(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 October 2022 (20.10.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/221774 A1

(51) International Patent Classification:
C07D 205/04 (2006.01) *A61K 31/397* (2006.01)

(21) International Application Number:
PCT/US2022/025241

(22) International Filing Date:
18 April 2022 (18.04.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/175,985 16 April 2021 (16.04.2021) US

(71) Applicant: **ELEUSIS THERAPEUTICS US, INC.** [US/US]; 99 Wall Street, #2205, New York, NY 10005 (US).

(72) Inventors: **JOHNSON, Graham**; 3 Lakeside Drive, Sanbornton, NH 03269 (US). **NICHOLS, David, E.**; 56702 Nash, Chapel Hill, NC 27517 (US). **MAILLET, Emeline, L.**; 8216 Birch St, #c, New Orleans, LA 70118 (US).

(74) Agent: **ELLISON, Jefffrey, J.**; Clark & Elbing LLP, 101 Federal Street, 15th Floor, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2022/221774 A1

(54) Title: ARYL-RING-SUBSTITUTED 3-PHENYLAZETIDINES AND THEIR USE IN METHODS FOR TREATING 5-HT2 RESPONSIVE CONDITIONS

(57) Abstract: The invention features compounds and pharmaceutical compositions useful for treating 5-HT2 responsive conditions. Also provided are methods of using the compounds or compositions of the invention for treating 5-HT2 responsive conditions in a subject in need thereof.

ARYL-RING-SUBSTITUTED 3-PHENYLAZETIDINES AND THEIR USE IN METHODS FOR TREATING 5-HT2 RESPONSIVE CONDITIONS

FIELD OF THE INVENTION

In general, the invention features compositions and methods for treating 5-HT2 responsive conditions.

BACKGROUND OF THE INVENTION

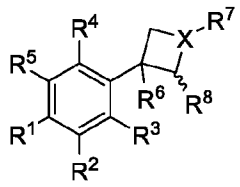
Significant interest in the therapeutic application of 5-HT2 receptor ligands has developed, based upon evidence of possible therapeutic effects in a wide array of 5-HT2 responsive conditions (e.g., mitigating or improving conditions and disorders via 5-HT2 receptor target modulation), including psychiatric conditions, pain disorders, immunological conditions, and neurological conditions.

There is a need in the field for discovery and development of small molecule 5-HT2 receptor ligands with more desirable therapeutic, absorption, distribution, pharmacokinetic, and/or safety profiles.

SUMMARY OF THE INVENTION

The present invention discloses a new chemotype class of ligands of the 5-HT2 receptors that have potent pharmacological properties. Also provided are methods of using the compounds or compositions of the invention, e.g., for treating an inflammatory or a neurological disorder in a subject in need thereof.

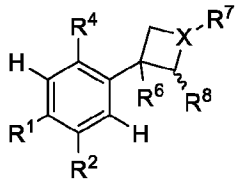
An aspect of the invention features a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

In formula (I), X is N or $N(CH_3)$; R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, C_1-C_8 alkylthio, or combined with R^2 or R^5 to form a cyclic ketal ring of formula $-OCH_2O-$; R^2 is H, OH, OCH_3, OCH_2CH_3, OBn, or combined with R^1 forms a cyclic ketal ring of formula $-OCH_2O-$; R^3 is H, OH, OCH_3, or OCH_2CH_3; R^4 is H, OH, OCH_3, OCH_2CH_3, or OBn; R^5 is H, OH, OCH_3, OCH_2CH_3, or combined with R^1 forms a cyclic ketal ring of formula $-OCH_2O-$; R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl; R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl, and R_8 is H or methyl, the latter being in either the R or S stereochemical configuration. In particular embodiments, R^1 is an optionally substituted C_{2-8} alkenyl having a cis configuration.

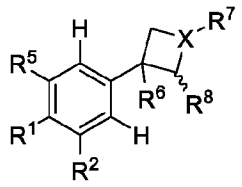
In particular embodiments, the compound of formula (I) is further described by formula (II), or a pharmaceutically acceptable salt thereof:



(II)

In formula (II), wherein X is N or $N(CH_3)$; R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, C_1-C_8 alkylthio, or combined with R^2 to form a cyclic ketal ring of formula $-OCH_2O-$; R^2 is OH, OCH_3, OCH_2CH_3, OBn, or combined with R^1 forms a cyclic ketal ring of formula $-OCH_2O-$; R^4 is OH, OCH_3, OCH_2CH_3, or OBn; R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl; R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl and R_8 is H or methyl, the latter being in either the R or S stereochemical configuration.

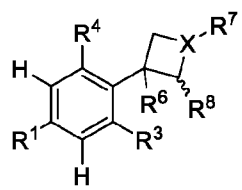
In particular embodiments, the compound of formula (I) is further described by formula (III), or a pharmaceutically acceptable salt thereof:



(III)

In formula (III), X is N or $N(CH_3)$; R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, C_1-C_8 alkylthio, or combined with R^2 to form a cyclic ketal ring of formula $-OCH_2O-$; R^2 is OH, OCH_3, OCH_2CH_3, OBn, or combined with R^1 forms a cyclic ketal ring of formula $-OCH_2O-$; R^5 is OH, OCH_3, or OCH_2CH_3; R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl; R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl, and R_8 is H or methyl, the latter being in either the R or S stereochemical configuration.

In particular embodiments, the compound of formula (I) is further described by formula (IV), or a pharmaceutically acceptable salt thereof:

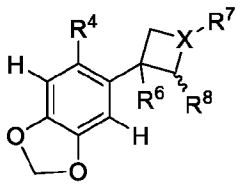


(IV)

In formula (IV), X is N or $N(CH_3)$; R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, or C_1-C_8 alkylthio; R^3 is OH, OCH_3, or OCH_2CH_3; R^4 is OH, OCH_3, OCH_2CH_3, or OBn; R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl; and R^7 is H,

optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl and R_8 is H or methyl, the latter being in either the R or S stereochemical configuration.

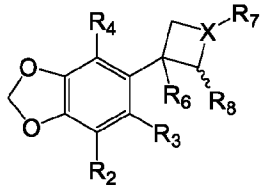
In particular embodiments, the compound of formula (I) is further described by formula (V), or a pharmaceutically acceptable salt thereof:



(V)

In formula (V), X is N or $N(CH_3)$; R^4 is H, OH, OCH_3, OCH_2CH_3, or OBn; R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl; R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl and R_8 is H or methyl, the latter being in either the R or S stereochemical configuration.

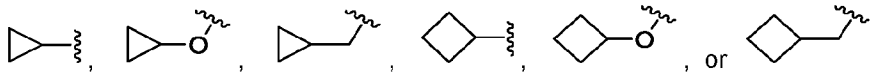
In particular embodiments, the compound of formula (I) is further described by formula (VI), or a pharmaceutically acceptable salt thereof:



(VI)

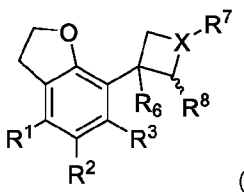
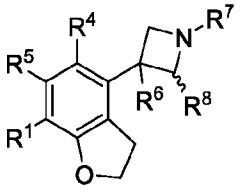
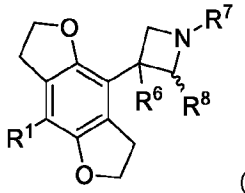
In formula (VI), X is N or $N(CH_3)$; R^2 is H, OH, OCH_3, OCH_2CH_3, or OBn; R^3 is H, OH, OCH_3, or OCH_2CH_3; R^4 is H, OH, OCH_3, OCH_2CH_3, or OBn; R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl; R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl and R_8 is H or methyl, the latter being in either the R or S stereochemical configuration.

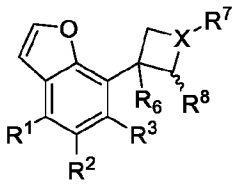
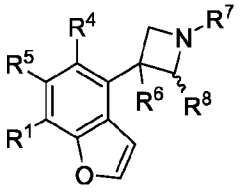
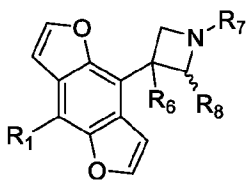
In one embodiment of any one of formulas (I)-(IV), R^1 is bromo, CN, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-C(CH_3)_3$, $-CH_2C(CH_3)_3$; $-OCH(CH_3)_2$, $-OC(CH_3)_3$, C_1-C_8 alkylthio, or a group selected from:



In a particular embodiment of any one of formulas (I)-(VI), R^7 is selected from H, CH_3, CH_2CH_3, and optionally substituted C_{7-14} alkaryl. In an embodiment of any one of formulas (I)-(VI), R^6 is H, OH, or OCH_3.

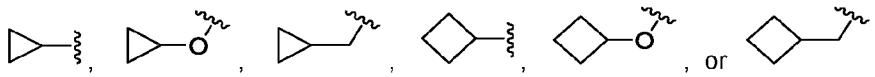
A further aspect of the invention features a compound of any one of formulas (VIa)-(VIf), or a pharmaceutically acceptable salt thereof:


(VIa);

(VIb);

(VIc);


(VId);

(VIe); or

(VIf).

In formulas (VIa)-(VIf), X is N or $N(CH_3)$; R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, or C_1-C_8 alkylthio; R^2 is OH, OCH_3, OCH_2CH_3; R^3 is H, OH, OCH_3, OCH_2CH_3, or OBn; R^4 is H, OH, OCH_3, OCH_2CH_3, or OBn; R^5 is H, OH, OCH_3, or OCH_2CH_3; R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl; R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl, and R_8 is H or methyl, the latter being in either the R or S stereochemical configuration. In particular embodiments, R^1 is an optionally substituted C_{2-8} alkenyl having a cis configuration.

In one embodiment of any one of formulas (VIa)-(VIf), R^1 is bromo, CN, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-C(CH_3)_3$, $-CH_2C(CH_3)_3$; $-OCH(CH_3)_2$, $-OC(CH_3)_3$, C_1-C_8 alkylthio, or a group selected from:



In a particular embodiment of any one of formulas (VIa)-(VIf), R^7 is selected from H, CH_3, CH_2CH_3, and optionally substituted C_{7-14} alkaryl. In an embodiment of any one of formulas (VIa)-(VIf), R^6 is H, OH, or OCH_3.

In another aspect, the invention includes a composition of any of the preceding aspects (e.g., a compound of any one of formulas (I)-(VIf), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. Such a pharmaceutical composition can be formulated, e.g., for oral, intranasal, subcutaneous, intramuscular, parenteral, topical, intraocular or pulmonary administration.

In another aspect, provided herein is a method of treating 5-HT2 responsive conditions in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of the compound or the pharmaceutical composition of any of the preceding aspects. In particular embodiments the 5-HT2 responsive condition is an inflammatory or neurological disorder.

In some embodiments of any of the preceding embodiments or any of the methods described herein, the 5-HT2 responsive condition is an inflammatory disorder selected from asthma, chronic obstructive pulmonary disease, neuroinflammation, rheumatoid arthritis, atherosclerosis, psoriasis, type II diabetes, inflammatory bowel disease, Crohn's disease, multiple sclerosis, septicemia, conjunctivitis, Alzheimer's disease, or any inflammatory condition described herein.

In another aspect, provided herein is a method of treating a psychological condition in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of the compound or the pharmaceutical composition of any of the preceding aspects. In particular embodiments, the psychological condition is depression, anxiety, addiction, post-traumatic stress disorder, an eating disorder, compulsive behavior, autism spectrum disorders, or any psychological condition described herein.

In another aspect, provided herein is a method of treating chronic pain in a subject in need thereof, the method including administering to the subject a therapeutically effective amount of the compound or the pharmaceutical composition of any of the preceding aspects.

In another aspect, the described composition of matter embodies a new chemotype class of ligands targeting the 5-HT2 receptors that offers structural differentiation from previously known chemotype ligand classes for these receptors, namely substituted phenethylamines, lysergamides, and tryptamines non exhaustively. A different structural chemotype will likely not replicate the extended pharmacology at secondary and complementary targets known for these other ligand classes. Thus, any additional activities at secondary metabotropic, ionotropic, or enzymes targets for the molecules described in this application could contribute to an overall distinctive pharmacological profile compared to existing 5-HT2 receptor targeting medicines.

In any of the methods provided herein, the compound can be administered by any suitable route of administration, e.g., orally, intranasally, or by inhalation. In some embodiments, the present compound or pharmaceutical composition thereof is administered by one or more of a variety of routes, including nasal, buccal, oral, by inhalation (e.g., as an oral spray, nebulizer, nasal spray, or aerosol), intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (e.g., by powders, ointments, creams, gels, lotions, and/or drops), mucosal, enteral, vitreal, intratumoral, sublingual; by intratracheal instillation, bronchial instillation, and/or through a portal vein catheter. In some embodiments the composition is administered by systemic intravenous injection. In specific embodiments the composition is administered intravenously and/or orally.

Definitions

To facilitate the understanding of this invention, a number of terms are defined below and throughout the disclosure. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The terminology herein is used to describe specific embodiments of the invention, but their usage does not limit the invention, except as outlined in the claims.

At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-8} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, C_6 alkyl, C_7 alkyl, and C_8 alkyl. Herein a phrase of the form "optionally substituted X" (*e.g.*, optionally substituted alkyl) is intended to be equivalent to "X, wherein X is optionally substituted" (*e.g.*, "alkyl, wherein the alkyl is optionally substituted"). It is not intended to mean that the feature "X" (*e.g.*, alkyl) *per se* is optional.

As used herein, the terms "alkyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e., cycloalkyl, and combinations thereof. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 6 ring carbon atoms, inclusive. Exemplary cyclic groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl groups. The C_{1-8} alkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, cyano, nitrilo, NH-acyl, amino, aminoalkyl, disubstituted amino, C_{2-7} heterocyclyl, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{1-8} alkyls include, without limitation, methyl; ethyl; n-propyl; isopropyl; cyclopropyl; cyclopropylmethyl; cyclopropylethyl; n-butyl; iso-butyl; sec-butyl; tert-butyl; cyclobutyl; cyclobutylmethyl; cyclobutylethyl; n-pentyl; cyclopentyl; cyclopentylmethyl; cyclopentylethyl; 1-methylbutyl; 2-methylbutyl; 3-methylbutyl; 2,2-dimethylpropyl; 1-ethylpropyl; 1,1-dimethylpropyl; 1,2-dimethylpropyl; 1-methylpentyl; 2-methylpentyl; 3-methylpentyl; 4-methylpentyl; 1,1-dimethylbutyl; 1,2-dimethylbutyl; 1,3-dimethylbutyl; 2,2-dimethylbutyl; 2,3-dimethylbutyl; 3,3-dimethylbutyl; 1-ethylbutyl; 2-ethylbutyl; 1,1,2-trimethylpropyl; 1,2,2-trimethylpropyl; 1-ethyl-1-methylpropyl; 1-ethyl-2-methylpropyl; and cyclohexyl.

By "C_{2-8} alkenyl" is meant a branched or unbranched hydrocarbon group containing one or more double bonds and having from 2 to 8 carbon atoms. A C_{2-8} alkenyl may optionally include monocyclic or polycyclic rings, in which each ring desirably has from three to six members. The C_{2-8} alkenyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, cyano, nitrilo, NH-acyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. C_{2-8} alkenyls include, without limitation, vinyl; allyl; 2-cyclopropyl-1-ethenyl; 1-propenyl; 1-butenyl; 2-butenyl; 3-butenyl; 2-methyl-1-propenyl; 2-methyl-2-propenyl; 1-pentenyl; 2-pentenyl; 3-pentenyl; 4-pentenyl; 3-methyl-1-butenyl; 3-methyl-2-butenyl; 3-methyl-3-butenyl; 2-methyl-1-butenyl; 2-methyl-2-butenyl; 2-methyl-3-butenyl; 2-ethyl-2-propenyl; 1-methyl-1-butenyl; 1-methyl-2-butenyl; 1-methyl-3-butenyl; 2-methyl-2-pentenyl; 3-methyl-2-pentenyl; 4-methyl-2-pentenyl; 2-methyl-3-pentenyl; 3-methyl-3-pentenyl; 4-methyl-3-pentenyl; 2-methyl-4-pentenyl; 3-methyl-4-pentenyl; 1,2-dimethyl-1-propenyl; 1,2-dimethyl-1-butenyl; 1,3-dimethyl-1-butenyl; 1,2-dimethyl-2-butenyl; 1,1-dimethyl-2-butenyl; 2,3-dimethyl-2-butenyl; 2,3-dimethyl-3-butenyl; 1,3-dimethyl-3-butenyl; 1,1-dimethyl-3-butenyl and 2,2-dimethyl-3-butenyl. In particular embodiments the C_{2-8} alkenyl has a cis configuration around the double bond.

By "C_{2-7} heterocyclyl" is meant a stable 5- to 7-membered monocyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated (aromatic), and which consists of 2 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, hydroxy, fluoroalkyl, perfluoralkyl, cyano, nitrilo, NH-acyl, amino, aminoalkyl, disubstituted amino, quaternary amino, hydroxyalkyl, carboxyalkyl, and carboxyl groups. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be covalently attached via any heteroatom or carbon atom that results in a stable structure, e.g., an imidazolinyl ring may be linked at either of the ring-carbon atom positions or at the nitrogen atom. A nitrogen atom in the heterocycle may optionally be quaternized. Preferably when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. Heterocycles include, without limitation, 1H-indazole, 2-

pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, beta-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred 5 to 10 membered heterocycles include, but are not limited to, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, tetrazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, isoxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, quinolinyl, and isoquinolinyl. Preferred 5 to 6 membered heterocycles include, without limitation, pyridinyl, pyrimidinyl, triazinyl, furanyl, thienyl, thiazolyl, pyrrolyl, piperazinyl, piperidinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, and tetrazolyl.

By "C_{6-12} aryl" is meant an aromatic group having a ring system comprised of carbon atoms with conjugated π electrons (e.g., phenyl). The aryl group has from 6 to 12 carbon atoms. Aryl groups may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has five or six members. The aryl group may be substituted or unsubstituted. Exemplary subsituents include alkyl, hydroxy, alkoxy, aryloxy, sulfhydryl, alkylthio, arylthio, halide, fluoroalkyl, carboxyl, hydroxyalkyl, carboxyalkyl, amino, aminoalkyl, monosubstituted amino, disubstituted amino, and quaternary amino groups.

By "C_{7-14} alkaryl" is meant an alkyl substituted by an aryl group (e.g., benzyl, phenethyl, or 3,4-dichlorophenethyl) having from 7 to 14 carbon atoms.

By "C_{3-10} alkheterocyclyl" is meant an alkyl substituted heterocyclic group having from 7 to 14 carbon atoms in addition to one or more heteroatoms (e.g., 3-furanylmethyl, 2-furanylmethyl, 3-tetrahydrofuranylmethyl, or 2-tetrahydrofuranylmethyl).

By "C_{1-8} heteroalkyl" is meant a branched or unbranched alkyl, alkenyl, or alkynyl group having from 1 to 8 carbon atoms in addition to1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O, S, and P. Heteroalkyls include, without limitation, tertiary amines, secondary amines, ethers, thioethers, amides, thioamides, carbamates, thiocarbamates, hydrazones, imines, phosphodiesters, phosphoramidates, sulfonamides, and disulfides. A heteroalkyl may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has three to six members. The heteroalkyl group may be substituted or unsubstituted. Exemplary substituents include alkoxy, aryloxy,

sulfhydryl, alkylthio, arylthio, halide, hydroxyl, fluoroalkyl, perfluoralkyl, cyano, nitrilo, NH-acyl, amino, aminoalkyl, disubstituted amino, quaternary amino, C_{2-7} heterocyclyl, hydroxyalkyl, hydroxyalkyl, carboxyalkyl, and carboxyl groups. Examples of C_{1-8} heteroalkyls include, without limitation, methoxymethyl and ethoxyethyl.

By “halide” is meant bromine, chlorine, iodine, or fluorine.

By “fluoroalkyl” is meant an alkyl group that is substituted with one or more fluorine atoms.

By “carboxyalkyl” is meant a chemical moiety with the formula -(R)-COOH, wherein R is selected from C_{1-8} alkyl, C_{2-7} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-8} heteroalkyl.

By “hydroxyalkyl” is meant a chemical moiety with the formula -(R)-OH, wherein R is selected from C_{1-8} alkyl, C_{2-7} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-8} heteroalkyl.

By “alkoxy” is meant a chemical substituent of the formula -OR, wherein R is selected from C_{1-8} alkyl, C_{2-7} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-8} heteroalkyl.

By “aryloxy” is meant a chemical substituent of the formula -OR, wherein R is a C_{6-12} aryl group.

By “alkylthio” is meant a chemical substituent of the formula -SR, wherein R is selected from C_{1-8} alkyl, C_{2-7} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-8} heteroalkyl.

By “arylthio” is meant a chemical substituent of the formula -SR, wherein R is a C_{6-12} aryl group.

By “quaternary amino” is meant a chemical substituent of the formula -(R)-N(R’)(R”)(R’”)$^+$, wherein R, R’, R”, and R’” are each independently an alkyl, alkenyl, alkynyl, or aryl group. R may be an alkyl group linking the quaternary amino nitrogen atom, as a substituent, to another moiety. The nitrogen atom, N, is covalently attached to four carbon atoms of alkyl and/or aryl groups, resulting in a positive charge at the nitrogen atom.

By “acyl” is meant a chemical moiety with the formula R-C(O)-, wherein R is selected from C_{1-8} alkyl, C_{2-7} heterocyclyl, C_{6-12} aryl, C_{7-14} alkaryl, C_{3-10} alkheterocyclyl, or C_{1-8} heteroalkyl.

Terms such as "a", "an," and "the" are not intended to refer to only a singular entity but include the general class of which a specific example may be used for illustration.

As used herein, the term “about” refers to a value that is within 10% above or below the value being described.

As used herein, the terms “acute stress disorder” and “ASD” refer to a condition that arises as a response to a stressful event or situation of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in an individual (e.g., natural or man-made disaster, combat, serious accident, witnessing the violent death of others, or being the victim of torture, terrorism, rape, or other crime). Like PTSD, acute stress disorder is an anxiety disorder that involves a very specific reaction following exposure to a traumatic event or stressor. However, the duration of acute stress disorder is shorter than that for PTSD, such that the symptoms are present for at least one, two, or three days, but no more than four, five, or six weeks. For individuals exhibiting symptoms persisting for a longer period of time, a diagnosis of PTSD may be warranted.

The term “administration” or “administering” refers to a method of giving a dosage of a compound or pharmaceutical composition to a subject.

By "dysthymia" or "dysthymic disorder" is meant a chronically depressed mood that occurs for most of the day, more days than not, for at least two years. In children and adolescents, the mood may be irritable rather than depressed, and the required minimum duration is one year. During the two year period (one year for children or adolescents), any symptom-free intervals last no longer than 2 months.

During periods of depressed mood, at least two of the following additional symptoms are present: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration, or difficulty making decisions, and feelings of hopelessness. The symptoms cause clinically significant distress or impairment in social, occupational (or academic), or other important areas of functioning. The diagnosis of dysthymia is not made if: the individual has ever had a manic episode, a mixed episode, a hypomanic episode; has ever met the criteria for a cyclothymic disorder; the depressive symptoms occur exclusively during the course of a chronic psychotic disorder (e.g., schizophrenia); or if the disturbance is due to the direct physiological effects of a substance or a general medical condition. After the initial two-years of dysthymic disorder, major depressive episodes may be superimposed on the dysthymic disorder ("double depression"). Diagnostic and Statistical Manual of Mental Disorders (OSM IV), American Psychiatric Press, 4th Edition, I 994. Diagnostic guidance for psychological disorders can be found, for example, in the ICD-10 (The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research, Geneva: World Health Organization, 1993) and the DSM-V (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) Arlington, VA.; American Psychiatric Association, 2013).

As used herein, the term “generalized anxiety disorder” refers to a condition characterized by excessive anxiety and worry (i.e., apprehensive expectation). Typically, the excessive anxiety and worry occur on more days than not for a period of time (e.g., one, two, three, or four months or more). The anxiety and worry can be associated with (i) restlessness, feeling keyed up, or on edge; and/or (ii) muscle tension. The anxiety and worry can be associated with (a) a marked avoidance of situations in which a negative outcome could occur; (b) a marked time and effort preparing for situations in which a negative outcome could occur; (c) a marked procrastination in behavior or decision-making due to worries; and (d) repeatedly seeking reassurance due to worries. The anxiety, worry, or physical symptoms can cause clinically significant distress or impairment in social, occupational, or other important areas of functioning in many, but not necessarily all individuals with GAD.

As used herein, the terms “obsessive compulsive disorder,” “OCD,” and “anxiety and obsessive-compulsive spectrum disorders” refer to a condition characterized by obsessions and/or compulsions. Obsessions are recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted and that usually cause marked anxiety or distress in which the obsessed individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion). Compulsions are repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the person feels driven to perform in response to an obsession, or according to rules that must be applied rigidly. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts either are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive. Typically the obsessions or compulsions are time consuming (for example, take more than 1 hour a day), or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

As used herein, the term “pharmaceutically acceptable salt” refers to those salts of the compounds described herein that are suitable for pharmaceutical use. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al.,

J. Pharmaceutical Sciences 66:1-19, 1977 and in *Pharmaceutical Salts: Properties, Selection, and Use*, (Eds. P.H. Stahl and C.G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final isolation and purification of the compounds described herein or separately, e.g., by reacting the free base of the compound with a suitable organic acid or inorganic acid, or by reacting the free acid of the compound with a suitable organic acid or inorganic base.

As used herein, the term "panic disorder" refers to a condition characterized by recurrent and unexpected panic attacks. Panic disorder includes both panic disorder with agoraphobia and panic disorder without agoraphobia. Subjects with this condition can exhibit one or both of the following: (i) a persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, going crazy); and/or (ii) significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks), which may include agoraphobic avoidance.

As used herein, the terms "post traumatic stress disorder" and "PTSD" refer to a condition that arises as a delayed and/or protracted response to a stressful event or situation (either short- or long-lasting) of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress in an individual (e.g., natural or man-made disaster, combat, serious accident, witnessing the violent death of others, or being the victim of torture, terrorism, rape, or other crime). Predisposing factors such as personality traits (e.g., compulsive, asthenic) or previous history of neurotic illness may lower the threshold for the development of the condition or aggravate its course, but they are neither necessary nor sufficient to explain its occurrence. PTSD is a less frequent and more enduring consequence of psychological trauma than the more frequently seen acute stress response. PTSD has been recognized in the past as railway spine, stress syndrome, shell shock, battle fatigue, traumatic war neurosis, and post-traumatic stress syndrome. Diagnostic symptoms include re-experiencing original trauma(s), by means of flashbacks or nightmares; avoidance of stimuli associated with the trauma; and increased arousal, such as difficulty falling or staying asleep, anger, and hypervigilance. Formal diagnostic criteria (DSM-V, DSM-IV, and/or ICD-9) require that the symptoms last more than one month and cause significant impairment in social, occupational, or other important areas of functioning (e.g., problems with work and/or relationships). Formal diagnostic criteria can include: (i) intrusion symptoms that are associated with the traumatic event (e.g., (a) spontaneous or cued recurrent, involuntary, and intrusive distressing memories of the traumatic event; (b) recurrent distressing dreams in which the content and/or affect of the dream is related to the event; (c) dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event were recurring (such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings; (d) intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event; and/or (e) marked physiological reactions to reminders of the traumatic event); (ii) persistent avoidance of stimuli associated with the traumatic event (e.g., (a) thoughts, feelings, or physical sensations that arouse recollections of the traumatic event; (b) activities, places, physical reminders, or times (e.g., anniversary reactions) that arouse recollections of the traumatic event; and/or (c) people, conversations, or interpersonal situations that arouse recollections of the traumatic event); (iii) negative alterations in cognitions and mood that are associated with the traumatic event (e.g., (a) inability to remember an important aspect of the traumatic event (typically dissociative amnesia); (b) persistent and exaggerated negative expectations about one's self, others, or

the world; (c) persistent distorted blame of self or others about the cause or consequences of the traumatic event; (d) pervasive negative emotional state (e.g., fear, horror, anger, guilt, or shame); (e) markedly diminished interest or participation in significant activities; (f) feeling of detachment or estrangement from others; and/or (g) persistent inability to experience positive emotions (e.g., unable to have loving feelings, psychic numbing); and (iv) alterations in arousal (i.e., hyperarousal) and reactivity that are associated with the traumatic event (e.g., (a) irritable, angry, or aggressive behavior; (b) reckless or self-destructive behavior; (c) hypervigilance; (d) exaggerated startle response; (e) problems with concentration; and/or (f) sleep disturbance (e.g., difficulty falling or staying asleep, or restless sleep)). Formal diagnostic criteria can further include that the duration of disturbance is more than a certain period of time (e.g., one month, three months, or six months) and that the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. In a small proportion of patients the condition may show a chronic course over many years and a transition to an enduring personality change. The three main symptoms associated with PTSD are (1) "reliving" the traumatic event, such as flashbacks, nightmares, intrusive thoughts and recollections, (2) avoidance behaviors and emotional numbing, and (3) hypersensitivity such as an inability to sleep, anxious feelings, overactive startle response, hyperarousal, hypervigilance, irritability, and outbursts of anger.

As used herein, the terms "psychological disorder" and "psychological condition" refer to a condition characterized by a disturbance in one's emotional or behavioral regulation that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental function. Psychological disorders include, but are not limited to depressive disorders (major depression, treatment resistant depression, melancholic depression, atypical depression, or dysthymia), anxiety disorders (end of life anxiety, generalized anxiety disorder, panic disorder, social anxiety, post-traumatic stress disorder, acute stress disorder, obsessive compulsive disorder, or social phobia), addictions (e.g., substance abuse, e.g., alcoholism, tobacco abuse, or drug abuse)), eating disorders (e.g., anorexia nervosa, bulimia nervosa, and binge eating disorder) and compulsive behavior disorders (e.g., primary impulse-control disorders or obsessive-compulsive disorder). Psychological disorders can be any psychological condition associated with one or more symptoms, e.g., somatic symptoms (e.g., chronic pain, anxiety disproportionate to severity of physical complaints, pain disorder, body dysmorphia, conversion (i.e., loss of bodily function due to anxiety), hysteria, or neurological conditions without identifiable cause), or psychosomatic symptoms (e.g., back pain, fibromyalgia, migraines, and chronic fatigue syndrome). Psychological disorders also include repetitive body-focused behaviors, such as tic disorders (e.g., Tourette's Syndrome, trichotillomania, nail-biting, temporomandibular disorder, thumb-sucking, repetitive oral-digital, lip-biting, fingernail biting, eye-rubbing, skin-picking, or a chronic motor tic disorder). In some cases, development of a psychological disorder is associated with or characterized by a prodromal symptom, such as depressed mood, decreased appetite, weight loss, increased appetite, weight gain, initial insomnia, middle insomnia, early waking, hypersomnia, decreased energy, decreased interest or pleasure, self-blame, decreased concentration, indecision, suicidality, psychomotor agitation, psychomotor retardation, crying more frequently, inability to cry, hopelessness, worrying/brooding, decreased self-esteem, irritability, dependency, self-pity, somatic complaints, decreased effectiveness, helplessness, and decreased initiation of voluntary responses.

As used herein, the terms "social phobia" and "social anxiety disorder" refer to a condition characterized by fear or anxiety associated with one or more social situations. Subjects with this

condition typically exhibit a marked fear or anxiety about one or more social situations in which the person is exposed to possible scrutiny by others. Examples include social interactions (e.g., having a conversation), being observed (e.g., eating or drinking), or performance in front of others (e.g., giving a speech). Typically, an individual with this condition (i) fears that he or she will act in a way, or show anxiety symptoms that will be negatively evaluated (i.e., be humiliating, embarrassing, lead to rejection, or offend others); (ii) the social situations almost invariably provoke immediate fear or anxiety; (iii) the social situations are avoided or endured with intense fear or anxiety; and (iv) the fear or anxiety is out of proportion to the danger posed by the social situation. In children, the fear or anxiety may be expressed by crying, tantrums, freezing, clinging, shrinking or refusal to speak in social situations. The fear, anxiety, and avoidance can cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The term "therapeutically effective amount," as used herein, refers to an amount, e.g., pharmaceutical dose, effective in inducing a desired effect in a subject or in treating a subject having a condition or disorder described herein (e.g., an inflammatory disorder). It is also to be understood herein that a "therapeutically effective amount" may be interpreted as an amount giving a desired therapeutic and/or preventative effect, taken in one or more doses or in any dosage or route, and/or taken alone or in combination with other therapeutic agents. For example, in the context of administering a composition described herein that is used for the treatment of a disorder or condition, an effective amount of a compound is, for example, an amount sufficient to prevent, slow down, or reverse the progression of the disorder or condition as compared to the response obtained without administration of the compound.

As used herein, the terms "treat," "treating," or "treatment" refer to administration of a compound or pharmaceutical composition for a therapeutic purpose. To "treat a disorder" or use for "therapeutic treatment" refers to administering treatment to a patient already suffering from a disease to ameliorate the disease or one or more symptoms thereof to improve the patient's condition (e.g., by reducing one or more symptoms of a 5-HT2 responsive condition, such as inflammation, depression, anxiety, Alzheimer's disease, etc.). The term "therapeutic" includes the effect of mitigating deleterious clinical effects of certain inflammatory processes (i.e., consequences of the inflammation, rather than the symptoms of inflammation). The methods of the invention can be used as a primary prevention measure, i.e., to prevent a condition or to reduce the risk of developing a condition. Prevention refers to prophylactic treatment of a patient who may not have fully developed a condition or disorder, but who is susceptible to, or otherwise at risk of, the condition. Thus, in the claims and embodiments, the methods of the invention can be used either for therapeutic or prophylactic purposes.

By "unipolar depression" or "major depressive disorder" is meant a clinical course that is characterized by one or more major depressive episodes in an individual without a history of manic, mixed, or hypomanic episodes. The diagnosis of unipolar depression is not made if: manic, mixed, or hypomanic episodes develop during the course of depression; if the depression is due to the direct physiological effects of a substance; if the depression is due to the direct physiological effects of a general medical condition; if the depression is due to a bereavement or other significant loss ("reactive depression"); or if the episodes are better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder. If manic, mixed, or hypomanic episodes develop, then the diagnosis is changed to a bipolar disorder. Depression may be associated with chronic general medical conditions (e.g., diabetes, myocardial

infarction, carcinoma, and stroke). Generally, unipolar depression is more severe than dysthymia. The essential feature of a major depressive episode is a period of at least two15 weeks during which there is either depressed mood or loss of interest or pleasure in nearly all activities. In children and adolescents, the mood may be irritable rather than sad. The episode may be a single episode or may be recurrent. The individual also experiences at least four additional symptoms drawn from a list that includes changes in appetite or weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts. Each symptom must be newly present or must have clearly worsened compared with the person's pre-episode status. The symptoms must persist for most of the day, nearly every day, for at least two consecutive weeks, and the episode must be accompanied by clinically significant distress or impairment in social, occupational (or academic), or other important areas of functioning (Diagnostic and Statistical Manual of Mental Disorders (OSM IV), American Psychiatric Press, 4th Edition, 1994). Diagnostic guidance for psychological disorders can be found, for example, in the ICD-10 (The ICD-10 Classification of Mental and Behavioral Disorders: Diagnostic Criteria for Research, Geneva: World Health Organization, 1993) and the DSM-V (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) Arlington, VA.; American Psychiatric Association, 2013).

Other features and advantages of the invention will be apparent from the following Detailed Description, Examples, and Claims.

DETAILED DESCRIPTION OF THE INVENTION

The invention features compounds of any one of formulas (I)-(VIf). The compounds are useful for treating 5-HT2 responsive conditions (e.g., inflammation, pain, depression, anxiety, PTSD, and Alzheimer's disease). The compounds can be resistant to metabolism (e.g., by monoamineoxidase degradation in vivo), and can exhibit a longer in-vivo half-life and hence longer lasting pharmacological effect.

Serotonin (also referred to as 5-hydroxytryptamine or 5-HT) is a neurotransmitter that has been strongly implicated in the pathophysiology and treatment of a wide variety of neuropsychiatric disorders. Serotonin exerts its effects through a diverse family of serotonin receptor molecules or serotonin reuptake sites (referred to herein as "5-HT receptors," "5-HTRs," or the SERT). Classically, members of the serotonin receptor family have been grouped into seven (7) subtypes pharmacologically, i.e., according to their specificity of various serotonin antagonists. Thus, although all the 5-HT receptors specifically bind with serotonin, they are pharmacologically distinct and are encoded by separate genes. To date, fourteen (14) mammalian serotonin receptors have been identified and sequenced. More particularly, these fourteen separate 5-HT receptors have been grouped into seven (7) pharmacological subtypes, designated 5-HT1, 5-HT2, 5-HT3, 5-HT4, 5-HT5, 5-HT6, and 5-HT7. Several of the subtypes are further subdivided such that the receptors are grouped pharmacologically as follows: 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3A, 5-HT3B, 5-HT4, 5-HT5A, 5-HT6, 5-HT7.

Of the fourteen different mammalian serotonin receptors that have been cloned, all but one are members of the G-protein coupled receptor superfamily. Serotonin receptors 5-HT1A, 5-HT1B, and 5-HT1D inhibit adenylate cyclase, and 5-HT2 receptors activate phospholipase C pathways, stimulating

breakdown of polyphosphoinositides. The 5-HT2 receptor belongs to the family of rhodopsin-like signal transducers that are distinguished by a seven-transmembrane configuration and functional linkage to G-proteins. The 5-HT3 receptor family includes ligand-gated ion channel receptors that have four putative TMDs.

Serotonin regulates a wide variety of sensory, motor, and behavioral functions in the mammalian CNS, including behaviors such as learning and memory, sleep, thermoregulation, motor activity, pain, sexual and aggressive behaviors, appetite, neuroendocrine regulation, and biological rhythms. Serotonin has also been linked to pathophysiological conditions such as anxiety, depression, obsessive-compulsive disorders, schizophrenia, suicide, autism, migraine, emesis, alcoholism and neurodegenerative disorders. This biogenic amine neurotransmitter is synthesized by neurons of the brain stem that project throughout the CNS, with highest density in basal ganglia and limbic structures (Steinbusch, 1984, In: Handbook of Chemical Neuroanatomy 3:68-125, Bjorklund et al., Eds., Elsevier Science Publishers, B. V.).

Studies have suggested that serotonin may play a role in the immune system because data demonstrate that serotonin receptors are present on various cells of the immune system. There have been reports in the literature about the immunomodulatory effects of adding serotonin exogenously to mitogenically stimulated lymphocyte cultures. Under some circumstances, serotonin has been shown to stimulate activated T cells (Foon et al., 1976, J. Immunol. 117:1545-1552; Kut et al., 1992, Immunopharmacol. Immunotoxicol. 14:783-796; Young et al., 1993, Immunology 80:395-400), whereas other laboratories report that high concentrations of added serotonin inhibit the proliferation (Slauson et al., 1984, Cell. Immunol. 84:240-252; Khan et al., 1986, Int. Arch. Allergy Appl. Immunol. 81:378-380; Mossner & Lesch, 1998, Brain, Behavior, and Immunity 12:249-271).

Of the fourteen known pharmacologically distinct serotonin receptors, lymphocytes express type 2A, type 2B, type 2C, type 6 and type 7 on resting cells (Ameisen et al., 1989, J. Immunol. 142:3171-3179; Stefulj et al., 2000, Brain, Behavior, and Immunity 14:219-224) and that the type 1A and type 3 receptors are up-regulated upon activation (Aune et al., 1993, J. Immunol. 151:1175-1183; Meyniel et al., 1997, Immunol. Lett. 55:151-160; Stefulj et al., 2000, Brain, Behavior, and Immunity 14:219-224).

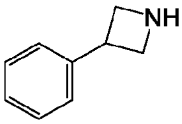
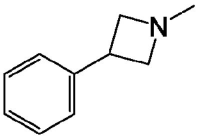
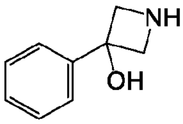
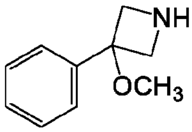
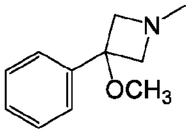
The involvement of 5-HT1A receptors in human and murine T cells has also been demonstrated (Aune et al., 1990, J. Immunol. 145:1826-1831; Aune et al., 1993, J. Immunol. 151:1175-1183; Aune et al., 1994, J. Immunol. 153:1826-1831). These studies established that IL-2-stimulated human T cell proliferation could be inhibited by a blockade of tryptophan hydroxylase, i.e., the first enzyme involved in the conversion of tryptophan to serotonin, and that the inhibition could be reversed by the addition of 5-hydroxytryptophan. Furthermore, human T cell proliferation was blocked in vitro with a 5-HT1A-specific receptor antagonist. In a murine model, a type 1A receptor antagonist, but not a type 2 receptor antagonist, was able to inhibit the in vivo contact sensitivity response, but not antibody responses, to oxazalone.

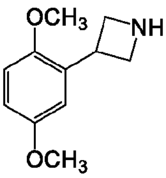
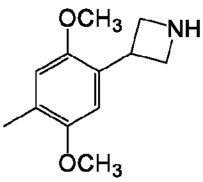
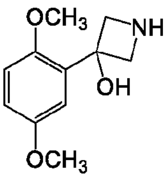
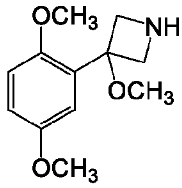
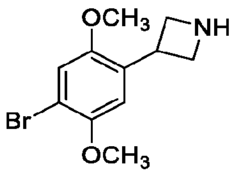
PCT Publication No. WO 03/106660 discloses the use of fluphenazine, an antagonist of 5-HT(1B/1D) and 5-HT(2C) receptors, for inhibiting proliferation and inducing cell death in lymphocytes.

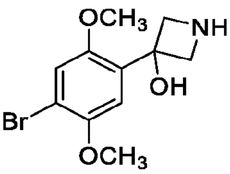
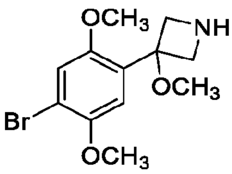
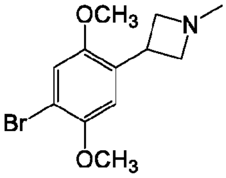
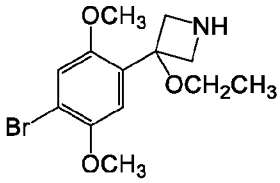
The new chemotypes of the invention can be screened for activity at the various 5-HT subtypes or monoamine transporters as described in Example 2.

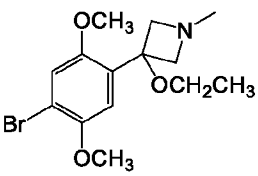
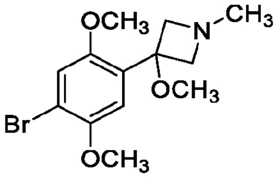
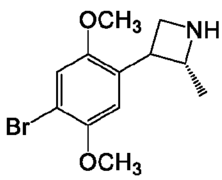
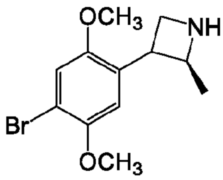
Compounds

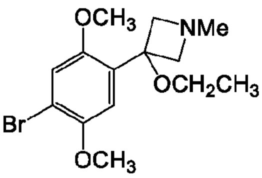
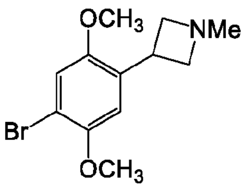
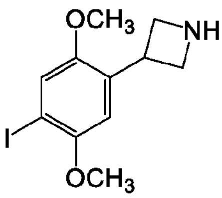
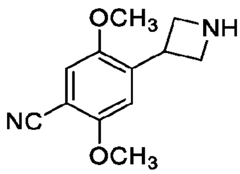
The invention features compounds of any one of formulas (I)-(VI). In particular embodiments, the compound of formula (I) is selected from:

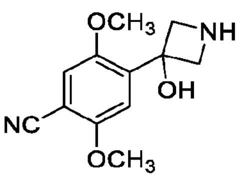
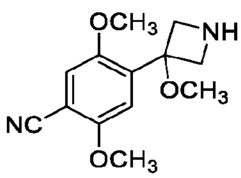
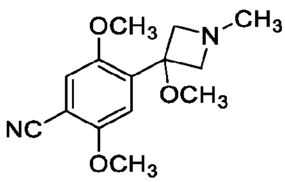
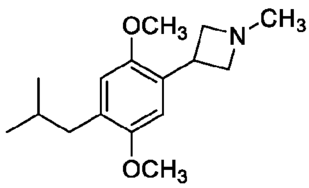
 ,  ,  ,  ,  ,

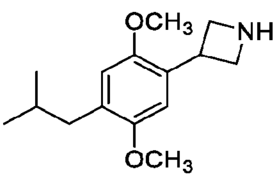
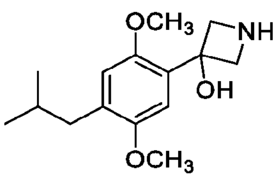
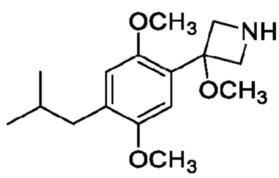
 ,  ,  ,  ,  ,

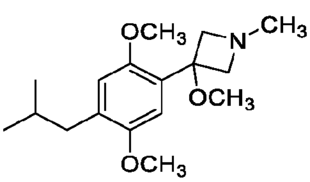
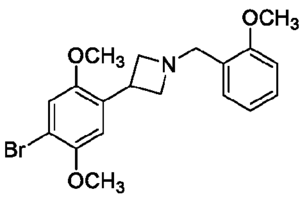
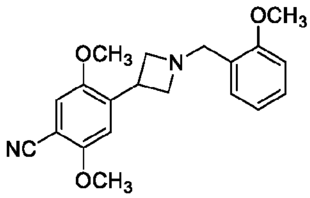
 ,  ,  ,  ,

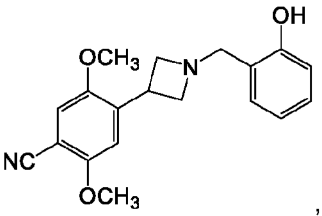
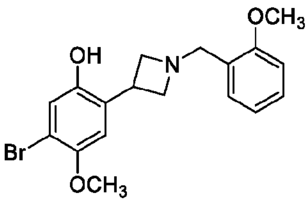
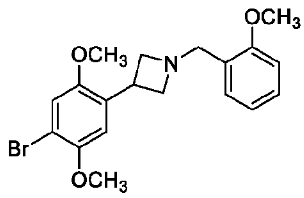
 ,  ,  ,  ,

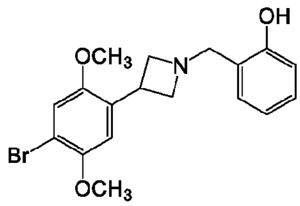
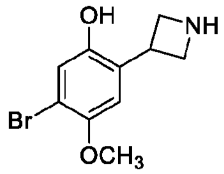
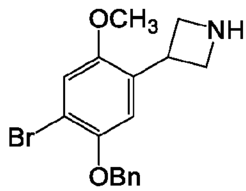
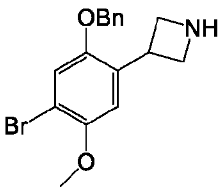
 ,  ,  ,  ,

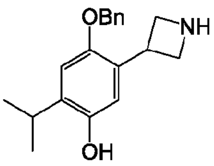
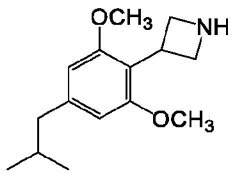
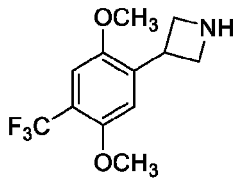
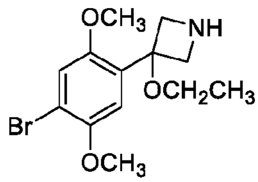
 ,  ,  ,  ,

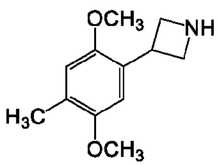
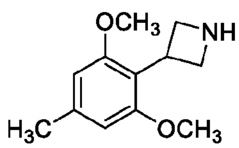
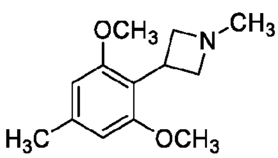
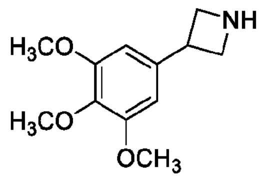
 ,  ,  ,

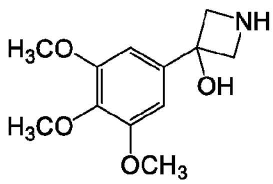
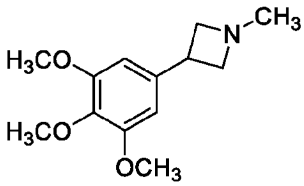
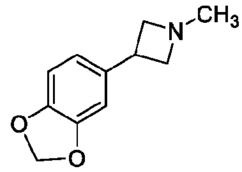
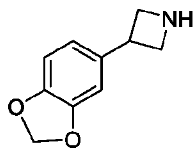
 ,  ,  ,

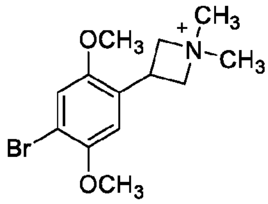
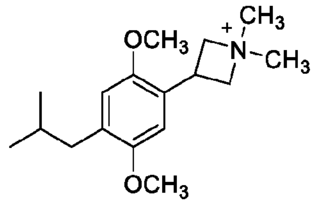
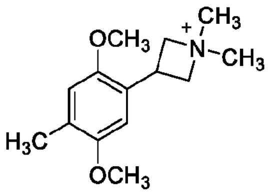

OH
OCH3
N
NC
OCH3
,

OCH3
OH
N
Br
OCH3
,

OCH3
OCH3
N
Br
OCH3
,

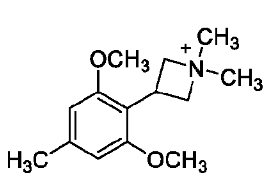
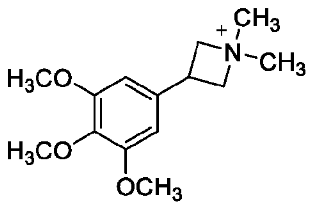
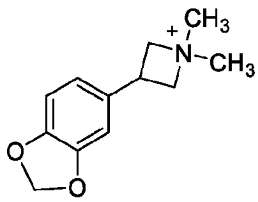
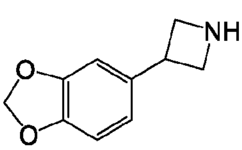

OH
OCH3
N
Br
OCH3
,

OH
NH
Br
OCH3
,

OCH3
NH
Br
OBn
,

OBn
NH
Br
O
,

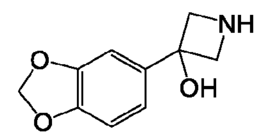
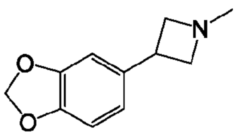
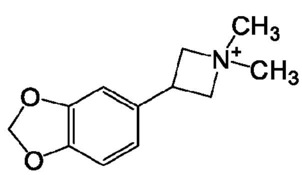
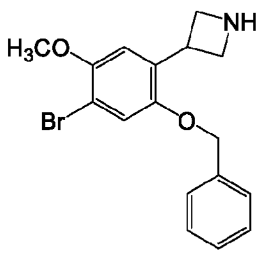

OBn
NH
OH
,

OCH3
NH
OCH3
,

OCH3
NH
F3C
OCH3
,

OCH3
NH
OCH2CH3
Br
OCH3
,

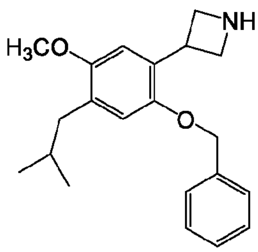
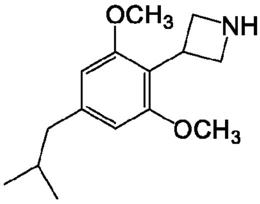
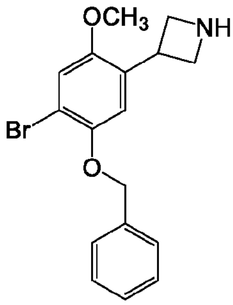

OCH3
NH
H3C
OCH3
,

OCH3
NH
H3C
OCH3
,

OCH3
N
CH3
H3C
OCH3
,

NH
H3CO
H3CO
OCH3
,

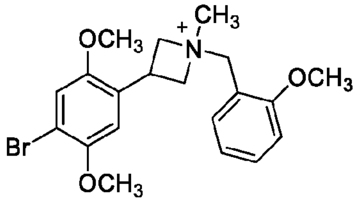

NH
H3CO
OH
H3CO
OCH3
,

N
CH3
H3CO
H3CO
OCH3
,

N
CH3
O
O
,

NH
O
O
,


OCH3
+
CH3
N
CH3
Br
OCH3
,

OCH3
+
CH3
N
CH3
OCH3
,

OCH3
+
CH3
N
CH3
H3C
OCH3
,


OCH3
+
CH3
N
CH3
H3C
OCH3
,

+
CH3
N
CH3
H3CO
H3CO
OCH3
,

+
CH3
N
CH3
O
O
,

NH
O
O
,


NH
O
OH
O
,

N
O
O
,

CH3
N
+
CH3
O
O
,

NH
H3CO
Br
O
,

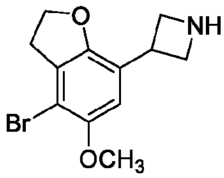
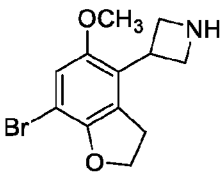
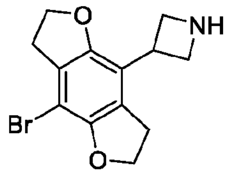
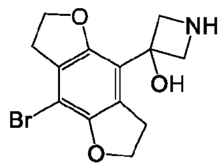
 ,  ,  ,and

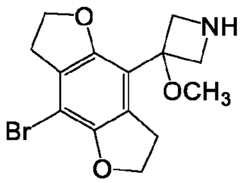
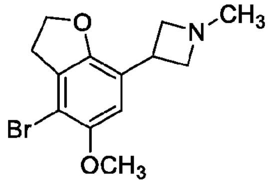
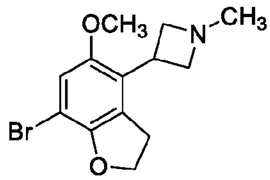
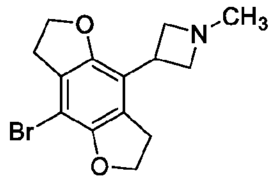
 ,

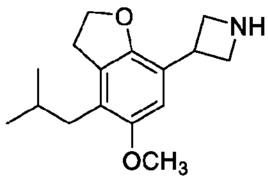
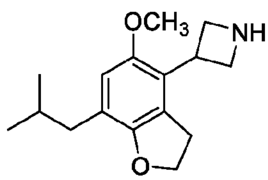
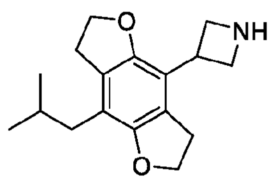
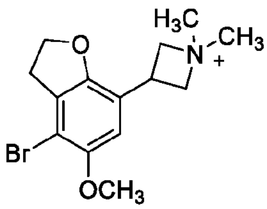
and pharmaceutically acceptable salts thereof.

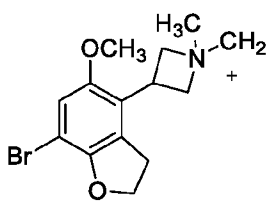
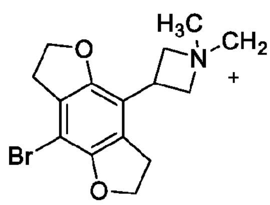
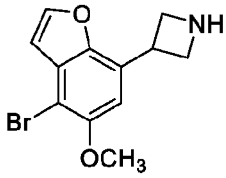
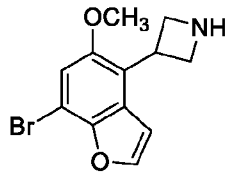
The compounds of formula (I) can be synthesized using methods analogous to those described in the examples.

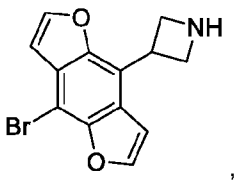
The invention further features compounds of any one of formulas (VIa)-(VIf). In particular embodiments, the compound of any one of formulas (VIa)-(VIf) is selected from:

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

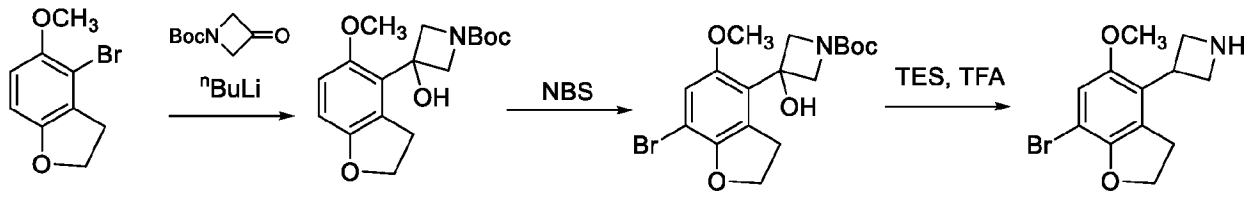
 ,  ,  ,  , and



and pharmaceutically acceptable salts thereof.

The compounds of formulas (VIa)-(VIf) can be synthesized using methods analogous to those described, e.g., in Isberg et al., PLOS One; 8(11): e78515 (2013); Parker et al., J. Med. Chem. 41:5148 (1998); Chambers et al., J. Med. Chem. 44:1003 (2001); and Monte et al., J. Med. Chem. 39:2953 (1996); the synthetic methods described in the examples, and in Scheme 1.

Scheme 1



Pharmaceutical Compositions

Pharmaceutical Compositions of any of the aforementioned compounds include tablets for oral use containing the compound in a mixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, starches including potato starch, sodium chloride, or lactose); granulating and disintegrating agents (e.g., cellulose derivatives including microcrystalline cellulose, starches including potato starch, croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose, glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch, pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.

In some embodiments, a pharmaceutically acceptable excipient is at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use in humans and for veterinary use. In some embodiments, an excipient is approved by the United States Food and Drug Administration. In some embodiments, an excipient is pharmaceutical grade. In some embodiments, an excipient meets the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

In some embodiments, the pharmaceutical composition is prepared, packaged, and/or sold in a formulation suitable for pulmonary administration, e.g., via a nebulizer. Such a formulation may

include dry particles that include the active ingredient and which have a diameter in the range from about 0.5 nm to about 7 nm or from about 1 nm to about 6 nm. Such compositions are conveniently in the form of dry powders for administration using a device including a dry powder reservoir to which a stream of propellant may be directed to disperse the powder and/or using a self-propelling solvent/powder dispensing container such as a device including the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders include particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nm and at least 95% of the particles by number have a diameter less than 7 nm. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nm and at least 90% of the particles by number have a diameter less than 6 nm. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50% to 99.9% (w/w) of the composition, and active ingredient may constitute 0.1% to 20% (w/w) of the composition. A propellant may further include additional ingredients such as a liquid non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles including the active ingredient).

Pharmaceutical compositions formulated for pulmonary delivery may provide an active ingredient in the form of droplets of a solution and/or suspension. Such formulations may be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, including active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further include one or more additional ingredients including, but not limited to, a flavoring or sweetening agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. Droplets provided by this route of administration may have an average diameter in the range from about 0.1 nm to about 200 nm.

Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder including the active ingredient and having an average particle from about 0.2 μm to 500 μm. Such a formulation is administered in the manner in which snuff is taken, *i.e.* by rapid inhalation through the nasal passage from a container of the powder held close to the nose.

Formulations suitable for nasal administration may, for example, include from about as little as 0.1% (w/w) and as much as 100% (w/w) of active ingredient, and may include one or more of the additional ingredients described herein. A pharmaceutical composition may be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration. Alternately, formulations suitable for buccal administration may include a powder and/or an aerosolized and/or atomized solution and/or suspension including active ingredient. Such powdered, aerosolized, and/or aerosolized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 nm to about 200 nm, and may further include one or more of any additional ingredients described herein.

Pharmaceutical compositions may be in the form of tablets and/or lozenges made using conventional methods, and may contain from 0.1% to 20% (w/w) active ingredient, the balance including

an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Tablets may be uncoated or they may be coated by known techniques, optionally to delay disintegration and absorption in the gastrointestinal tract and thereby providing a sustained action over a longer period. For example, the coating may be adapted to release the compound in a predetermined pattern (e.g., in order to achieve a controlled release formulation) or it may be adapted not to release the compound until after passage through the stomach. The coating may be a sugar coating, a film coating (e.g., based on hydroxypropyl methylcellulose, methylcellulose, methyl hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, acrylate copolymers, polyethylene glycols and/or polyvinylpyrrolidone), or an enteric coating (e.g., based on methacrylic acid copolymer, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, shellac, and/or ethylcellulose). Additionally or alternatively, a time-delay material such as, e.g., glyceryl monostearate or glyceryl distearate may be incorporated in a tablet.

Solid tablet compositions may include a coating adapted to protect the compound from unwanted chemical changes, (e.g., chemical degradation prior to the release of the compound). The coating may be applied on the solid dosage form in a similar manner to that described in Encyclopedia of Pharmaceutical Technology (eds. J. Swarbrick and J. C. Boylan, 1988-1999, Marcel Dekker, New York).

Pharmaceutical compositions for oral use may also be presented as chewable tablets, or as hard gelatin capsules in which the compound is mixed with an inert solid diluent (e.g., potato starch, lactose, microcrystalline cellulose, calcium phosphate, or kaolin), or as soft gelatin capsules wherein the compound is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Powders and granulates may be prepared using the ingredients mentioned above under tablets and capsules in a conventional manner using, e.g., a mixer, a fluid bed apparatus or a spray drying equipment.

Powders, dispersible powders, or granules suitable for preparation of an aqueous suspension by addition of water are convenient dosage forms for oral administration of compounds. Formulation as a suspension provides the compound in a mixture with a dispersing or wetting agent, suspending agent, and one or more preservatives. Suitable dispersing or wetting agents are, for example, naturally-occurring phosphatides (e.g., lecithin or condensation products of ethylene oxide with a fatty acid, a long chain aliphatic alcohol, or a partial ester derived from fatty acids) and a hexitol or a hexitol anhydride (e.g., polyoxyethylene stearate, polyoxyethylene sorbitol monooleate, polyoxyethylene sorbitan monooleate, and the like). Suitable suspending agents are, for example, sodium carboxymethylcellulose, methylcellulose, sodium alginate, and the like.

The pharmaceutical composition may also be administered parenterally by injection, infusion or implantation (intravenous, intramuscular, subcutaneous, or the like) in dosage forms, formulations, or via suitable delivery devices or implants containing conventional, non-toxic pharmaceutically acceptable carriers, and adjuvants. The formulation and preparation of such compositions are well known to those skilled in the art of pharmaceutical formulation. Formulations can be found in Hayes (Remington: The Science and Practice of Pharmacy, volume I and volume II. Twenty-second edition. Philadelphia, 2012).

Compositions for parenteral use (e.g., intravenous administration) may be provided in unit dosage forms (e.g., in single-dose ampoules), or in vials containing several doses and in which a suitable preservative may be added (see below). The composition may be in form of a solution, a suspension, an

emulsion, an infusion device, or a delivery device for implantation, or it may be presented as a dry powder to be reconstituted with water or another suitable vehicle before use. Apart from the compound (e.g., a compound having the structure of any one of formulas (I)-(VI)), the composition may include suitable parenterally acceptable carriers and/or excipients. The compound may be incorporated into microspheres, microcapsules, nanoparticles, liposomes, or the like for controlled release. Furthermore, the composition may include suspending, solubilizing, stabilizing, pH-adjusting agents, and/or dispersing agents.

As indicated above, the pharmaceutical compositions according to the invention may be in a form suitable for sterile injection. To prepare such a composition, the compound is dissolved or suspended in a parenterally acceptable liquid vehicle. Among acceptable vehicles and solvents that may be employed are water, water adjusted to a suitable pH by addition of an appropriate amount of hydrochloric acid, sodium hydroxide or a suitable buffer, 1,3-butanediol, Ringer's solution, and isotonic sodium chloride solution. The aqueous formulation may also contain one or more preservatives (e.g., methyl, ethyl or n-propyl p-hydroxybenzoate). In cases where one of the compound is only sparingly or slightly soluble in water, a dissolution enhancing or solubilizing agent can be added, or the solvent may include 10-60% w/w of propylene glycol or the like.

Methods

Provided herein are methods of using a compound or pharmaceutical composition described herein to treat 5-HT2 responsive conditions in a subject. Methods of treating 5-HT2 responsive conditions include administering to a subject in need thereof a therapeutically effective amount of a compound or pharmaceutical composition of the invention.

The exact amount of the compound or composition required for therapeutic effect can vary from subject to subject, depending on the species, age, weight, and general condition of the subject, the severity of the disease, the particular composition, its mode of administration, its mode of activity, and the like. Pharmaceutical compositions in accordance with the present disclosure are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of the compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective level for any particular subject will depend upon a variety of factors including the particular inflammatory disorder being treated and the severity thereof; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

Compositions described herein may be administered to subjects, such as human patients or, alternatively, to other mammals, such as domesticated animals, cats, dogs, mice, or rats.

Compositions described herein may be administered by any route. In some embodiments, the present compound or pharmaceutical composition thereof is administered by one or more of a variety of routes, including nasal, buccal, oral, by inhalation (e.g., as an oral spray, nasal spray, or aerosol), intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (e.g., by

powders, ointments, creams, gels, lotions, and/or drops), mucosal, enteral, vitreal, intratumoral, sublingual; by intratracheal instillation, bronchial instillation, and/or through a portal vein catheter. In some embodiments the composition is administered by systemic intravenous injection. In specific embodiments the composition is administered intravenously and/or orally.

A compound of the invention can be administered in a therapeutically effective amount (e.g., an amount that results in the desired therapeutic effect, e.g., within the therapeutic window between a dose sufficient to reduce inflammation and a dose that elicits a psychoactive effect (about a ten-fold difference)). In some embodiments, the compound is administered in an amount resulting in circulating drug plasma levels of less than 20 ng/mL (e.g., 0.05 to 20 ng/mL, e.g., 0.1 to 15 ng/mL, 0.5 to 10 ng/mL, or 1 to 5 ng/mL, e.g., 0.05 to 0.1 ng/mL, 0.1 to 0.2 ng/mL, 0.2 to 0.3 ng/mL, 0.3 to 0.4 ng/mL, 0.4 to 0.5 ng/mL, 0.5 to 1.0 ng/mL, 1.0 to 5 ng/mL, 5 to 10 ng/mL, 10 to 15 ng/mL, or 15 to 20 ng/mL, e.g., about 0.05 ng/mL, 0.1 ng/mL, 0.2 ng/mL, 0.5 ng/mL, 1.0 ng/mL, 2.0 ng/mL, 2.5 ng/mL, 5.0 ng/mL, 7.5 ng/mL, 10 ng/mL, 12 ng/mL, 15 ng/mL, or 20 ng/mL), e.g., in a human subject. In some embodiments, the circulating drug plasma level of the compound is below the limit of detection (e.g., 0.1 ng/mL or less). In some embodiments, a therapeutically effective amount of the compound can be less than about 20 µg/kg body weight (e.g., less than 20 µg/kg, less than 15 µg/kg, less than 10 µg/kg, or less than 5 µg/kg body weight, e.g., from 1 to 20 µg/kg body weight, e.g., from 1 to 5 µg/kg, from 5 to 10 µg/kg, from 10 to 15 µg/kg, or from 15 to 10 µg/kg, e.g., about 5 µg/kg, about 10 µg/kg, about 15 µg/kg, or about 20 µg/kg).

In certain embodiments, compositions in accordance with the present disclosure may be administered at dosage levels sufficient to deliver from about 0.0001 µg/kg to about 1 mg/kg, from about 0.01 µg/kg to about 500 µg/kg, from about 0.1 µg/kg to about 400 µg/kg, from about 0.5 µg/kg to about 30 µg/kg, from about 0.01 µg/kg to about 10 µg/kg, from about 0.1 µg/kg to about 10 µg/kg, or from about 1 µg/kg to about 25 µg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect. The desired dosage may be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In some embodiments, the compound is administered at a frequency of one to three times per week (e.g., once per week, twice per week, three times per week, four times per week, five times per week, six times per week, seven times per week, or more, e.g., once daily, twice daily, three times daily, etc.). In some embodiments, the compound is administered intermittently, e.g., every other day, every other week, once per month, etc. In certain embodiments, the desired dosage may be delivered using multiple administrations (e.g., two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

Compositions described herein may be used in combination with one or more other therapeutic, prophylactic, diagnostic, or imaging agents. By "in combination with," it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Pharmaceutical compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, diagnostic, or imaging compositions in

combination with agents that improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

It will further be appreciated that compounds or compositions utilized in combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that agents utilized in combination with be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

Psychological Conditions

In particular embodiments, the 5-HT2 responsive condition to be treated is a psychological condition. Disclosed herein are methods of treating psychological conditions. The psychological condition may be any psychological condition described herein. In some embodiments the psychological condition is depression, anxiety, addiction, post-traumatic stress disorder (PTSD), an eating disorder, or compulsive behavior. In some embodiments, the psychological condition may be depression. The psychological condition may also be anxiety. The anxiety may be experienced by a subject who is receiving palliative care or is enrolled in a hospice program. In certain embodiments, the subject who is experiencing anxiety has symptoms such as hypervigilance, fatigue, racing thoughts, irritability, excessive worry, and/or fear.

A subject with a psychological condition may be diagnosed by a clinician, a physician, or a therapist. The subject may be diagnosed with a psychological condition by evaluation of the subject's symptoms by a physician, clinician, or therapist based on a physical examination. For example, a blood test may be used to evaluate blood concentration levels of certain biomarkers such as hormones, calcium, vitamin D, electrolytes, and iron in diagnosing depression. Additionally or alternatively, for patients with a possible depression condition a depression screening test may be performed by the physician, clinician, or therapist to aid in the diagnosis of depression. The depression screening test may be the Patient Health Questionnaire-9 (PHQ-9), the Beck Depression Inventory (BDI), the Zung Self-Rating Depression Scale, the Center for Epidemiological Studies Depression Scale (CES-D), the Hamilton Rating Scale for Depression (HRSD), or the Montgomery-Asberg Depression Rating Scale (MADRS-C). In some embodiments, the methods described herein may be used to treat psychosomatic pain conditions. In some embodiments, the psychosomatic pain condition may be fibromyalgia, chronic fatigue, migraines, or back pain.

In some embodiments, the patient is being treated for depression with a compound of any one of formulas (I)-(VI). The patient may have their symptoms of depression evaluated using a depression screening test. The symptoms of depression may be evaluated by a clinician using the Clinical Global Impression (CGI) rating. The depression screening test may be the Patient Health Questionnaire-9 (PHQ-9), the Beck Depression Inventory (BDI), the Zung Self-Rating Depression Scale, the Center for Epidemiological Studies Depression Scale (CES-D), the Hamilton Rating Scale for Depression (HRSD), and/or the Montgomery-Asberg Depression Rating Scale (MADRS). The patient being treated for depression with a compound of any one of formulas (I)-(VI) may have their symptoms of depression evaluated using the Montgomery-Asberg Depression Rating Scale (MADRS-C). In some embodiments, the patient evaluated using the MADRS-C by a clinician, physician, or third party rater. In certain embodiments, the patient may self-evaluate using the MADRS. The patient's score obtained using the

MADRS-C may be decreased compared to the score before treatment. The patient's score may decreased by at least 50% compared to the score before treatment. The patient's score obtained using the MADRS-C may be less than 10. In some embodiments, the decrease in the patient's score using the MADRS-C is decreased for 1 week after treatment. In certain embodiments, the decrease in the patient's score using the MADRS-C is decreased for 4 weeks after treatment. In particular embodiments, the patient's score using the MADRS-C is decreased for more than 4 weeks after treatment.

In certain embodiments, the patient is being treated for anxiety with a compound of any one of formulas (I)-(VI). The patient may have their symptoms of anxiety evaluated using an anxiety screening test. The anxiety screening test may be the Zung Self-Rating Anxiety Scale, the Hamilton Anxiety Scale, the Beck Anxiety Inventory, the Social Phobia Inventory, the Penn State Worry Questionnaire, the Yale-Brown Obsessive-Compulsive Scale, or the - General Anxiety Disorder-7. In some embodiments, the patient's anxiety score using any one of these screening tests decreases in comparison to the patient's score before receiving treatment. In certain embodiments, the patient's anxiety score using any one of the above screening tests decreases by 50% in comparison to the patient's score before receiving treatment. In particular embodiments, the patient meets fewer criteria for anxiety as described by the Diagnostic and Statistical Manual of Mental Disorders in comparison before receiving treatment.

In one embodiment, the methods of the invention are used to treat psychological conditions, e.g., depression, anxiety, PTSD, an eating disorder, and compulsive behavior , by administering a compound of any one of formulas (I)-(VI) as needed to treat the symptoms associated with the psychological condition.

Neurological Injuries

In particular embodiments, the 5-HT2 responsive condition to be treated is a neurological injury. Also disclosed herein are methods of treating a neurological injury. The neurological injury may be any neurological injury. In some embodiments, the neurological injury is a stroke, a traumatic brain injury, or a spinal cord injury. The methods of treating a neurological injury described herein may reduce acute inflammation. In certain embodiments, hippocampal hyperactivity is reduced. Also, the methods described herein for treating a neurological injury may be administered in combination with a behavioral, physical, or speech therapy.

In particular embodiments, the methods of the invention are used to treat a neurological injury, e.g., stroke, traumatic brain injury, and spinal cord injury, by administering a compound of any one of formulas (I)-(VI) as needed to pain, inflammation, and/or other symptoms associated with the neurological injury.

Inflammatory Conditions

In particular embodiments, the 5-HT2 responsive condition to be treated is an inflammatory condition. An inflammatory condition in a subject can be treated with a compound of any one of formulas (I)-(VI) using the methods of the invention. The inflammatory condition to be treated can be a lung inflammation (e.g., chronic obstructive pulmonary disease (COPD)), neuroinflammation (e.g., Alzheimer's disease), chronic inflammation, rheumatoid arthritis, atherosclerosis, psoriasis, type II

diabetes, inflammatory bowel disease, Crohn's disease, conjunctivitis, multiple sclerosis, and/or septicemia.

In one embodiment, inflammation is treated by administering a compound of any one of formulas (I)-(VI) as needed to treat (i) acute attacks of inflammation (e.g., inflammatory bowel disease), or (ii) chronic inflammatory conditions (e.g., arthritis).

Chronic Pain

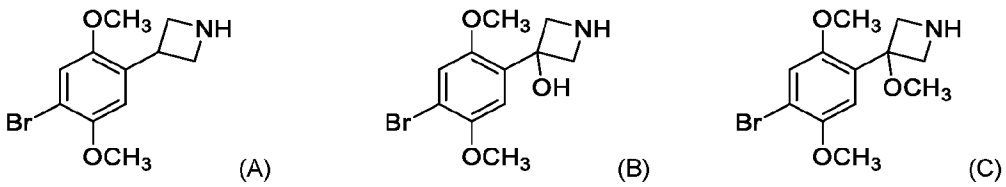
In particular embodiments, the 5-HT2 responsive condition to be treated is chronic pain. A disorder of condition associated with chronic pain can be treated with a compound of any one of formulas (I)-(VI) using the methods of the invention. The chronic pain may result from post-operative pain, tension headaches, chronic lower back pain, fibromyalgia, nephropathy, multiple sclerosis, shingles, complex regional pain syndrome, cephalic pain, or sciatica. The chronic pain may arise from an operation. The chronic pain may also be pain associated with a particular disease or condition such as nephropathy, multiple sclerosis, shingles, or complex regional pain syndrome. One particular disorder or condition associated with cephalic pain can be treated with a compound of any one of formulas (I)-(VI) using the methods of the invention. As used herein, a disorder or condition associated with cephalic pain is a disorder or condition which has as one of its symptoms cephalic/head pain (e.g., headache). Examples of such disorders or conditions include trigeminal autonomic cephalalgias such as episodic and chronic cluster headache (CH), episodic and chronic paroxysmal hemicrania (PH), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). Other examples of disorders or conditions which can be treated according to the present invention include vascular headaches (e.g., migraine headaches), tension headaches, headaches associated with the use of a substance (e.g., triptans such as sumatriptan, benzodiazepines such as alprazolam, analgesics such as ibuprofen, ergots such as ergotamine, opioids such as morphine, recreational drugs such as caffeine, nicotine, alcohol, and hormone replacement therapy containing, for example, estrogen) or its withdrawal. Yet additional examples of disorders or conditions associated with cephalic pain include miscellaneous headache unassociated with a structural lesion, headache associated with a nonvascular intracranial disorder, headache associated with a non-cephalic infection, headache associated with a metabolic disorder, headache associated with a disorder of the cranium, neck, eyes, nose, sinuses, teeth, mouth, or other facial or cranial structure, nerve trunk pain and deafferentiation pain.

EXAMPLES

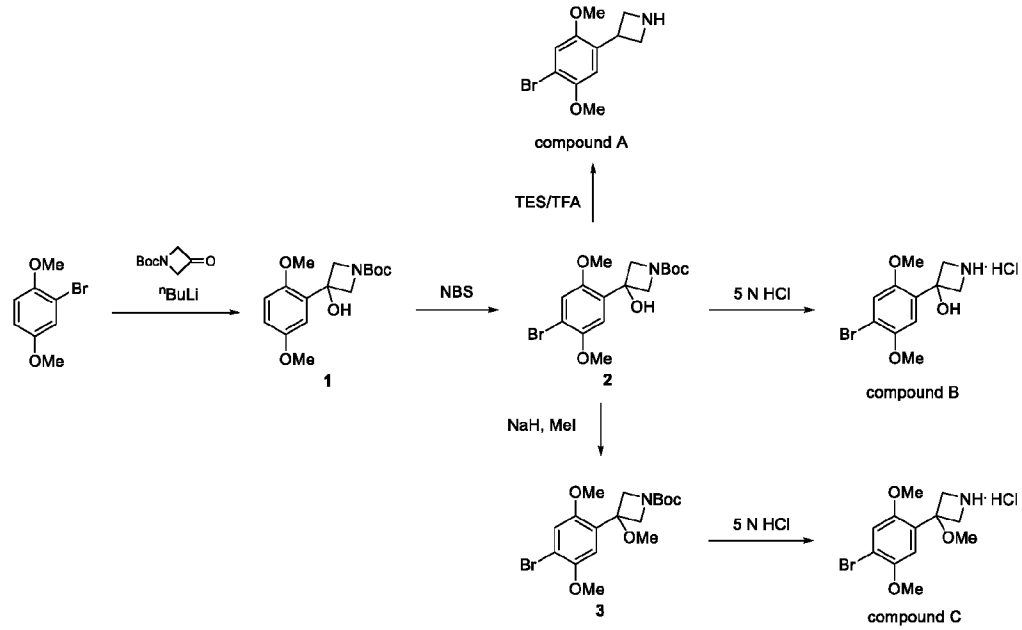
The following examples are put forth so as to provide those of ordinary skill in the art with a description of how the compositions and methods claimed herein can be performed, made, and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventor regards as his or her invention.

Example 1. Synthesis and characterization of Compounds (A)-(C).

Compounds (A)-(C) can be synthesized according to Scheme 1 (details below).



Scheme 1.



Procedures

Synthesis of tert-Butyl 3-(2,5-dimethoxyphenyl)-3-hydroxyazetidine-1-carboxylate (1).

A solution of 2-bromo-1,4-dimethoxybenzene (1.00 g, 4.6 mmol) in THF (15 mL) was cooled to -78ºC, and n-BuLi (1.6 M solution in hexane, 3.5 mL, 5.6 mmol) was added dropwise at -78°C over 5 min. The mixture was stirred for 0.5 h at this temperature, then a solution of N-Boc-azetidin-3-one (1.36g, 8 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 0.5 h and then allowed to warm to 0ºC and quenched with aqueous 10% NH_4Cl (20 mL) and EtOAc (20 mL×2). The organic phase was collected and washed with water (20 mL×2), saturated aqueous $NaHCO_3$ (20 mL×2), and brine (20 mL×1), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/Hexane =1:5 to 1:3) and afforded compound **1** (0.70 g, 49% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): ppm 7.12 (s, 1H), 6.88 (s, 1H), 5.30 (s, 1H), 4.30~4.33 (dd, *J* = 0.8 and 9.6 Hz, 2H), 4.10~4.13 (dd, *J* = 0.8 and 9.6 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 1.45 (s, 9H).

Synthesis of tert-Butyl 3-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxyazetidine-1-carboxylate (2)

NBS (480 mg, 27 mmol) was added to a solution of compound **1** (0.70 g, 2.3 mmol) in acetonitrile (15 mL) at room temperature. The mixture was stirred for 16h at room temperature, then concentrated. The crude was purified by silica gel chromatography (EtOAc/Hexane =1:5) and afforded compound **2** (293 mg, 33% yield).

Synthesis of Compound (B)

Compound 2 (950 mg, 2.56 mmol) was dissolved in EtOAc (3 mL), cooled to 0°C, then 5N HCl-EtOAc (10 mL) was added. The mixture was stirred at 0°C for 1 h, then allowed to warm to room temperature. The mixture was concentrated to dryness to afford crude. The crude was triturated with EtOAc/hexane (3 mL/6 mL), dried to afford compound **(B)** (239 mg, 58% yield) as HCl salt as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): ppm 9.36 (bs, 1H), 9.03 (bs, 1H), 7.30 (s, 1H), 7.06 (s, 1H), 4.39~4.46 (m, 2H), 3.94~3.99 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H). LC-MS: m/z 288.2 $[M+H]^+$.

Synthesis of Compound (A)

Compound **2** (300 mg, 0.77 mmol) was dissolved in TFA (3 mL), cooled to 0°C, then triethylsilane (1 mL) was added. The mixture was stirred at 0°C for 1 h, then allowed to warm to room temperature and stirred overnight. The mixture was concentrated, and the crude was purified by prep-HPLC to afford TFA salt. The TFA salt was dissolved in DCM, alkalized with aqueous 5% NaHCO3, extracted with DCM, dried and concentrated to afford compound **(A)** (120.8 mg, 57% yield) as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): ppm 8.79 (bs, 1H), 7.23 (s, 1H), 7.06 (s, 1H), 4.10~4.20 (m, 4H), 3.83 (s, 3H), 3.78 (s, 3H). LC-MS: m/z 272.2 $[M+H]^+$.

Synthesis of tert-Butyl 3-(4-bromo-2,5-dimethoxyphenyl)-3-methoxyazetidine-1-carboxylate (3)

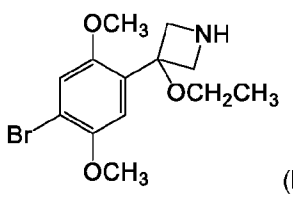
NaH (60% suspension on oil, 154 mg, 3.9 mmol) was added to a solution of compound **2** (1.00 g, 2.6 mmol) in THF (10 mL) at 0°C. The mixture was stirred for 5 min, and then MeI (0.5 mL) was added. The mixture was stirred for 0.5 h and then allowed to warm to room temperature, quenched with aqueous 10% NH_4Cl (10 mL), extracted with EtOAc (10 mL×3). The organic phase was collected and washed with water (20 mL×2), saturated aqueous $NaHCO_3$ (20 mL×2), and brine (20 mL×1), dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel chromatography (EtOAc/Hexane =1:6) and afforded compound **3** (870 mg, 84% yield).

Synthesis of Compound (C)

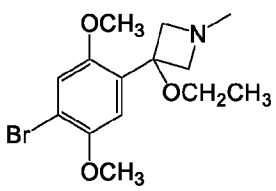
Compound **3** (870 mg, 2.17 mmol) was dissolved in EtOAc (3 mL), cooled to 0°C, then 5N HCl-EtOAc (10 mL) was added. The mixture was stirred at 0°C for 1 h, then allowed to warm to room temperature. The mixture was concentrated to dryness to afford crude. The crude was triturated with EtOAc/hexane (3 mL/6 mL), dried to afford compound **(C)** (499 mg, 67% yield) as HCl salt as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): ppm 9.36 (bs, 1H), 8.93 (bs, 1H), 7.34 (s, 1H), 6.95 (s, 1H), 4.33~4.37 (m, 2H), 4.09~4.13 (m, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.00 (s, 3H). LC-MS: m/z 303.9 $[M+H]^+$.

Example 2. Synthesis and characterization of Compounds (D)-(H).

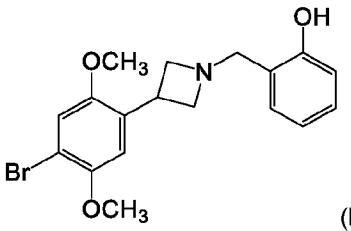
Compounds (D)-(H) shown below can be synthesized according to Scheme 2 (details below).



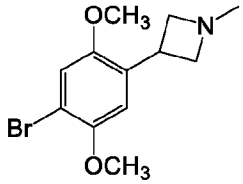
(D)



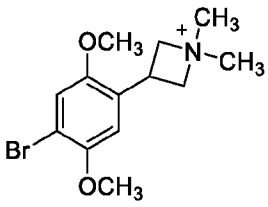
(E)



(F)

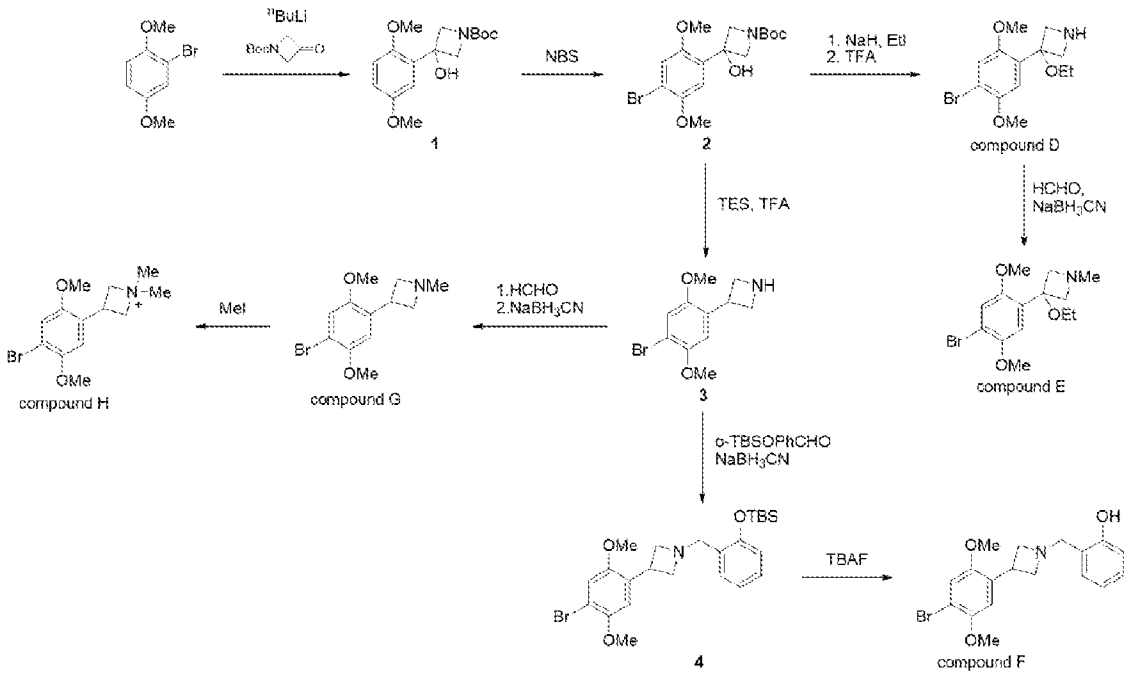


(G)



(H)

Scheme 2.



Procedures

Synthesis of tert-Butyl-3-(2,5-dimethoxyphenyl)-3-hydroxyazetidine-1-carboxylate (1)

A 1.6 M solution of n-BuLi in hexane (75.6 mL, 121 mmol) was added dropwise to a solution of 2-bromo-1,4-dimethoxybenzene (22.0 g, 101 mmol) in THF (120 mL) at -78 °C over 30 min. The mixture was stirred at -78 °C for 1 h. A solution of N-Boc-azetidine-3-one (24.2 g, 141 mmol) in THF (50 mL) was added dropwise over 30 min. The mixture was stirred for an additional 1 h and then quenched with aqueous 10% NH4Cl (100 mL), extracted with EtOAc (2 x 150 mL). The organic phase was collected and washed with brine (100 mL), dried (Na2SO4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:2) to afford compound **1** of Scheme 2 (20.1 g, 64% yield).

Synthesis of tert-Butyl33-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxyazetidine-1-carboxylate (2)

N-bromosuccinimide (NBS) (4.2 g, 23.3 mmol) and p-toluenesulfonic acid monohydrate (386 mg, 1.9 mmol) were added to a solution of compound **1** of Scheme 2 (6.0 g, 19.4 mmol) in acetonitrile (60 mL) at 0°C. The mixture was stirred for 16 h at room temperature and concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/hexane =1:2) to afford compound **2** of Scheme 2 (6.1 g, 81% yield).

Synthesis of 3-(4-Bromo-2,5-dimethoxyphenyl)azetidine (3)

Triethylsilane (28.6 mL, 157 mmol) was added to a solution of compound 2 (6.1 g, 15.7 mmol) in DCM (20 mL) and TFA (30.0 mLmL) at 0 °C. The resulting mixture was stirred for 0.5 h at 0 °C, and then allowed to warm to room temperature and stirred overnight. The mixture was concentrated, and the crude

was dissolved in DCM, alkalinized with aqueous 5% NaHCO3, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH=15:1) to afford compound **3** of Scheme 2 (3.6 g, 86% yield).

Synthesis of Compound (G)

Sodium cyanoborohydride (710 mg, 10.0 mmol) and AcOH (1.0 mL) were added to a solution of compound **3** of Scheme 2 (280 mg, 1.0 mmol) and formaldehyde (37% aq, 0.47 mL, 6.0 mmol) in MeOH/THF (6 mL/6 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred for 2h. The mixture was diluted with ice water (10 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried (Na2SO4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (MeOH/DCM=1:20) and afforded compound (G) (62 mg, 20% yield) as the free base, which was converted to compound (G) oxalate as a white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.24 (s, 1H), 7.02 (s, 1H), 4.10~4.40 (m, 5H), 3.83 (s, 3H), 3.77 (s, 3H), 2.83 (s, 3H). LC-MS: m/z 288.0 $[M+H]^+$.

Synthesis of Compound (H)

K2CO3 (304 mg, 2.2 mmol) and MeI (313 mg, 2.2 mmol) were added to a solution of compound **(G)** (300 mg,1.1 mmol) in ACN (10 mL) at room temperature. The mixture was stirred at room temperature for 3 h, then filtered. The filtrate was concentrated in vacuo. The crude product was triturated with EtOAc/ACN (3 mL/3 mL×2), then filtered to afford compound **(H)** (286 mg, 90% yield) as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.25 (s, 1H), 6.95 (s, 1H), 4.50~4.60 (m, 2H), 4.35~4.50 (m, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.32 (s, 3H), 3.13 (s, 3H). LC-MS: m/z 301.9 $[M]^+$.

Synthesis of 3-(4-Bromo-2,5-dimethoxyphenyl)-1-(2-(tert-butyldimethylsilyloxy)benzyl)-azetidine (4)

Sodium cyanoborohydride (1.1 g, 15.0 mmol) and AcOH (1.0 mL) were added to a solution of compound **3** of Scheme 2 (420 mg, 1.5 mmol) and 2-(tert-butyldimethylsilyloxy) benzaldehyde (1.82 g, 7.5 mmol) in MeOH/THF (6 mL/6 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred for 2h. The mixture was diluted with ice water (10 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried (Na2SO4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (MeOH/DCM=1:50) to afford compound **3** of Scheme 2 (340 mg, 45% yield).

Synthesis of Compound (F)

A 1.0 M solution of tetrabutylammonium fluoride (TBAF) in THF (1.0 mL, 1.03 mmol) was added to a solution of compound **3** of Scheme 2 (340 mg, 0.69 mmol) in THF (10 mL) at room temperature. The mixture was stirred for 4 h at room temperature, then quenched with water (20 mL) and extracted with EtOAc (2 x 20 mL). The organic phase was washed with brine (30 mL), dried (Na2SO4), then filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH =8:1) to afford compound **F** (75 mg, 29% yield) as an oil. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.12 (s, 1H), 7.05~7.10 (m, 2H), 6.98 (s, 1H), 6.70~6.80 (m, 2H), 3.83 (s, 3H), 3.55~3.85 (m, 8H), 3.10~3.20 (t, J = 6.8 Hz, 2H). LC-MS: m/z 377.3 $[M+H]^+$.

Synthesis of Compound (D)

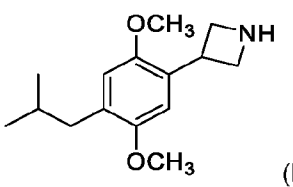
NaH (60%, 86 mg, 2.2 mmol) was added to a solution of compound **2** of Scheme 2 (600 mg, 1.55 mmol) in THF (20 mL) at 0ºC. The mixture was stirred at 0ºC for 1 h, and to it a solution of ethyl iodide (EtI) (482 mg, 3.1 mmol) in THF (10 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was quenched with ice water (40 mL), extracted with EtOAc (30 mL×2). The combined organic phases were washed with brine (50 mL×3), dried (Na2SO4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:4) and afforded the ethyl ether. This ether was dissolved in DCM (10 mL), and TFA (15 mL) was added at 0°C. The mixture was allowed to warm to room temperature and stirred for 3 h, then concentrated. The crude was dissolved in DCM, alkalinized with aqueous 5% NaHCO3, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH=15:1) to afford compound **(D)** (350 mg, 71% yield) as oil. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.24 (s, 1H), 6.88 (s, 1H), 3.87~3.95 (d, J = 9.6 Hz, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.60~3.70 (d, J = 9.6 Hz, 2H), 3.00~3.20 (q, J = 6.8 Hz, 2H), 0.95~1.05 (t, J = 6.8 Hz, 3H). LC-MS: m/z 317.6 $[M+H]^+$.

Synthesis of Compound (E)

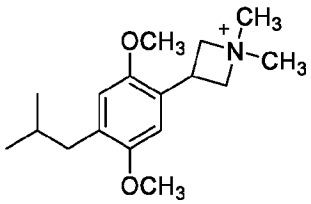
Sodium cyanoborohydride (270 mg, 3.8 mmol) and AcOH (0.5 mL) were added to a solution of compound **(D)** (120 mg, 0.38 mmol) and formaldehyde (37% aq, 0.17 mL, 2.3 mmol) in MeOH/THF (3 mL/3 mL) at 0°C. The mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred for 2h. The mixture was diluted with ice water (10 mL), extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine (20 mL), dried (Na2SO4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (MeOH/DCM=1:20) to afford compound **E** (57 mg, 46% yield) as oil. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.24 (s, 1H), 6.87 (s, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.50~3.60 (d, J = 8.0 Hz, 2H), 3.40~3.45 (d, J = 8.0 Hz, 2H), 3.10~3.20 (q, J = 6.8 Hz, 2H), 0.95~1.05 (t, J = 6.8 Hz, 3H). LC-MS: m/z 332.0 $[M+H]^+$.

Example 3. Synthesis and characterization of Compounds (I)-(J).

Compounds (I)-(J), as shown below, can be synthesized according to Scheme 3 (details below).

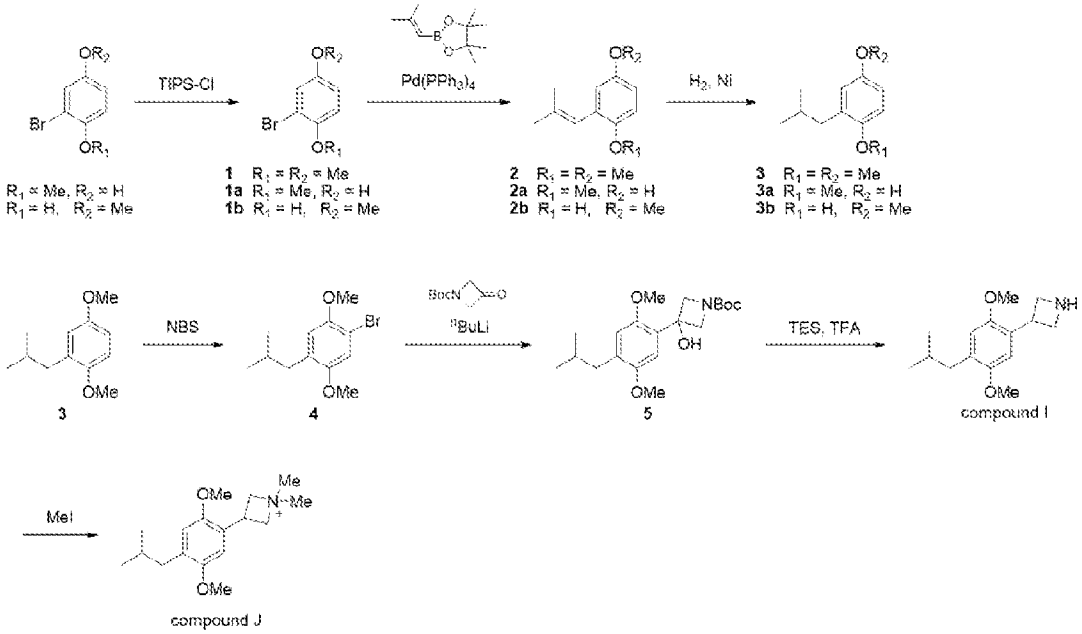


(I)



(J)

Scheme 3.



Procedures

Synthesis of (3-Bromo-4-methoxyphenoxy)triisopropylsilane (1a)

TIPS-Cl (5.67 g, 29.5 mmol) and imidazole (2.51 g, 36.9 mmol) was added to a solution of 3-bromo-4-methoxyphenol (5.0 g, 24.6 mmol) in DCM (60 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. The mixture was quenched with ice water (40 mL), separated, and the aqueous layer re-extracted with DCM (2 x 30 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:6) to provide compound **1a** of Scheme 3 (7.2 g, 82% yield).

Synthesis of (2-Bromo-4-methoxyphenoxy)triisopropylsilane (1b)

This compound was synthesized with a procedure similar to compound **1a** of Scheme 3 from 2-bromo-4-methoxyphenol with TIPS-Cl to give title compound **1b** of Scheme 3 (7.4 g, 84% yield).

Synthesis of Triisopropyl(4-methoxy-3-(2-methylprop-1-enyl)phenoxy)silane (2a)

$Pd(PPh_3)_4$ (1.2 g, 1.0 mmol) and K_2CO_3 (6.92 g, 50 mmol), were added to a solution of 4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane (3.64 g, 20 mmol) and compound **1a** of Scheme 3 (6.0 g, 17 mmol) in dioxane/H_2O (150 mL/15 mL). The resulting mixture was heated to 105 °C and stirred overnight under an N_2 atmosphere. After cooling to room temperature, the mixture was diluted with H_2O (300 mL), then extracted with EtOAc (3 x 300 mL). The combined organic phases were washed with water (2 x 500 mL) and brine (300 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane =1:10) to afford compound **2a** of Scheme 3 (4.9 g, 86% yield).

Synthesis of Triisopropyl(4-methoxy-2-(2-methylprop-1-enyl)phenoxy)silane (2b)

This compound was synthesized with a procedure similar to compound **2a** of Scheme 3 from compound **1b** of Scheme 3 with 4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane to give title compound **2b** of Scheme 3 (4.8 g, 84% yield).

Synthesis of 1,4-Dimethoxy-2-(2-methylprop-1-enyl)benzene (2)

This compound was synthesized with a procedure similar to compound **2a** of Scheme 3 using 2,4-dimethoxyphenol and 4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane to give title compound **2** of Scheme 3 (3.5 g, 65% yield).

Synthesis of (3-Isobutyl-4-methoxyphenoxy)triisopropylsilane (3a)

Pd/C (10% on carbon, 1 g) was added to a solution of compound **2a** of Scheme 3 (4.5 g, 13.4 mmol) in MeOH (20 mL). The mixture was stirred at room temperature under 1 atmosphere of H_2 for 5 h. The Pd/C was removed by filtration, and the filtrate was concentrated to dryness. The crude was purified by silica gel chromatography (EtOAc/hexane =1:11) to provide compound **3a** of Scheme 3 (4.3 g, 95% yield).

Synthesis of (2-Isobutyl-4-methoxyphenoxy)triisopropylsilane (3b)

This compound was synthesized with a procedure similar to compound **3a** of Scheme 3 from compound **2b** of Scheme 3 to give title compound **3b** of Scheme 3 (4.1 g, 90% yield).

Synthesis of (3-Isobutyl-2,4-dioxyphenoxy)benzene (3)

This compound was synthesized with a procedure similar to compound **3a** of Scheme 3 from compound **2** to give title compound **3** (2.9 g, 93% yield).

Synthesis of 1-Bromo-4-isobutyl-2,5-dimethoxybenzene (4)

NBS (1.55 g, 8.7 mmol) was added dropwise to a solution of compound **3** of Scheme 3 (1.3 g, 6.7 mmol) in AcOH (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then quenched with aqueous saturated Na_2SO_3 (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (3 x 100 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:20) to provide compound **4** of Scheme 3 (1.5 g, 82% yield).

Synthesis of *tert*-Butyl-3-hydroxy-3-(4-isobutyl-2,5-dimethoxyphenyl)azetidine-1-carboxylate (5)

n-BuLi (1.6 M solution in hexane, 3.4 mL, 5.5 mmol) was added dropwise to a solution of compound **4** of Scheme 3 (1.0 g, 3.7 mmol) in THF (20 mL) at -78 °C over 5 min. The mixture was stirred at -78 °C for 0.5 h, then a solution of N-Boc-azetidin-3-one (1.26 g, 7.4 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for an additional 0.5 h, then quenched with aqueous 10% NH_4Cl (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:1) to afford compound **5** of Scheme 3 (550 mg, 41% yield).

Synthesis of Compound (I)

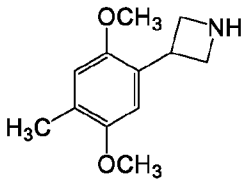
Triethylsilane (1.7 g, 15 mmol) and $BF_3 \cdot Et_2O$ (2.0 M solution in THF, 3 mL) were added to a solution of compound **5** of Scheme 3 (550 mg, 1.5 mmol) in DCM (10 mL).The mixture was heated under reflux and stirred overnight. After cooling to room temperature, the solvent was removed in vacuo, and the residue was diluted with EtOAc (100 mL), and wished with brine, dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (MeOH/DCM =10:1) to afford compound **(I)** (130 mg, 35% yield) as an oil. ^{1}H-NMR (400 MHz, DMSO-d6): δ 6.87 (s, 1H), 6.67 (s, 1H), 3.90~4.05 (m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.60~3.70 (m, 4H), 2.35~2.45 (d, J = 7.2 Hz, 2H), 1.80~1.90 (m, 1H), 0.80~0.90 (d, J = 6.4 Hz, 6 H). LC-MS: m/z 250.1 $[M+H]^+$.

Synthesis of Compound (J)

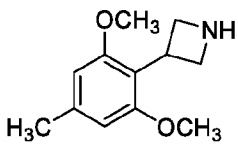
K_2CO_3 (345 mg, 2.5 mmol) and iodomethane (MeI) (360 mg, 2.5 mmol) were added to a solution of compound **(I)** (200 mg, 0.8 mmol) in ACN (10 mL) at room temperature. The mixture was heated under reflux and stirred for 3 h. After cooling to room temperature, the mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH / DCM =10:1) to provide compound **(J)** (132 mg, 59% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d6): δ 6.79 (s, 1H), 6.77 (s, 1H), 4.50~4.55 (m, 2H), 4.40~4.55 (m, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.31 (s, 3H), 3.14 (s, 3H), 2.40~2.45 (d, J = 7.2 Hz, 2H), 1.80~1.90 (m, 1H), 0.80~0.90 (d, J = 6.8 Hz, 6H). LC-MS: m/z 279.3 $[M]^+$.

Example 4. Synthesis and characterization of Compounds (K)-(N).

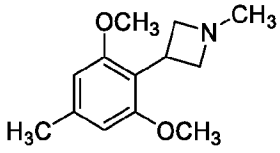
Compounds (K)-(N), described below,can be synthesized according to Scheme 4 (details below).



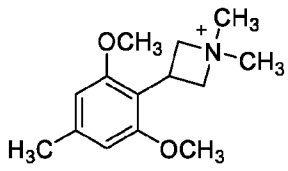
(K)



(L)

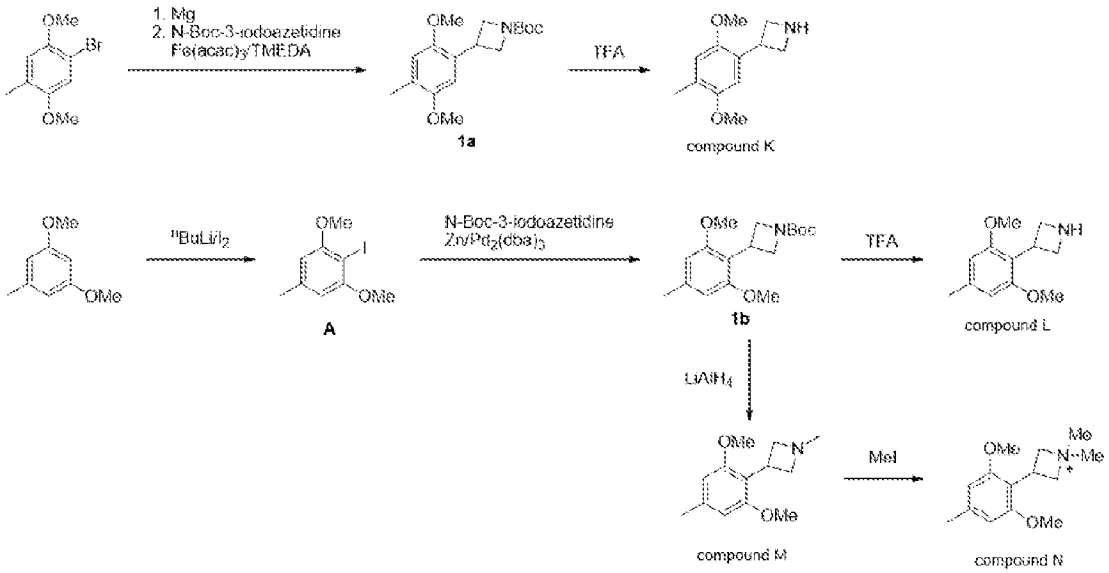


(M)



(N)

Scheme 4.



Procedure

Synthesis of *tert*-Butyl-3-(2,5-dimethoxy-4-methylphenyl)azetidine-1-carboxylate (1a)

(2,5-Dimethoxy-4-methylphenyl)magnesium bromide solution freshly prepared from Mg chips and 1-bromo-2,5-dimethoxy-4-methyl benzene (2.0 g, 9 mmol) in THF (20 mL)] was added to a suspension of tert-butyl-3-iodoazetidine-1-carboxylate (1.0 g, 3.5 mmol), iron (III) acetylacetonate (125 mg, 0.35 mmol) and TMEDA (1.0 g, 8.6 mmol) in THF (15 mL) at -20 °C. The mixture was allowed to warm to room temperature and stirred for 0.5 h and then quenched with aqueous 10% NH_4Cl (20 mL) and EtOAc (2 x 20 mL). The organic phase was collected and washed with water (2 x 20 mL), saturated aqueous $NaHCO_3$ (2 x 20 mL), and brine (20 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:10) to afford compound **1a** (1.1 g, 42% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 6.74 (s, 1H), 6.68 (s, 1H), 4.24~4.28 (t, 2H), 4.00~4.03 (t, 2H), 3.91~3.99 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 2.22 (s, 3H), 1.46 (s, 9H).

Synthesis of Compound (K)

TFA (4 mL) was added was added to a solution of compound **1a** of Scheme 4 (400 mg, 1.3 mmol) in DCM (4 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred for 1 h. The mixture was concentrated, and the TFA salt was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH =10:1) to afford compound **(K)** (120 mg, 44% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 6.85 (s, 1H), 6.76 (s, 1H), 3.96~4.00 (m, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 3.59~3.67 (m, 4H), 2.12 (s, 3H). LC-MS: m/z 208.5 $[M+H]^+$.

Synthesis of 2-Iodo-1,3-dimethoxy-5-methylbenzene (A)

n-BuLi (1.6 M solution in hexane, 19.8 mL, 31.7 mmol) was added dropwise over 20 min to a solution of 3,5-dimethoxytoluene (4.0 g, 26.0 mmol) in THF (40 mL) at -78 °C. After the addition was

completed, the mixture was stirred at -78 °C for 1.5 h, then a solution of iodine (8.1 g, 32 mmol) in THF (15 mL) was added dropwise over 10 min. The mixture was stirred at -78°C for 2 h, then allowed to warm to 0°C. The mixture was quenched with aqueous saturated NH_4Cl (60 mL), and then extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with aqueous saturated Na_2SO_3 (100 mL) and brine (60 mL), dried (Na_2SO_4) and filtered, concentrated to dryness. The residue was purified by silica gel chromatography (hexane/EtOAc =12:1) and afforded compound **A** of Scheme 4 (5.2 g, 72% yield).

Synthesis of *tert*-Butyl 3-(2,6-dimethoxy-4-methylphenyl)azetidine-1-carboxylate (1b)

TMSCl (300 mg, 3 mmol) was added to a suspension of Zn powder (1.5 g, 23 mmol) in DMF (20 mL). The mixture was stirred at room temperature for 30 min, then iodine (250 mg, 1 mmol) was added and stirred at room temperature for 30 min. Boc-3-iodoazetidine (2.25 g, 8 mmol) was added to the mixture, and then heated at 55 °C for 30 min. The mixture was allowed to cool to room temperature, then compound **A** of Scheme 4 (2.22 g, 8 mmol), $Pd_2(dba)_3$ (100 mg, 0.10 mmol), and SPhos (80 mg, 0.19 mmol) were added. The resulting mixture was heated at 55 °C and stirred for 3 h. After cooling to room temperature, the mixture was quenched with aqueous 10% NH_4Cl (80 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (2 x 100 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane =2:3) to provide compound **1b** of Scheme 4 (950 mg, 39% yield).

Synthesis of Compound (L)

This compound was synthesized with a procedure similar to compound **(K)** from compound **1b** with TFA to give title compound **(L)** as the free base (370 mg, 40% yield). This free base was converted to its HCl salt using HCl-dioxane. ^{1}H-NMR (400 MHz, DMSO-d*6*): □ 8.62 (bs, 1H), 6.51 (s, 2H), 4.20~4.35 (m, 1H), 4.05~4.20 (m, 4H), 3.76 (s, 3H), 2.29 (s, 3H). LC-MS: m/z 207.9 $[M+H]^+$.

Synthesis of Compound (M)

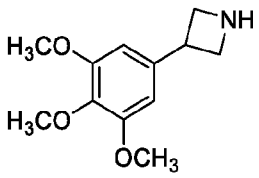
Lithium aluminum hydride (500 mg, 13 mmol) was added to a solution of compound **1b** of Scheme 4 (380 mg, 1.23 mmol) in THF (20 mL) at 0°C. The mixture was heated under reflux and stirred overnight. The mixture was cooled to 0°C and quenched by addition of water (0.5 mL), followed by 15% sodium hydroxide (0.5 mL), and finally water (1.5 mL). The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography (DCM/MeOH = 9:1) and afforded compound **(M)** (190 mg, 46% yield) as oil. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 6.42 (s, 2H), 3.70~3.80 (m, 2H), 3.69 (s, 6H), 3.45~3.55 (m, 1H), 2.90~2.98 (m, 2H), 2.26 (s, 3H), 2.17 (s, 3H). LC-MS: m/z 222.4 $[M+H]^+$.

Synthesis of Compound (N)

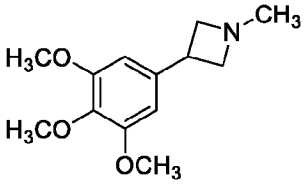
K_2CO_3 (180 mg, 1.3 mmol) and MeI (183 mg, 1.3 mmol) was added to a solution of compound **(M)** (133 mg, 0.6 mmol) in ACN (10 mL) at room temperature. The mixture was stirred at room temperature for 3 h. The solid was filtered and the filtrate was concentrated in vacuo. The crude solid was triturated with EtOAc/ACN (3 mL/3 mL×2) to afford compound **(N)** (71 mg, 55% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 6.53 (s, 1H), 4.30~4.50 (m, 5H), 3.74 (s, 6H), 3.26 (s, 3H), 3.08 (s, 3H). LC-MS: m/z 237.1 $[M]^+$.

Example 5. Synthesis and characterization of Compounds (O)-(U).

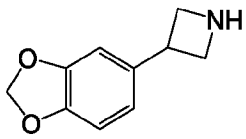
Compounds (O)-(U), as described below, can be synthesized according to Scheme 5 (details below).



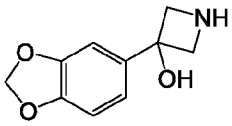
(O)



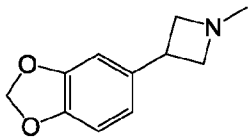
(P)



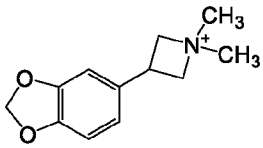
(Q)



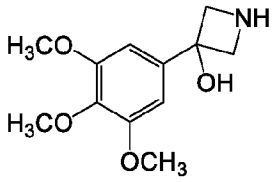
(R)



(S)

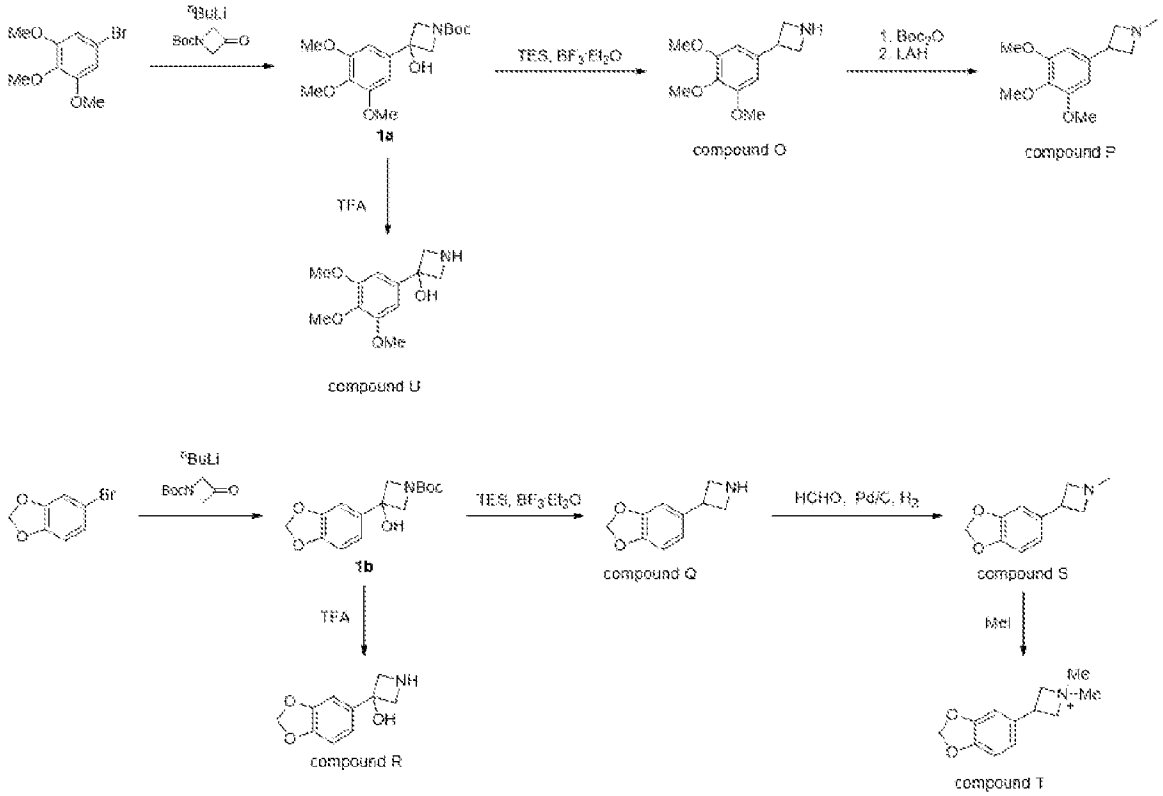


(T)



(U)

Scheme 5.



Procedures

Synthesis of *tert*-Butyl 3-hydroxy-3-(3,4,5-trimethoxyphenyl)azetidine-1-carboxylate (1a)

n-BuLi (1.6 M solution in hexane, 12.2 mL, 19.5 mmol) was added dropwise over 5 min to a solution of 5-bromo-1,2,3-trimethoxybenzene (4.0 g, 16.0 mmol) in THF (20 mL) at -78 °C. The mixture was stirred at -78 °C for 0.5 h, then a solution of N-Boc-azetidin-3-one (3.9 g, 0.023 mol) in THF (10 mL) was added dropwise. The mixture was stirred for 0.5 h and quenched with aqueous 10% NH_4Cl (20 mL), extracted with EtOAc (2 x 20 mL). The organic phase was collected and washed with brine (20 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =2:1) and afforded **1a** of Scheme 5 (2.7 g, 49% yield).

Synthesis of *tert*-Butyl 3-(benzo[*d*][1,3]dioxol-5-yl)-3-hydroxyazetidine-1-carboxylate (1b)

This compound was synthesized with a procedure similar to compound **1a** of Scheme 5 from 5-bromobenzo[d][1,3]dioxole and N-Boc-azetidin-3-one to give title compound **1b** of Scheme 5 (4.6 g, 63% yield).

Synthesis of Compound (O)

Triethylsilane (6.9 g, 59 mmol) and $BF_3 \cdot Et_2O$ (2.0 M solution in THF, 10 mL) were added to a solution of compound **1a** of Scheme 5 (2.0 g, 5.89 mmol) in DCM (10 mL). The mixture was heated under reflux and stirred overnight. After cooling to room temperature, the solvent was removed in vacuo, and

the residue was diluted with EtOAc (100 mL), wished with brine, dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (MeOH / DCM=10:1) to provide compound **(O)** (1.2 g, 90% yield) as an oil. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 6.64 (s, 2H), 3.78 (s, 6H), 3.69~3.77 (m, 3H), 3.63~3.70 (m, 2H), 3.34 (s, 3H). LC-MS: m/z 223.9 $[M+H]^+$.

Synthesis of Compound (P)

Boc_2O (1.1 g, 4.93 mmol) and TEA (680 mg, 6.73 mmol) were added to a solution of compound **(O)** (1.0 g, 4.48 mmol) in DCM (20 mL) at 0 ºC. The mixture was stirred overnight at room temperature. The reaction mixture was washed with brine (20 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:5) to afford Boc-protected product. This product was dissolved in THF (20 mL), and to it was added powdered $LiAlH_4$ (0.5 g, 13.2 mmol). The mixture was heated under reflux and stirred overnight. After cooling to 0 ºC, the mixture was quenched with water (0.5 mL), followed by 15% sodium hydroxide (0.5 mL), and finally water (1.5 mL). The mixture was filtered and washed with EtOAc (50 mL). The combined filtrate was washed with brine (2 x 20 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH =10:1) to afford compound **(P)** (360 mg, 49% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 6.71 (s, 2H), 4.18~4.39 (m, 3H), 3.95~4.14 (m, 2H) 3.81 (s, 6H), 3.63 (s, 3H), 2.87 (s, 3H). LC-MS: m/z 238.2 $[M+H]^+$.

Synthesis of Compound (Q)

This compound was synthesized with a procedure similar to compound **(O)** from compound **1b** of Scheme 5 to give the title compound as the free base (400 mg, 60% yield). Th free base was converted with HCl-dioxane to its HCl salt as a white solid.^{1}H-NMR (400 MHz, DMSO-d*6*): δ 9.46 (bs, 2H), 7.10~7.15 (m, 1H), 6.80~6.95 (m, 2H), 6.01 (s, 2H), 4.15~4.25 (m, 2H), 3.95~3.10 (m, 3H). LC-MS: m/z 177.9 $[M+H]^+$.

Synthesis of Compound (R)

TFA (3 mL) was added to a solution of compound **1a** of Scheme 5 (500 mg, 1.47 mmol) in DCM (3 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred overnight. The mixture was concentrated, and the crude was purified by prep-HPLC to afford the TFA salt. The TFA salt was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried, and concentrated to afford compound **(R)** (90 mg, 40% yield) as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.16~7.17 (d, *J* = 1.6 Hz, 1H), 7.07~7.12 (dd, *J* = 1.6 and 8.0 Hz, 1H), 6.85~6.90 (d, *J* = 8.0 Hz, 1H), 5.98 (s, 2H), 5.85 (bs, 1H), 3.73~3.76 (d, *J* = 8.8 Hz, 2H), 3.48~3.52 (d, *J* = 8.8 Hz, 2H). LC-MS: m/z 149.9 $[M+H]^+$.

Synthesis of Compound (S)

Sodium cyanoborohydride (1.2 g, 1.7mmol) and formaldehyde (37% wt, 0.8 mL, 0.8 mmol) were added to a solution of compound **(Q)** (360 mg, 1.7 mmol) in MeOH/THF/AcOH (3mL/3mL/0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, then stirred at room temperature for 2 h. The mixture was quenched with aqueous saturated $NaHCO_3$ (20 mL), then extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), then filtered and

concentrated. The residue was purified by silica gel chromatography (DCM/MeOH =10:1) to provide compound **(S)** (150 mg, 46% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.00~7.05 (d, *J* = 1.6 Hz, 1H), 6.85~6.90 (d, *J* = 8.0 Hz, 1H), 6.75~6.85 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 6.00 (s, 2H), 3.90~9.98 (m, 2H), 3.70~3.80 (m, 1H), 3.50~3.60 (m, 2H), 2.57 (s, 3H). LC-MS: m/z 192.0 $[M+H]^+$.

Synthesis of Compound (T)

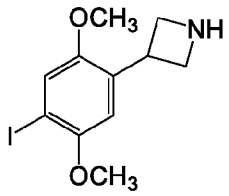
K_2CO_3 (173 mg, 1.26 mmol) and MeI (179 mg, 1.26 mmol) were added to a solution of compound **(S)** (120 mg, 0.63 mmol) in ACN (10 mL) at room temperature. The mixture was stirred at room temperature for 3 h. K_2CO_3 and then filtered. The filtrate was concentrated in vacuo. The crude was triturated with EtOAc/ACN (3 mL/3 mL×2) to afford compound (T) (71 mg, 55% yield) as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.15~7.17 (d, *J* = 1.6 Hz, 1H), 6.90~6.93 (d, *J* = 8.0 Hz, 1H), 6.80~6.85 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 6.03 (s, 2H), 4.30~4.60 (m, 5H), 3.34 (s, 3H), 3.18 (s, 3H). LC-MS: m/z 206.1 $[M]^+$.

Synthesis of Compound (U)

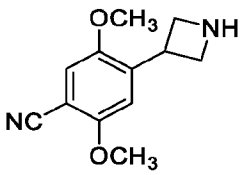
This compound was synthesized with a procedure similar to compound **(R)** from compound **1a** to give Compound **(U)** as the free base (120 mg, 24% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): 6.93 (s, 2H), 5.89 (bs, 1H), 3.80 (s, 6H), 3.75~3.80 (d, *J* = 8.4, 2H), 3.64 (s, 3H), 3.56~3.60 (d, *J* = 8.4, 2H). LC-MS: m/z 240.1 $[M+H]^+$.

Example 6. Synthesis and characterization of Compounds (U)-(Y).

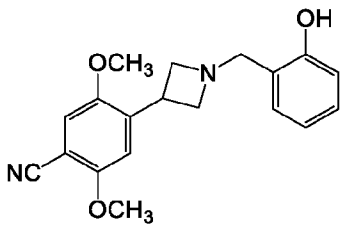
Compounds (U)-(Y), as described below, can be synthesized according to Scheme 6 (details below).



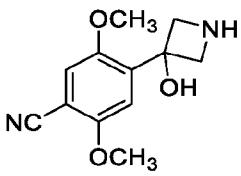
(V)



(W)

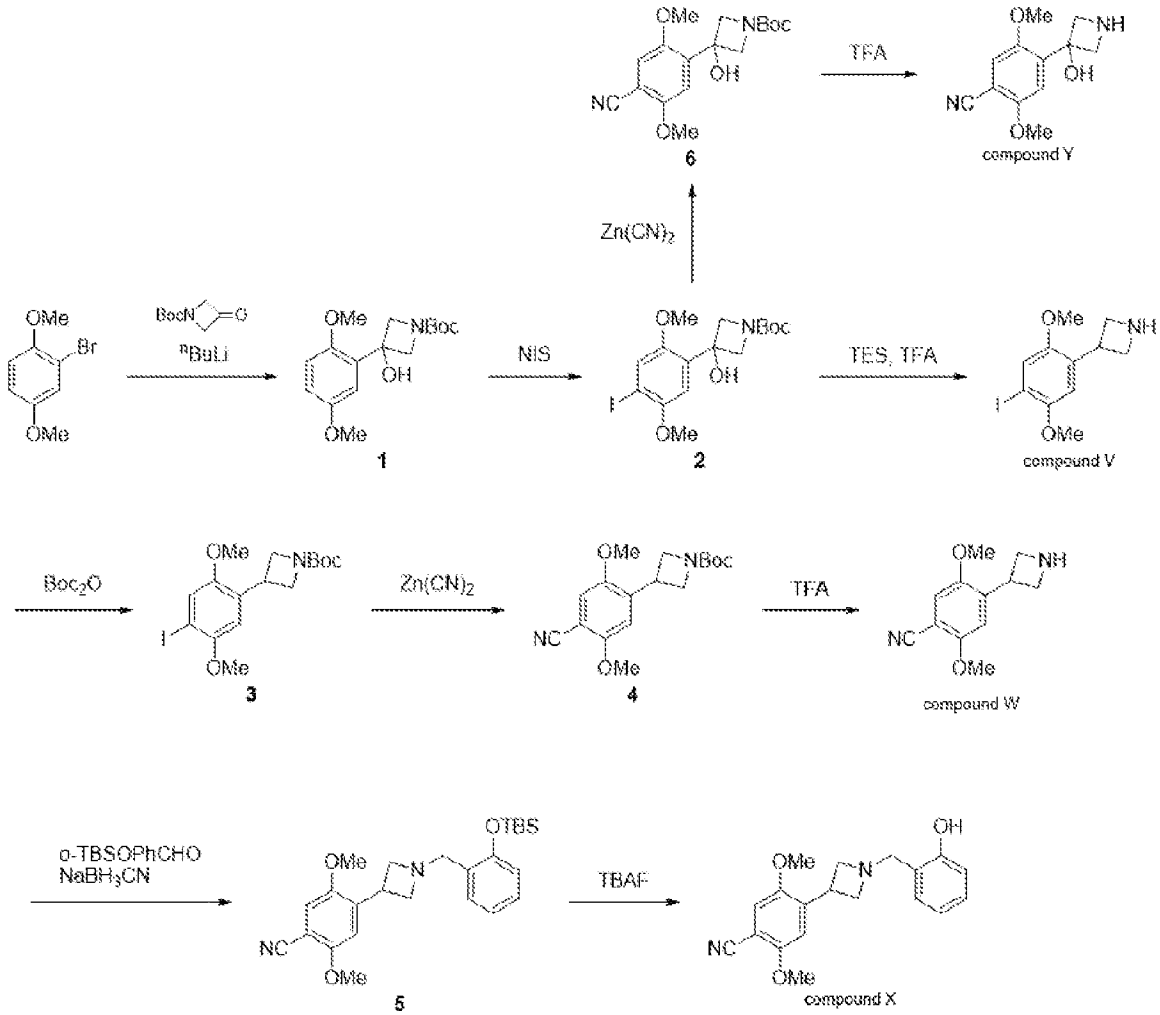


(X)



(Y)

Scheme 6.



Procedures

Synthesis of *tert*-Butyl 3-(2,5-dimethoxyphenyl)-3-hydroxyazetidine-1-carboxylate (1)

n-BuLi (1.6 M solution in hexane, 69.1 mL, 110.5 mmol) was added dropwise over 5 min to a solution of 2-bromo-1,4-dimethoxybenzene (20.0 g, 92.2 mmol) in THF (200 mL) at -78 °C. The mixture was stirred at -78 °C for 0.5 h, then a solution of N-Boc-azetidin-3-one (22.1 g, 129.0 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 0.5 h at -78 °C and then allowed to warm to 0 °C. The reaction mixture was quenched with aqueous 10% NH_4Cl (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine (200 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:1) to provide compound **1** (16.0 g, 70% yield).

Synthesis of *tert*-Butyl 3-hydroxy-3-(4-iodo-2,5-dimethoxyphenyl)azetidine-1-carboxylate (2)

N-iodosuccinimide (NIS) (3.2 g, 14.2 mmol) was added to a solution of compound **1** of Scheme 6 (4.0 g, 12.9 mmol) in acetonitrile (50 mL) at room temperature. The mixture was stirred for 16 h at room temperature, the solvent was removed, and the crude was purified by silica gel chromatography (EtOAc/hexane =1:5) to afford compound **2** of Scheme 6 (3.5 g, 62% yield).

Synthesis of Compound (V)

Triethylsilane (1.5 mL, 9.2 mmol) and TFA (5.0 mL) were added to a solution of compound **2** of Scheme 6 (400 mg, 0.92 mmol) in DCM (4 mL) at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C, and then allowed to warm to room temperature and stirred overnight. The mixture was concentrated, and the crude was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH=15:1) to afford compound **(V)** (111 mg, 38% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.25 (s, 1H), 6.93 (s, 1H), 3.90~4.00 (t, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.70(s, 3H), 3.60~3.70 (m, 4H). LC-MS: m/z 320.4 $[M+H]^+$.

Synthesis of *tert*-Butyl 3-(4-iodo-2,5-dimethoxyphenyl)azetidine-1-carboxylate (3)

Boc_2O (2.2 g, 10 mmol) and TEA (1 mL) were added to a solution of compound **(V)** (1.2 g, 3.7 mmol) in DCM (40 mL) at room temperature. The reaction mixture was stirred overnight, then washed with 1*N* aq HCl (20 mL), and brine (2 x 20 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:10) to afford compound **3** of Scheme 6 (0.95 g, 61% yield).

Synthesis of *tert*-Butyl 3-(4-cyano-2,5-dimethoxyphenyl)azetidine-1-carboxylate (4)

A mixture of $Pd(dppf)_2Cl_2$ (20 mg, 0.03 mmol), zinc powder (24 mg, 0.35 mmol), compound **3** (630 mg, 1.5 mmol), and zinc cyanide (525 mg, 4.5 mmol) in DMF (15 mL) was stirred overnight at 120 °C under an N_2 atmosphere. After cooling to room temperature, the mixture was quenched with aqueous 10% NH_4Cl (50 mL), extracted with EtOAc (3 x 50 mL). The organic phase was collected and washed with water (2 x 30 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL), and brine (30 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:3) to provide compound **4** of Scheme 6 (220 mg, 46% yield).

Synthesis of Compound (W)

TFA (3 mL) was added to a solution of compound **4** of Scheme 6 (200 mg, 0.63 mmol) in DCM (3 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred overnight. The mixture was concentrated, and the crude was purified by prep-HPLC to afford the TFA salt. The TFA salt was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried and concentrated to afford compound **(W)** (120 mg, 86% yield) as the free base. This free base was converted to its HCl salt with HCl-dioxane to afford compound **(W)** salt. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 8.90~9.30 (bs, 2H), 7.38 (s, 1H), 7.10~7.20 (m, 1H), 4.10~4.30 (m, 5H), 3.92 (s, 3H), 3.49 (s, 3H). LC-MS: m/z 219.0 $[M+H]^+$.

Synthesis of 4-(1-(2-(*tert*-Butyldimethylsilyloxy)benzyl)azetidin-3-yl)-2,5-dimethoxybenzonitrile (5)

Sodium cyanoborohydride (1.2 g, 1.7 mmol) and 2-(tert-butyldimethylsilyloxy) benzaldehyde (200 mg, 0.85 mmol) were added to a solution of compound **(W)** (100 mg, 0.46 mmol) in MeOH/THF/AcOH (3 mL/3 mL/0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, then stirred overnight at room temperature. The mixture was quenched with aqueous saturated $NaHCO_3$ (20 mL), then extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH =10:1) to afford compound **5** of Scheme 6 (90 mg, 45% yield).

Synthesis of Compound (X)

TBAF (1.0 M solution in THF, 1.0 mL, 1.03 mmol) was added to a solution of compound **5** (250 mg, 0.57 mmol) in ACN (10 mL) at room temperature. The mixture was stirred at room temperature for 3 h. The mixture was concentrated in vacuo, and the residue was purified by silica gel chromatography (DCM/MeOH=15:1) to provide compound **(X)** (75 mg, 40% yield) as the free base. The free base was converted to its HCl salt with HCl-dioxane to afford compound **(X) HCl salt** as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 10.28 (s, 1H), 10.73 (bs, 1H), 7.40 (s, 1H), 7.20~7.40 (m, 2H), 7.06 (s, 1H), 6.80~6.95 (m, 2H), 4.20~4.40 (m, 6H), 4.05~4.15 (m, 1H), 3.91 (s, 3H), 3.78 (s, 3H). LC-MS: m/z 325.4 $[M+H]^+$.

Synthesis of *tert*-Butyl 3-(4-cyano-2,5-dimethoxyphenyl)-3-hydroxyazetidine-1-carboxylate (6)

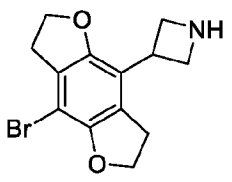
This compound was synthesized using a procedure similar to compound **4** of Scheme 6 from compound **2** of Scheme 6 with zinc cyanide to give title compound (510 mg, 54% yield).

Synthesis of Compound (Y)

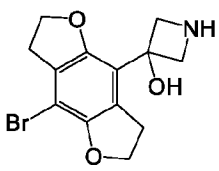
This compound was synthesized with a procedure similar to compound **(W)** from compound **6** of Scheme 6 to give title compound **(Y)** free base (190 mg, 66% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.35 (s, 1H), 7.08 (s, 1H), 5.80 (bs, 1H), 3.95~4.00 (d, *J* = 9.2 Hz, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.50~3.60 (d, *J* = 9.2 Hz, 2H), 2.60 (bs, 1H) . LC-MS: m/z 320.4 $[M+H]^+$.

Example 7. Synthesis and characterization of Compounds (Z)-(AC).

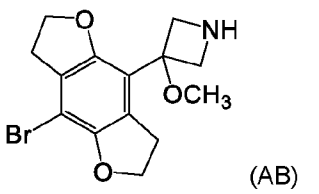
Compounds (Z)-(AC) can be synthesized according to Scheme 7 (details below).



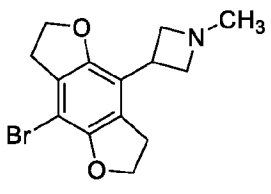
(Z)



(AA)

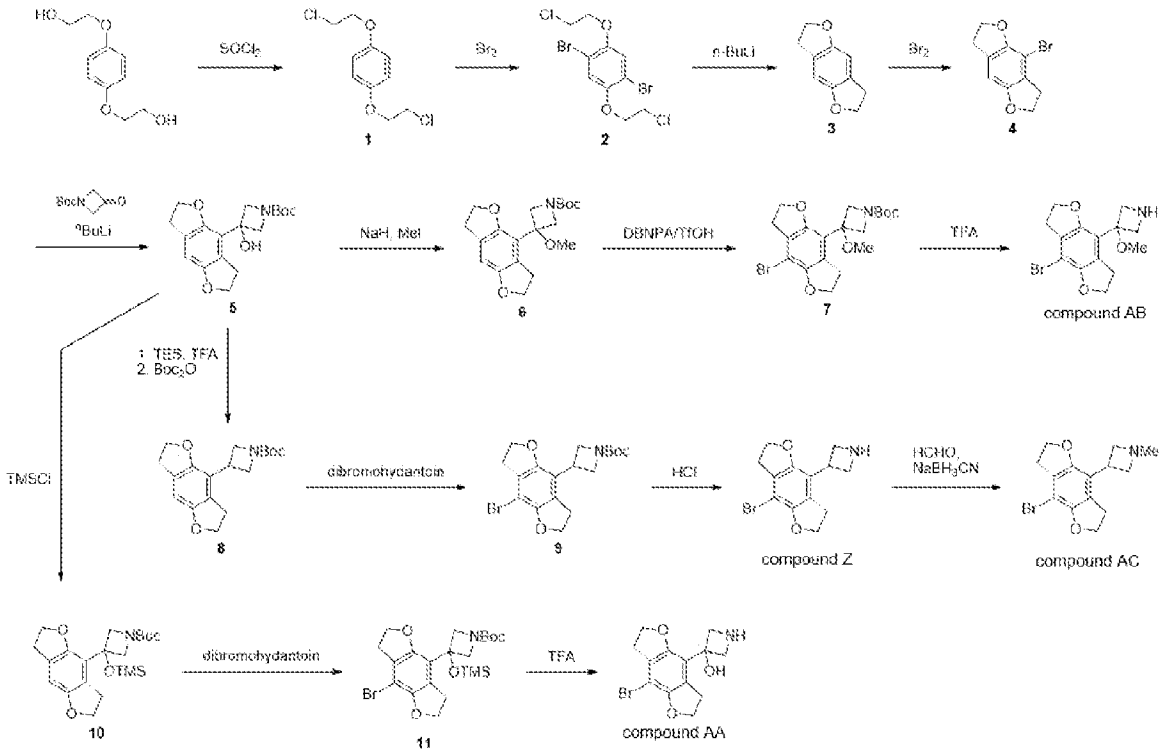


(AB)



(AC)

Scheme 7.



Procedures

Synthesis of 1,4-Bis(2-chloroethoxy)benzene (1)

Thionyl chloride (55.5 g, 460 mmol) was added dropwise over 10 min to a solution of 2,2'-(1,4-phenylenebis(oxy))bis(ethan-1-ol) (40.0 g, 200 mmol) in DCM (350 mL) and pyridine (39.0 g, 480 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stir overnight. The mixture was quenched with ice water (200 mL). The layers were separated, and the aqueous phase was re-extracted with DCM (2 x 200 mL). The combined organic phases were washed with brine (300 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane=1:9) to provide compound **1** of Scheme 7 (42.5 g, 90% yield).

Synthesis of 1,4-Dibromo-2,5-bis(2-chloroethoxy)benzene (2)

Zinc chloride (28.0 g, 204 mmol) was added to a solution of compound **1** of Scheme 7 (20.0 g, 85 mmol) in AcOH (300 mL) at 0 °C, and then bromine (29.0 g, 180 mmol) was added dropwise over 15 min. The resulting mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stir overnight. The mixture was quenched with aqueous 10% NH_4Cl (500 mL), and then extracted with EtOAc

(2 x 500 mL). The combined organic phases were washed with brine (2 x 500 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:12 to 1:5) to afford compound **2** of Scheme 7 (24.0 g, 72% yield).

Synthesis of 2,3,6,7-Tetrahydrobenzo[1,2-b:4,5-b']difuran (3)

n-BuLi (1.6 M solution in hexane, 56.0 mL, 89 mmol) was added dropwise over 10 min to 0 °C a solution of compound **2** of Scheme 7 (16.0 g, 41mmol) in THF (150 mL). The mixture was stirred at 0 °C for 1 h, then quenched with aqueous 10% NH_4Cl (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic phases were washed with aqueous saturated Na_2SO_3 (300 mL), brine (200 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:10) to provide compound **3** of Scheme 7 (4.3 g, 65% yield).

Synthesis of 4-Bromo-2,3,6,7-tetrahydrobenzo[1,2-b:4,5-b']difuran (4)

Bromine (0.17 mL, 3.1 mmol) was added dropwise to a solution of compound **3** of Scheme 7 (0.5 g, 3.1 mmol) in AcOH (10 mL) at 0°C. The mixture was stirred at 0 °C for 1 h, then quenched with aqueous satd Na_2SO_3 (50 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (3 x 100 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:20) to provide compound **4** of Scheme 7 (0.41 g, 55% yield).

Synthesis of *tert*-Butyl 3-hydroxy-3-(2,3,6,7-tetrahydrobenzo[1,2-b:4,5-b']difuran-4-yl)azetidine-1-carboxylate (5)

n-BuLi (1.6 M solution in hexane, 7.2 mL, 11.4 mmol) was added dropwise over 5 min to a solution of compound **4** of Scheme 7 (2.3 g, 9.5 mmol) in THF (20 mL) at -78 °C. The mixture was stirred at -78 °C for 0.5 h, then a solution of N-Boc-azetidin-3-one (2.3g, 13.4 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for an additional 0.5 h, then quenched with aqueous 10% NH_4Cl (50 mL), extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:1) to provide compound **5** of Scheme 7 (1.4 g, 45% yield).

Synthesis of *tert*-Butyl-3-methoxy-3-(2,3,6,7-tetrahydrobenzo[1,2-b:4,5-b']difuran-4-yl)-azetidine-1-carboxylate (6)

NaH (60% in mineral oil, 76 mg, 1.89 mmol) was added to a solution of compound **5** (450 mg, 1.35 mmol) in THF (15 mL) at 0 ºC. The mixture was stirred at 0 ºC for 1 h, then a solution of MeI (390 mg, 2.70 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with ice water (20 mL), extracted with EtOAc (2 x 20 mL). The organic phase was washed with brine (30 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:6) to provide compound **6** of Scheme 7 (312 mg, 67% yield).

Synthesis of *tert*-Butyl-3-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-b:4,5-b']difuran-4-yl)-3-methoxyazetidine-1-carboxylate (7)

Dibromohydantoin (DBNPA, 62 mg, 0.22 mmol) and trifluoromethanesulfonic acid (130 mg, 0.87 mmol) were added to a solution of compound **6** of Scheme 7 (150 mg, 0.43 mmol) in DCM (5 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h, and then quenched with aqueous saturated $NaHCO_3$ (50 mL), and extracted with EtOAc (2 x 50 mL). The combined organic phases were dried and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:6) to afford compound **7** of Scheme 7 (159 mg, 87% yield).

Synthesis of *tert*-Butyl-3-(2,3,6,7-tetrahydrobenzo[1,2-b:4,5-b']difuran-4-yl)azetidine-1-carbo xylate (8)

Triethylsilane (5.9 g, 50 mmol) was added to a solution of compound **7** of Scheme 7 (1.7 g, 5 mmol) in DCM (10 mL) and trifluoroacetic acid (10 mL) at 0 °C. The mixture was stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was diluted with aqueous saturated $NaHCO_3$ (50 mL), then extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (2 x 100 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was dissolved in DCM (10 mL) and cooled to 0 °C. Then Boc_2O (0.75 g, 3.45 mmol) and TEA (0.46 g, 4.6 mmol) were added. The mixture was stirred overnight at room temperature. The mixture was quenched with aqueous satd $NaHCO_3$ (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:5) to provide compound **8** of Scheme 7 (470 mg, 64% yield).

Synthesis of *tert*-Butyl-3-(8-bromo-2,3,6,7-tetrahydrobenzofuro[5,6-b]furan-4-yl)azetidine-1-carboxylate (9)

This compound was synthesized with a procedure similar to compound **7** of Scheme 7 from compound **8** of Scheme 7 and DBNPA to give title compound **9** of Scheme 7 (330 mg, 76% yield).

Synthesis of *tert*-Butyl-3-(2,3,6,7-tetrahydrobenzo[1,2-b:4,5-b']difuran-4-yl)-3-((trimethylsilyl)oxy)azetidine-1-carboxylate (10)

A solution of compound **5** (300 mg, 0.91 mmol) in DCM (10 mL) was cooled to 0 °C, and imidazole (100 mg, 1.35 mmol) was added at 0 °C. Then chlorotrimethylsilane (120 g, 1.08 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h. The mixture was quenched with ice water (10 mL) and extracted with DCM (2 x 20 mL). The organic phase was washed with brine (20 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:5) to provide compound **10** of Scheme 7 (295 mg, 81% yield).

Synthesis of *tert*-Butyl-3-(8-bromo-2,3,6,7-tetrahydrobenzofuro[5,6-b]furan-4-yl)-3-(trimethylsilyloxy)azetidine-1-carboxylate (11)

This compound was synthesized with a procedure similar to compound **7** of Scheme 7 from compound **10** and DBNPA to give title compound **11** of Scheme 11 (366 mg, 61% yield).

Synthesis of Compound (Z)

HCl in EtOAc (5N, 5 mL) was added to a solution of compound **9** of Scheme 7 (300 mg, 0.76 mmol) in EtOAc (3 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature. The mixture was concentrated to dryness in vacuo. The crude was triturated with EtOAc/hexane (3 mL/6 mL) and dried to afford compound **(Z)** as the HCl salt (120 mg, 53% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): 8.81 (bs, 1H), 8.55 (bs, 1H), 4.61~4.66 (t, *J* = 8.8 Hz, 2H), 4.53~4.58 (t, *J* = 8.8 Hz, 2H), 4.27~4.31 (m, 2H), 4.07~4.14 (m, 2H), 4.04~4.06 (m, 1H), 3.17~3.21 (t, *J* = 8.8 Hz, 2H), 3.10~3.14 (t, *J* = 8.8 Hz, 2H). LC-MS: m/z 296.3 $[M+H]^+$.

Synthesis of Compound (AA)

This compound was synthesized with a procedure similar to compound **(Z)** from compound **11** of Scheme 7 and HCl-EtOAc to give the title compound **(AA)** as the HCl salt (55 mg, 21% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): 9.48 (bs, 1H), 9.09 (bs, 1H), 6.63 (s, 1H), 4.54~4.61 (m, 4H), 4.43~4.46 (m, 2H), 3.90~3.94 (m, 2H), 3.13~3.21 (t, *J* = 8.8 Hz, 2H), 3.09~3.13 (t, *J* = 8.8 Hz, 2H). LC-MS: m/z 313.9 $[M+H]^+$.

Synthesis of Compound (AB)

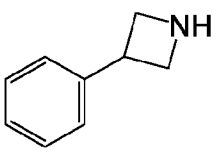
A solution of compound **9** of Scheme 7 (150 mg, 0.35 mmol) in DCM (10 mL) was cooled to 0 ºC, and trifluoroacetic acid (10 mL) was added dropwise at 0 ºC. The mixture was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was dissolved in aqueous satd sodium bicarbonate (5 mL), extracted with EtOAc (2 x 20 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (MeOH/DCM=1:10) to afford compound **(AB)** (55 mg, 48% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): 4.57~4.61 (t, *J* = 8.8 Hz, 2H), 4.56~4.60 (t, *J* = 8.8 Hz, 2H), 4.35~4.43 (m, 2H), 4.05~4.08 (m, 2H), 4.31~4.32 (m, 4H), 3.04 (s, 3H). LC-MS: m/z 328.1 [M+H]+

Synthesis of Compound (AC)

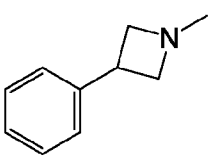
Sodium cyanoborohydride (240 mg, 3.37 mmol) and formaldehyde (37% wt, 0.4 mL, 2 mmol) were added to a solution of compound **(Z)** (100 mg, 0.34 mmol) in MeOH/THF/AcOH (3mL/3mL/0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, then stirred at room temperature for 2 h. The mixture was quenched with aqueous satd $NaHCO_3$ (20 mL), then extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH =10:1) to afford compound **(AC)** (75 mg, 72% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): 4.61~4.66 (t, *J* = 8.8 Hz, 2H), 4.53~4.58 (t, *J* = 8.8 Hz, 2H), 4.21~4.41 (m, 4H), 3.93~4.04 (m, 1H), 3.15~3.19 (t, *J* = 8.8 Hz, 2H), 3.10~3.15 (t, *J* = 8.8 Hz, 2H), 2.87 (s, 3H). LC-MS: m/z 310.0 $[M+H]^+$.

Example 8. Synthesis and characterization of Compounds (AD)-(AK).

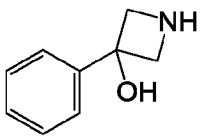
Compounds (AD)-(AK) can be synthesized according to Scheme 8 (details below).



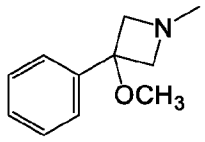
(AD)



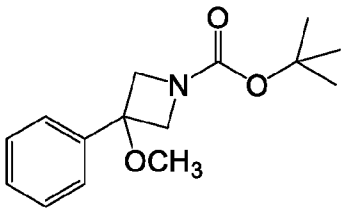
(AE)



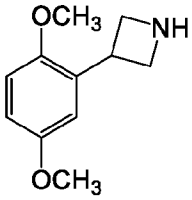
(AF)



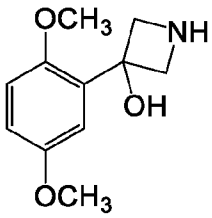
(AG)



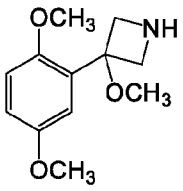
(AH)



(AI)



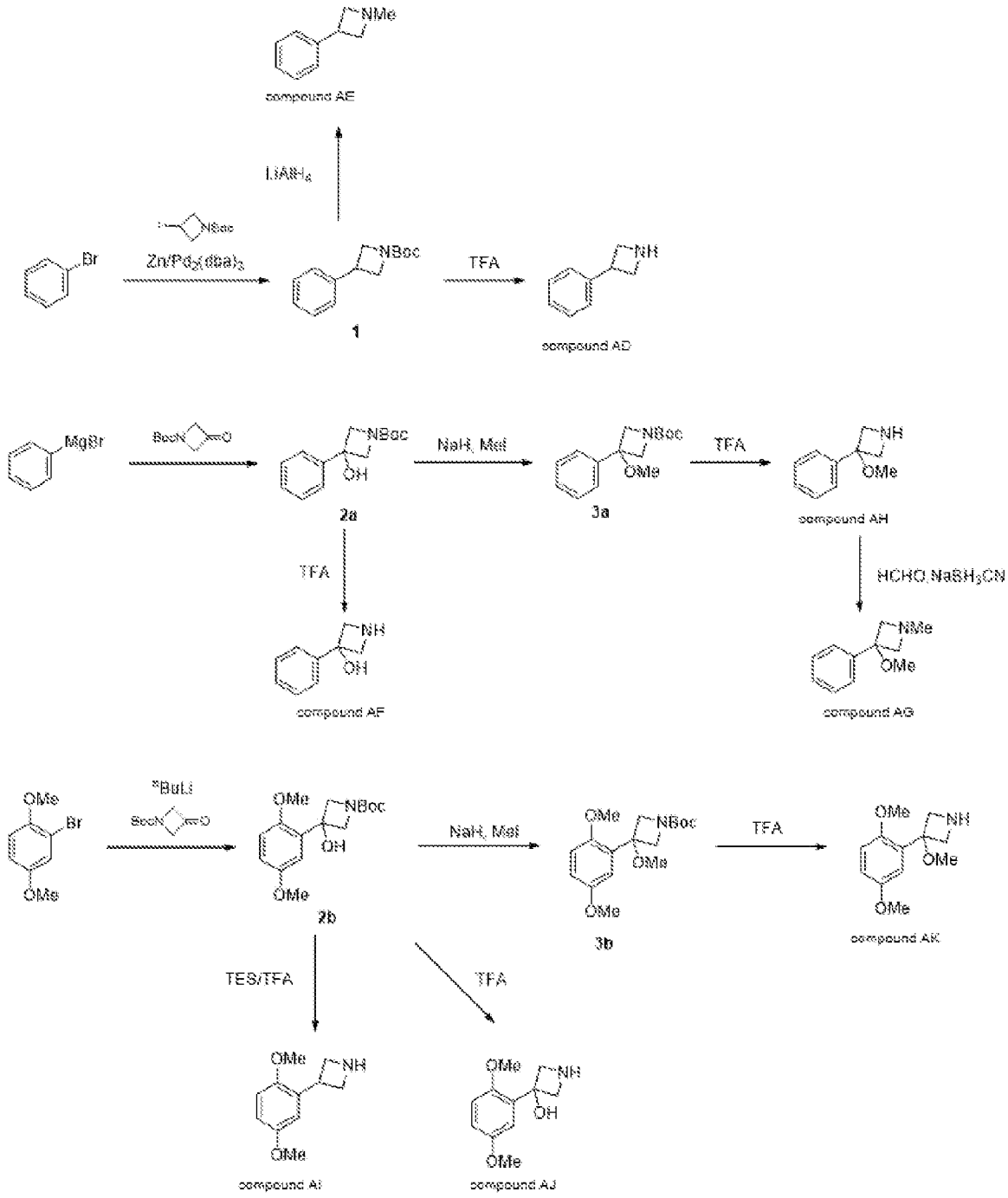
(AJ)



(AK)

5

Scheme 8.



Procedures

Synthesis of *tert*-Butyl-3-phenylazetidine-1-carboxylate (1)

TMSCl (268 mg, 2.3 mmol) was added to a solution of Zn (1.2 g, 19.2 mmol) in DMF (20 mL). The mixture was stirred at room temperature for 30 min under an N_2 atmosphere, then iodine (163 mg, 0.64 mmol) was added and stirred at room temperature for 30 min. N-Boc-3-iodoazetidine (1.8 g, 6.4 mmol) was added, the mixture was heated to 55°C for 30 min. The mixture was allowed to warm to room

temperature and bromobenzene (1.0 g, 6.4 mmol), $Pd_2(dba)_3$ (100 mg, 0.10 mmol), and S-Phos (80 mg, 0.19 mmol) were then added. The resulting mixture was heated to 55 °C and stirred for 3 h. After cooling to room temperature, the mixture was quenched with aqueous 10% NH_4Cl (80 mL) and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine (2 x 100 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane =1:15) to provide compound **1** (550 mg, 37% yield).

Synthesis of Compound (AD)

Compound **1** of Scheme 8 (300 mg, 1.3 mmol) was dissolved in DCM (5 mL), cooled to 0 °C, then TFA (5 mL) was added. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred for 1 h. The mixture was concentrated, and the TFA salt was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried, and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH =9:1) to afford compound **(AD)** as a white solid (110 mg, 65% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.20~7.50 (m, 5H), 4.10~4.20 (m, 2H), 4.05~4.10 (m, 1H), 3.95~4.00 (m, 3H). LC-MS: m/z 133.9 $[M+H]^+$.

Synthesis of Compound (AE)

Lithium aluminum hydride (200 mg, 5.3 mmol) was added to a solution of compound **1** of Scheme 8 (200 mg, 0.86 mmol) in THF (40 mL). The resulting mixture was heated under reflux for 18 h. After cooling to 0 °C, the reaction was quenched with water (0.2 mL), followed by 15% sodium hydroxide (0.2 mL), and finally water (0.6 mL). The mixture was filtered, and alumina salts on the filter were washed with EtOAc (50 mL). The combined filtrate was washed with brine (2 x 20 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH =15:1) to provide compound **(AE)** as an oil (80 mg, 63% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.25~7.40 (m, 4H), 7.15~7.25 (m, 1H), 3.61~3.64 (m, 2H), 3.55~3.60 (m, 1H), 3.06~3.09 (m, 2H), 2.27 (s, 3H). LC-MS: m/z 148.2 $[M+H]^+$.

Synthesis of *tert*-Butyl-3-hydroxy-3-phenylazetidine-1-carboxylate (2a)

Phenylmagnesium bromide (1.0 M solution in hexane, 40.9 mL, 40.9 mmol) was added dropwise over 5 min to a solution of N-Boc-azetidin-3-one (7.0 g, 40.9 mmol) in THF (100 mL) at -20 °C. The resulting mixture was stirred for 2 h and quenched with aqueous 10% NH_4Cl (100 mL), extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:2) to afford compound **2a** of Scheme 8 (6.0 g, 59% yield).

Synthesis of *tert*-butyl-3-(2,5-dimethoxyphenyl)-3-hydroxyazetidine-1-carboxylate (2b)

This compound was synthesized with a procedure similar to compound **2a** of Scheme 8 from 2-bromo-1,4-dimethoxybenzene and N-Boc-azetidin-3-one to give the title compound **2b** of Scheme 8 (1.2 g, 45% yield).

Synthesis of *tert*-Butyl-3-methoxy-3-phenylazetidine-1-carboxylate (3a)

NaH (60% mineral oil suspension, 180 mg, 4.5 mmol) was added to a solution of compound **2a** of Scheme 8 (800 mg, 3.2 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then a solution of MeI (921 mg, 6.4 mmol) in THF (5 mL) was added dropwise, then allowed to warm to room temperature and stirred overnight. The mixture was quenched with ice water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:5) to provide compound **3a** of Scheme 8 (450 mg, 53% yield).

Synthesis of *tert*-Butyl-3-(2,5-dimethoxyphenyl)-3-methoxyazetidine-1-carboxylate (3b)

This compound was synthesized with a procedure similar to compound **2b** of Scheme 8 from **3a** of Scheme 8 and MeI to give title compound **3b** of Scheme 8 (350 mg, 55% yield).

Synthesis of Compound (AF)

Compound **2a** of Scheme 8 (500 mg, 2.0 mmol) was dissolved in DCM (5 mL), the solution cooled to 0 °C, then TFA (5 mL) was added. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred for 1 h. The mixture was concentrated, the TFA salt was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH =9:1) to afford the title compound as a white solid (117 mg, 39% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.60~7.65 (d, *J* = 7.2 Hz, 2H), 7.30~7.40 (m, 2H), 7.23~7.30 (m, 1H), 5.91 (bs, 1H), 3.75~3.85 (d, *J* = 8.4 Hz, 2H), 3.50~3.58 (d, *J* = 8.4 Hz, 2H), 3.20~3.30 (m, 1H) . LC-MS: m/z 149.9 $[M+H]^+$.

Synthesis of Compound (AH)

Compound **3a** of Scheme 8 (400 mg) was treated with TFA (10 mL)/DCM (10 mL) at 0 °C for 1 h, then concentrated to afford the TFA salt. This TFA salt was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH =10:1) to afford the title compound as an oil (130 mg, 52% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.35~7.50 (m, 4H), 7.30~7.40 (m, 1H), 3.75~3.85 (d, *J* = 9.2 Hz, 2H), 3.60~3.70 (d, *J* = 9.2 Hz, 2H), 3.40~3.50 (bs, 1H), 2.93 (s, 3H). LC-MS: m/z 163.9 $[M+H]^+$.

Synthesis of Compound (AG)

Sodium cyanoborohydride (1.55 g, 24.5 mmol) and AcOH (1 mL) were added to a solution of compound (AH) (400 mg, 2.45 mmol) and formaldehyde (37% aq 2.9 mL, 14.7 mmol) in MeOH/THF (6 mL/6 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred for 2 h. The mixture was diluted with ice water (10 mL), extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (MeOH/DCM=1:10) and afforded the title compound as the free base. The free base was converted to the HCl salt with HCl-dioxane to afford compound **(AH)** HCl salt (80 mg, 16% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 10.4~10.65 (bs, 1H), 7.42~7.50 (m, 4H), 7.35~7.40 (d, *J* = 8.8 Hz, 1H), 4.60~4.70 (m, 1H), 4.30~4.50 (m, 2H), 4.10~4.20 (m, 1H), 2.95 (s, 3H), 2.94~9.95 (d, *J* = 4.4 Hz, 1.5H), 2.83~2.85 (d, *J* = 4.4 Hz, 1.5H). LC-MS: m/z 172.9 $[M+H]^+$.

Synthesis of Compound (AI)

Compound **2b** of Scheme 8 (600 mg, 2 mmol) was dissolved in TFA (9 mL), cooled to 0 °C, then triethylsilane (3 mL) was added. The mixture was stirred at 0 °C for 1 h, then allowed to warm to room temperature and stirred overnight. The mixture was concentrated, and the crude was purified by prep-HPLC to afford the TFA salt. The TFA salt was dissolved in DCM, alkalinized with aqueous 5% NaHCO3, extracted with DCM, dried and concentrated with 1 mL of 4N HCl-dioxane to afford the HCl salt as a white solid (150 mg, 32% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 8.48 (bs, 1H), 6.82~9.95 (d, J = 8.8 Hz, 1H), 6.80~6.90 (m, 2H), 4.05~4.20 (m, 4H), 3.74 (s, 3H), 3.70 (s, 3H). LC-MS: m/z 194.1 $[M+H]^+$.

Synthesis of Compound (AJ)

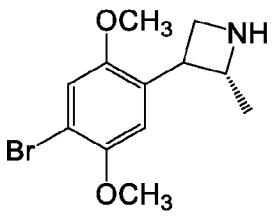
Compound **2b** of Scheme 8 (200 mg) was treated with TFA (10 mL)/DCM (10 mL) at 0 °C for 1 h, then concentrated. This TFA salt was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH =10:1) to provide the title compound as the free base. The free base was converted to its HCl salt with HCl-dioxane to afford the compound **(AJ)** HCl salt (85 mg, 53% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 9.31 (bs, 1H), 8.90 (bs, 1H), 6.95~7.05 (d, *J* = 8.8 Hz, 1H), 6.80~6.90 (m, 2H), 6.40~6.50 (m,1H), 4.40~4.45 (m, 2H), 3.90~4.05 (m, 2H), 3.79 (s, 3H), 3.72 (s, 3H). LC-MS: m/z 209.9 $[M+H]^+$.

Synthesis of Compound (AK)

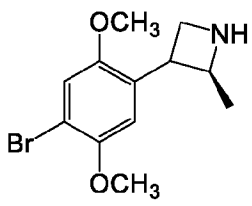
Compound **3b** of Scheme 8 (200 mg) was treated with TFA (10 mL)/DCM (10 mL) at 0 °C for 1 h, then concentrated. This TFA salt was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH =10:1) to afford the title compound as the free base. The free base was converted to its HCl salt with HCl-dioxane to afford compound **(AK)** HCl salt (50 mg, 62% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 9.34 (bs, 1H), 8.82 (bs, 1H), 6.95~7.05 (m, 2H), 6.80~6.82 (d, *J* = 2.8 Hz, 1H), 4.30~4.35 (m, 2H), 4.05~4.15 (m, 2H), 3.73 (s, 6H), 2.97 (s, 3H). LC-MS: m/z 224.0 $[M+H]^+$.

Example 9. Synthesis and characterization of Compounds (AL)-(AM).

Compounds (AL)-(AM) can be synthesized according to Scheme 9 (details below).

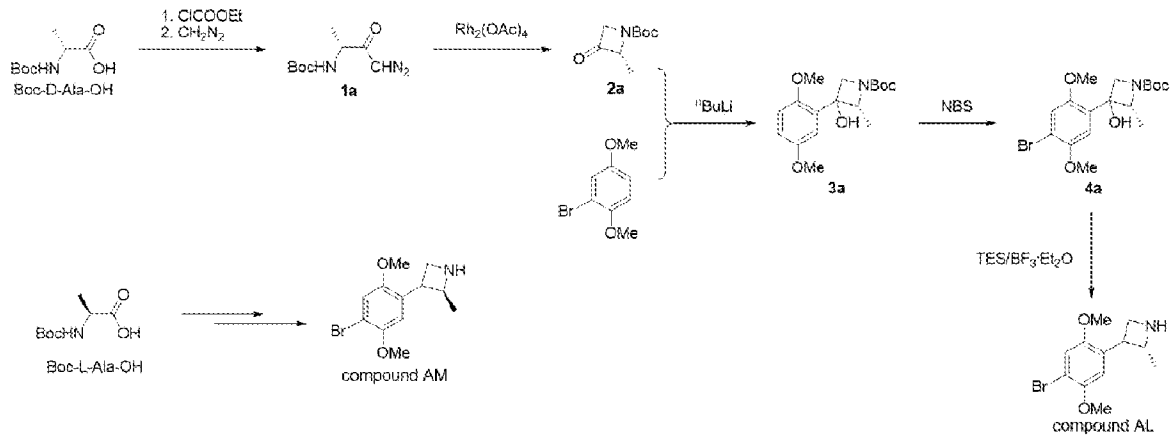


(AL)



(AM)

Scheme 9.



Procedures

Synthesis of tert-Butyl-(*R*)-(4-diazo-3-oxobutan-2-yl)carbamate (1a)

Ethyl chloroformate (3.14 g, 29.1 mmol) was added to a solution of N-Boc-D-alanine (5 g, 26.4 mmol) in THF (100 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then diazomethane (60 mmol)/ethyl ether solution (110 mL) was added and the resulting mixture was stirred at 0 °C for 0.5 h, then allowed stir for 2 h at room temperature. The mixture was quenched with AcOH (5 mL), then diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane =1:2) to afford compound **1** of Scheme 9 (3.9 g, 69% yield).

Synthesis of *tert*-Butyl-(*R*)-2-methyl-3-oxoazetidine-1-carboxylate (2a)

$Rh_2(OAc)_4$ (40.3 mg, 0.091 mmol) was added to a solution of compound **1** (3.9 g, 18.2 mmol) in DCM (50 mL) and TEA (25 µL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was quenched with water (20 mL), extracted with DCM (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), then filtered and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane =1:4) to provide compound **2a** of Scheme 9 (1.6 g, 47% yield). ^{1}H-NMR (400 MHz, CDCl3): 4.90~5.30 (m, 1H), 4.72 (s, 0.3H), 4.68 (s, 0.7H), 4.58~4.59 (d, *J* = 4.4 Hz, 0.7H), 4.54~4.55 (d, *J* = 4.4 Hz, 0.3H), 1.49 (s, 9H), 1.45~1.46 (d, *J* = 7.2 Hz, 3H).

Synthesis of tert-Butyl-(2*R*)-3-(2,5-dimethoxyphenyl)-3-hydroxy-2-methylazetidine-1-carboxylate (3a)

n-BuLi (1.6 M solution in hexane, 7.6 mL, 12.1 mmol) was added dropwise to a solution of 2-bromo-1,4-dimethoxybenzene (1.88 g, 8.6 mmol) in THF (15 mL) at -78 ºC. The mixture was stirred at -78 °C for 0.5 h, then a solution of compound **2a** of Scheme 9 (1.6g, 8.6 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 0.5 h, then quenched with aqueous 10% NH_4Cl (20 mL) and EtOAc (2 x 50 mL). The organic phase was collected and washed with water (2 x 20 mL), saturated aqueous

$NaHCO_3$ (2 x 20 mL), and brine (20 mL), dried (Na_2SO_4), then filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:2) to afford compound **3** of Scheme 9 (1.0 g, 36% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): 6.81~6.86 (m, 3H), 4.40~4.45 (m, 1H), 4.35~4.40 (d, *J* = 9.6 Hz, 1H), 3.95~4.00 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 1.50~1.55 (d, *J* = 6.4 Hz, 3H), 1.44 (s, 9H).

Synthesis of *tert*-Butyl-(2*R*)-3-(4-bromo-2,5-dimethoxyphenyl)-3-hydroxy-2-methylazetidine-1-carboxylate (4a)

NBS (606 mg, 3.4 mmol) was added to a solution of compound **3** of Scheme 9 (1.0 g, 3.1 mmol) in acetonitrile (15 mL) at 0 °C. The mixture was stirred for 16 h at room temperature and then concentrated in vacuo. The crude product was purified by silica gel chromatography (EtOAc/hexane =1:2) to provide compound **4** of Scheme 9 (400 mg, 32% yield).

Synthesis of Compound (AL) oxalate

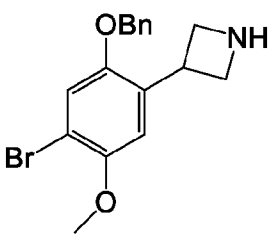
Compound **4** of Scheme 9 (400 mg, 1.00 mmol) was dissolved in DCM (4 mL), the solution cooled to 0 °C, then triethylsilane (2.0 mL, 10.0 mmol) and $BF_3.Et_2O$ (1.2 mL) were added at 0 °C. The mixture was stirred overnight at room temperature. The mixture was concentrated, and the crude was dissolved in DCM, alkalinized with aqueous 5% $NaHCO_3$, extracted with DCM, dried and concentrated to dryness. The residue was purified by silica gel chromatography (DCM/MeOH =15:1) to afford compound **(AL)** as the free base (180 mg, 63% yield), which was converted to compound **(AL)** oxalate and isolated as a white solid: ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 8.90 (bs, 1H), 7.20~7.30 (m, 1H), 7.04 (s, 1H), 4.40~4.60 (m, 1H), 4.05~4.20 (m, 2H), 3.70~3.90 (m, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 1.50~1.55 (m, 3H). LC-MS: m/z 288.0 $[M+H]^+$.

Synthesis of Compound (AM) oxalate

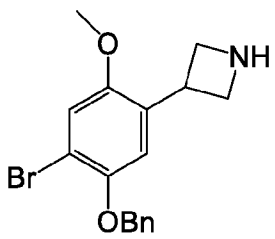
This compound was synthesized with a procedure similar to compound **(AL)** from Boc-L-Ala-OH to give compound **(AM)** oxalate (40 mg, 36% yield). ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 9.05 (bs, 2H), 7.20~7.30 (m, 1H), 7.04 (s, 1H), 4.40~4.60 (m, 1H), 4.05~4.20 (m, 2H), 3.70~3.90 (m, 2H), 3.85 (s, 3H), 3.75 (s, 3H), 1.50~1.55 (d, *J* = 6.8 Hz, 2.1H), 1.02~1.05 (d, *J* = 6.8 Hz, 0.7H). LC-MS: m/z 288.0 $[M+H]^+$.

Example 10. Synthesis and characterization of Compounds (AN)-(AO).

Compounds (AN)-(AO) can be synthesized according to Scheme 10 (details below).

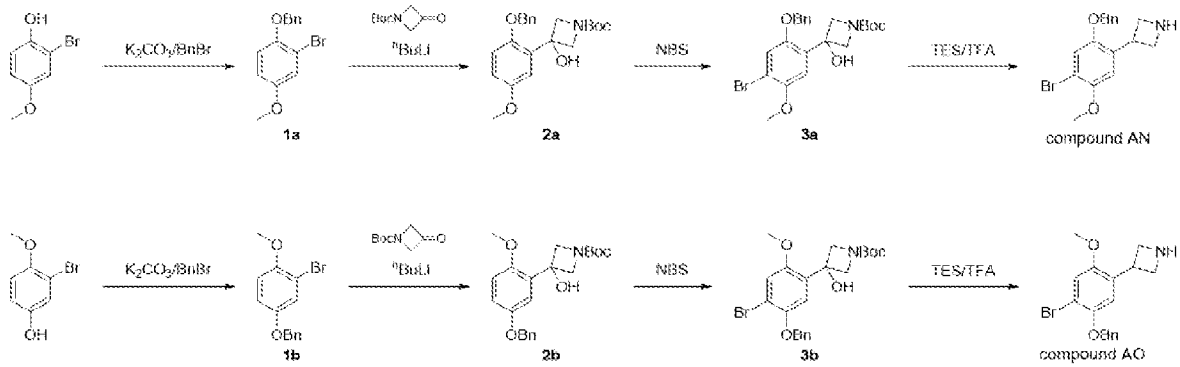


(AN)



(AO)

Scheme 10.



Procedures

Synthesis of 1-(Benzyloxy)-2-bromo-4-methoxybenzene (1a)

Benzylbromide (6.3g, 37 mmol) was added to a mixture of K_2CO_3 (6.8g, 49 mmol) and 2-bromo-4-methoxyphenol (5.0 g, 25 mmol) in DMF (70 mL). The mixture was heated at 60 °C and stirred overnight. The mixture was cooled to room temperature, quenched with water (200 mL), then extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine (2 x 200 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (EtOAc/hexane =1:50) to afford compound **1a** of Scheme 10 (4.9 g, 67% yield).

Synthesis of 4-(Benzyloxy)-2-bromo-1-methoxybenzene (1b)

This compound was synthesized with a procedure similar to that used for compound **1a** of Scheme 10 from 3-bromo-4-methoxyphenol (2.5 g, 12.5 mmol) to give title compound **1b** of Scheme 10 (2.3 g, 66% yield).

Synthesis of tert-Butyl-3-(2-(benzyloxy)-5-methoxyphenyl)-3-hydroxyazetidine-1-carboxylate (2a)

n-BuLi (1.6 M solution in hexane, 3.7 mL, 9.0 mmol) was added dropwise over 5 min to a solution of compound **1** of Scheme 10 (2.2 g, 7.5 mmol) in THF (20 mL) at -78 °C. The mixture was stirred for 0.5 h at -78 °C. A solution of Boc-azetidine-3-one (1.8 g, 11.0 mmol) in THF (25 mL) was added dropwise over 5 min. The mixture was allowed to warm to room temperature and stirred for 0.5 h, and then quenched with aqueous 10% NH_4Cl (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel column chromatography (EtOAc/Petroleum ether =2:1) to afford compound **2a** of Scheme 10 (1.20g, 42% yield).

Synthesis of tert-Butyl-3-(5-(benzyloxy)-2-methoxyphenyl)-3-hydroxyazetidine-1-carboxylate (2b)

This compound was synthesized from **1b** of Scheme 10 with a procedure similar to that used for compound **2a** of Scheme 10 (1.76 g, 6.0 mmol) to give the title compound **2b** of Scheme 10 (970 mg, 43% yield).

Synthesis of tert-Butyl-3-(2-(benzyloxy)-4-bromo-5-methoxyphenyl)-3-hydroxyazetidine-1-carboxylate (3a)

NBS (550 mg, 3.1 mmol) was added to a solution of compound **2** of Scheme 10 (1.5 g, 3.9 mmol) in acetonitrile (20 mL). The mixture was stirred at room temperature for 16 h. The solvent was concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane =1:3) to afford compound **3a** of Scheme 10 (1.59 g, 88% yield).

Synthesis of tert-Butyl 3-(5-(benzyloxy)-4-bromo-2-methoxyphenyl)-3-hydroxyazetidine-1-carboxylate (3b)

This compound was synthesized from compound **2b** of Scheme 10 with a procedure similar to that used for compound **3a** of Scheme 10 (3.0 g, 7.8 mmol) to give the title compound **3b** of Scheme 10 (3.2 g, 89% yield).

Synthesis of Compound (AN)

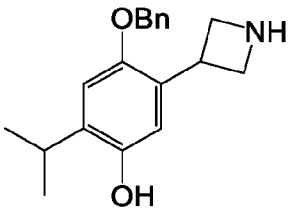
Trifluoroacetic acid (10 ml) was added dropwise to a solution of compound **3** of Scheme 10 (1.59 g, 3.4 mmol) and triethylsilane (4.0 g, 34.5 mmol) in DCM (10 mL). The mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was dissolved in a saturated aqueous solution of sodium bicarbonate (5 mL), then extracted with EtOAc (2 x 20 mL). The combined organic phases were concentrated. The residue was purified by silica gel chromatography (MeOH/DCM = 9:1) to afford the free base, which was converted to compound **(AN)** HCl salt (770 mg, 65% yield) as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 9.03 (bs, 1H), 9.81 (bs, 1H), 7.30~7.50 (m, 6H), 7.09 (s, 1H), 5.08 (s, 2H), 4.20~4.30 (m, 1H), 4.05~4.20 (m, 4H), 3.84 (s, 3H). LC-MS: m/z 349.9 $[M+H]^+$.

Synthesis of Compound (AO)

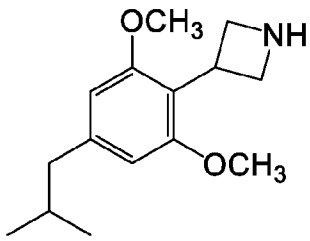
This compound was synthesized with a procedure similar to that used for compound **(AN)** from compound **3b** of Scheme 10 (3.0 g, 7.8 mmol) to give title compound **(AO)** tosylate (1:2, 330 mg, 55% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 7.30~7.60 (m, 6H), 7.15~7.25 (d, *J* = 13.2 Hz, 2H), 7.10~7.15 (d, *J* = 8.0 Hz, 1H), 5.17 (s, 2H), 3.90~4.10 (m, 5H), 3.73 (s, 3H), 2.29 (s, 1.5H). LC-MS: m/z 350.1 $[M+H]^+$.

Example 11. Synthesis and characterization of Compounds (AP)-(AQ).

Compounds (AP)-(AQ) can be synthesized according to Scheme 11 (details below).

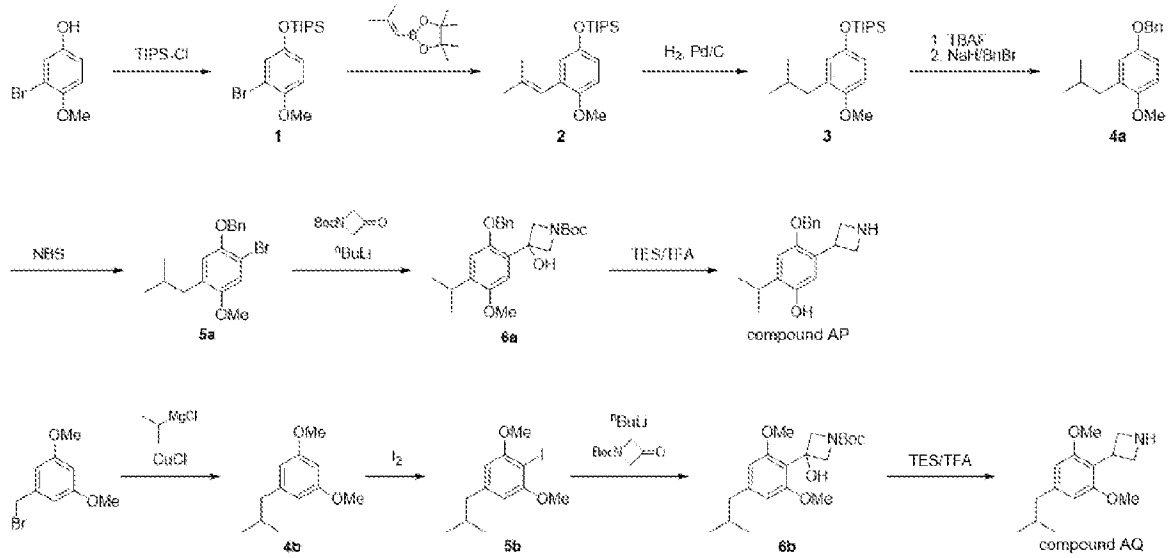


(AP)



(AQ)

Scheme 11.



Procedures

Synthesis of (3-Bromo-4-methoxyphenoxy)triisopropylsilane (1)

TIPS-Cl (5.67 g, 29.5 mmol) was added to a solution of 3-bromo-4-methoxyphenol (5 g, 24.6 mmol) and imidazole (2.51 g, 36.9 mmol) in DCM (60 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, then quenched with ice water (60 mL). The layers were separated and the aqueous phase was re-extracted with DCM (50 mL). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:6) to afford compound **1** of Scheme 11 (7.2 g, 82% yield).

Synthesis of Triisopropyl(4-methoxy-3-(2-methylprop-1-enyl)phenoxy)silane (2)

$Pd(PPh_3)_4$ (1.2 g, 1.0 mmol) was added to a mixture of K_2CO_3 (6.92 g, 50 mmol), 4,4,5,5-tetramethyl-2-(2-methylprop-1-enyl)-1,3,2-dioxaborolane (3.64 g, 20 mmol) and compound **1** of Scheme 11 (6.0 g, 17 mmol) in dioxane/H_2O (60/3 mL) under an N_2 atmosphere. The mixture was heated to 105 °C and stirred for 16 h. After cooling to room temperature, the mixture was diluted with water (120 mL), and then extracted with EtOAc (3 x 100 mL). The combined organic phase was washed with water (2 x 150 mL) and brine (100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by silica gel chromatography (EtOAc/hexane =1:11) to afford compound **2** of Scheme 11 (4.9 g, 86% yield).

Synthesis of (3-Isobutyl-4-methoxyphenoxy)triisopropylsilane (3)

Pd/C (10% on carbon, 1 g) was added to a solution of compound **2** of Scheme 11 (4.5 g, 13.4 mmol) in MeOH (20 mL). The mixture was stirred at room temperature under 1 atmosphere of hydrogen for 5 h. Pd/C was removed by filtration and the filtrate was concentrated to dryness. The crude material

was purified by silica gel chromatography (EtOAc/hexane =1:11) to afford compound **3** of Scheme 11 (4.3 g, 95% yield).

Synthesis of 4-(Benzyloxy)-2-isobutyl-1-methoxybenzene (4a)

TBAF (1.0M solution in THF, 15.3 mL, 15.3 mmol) was added to a solution of compound **3** of Scheme 11 (4.3 g, 12.8 mmol) in THF (20 mL). The mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water (100 mL), and then extracted with EtOAc (3 x 100 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH/DCM =9:1) to afford 3-isobutyl-4-methoxyphenol (2.1 g, 91% yield).

NaH (1.35 g, 33.3 mmol) was added to a solution of 3-isobutyl-4-methoxyphenol (5.0 g, 27.8 mmol) in DMF (100 mL) at 0 °C. The mixture was stirred for 0.5 h then benzyl bromide (7.2 g, 41.7 mmol) was added. The mixture was stirred at room temperature for 5 h. The reaction was diluted with water (300 mL), and then extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine (300 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:30) to afford compound **4a** of Scheme 11 (6.1 g, 81% yield).

Synthesis of 1-Isobutyl-3,5-dimethoxybenzene (4b)

Isopropylmagnesium chloride (2.0 M solution in THF, 6.9 mL, 13.8 mmol) was added dropwise over 5 min to a mixture of CuCl (42.8 mg, 0.43 mmol) and 1-(bromomethyl)-3,5-dimethoxybenzene (1.0 g, 4.33 mmol) in THF (20 mL) at -78 °C. The mixture was stirred for 2 h at -78 °C, and then allowed to warm to at room temperature and stirred for a further 16 h. The mixture was then quenched with aqueous 10% NH_4Cl (50 mL) and then extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with water (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL), and brine (50 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:9) to afford compound **4b** of Scheme 11 (730 mg, 87% yield).

Synthesis of 1-(Benzyloxy)-2-bromo-5-isobutyl-4-methoxybenzene (5a)

NBS (260 mg, 1.5 mmol) was added to a solution of compound **4** of Scheme 11 (500 mg, 1.9 mmol) in acetonitrile (10 mL). The mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography (EtOAc/hexane =1:20) to afford compound **5a** of Scheme 11 (460 mg, 72% yield).

Synthesis of 2-Iodo-5-isobutyl-1,3-dimethoxybenzene (5b)

Iodine (1.44 g, 5.8 mmol) was added to a mixture of $NaHCO_3$ (0.48 g, 5.8 mmol) and compound **1** (1.0 g, 5.2 mmol) in THF/H_2O (10 mL/10 mL) at 0 °C. The mixture was stirred at room temperature for 16 h. The mixture was diluted with water (20 mL), and extracted with EtOAc (2 x 30 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =1:10) to afford compound **5b** of Scheme 11 (1.3 g, 78% yield).

Synthesis of tert-Butyl-3-(2-(benzyloxy)-4-isobutyl-5-methoxyphenyl)-3-hydroxyazetidine-1-carboxylate (6a)

^{n}BuLi (1.6 M solution in hexane, 0.8 mL, 1.13 mmol) was added dropwise over 5 min to a solution of compound **5** of Scheme 11 (330 mg, 0.95 mmol) in THF (10 mL) at -78 °C. The mixture was stirred for 0.5 h at -78 °C and to it was added over 5 min a solution of Boc-azetidin-3-one (227 mg, 1.33 mmol) in THF (5 mL) . The mixture was allowed to warm to room temperature and stirred for 0.5 h, and then quenched with aqueous 10% NH_4Cl (10 mL). The mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated to dryness. The residue was purified by silica gel chromatography (EtOAc/hexane =2:1) to afford compound **6a** of Scheme 11 (320 mg, 76% yield).

Synthesis of tert-butyl-3-hydroxy-3-(4-isobutyl-2,6-dimethoxyphenyl)azetidine-1-carboxylate (6b)

This compound was synthesized from compound **5b** of Scheme 11 (2.8 g, 8.7 mmol) with a procedure similar to that used for compound **6a** of Scheme 11 with Boc-azetidin-3-one (2.1 g, 12.2 mmol) to provide the title compound **6b** of Scheme 11 (900 mg, 28% yield).

Synthesis of Compound (AP)

Trifluoroacetic acid (8 mL) was added dropwise to a solution of compound **6a** of Scheme 11 (1.1 g, 2.5 mmol) and triethylsilane (2.9 g, 24.9 mmol) in DCM (10 mL). The mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo, and the residue was dissolved in aqueous saturated solution of sodium bicarbonate (5 mL), extracted with EtOAc (2 x 20 mL). The combined organic phases was concentrated and the residue was purified by silica gel chromatography (MeOH/DCM = 9:1) to afford the free base, which was subsequently converted to compound **(AP)** HCl salt (470 mg, 58% yield) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 8.91 (bs, 2H), 7.25~7.50 (m, 5H), 6.91 (s, 1H), 6.86 (s, 1H), 5.06 (s, 2H), 4.20~4.40 (m, 1H), 4.10~4.20 (m, 4H), 3.77 (s, 3H), 2.35~2.45 (d, *J* = 7.2 Hz, 2H), 1.75~1.85 (m, 1H), 0.80~0.85 (d, *J* = 6.4 Hz, 6H). LC-MS: m/z 325.9 $[M+H]^+$.

Synthesis of Compound (AQ)

This compound was synthesized from compound **6b** of Scheme 11 (450 mg, 1.23 mmol) with a procedure similar to that used for compound **(AP)** to give the title compound **(AQ)** (130 mg, 42% yield) as HCl salt as white solid. ^{1}H-NMR (400 MHz, DMSO-d*6*): δ 8.65 (bs, 2H), 6.50~6.55 (d, *J* = 2.4 Hz, 1H), 6.30~6.35 (d, *J* = 2.4 Hz, 1H), 4.20~4.40 (m, 3H), 4.05~4.20 (m, 2H), 3.92 (s, 3H), 3.74 (s, 3H), 2.35~2.45 (d, *J* = 7.2 Hz, 2H), 1.50~1.65 (m, 1H), 0.80~0.85 (d, *J* = 6.8 Hz, 6H). LC-MS: m/z 250.5 $[M+H]^+$.

Example 12. 5-HT In Vitro Receptor Binding Studies.

This example describes testing of the present compounds in binding assays of various 5-HT2A, B,C and 5-HT1A receptors and potential adrenergic receptor off targets adrenergic 2a (ADRA2) and adrenergic 2B (ADRB2). Radioligand binding was assessed at equilibrium, using the ligands indicated in Table 1 and Table 3, at recombinantly expressed human receptors from membrane preparations using standard conditions at Cerep Eurofins Discovery and gold standard filtration methods, in accordance with generally accepted methodologies as described in Auld et al. (Receptor Binding Assays for HTS and

Drug Discovery. 2012. In: Sittampalam et al., editors. Assay Guidance Manual [Internet], Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences; 2004). Each test compound was titrated and tested at several concentrations under competitive binding conditions to determine radioligand binding inhibition, and half maximal inhibitory concentration (IC50) and apparent binding affinity (equilibrium dissociation constant (Ki)) where applicable. The IC50 values (concentration causing a half-maximal inhibition of control specific binding) by non-linear regression analysis of the competition curves were generated using Hill equation curve fitting. Hill coefficients (nH) were imposed to 1 due to limited data points and curve data points were checked for significant deviation from 1. This analysis was performed using the commercial software Graph-Pad Prism 8.0 (GraphPad Software, Inc.).

IC50 are described in nanomolar concentration units and are listed below for compounds (A)-(C) in Table 1.

Table 1.

ASSAY	Compound (A) IC50 binding (nM)	Compound (B) IC50 binding (nM)	Compound (C) IC50 binding (nM)
h5-HT1A (agonist radioligand, [3H]8-OH-DPAT)	291	>10000	>100
h5-HT2A (agonist radioligand, [125I](±)DOI)	3	140	~47
h5-HT2B (agonist radioligand, [125I](±)DOI)	61	199	~ 163
h5-HT2C (agonist radioligand, [125I](±)DOI)	2	61	<50
hAdrenergic A2 (antagonist radioligand, [3H]RX 821002)	> 1000	>1000	>1000
hAdrenergic B2 (agonist radioligand, [3H](-)CGP 12177)	>1000	>1000	>1000

Table 2 shows the apparent IC50 of the endogenous agonist serotonin in radioligand binding assays. Serotonin was used as a reference ligand for each 5-HT2 receptor tested under generally similar experimental conditions. Generally, the IC50 values of tested compounds (A), (B), and (C) (Table 1) indicate that these ligands have comparable to lower apparent affinities, along with differentiated specificity profile, for the 5-HT2 targets in comparison to the endogenous ligand serotonin.

Table 2.

ASSAY	Ligand	IC50 Binding (nM)
h5-HT2A (agonist radioligand, [125I](±)DOI)	serotonin	10
h5-HT2B (agonist radioligand, [125I](±)DOI)	serotonin	2.1
h5-HT2C (agonist radioligand, [125I](±)DOI)	serotonin	2.4

The specificity of compound (A) in regard to apparent affinity at tested receptors was 5-HT2A=5-HT2C>5-HT2B>5-HT1A>>ADRA2=ADRB2. The specificity of compound (B) in regard to apparent affinity at tested receptors was 2C>2A=2B>>1A=ADRA2=ADRB2. The specificity of compound (C) in regard to apparent affinity at tested receptors was 2A=2C>2B>1A=ADRA2=ADRB2.

Binding experiments demonstrated compound (A) to be a high affinity dual human 5-HT2A/C receptor ligand with a 20 fold preferential affinity for 5-HT2A/C over the 5-HT2B receptor subtype. Compound (B) featured a pan 5-HT2A/B/C receptor binding profile, with a modest 3-fold preferential

affinity for 5-HT2C. receptor subtype. Compound (C) was also a pan 5-HT2A/B/C ligand with a potential modest preferential affinity for 2A and 2C receptor subtypes over the 2B receptor subtype.

Table 3 shows IC50 results for additional compounds (G), (F), (L), (AL), and (AM).

Table 3.

ASSAY	Compound (G) IC50 Binding (nM)	Compound (F) IC50 Binding (nM)	Compound (L) IC50 Binding (nM)	Compound (AL) IC50 Binding (nM)	Compound (AM) IC50 Binding (nM)
h5-HT2A (Agonist Radioligand)	1	2.1	14	6	2.6
h5-HT2B (Agonist Radioligand)	32	41	7.4	9.4	43
h5-HT2C (Agonist Radioligand)	0.9	9.3	9.5	14	3.5

Table 4 shows EC50 values for a variety of compounds disclosed herein. An entry marked "N.C." indicates that the value was unable to be calculated.

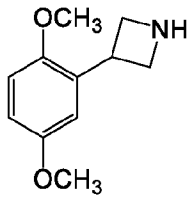
Table 4.

COMPOUND	Binding HT2A EC50 (nM)	Binding HT2B EC50 (nM)	Binding HT2C EC50 (nM)
D	N.C.	N.C.	2500
E	N.C.	N.C.	92
F	60	N.C.	31
G	9.4	N.C.	1.8
I	50	N.C.	15
J	9300	N.C.	N.C.
K	94	>10000	35
L	130	8600	99
M	N.C.	N.C.	8900
N	N.C.	N.C.	N.C.
Q	N.C.	N.C.	>10000
S	N.C.	N.C.	>10000
V	9.7	110	7.5
W	2300	N.C.	1900
X	2700	N.C.	3600
Z	85	160	24
AA	990	140	190
AB	500	68	7.8
AC	140	N.C.	17
AD	N.C.	N.C.	N.C.
AE	N.C.	N.C.	N.C.
AL	>10000	N.C.	600
AM	19	40	5

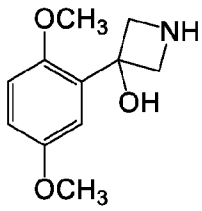
AR	N.C.	N.C.	2000
AS	N.C.	N.C.	N.C.
AT	N.C.	N.C.	2500

IC50 and EC50 analysis was performed using software developed at Cerep (Hill software) and validated by comparison with data generated by the commercial software SigmaPlot ® 4.0 for Windows ® (© 1997 by SPSS Inc.).

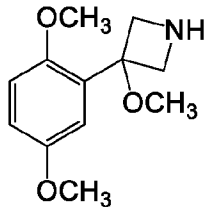
The inhibition constants (Ki) shown below in Table 5 were calculated for a variety of compounds disclosed herein using the Cheng Prusoff equation. Compounds (AR)-(AT) are:



(AR)



(AS)



(AT)

Table 5.

COMPOUND	h5-HT2A Ki Binding (nM)	h5-HT2B Ki Binding (nM)	h5-HT2C Ki Binding (nM)
D	1040	503	151
E	1030	1140	57.5
F	1.8[1]	20.6[1]	9.5[1]
G	25.8	148	14
G	0.755	15.9	0.808
H	1970	>10000	4950
I	0.175	41.4	>10000
J	346	1130	371
K	9.99	16.2	2.96
L	13[1]	35.5[1]	8.6[1]
M	66.3	640	177
N	7240	401	2430
O	>10000	972	1020
P	>10000	1780	1420
Q	203	70.4	566
R	>10000	2430	>10000
S	1880	147	320
T	>10000	>10000	>10000
U	>10000	2240	4620
V	1.01	6.02	1.26
W	109	529	59.3
X	91.4	446	337
Y	>10000	4660	5120
Z	8.63	5.55	2.4
AA	35.3	8.56	12.4
AB	16.5	7	1.86

AC	24.6	5.74	2.1
AD	704	>10000	>10000
AE	>10000	3060	>10000
AF	>10000	>10000	>10000
AG	3350	>10000	1210
AH	>10000	>10000	>10000
AL	276	168	174
AM	1.92	21.5	3.15
AR	567	199	80.3
AS	>10000	346	2480
AT	3740	1700	75.3

1. Average of two assay values.

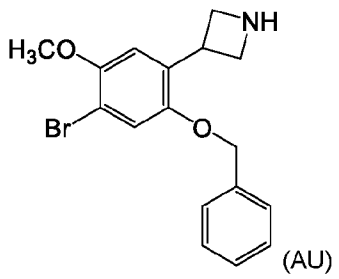
Example 13. 5-HT2A Receptor In Vitro Functional Studies Compound (A).

$G\alpha_q$-mediated calcium flux downstream of 5-HT_{2A} receptor activation was determined using HEK293 cells stably expressing the human 5-HT_{2A} receptor. Cells were seeded in DMEM supplemented with 10% fetal bovine serum, 100 units/mL penicillin, 100 mg/mL streptomycin, and 100 mg/mL Zeocin™ onto 96-well poly-D-lysine plates with clear bottoms (12,000 cells/well) and cultured at 37°C. The following day, media was aspirated and replaced with serum-free DMEM for 12 h. On the day of the experiment, the cells were washed once with HBSS supplemented with 20 mM HEPES, loaded with 75 μL of 3 μM Fluo-2 AM HA (Ion Indicators, LLC) diluted in HBSS-HEPES buffer, incubated for 1 h at 37°C, washed again with HBSS-HEPES, and maintained in 50 μL HBSS-HEPES at 25°C. The plate of dye-loaded cells were placed into a FlexStation 3 microplate reader (Molecular Devices, LLC) to monitor fluorescence (excitation, 485 nm; emission, 525 nm; cutoff, 515 nm). The plate was read for 20 s (2-second interval) to establish baseline fluorescence and then challenged with compound diluted in a range of 10 pM to 10 μM or buffer and read for an additional 80 s. After obtaining a calcium mobilization trace for each sample, the mean baseline fluorescence was subtracted from peak fluorescence in each well. E_{MAX} value was determined by normalization to the maximum 5-HT response (100%) on the same plate. The data were analyzed using non-linear regression curve-fitting routines in Graph-Pad Prism 8.0 (GraphPad Software, Inc.) to generate EC_{50} values.

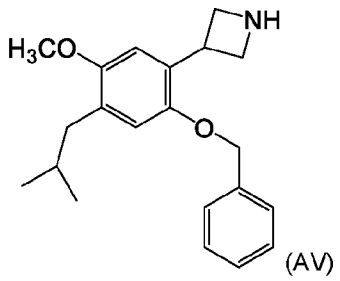
Compound (A) was observed to be a full agonist for calcium mobilization at heterologously expressed human 5-HT_{2A} receptors (calcium mobilization: EC_{50} = 3.7 nM, E_{Max} = 103%). Drug-induced Gq-mediated functional agonism at 5-HT2 receptors is generally associated with physiological stimulation in biological systems. In addition, drug-induced Gq-mediated functional agonism at 5-HT2 receptors is generally, but not always, associated with subsequent receptor transient receptor deactivation. In addition, drug-induced Gq-mediated functional agonism at 5-HT2 receptors is generally associated to varying degrees of physiological desensitization and/or post- signaling cellular adaptations with consequent modulation of physiological tone and responsiveness to endogenous stimuli.

Example 14. 5-HT2A and 5-HT2C In Vitro Receptor Binding Study.

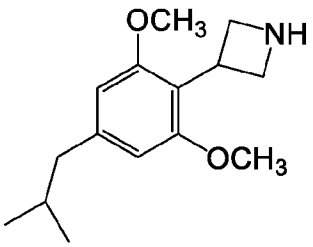
This example describes testing of compounds (AU)-(AX) in assays of 5-HT2A and 5-HT2C agonism and antagonism.



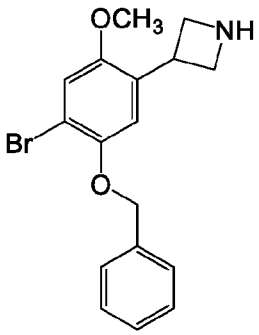
(AU)



(AV)



(AW)



(AX)

Cell Culture Procedure

Frozen adherent/epithelial HEK293 cells were thawed at 37°C water bath with a continuous agitation. Cells were gently added, drop by drop to a 15 ml centrifuge tube containing 5 ml of fresh pre-warmed complete DMEM medium. The cells were centrifuged at 1000 rpm for 10 minutes. Supernatant medium was discarded, and the cell pellet was resuspended in 5 ml of fresh pre-warmed complete DMEM medium. Cells were transferred to a T25 flask and incubated at 37°C with 5% CO2 until the cells reached >90% confluence. The recovery rate for frozen cells is usually 70% or above.

When the cells reached 90% confluence, the cells were split. Media was carefully aspirated off, the cell layer gently rinsed with the appropriate amount of 0.2% trypsin-EDTA, and the media aspirated off again. A minute passed, and the cells were dislodged by gently tapping of the sides of the flask. The cells were resuspended with the appropriate amount of cell culture medium. Media was changed every other day. Following a reiteration of the subculture, the cells were centrifuged at 1000 rpm for 10 minutes, the supernatant aspirated, the cells resuspended in 90% FBS and 10% DMSO at a density of 2-3 x 10^6 cells/ml, and frozen at -80 °C overnight, before being transferred into cryogenic storage in liquid nitrogen at -196 °C.

5-HT2A, 5-HT2B, 5-HT2B Agonism and Antagonism In Vitro Studies

Test compounds (AU)-(AX) were serially diluted with DMSO to 400X stock solution (top dose=4mM, 3-fold dilution, 11 points) in a LDV plate. Following the dilution, 250 nL of the compound solution was spotted and dispensed in a 20 uL/well assay buffer to make 5X working solutions in a 384-well compound plate by MultiDrop. The cells were cultured with DMEM medium (10% FBS). When the cells reached 80% confluence, the cells were dissociated with 0.25% Trypsin-EDTA. The cell density was measured and the cells diluted to 6.6 x10e5 cells/mL with DMEM (10% FBS). Following the dilution, 30µl of cells was dispensed into each well (20000 cells per well) of a 384-well plate (corning 3764#, pre-coated with Matrigel) with multidrop and cultured at 37℃ , 5% CO2 for 20-24hrs. 10ul was added per well of 4X loading dye into cell plate. The cells were incubated at 37°C, 5% CO2 in the dark for 1h.

Following 1 hour the Flipr program was loaded. The tips, cell plate and compound plates were placed into the machine and the program run. Per the Flipr program, 10ul to 40ul was added to the cell plate to obtain an agonist mode signal. The program was run repeatedly until all plates were tested, with fresh tips for each new cell plate. The plate was incubated at 25℃ in the dark for 15 min before antagonist mode signal readout. Following incubation, 20 µl/well in 384-well assay plate was prepared (greiner 784075#) of working solution (6X) of agonist (Serotonin) in 1X HBSS+20mM HEPES+0.1% BSA. The concentration of Serotonin used in this assay was determined by dose response in previous agonist mode. EC80 was used in the assay as final agonist concentration. Following 15 minutes elapsed, the

Flipr program was loaded. The tips, cell plate and compound plates were placed into the machine, and the program run. Per the Flipr program, 10ul to 50ul was added to the cell plate to obtain an antagonist mode signal. FLIPR results were read at room temperature using the specified settings. Data was analyzed by using XL-fit and is shown in Table 6 below.

Table 6.

ASSAY	Compound (AU)	Compound (AV)	Compound (AW)	Compound (AX)
5-HT2A FLIPR agonist EC50 (nM)	>10000	>10000	>10000	1032
5-HT2A FLIPR agonist Emax (M)	-0.164	9.9	6.5	74.55
5-HT2A FLIPR antagonist EC50 (nM)	145	461.9	>10000	
5-HT2A FLIPR antagonist Emax (M)	100.9	100.9	29.5	
5-HT2C FLIPR agonist EC50 (nM)	>10000	>10000	>10000	2450
5-HT2C FLIPR agonist Emax (M)	0	0	0	49.9
5-HT2C FLIPR antagonist EC50 (nM)	279.8	572.3	>10000	
5-HT2C FLIPR antagonist Emax (M)	100	100	26.15	

Example 15. 5-HT In Vitro Receptor Binding Studies.

This example describes testing of compounds disclosed herein in assays of 5-HT2A, 5-HT2B, and 5-HT2C agonism. The testing was in accordance with generally accepted methodologies as described in Porter et al. (Functional characterization of agonists at recombinant human 5-HT2A, 5-HT2B and 5-HT2C receptors in CHO-K1 cells. 1999), using HEK293 cells. IP1 results are shown in Table 7 below.

Table 7.

COMPOUND	5-HT2A IP1 EC50 (nM)	5-HT2A IP1 EMax (M)	5-HT2B IP1 EC50 (nM)	5-HT2A IP1 EMax (M)	5-HT2C IP1 EC50 (nM)	5-HT2A IP1 EMax (M)
D	>10000	13.9	>10000	100	1920	91
E	>10000	10.2	>10000	12.6	920	109
F	59.6	74.8	>10000	2.67	30.9	93.9
G	9.42	38	>10000	4.28	1.82	77.1
I	49.9	115	331	16.2	11.8	83.2
J	1480	53.2	>10000	0.268	1860	24.2
K	93.8	62.7	351	37	35.3	80.2
L	132	63	790	54.2	99.4	103
M	>10000	13.5	>10000	3.37	2530	69.8
N	>10000	5.83	>10000	2.12	>10000	9.11
Q	>10000	2.95	>10000	1.86	8380	78
S	>10000	-0.785	>10000	4.07	1550	54.2
V	8.84	95.9	109	54.3	7.46	103
W	758	69.6	>10000	100	814	76.9
X	576	63.2	>10000	0.986	1620	76.6
Z	85	83	157	44.9	23.6	109
AA	316	72.3	145	57.2	83.3	71.1

AB	198	78.8	68.1	73.2	7.83	84.8
AC	137	40.6	>10000	7.83	17	71.5
AE	>10000	-2.45	>10000	15.4	>10000	-0.307
AF	>10000	3.55	>10000	5.2	>10000	9.34
AL	>10000	100	>10000	7.6	601	89
AM	19.2	78.7	32.7	73.8	4.74	94.9
AR	2830	24.9	>10000	0.586	1460	90.6
AS	>10000	1.95	>10000	0.949	>10000	11.2
AT	>10000	-1.41	>10000	7.04	712	67.1

OTHER EMBODIMENTS

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

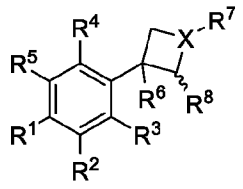
Although the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

Other embodiments are within the claims.

What is claimed is:

CLAIMS

1. A compound of formula (I):



(I),

wherein

X is N or $N(CH_3)$;

R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, C_1-C_8 alkylthio, or combined with R^2 or R^5 to form a cyclic ketal ring of formula $-OCH_2O-$;

R^2 is H, OH, OCH_3, OCH_2CH_3, OBn, or combined with R^1 forms a cyclic ketal ring of formula $-OCH_2O-$;

R^3 is H, OH, OCH_3, or OCH_2CH_3;

R^4 is H, OH, OCH_3, OCH_2CH_3, or OBn;

R^5 is H, OH, OCH_3, OCH_2CH_3, or combined with R^1 forms a cyclic ketal ring of formula $-OCH_2O-$;

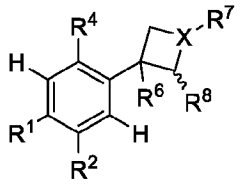
R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl; and

R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl; and

R_8 is H or methyl, wherein the methyl is in the R or S stereochemical configuration;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, further described by formula (II):



(II)

wherein

X is N or $N(CH_3)$;

R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, or optionally substituted C_{1-8} alkoxy, C_1-C_8 alkylthio, or combined with R^2 to form a cyclic ketal ring of formula $-OCH_2O-$;

R^2 is OH, OCH_3, OCH_2CH_3, OBn, or combined with R^1 forms a cyclic ketal ring of formula $-OCH_2O-$;

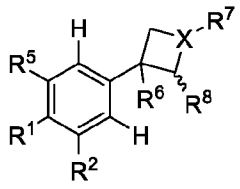
R^4 is OH, OCH_3, OCH_2CH_3, or OBn;

R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl;

R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl; and

R_8 is H or methyl, wherein the methyl is in the R or S stereochemical configuration;
or a pharmaceutically acceptable salt thereof.

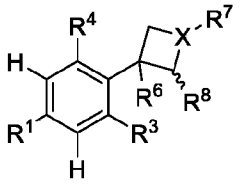
3. The compound of claim 1, further described by formula (III):



(III)

wherein
X is N or $N(CH_3)$;
R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, C_1-C_8 alkylthio, or combined with R^2 or R^5 to form a cyclic ketal ring of formula $-OCH_2O-$;
R^2 is OH, OCH_3, OCH_2CH_3, OBn, or combined with R^1 forms a cyclic ketal ring of formula $-OCH_2O-$;
R^5 is OH, OCH_3, or OCH_2CH_3;
R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl;
R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl; and
R_8 is H or methyl, wherein the methyl is in the R or S stereochemical configuration;
or a pharmaceutically acceptable salt thereof.

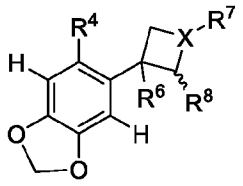
4. The compound of claim 1, further described by formula (IV):



(IV)

wherein
X is N or $N(CH_3)$;
R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, or C_1-C_8 alkylthio;
R^3 is OH, OCH_3, or OCH_2CH_3;
R^4 is OH, OCH_3, OCH_2CH_3, or OBn;
R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl;
R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl; and
R_8 is H or methyl, wherein the methyl is in the R or S stereochemical configuration;
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, further described by formula (V):



(V)

wherein

X is N or $N(CH_3)$;

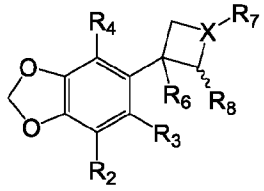
R^4 is OH, OCH_3, OCH_2CH_3, OBn;

R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl;

R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl and

R_8 is H or methyl, wherein the methyl is in the R or S stereochemical configuration.

6. The compound of claim 1, further described by formula (VI):



(VI)

wherein

X is N or $N(CH_3)$;

R^2 is H, OH, OCH_3, OCH_2CH_3, or OBn;

R^3 is H, OH, OCH_3, or OCH_2CH_3;

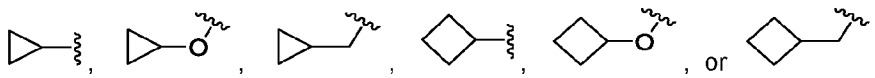
R^4 is H, OH, OCH_3, OCH_2CH_3, or OBn;

R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl;

R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl; and

R_8 is H or methyl, wherein the methyl is in the R or S stereochemical configuration.

7. The compound of any of claims 1-4, wherein R^1 is bromo, CN, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-C(CH_3)_3$, $-CH_2C(CH_3)_3$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, C_1-C_8 alkylthio, or a group selected from:

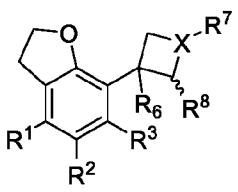
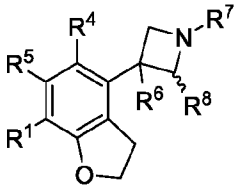
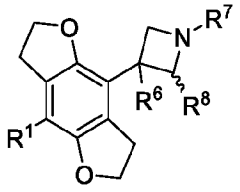


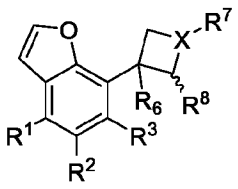
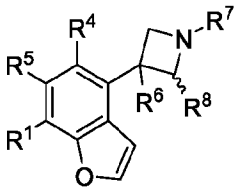
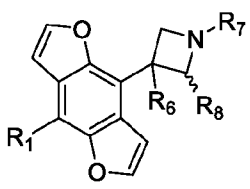
.

8. The compound of any of claims 1-7, wherein R^7 is selected from H, CH_3, CH_2CH_3, and optionally substituted C_{7-14} alkaryl.

9. The compound of any of claims 1-8, wherein R^6 is H, OH, or OCH_3.

10. A compound of any one of formulas (VIa)-(VIf)):


(VIa);

(VIb);

(VIc);


(VId);

(VIe); or

(VIf).

wherein

X is N or $N(CH_3)$;

R^1 is H, halogen, trifluoromethyl, CN, optionally substituted C_{1-8} alkyl, optionally substituted C_{2-8} alkenyl, optionally substituted C_{1-8} alkoxy, or C_1-C_8 alkylthio;

R^2 is OH, OCH_3, OCH_2CH_3, or OBn;

R^3 is H, OH, OCH_3, or OCH_2CH_3;

R^4 is H, OH, OCH_3, OCH_2CH_3, or OBn;

R^5 is H, OH, OCH_3, or OCH_2CH_3;

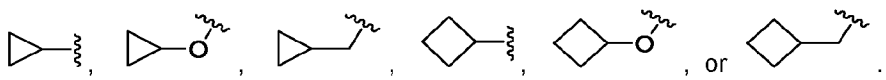
R^6 is H, OH, OCH_3, OCH_2CH_3, or C_{1-8} alkyl;

R^7 is H, optionally substituted C_1-C_8 alkyl, optionally substituted C_{2-7} heterocyclyl, optionally substituted C_{6-12} aryl, optionally substituted C_{7-14} alkaryl, optionally substituted C_{3-10} alkheterocyclyl, or optionally substituted C_{1-8} heteroalkyl, and

R_8 is H or methyl,

or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10, wherein R^1 is bromo, CN, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH_3$, $-C(CH_3)_3$, $-CH_2C(CH_3)_3$, $-OCH(CH_3)_2$, $-OC(CH_3)_3$, C_1-C_8 alkylthio, or a group selected from:


, or .

12. The compound of claim 10 or 11, wherein R^7 is selected from H, CH_3, CH_2CH_3, and optionally substituted C_{7-14} alkaryl.

13. A pharmaceutical composition comprising the compound of any one of claims 1-12, and a pharmaceutically acceptable excipient.

14. The pharmaceutical composition of claim 13, wherein the pharmaceutical composition is formulated for oral, intranasal, or pulmonary administration.

15. A method of treating an inflammatory disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-12.

16. The method of claim 15, wherein the inflammatory disorder is selected from the group consisting of asthma, chronic obstructive pulmonary disease, neuroinflammation, rheumatoid arthritis, atherosclerosis, psoriasis, type II diabetes, inflammatory bowel disease, Crohn's disease, multiple sclerosis, septicemia, Alzheimer's disease, and conjunctivitis.

17. A method of treating a psychological condition in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-12.

18. The method of claim 17, wherein the psychological condition is depression, anxiety, addiction, post-traumatic stress disorder, an eating disorder, or compulsive behavior.

19. A method of treating chronic pain in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-12.

20. The method of any one of claims 15-19, wherein the compound is administered orally, intranasally, or by inhalation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/025241

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 15/04; C07D 205/04 (2022.01)
CPC - C07C 15/04; C07D 205/04 (2022.05)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
see Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PUBCHEM, SID 440032533, Available Date: 03 February 2021 [retrieved on 07 June 2022].,Retrieved from the Internet <URL: https://pubchem.ncbi.nlm.nih.gov/substance/440032533> entire document	1
A	US 2014/0336378 A1 (VIVOZON INC.) 13 November 2014 (13.11.2014) entire document	1
A	US 6,310,208 B1 (BÖS et al) 30 October 2001 (30.10.2001) entire document	1

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 July 2022	SEP 02 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Taina Matos Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/025241

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8, 9, 13-20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/025241

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-7 and 10-12 are drawn to compounds of formula (I), or a pharmaceutically acceptable salt thereof, and compound of formulae (VIa)-(VIf), or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted to a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is N; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is H; R7 is H; and R8 is H. It is believed that claims 1 reads on this first named invention and thus this claim will be searched without fee to the extent that it reads on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is N; R1 is H; R2 is OH; R3 is H; R4 is H; R5 is H; R6 is H; R7 is H; and R8 is H. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables X, R1, R2, R3, R4, R5, R6, R7, R8, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound having the core structure of formula (I), or a pharmaceutically acceptable salt thereof, these shared technical features do not represent a contribution over the prior art as disclosed by the publication entitled "SID 440032533" by PubChem (hereinafter, "PubChem").

PubChem teaches a compound having the core structure of formula (I), or a pharmaceutically acceptable salt thereof (Pg. 2, compound as shown).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.