pharmaceutically acceptable salt thereof.

54. A compound selected from the group consisting of:



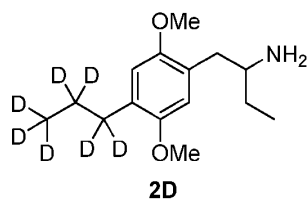
or a pharmaceutically acceptable salt thereof.

55. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

56. A compound having the structure:

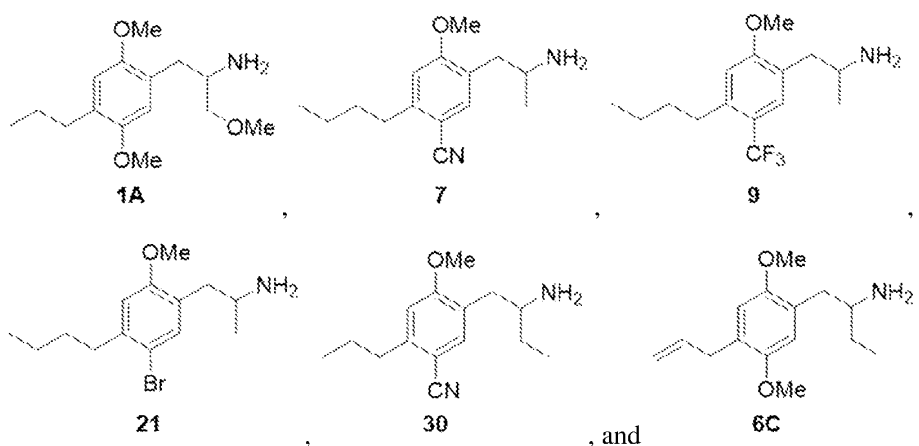


or a pharmaceutically acceptable salt thereof,
wherein each deuterium-enriched H-site is greater than 0.02% deuterium.

57. The compound of claim 56, wherein each deuterium-enriched H-site is greater than 90% deuterium.

58. The compound of claim 56, wherein each deuterium-enriched H-site is greater than 95% deuterium.

59. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

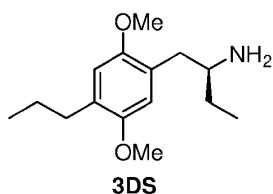
60. The compound of any one of claims 1 to 59 in the S-enantiomeric form.

61. The compound of any one of claims 1 to 59 in the R-enantiomeric form.

62. The compound of claim 60 or 61, wherein the compound is substantially enantiomerically pure.

63. The compound of claim 60 or 61, which optionally includes the compound of the opposite enantiomeric form, provided the compound contains >50% of the indicated enantiomeric form and <50% of the opposite enantiomeric form.

64. A composition comprising the following S-enantiomeric compound:

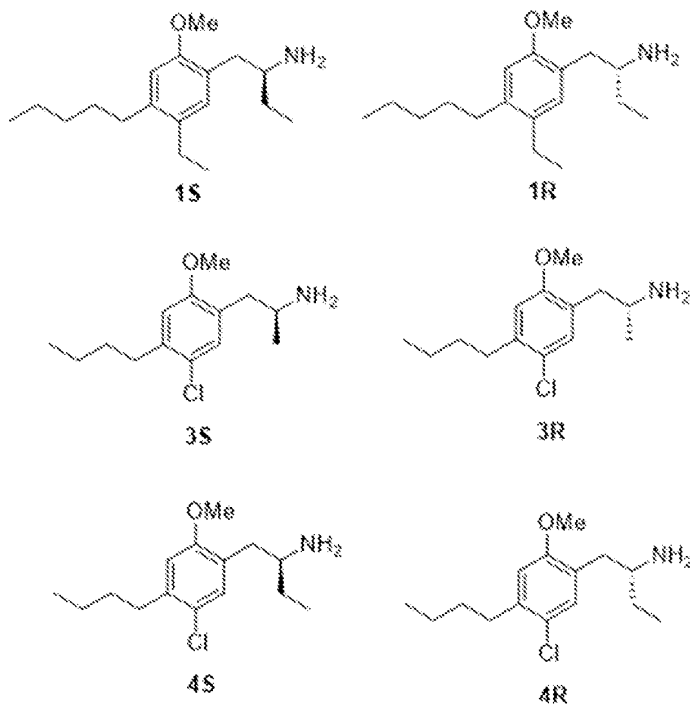


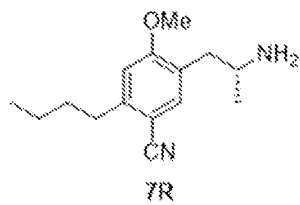
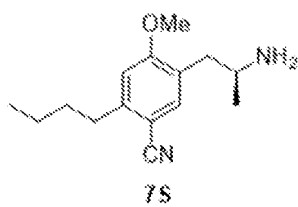
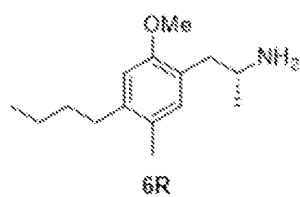
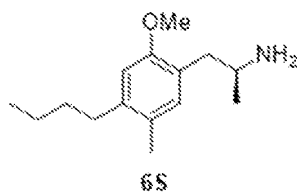
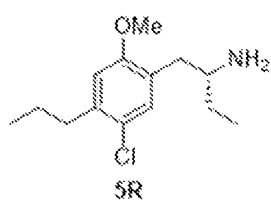
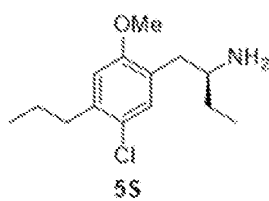
which optionally includes the R-enantiomeric form of the same compound, provided that the composition contains greater than 50% of the S-enantiomeric form.

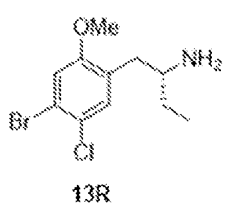
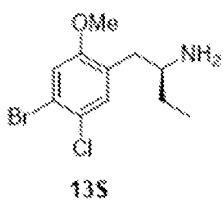
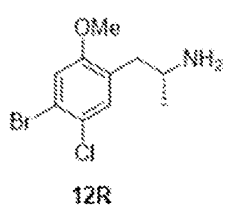
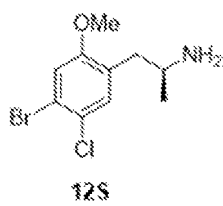
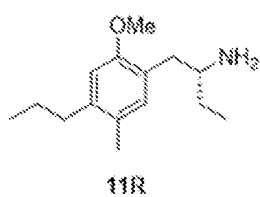
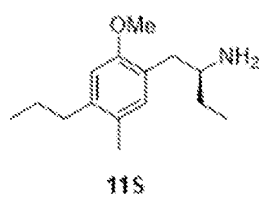
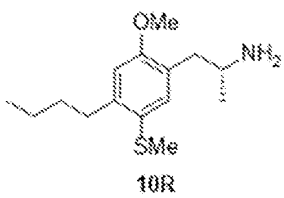
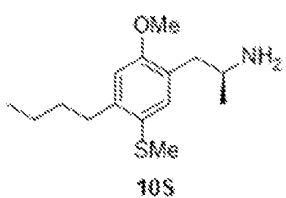
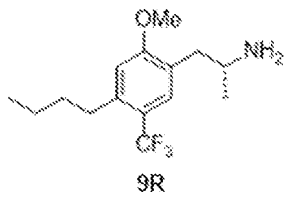
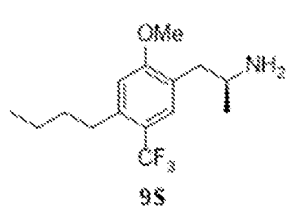
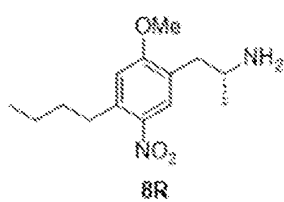
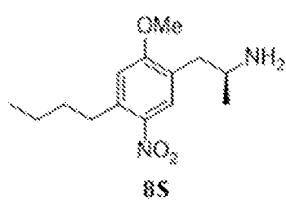
65. The composition of claim 64, which contains greater than 90% of the S-enantiomeric form.

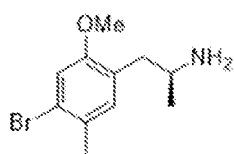
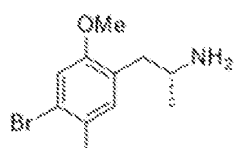
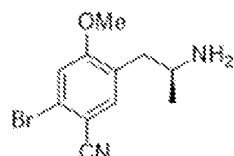
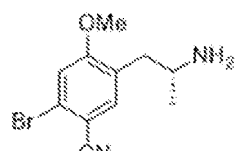
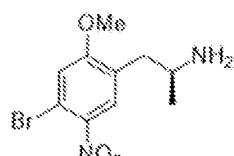
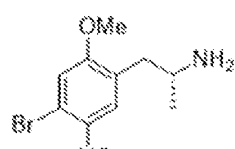
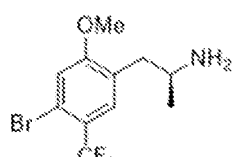
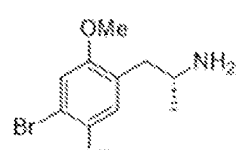
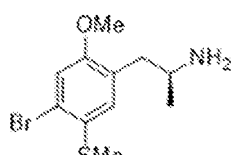
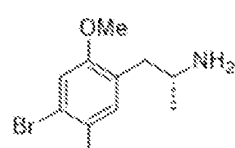
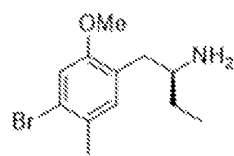
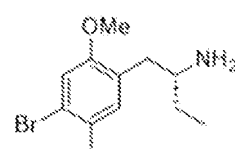
66. The composition of claim 64, which contains greater than 95% of the S-enantiomeric form.

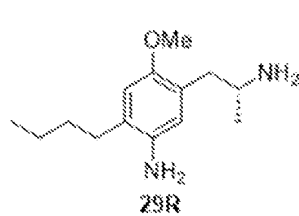
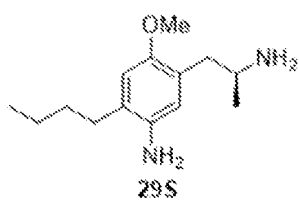
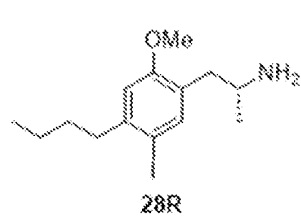
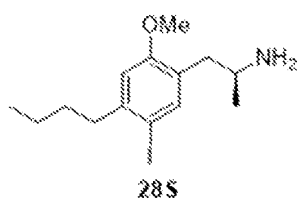
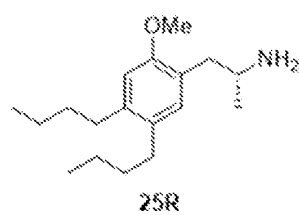
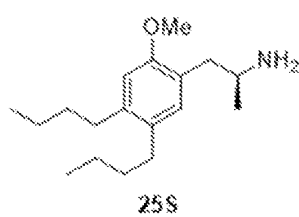
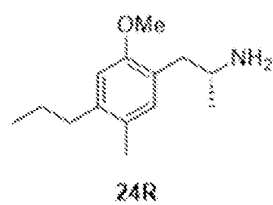
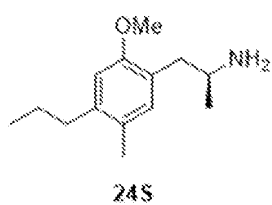
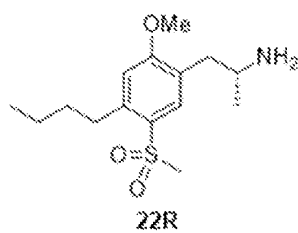
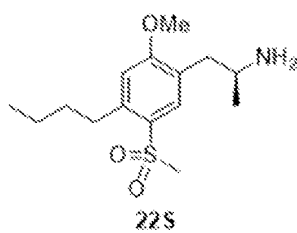
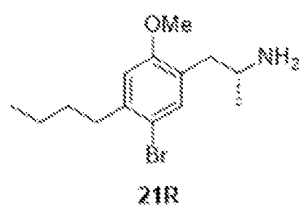
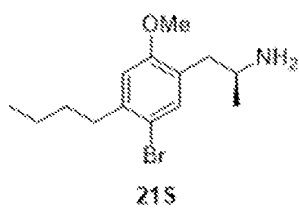
67. A compound selected from the group consisting of:

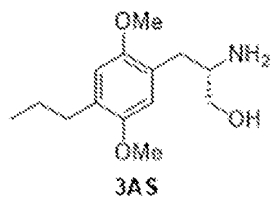
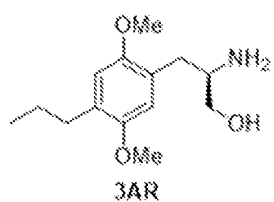
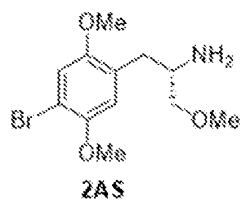
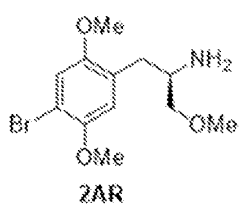
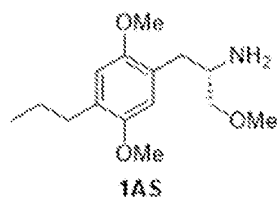
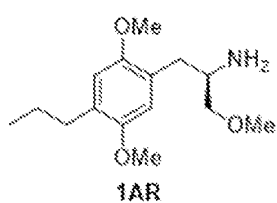
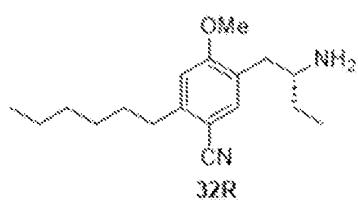
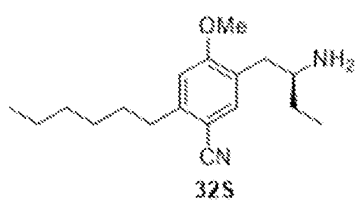
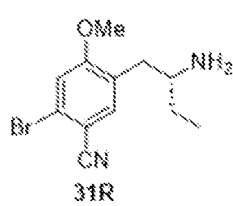
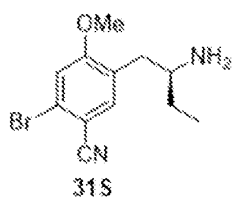
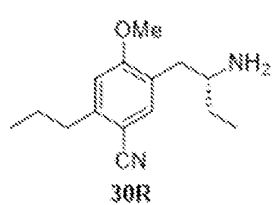
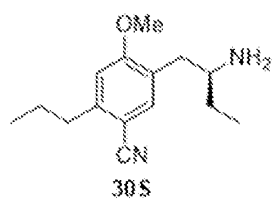


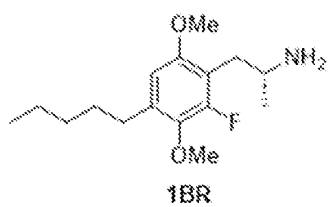
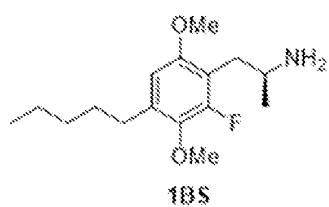
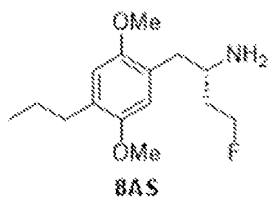
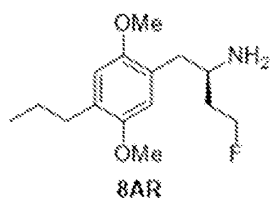
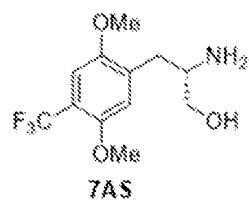
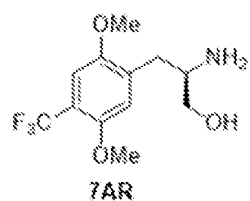
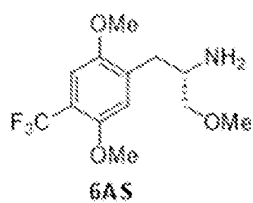
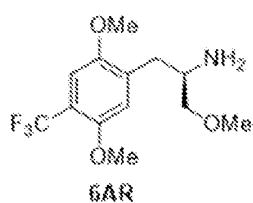
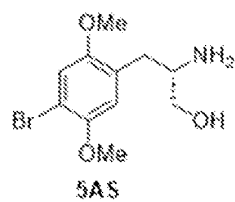
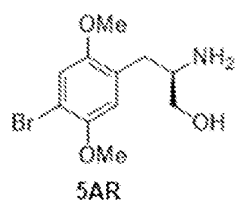
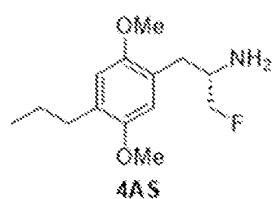
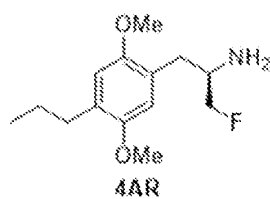


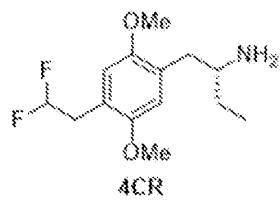
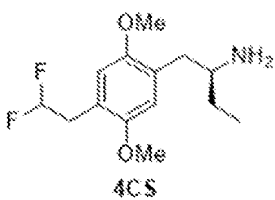
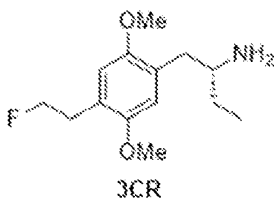
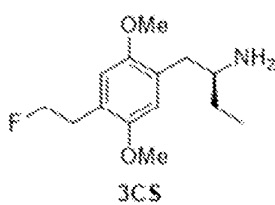
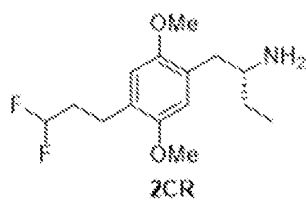
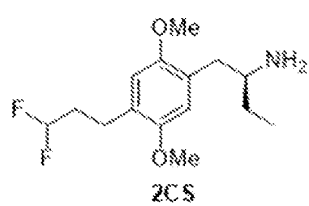
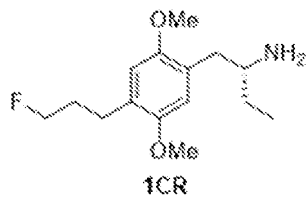
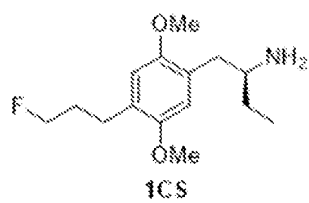
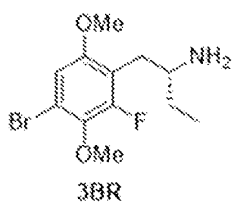
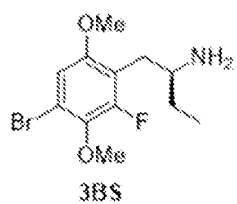
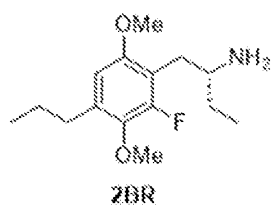
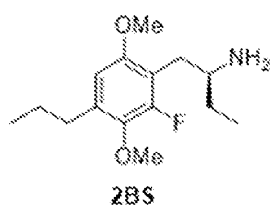


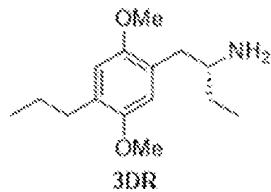
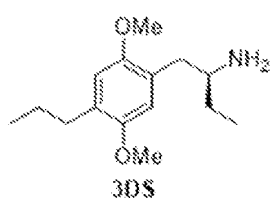
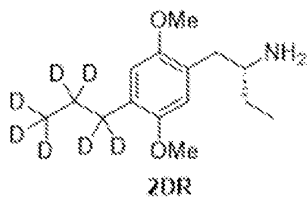
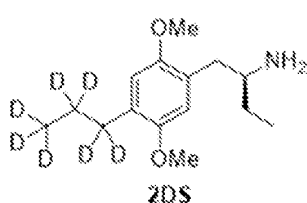
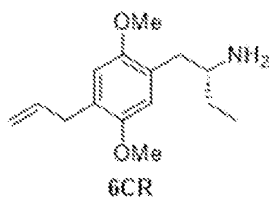
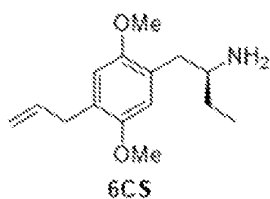
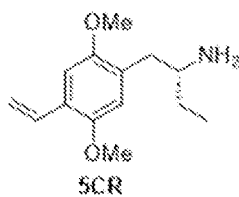
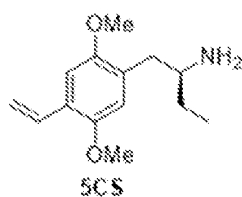
**14S****14R****15S****15R****16S****16R****17S****17R****18S****18R****19S****19R**











68. A pharmaceutical composition comprising the compound of any one of claims 1-63 or the composition of any one of claims 64-67, and a pharmaceutically acceptable carrier.

69. A method of treating a psychiatric disease or disorder, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1-63 or the composition of any one of claims 64-67.

70. The method of claim 69, wherein the psychiatric disease or disorder is selected from the group consisting of depressive disorders and bipolar disorders.

71. The method of claim 69, wherein the psychiatric disease or disorder is a depressive disorder.
72. The method of claim 69, wherein the psychiatric disease or disorder is a treatment-resistant depressive disorder.
73. The method of claim 69, wherein the psychiatric disease or disorder is selected from the group consisting of major depressive disorder, persistent depressive disorder, postpartum depression, premenstrual dysphoric disorder, seasonal affective disorder, psychotic depression, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition.
74. The method of claim 69, wherein the psychiatric disease or disorder is selected from the group consisting of bipolar disorder I, bipolar disorder II, cyclothymic disorder, substance/medication-induced bipolar and related disorder, and bipolar and related disorder due to another medical condition.
75. The method of claim 69, wherein the psychiatric disease or disorder is a substance-related disorder.
76. The method of claim 69, wherein the psychiatric disease or disorder is a substance-use disorder.
77. The method of claim 69, wherein the psychiatric disease or disorder is an anxiety disorder.
78. The method of claim 69, wherein the psychiatric disease or disorder is selected from the group consisting of obsessive-compulsive and related disorders, trauma- and stressor-related disorders, feeding and eating disorders, borderline personality disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder.

79. A method of treating a headache or headache disorder, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1-63 or the composition of any one of claims 64-67.

80. A method of treating an inflammatory disease or disorder, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1-63 or the composition of any one of claims 64-67.

81. A method of treating high intraocular pressure, comprising administering to a patient in need thereof a therapeutically effective amount of the compound of any one of claims 1-63 or the composition of any one of claims 64-67.