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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
04 July 2024 (04.07.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/145659 A1

(51) International Patent Classification:
A61K 31/4985 (2006.01) *A61P 25/24* (2006.01)
A61P 25/18 (2006.01) *C07D 487/16* (2006.01)
A61P 25/22 (2006.01)

(21) International Application Number:
PCT/US2023/086562

(22) International Filing Date:
29 December 2023 (29.12.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/478,010 30 December 2022 (30.12.2022) US
63/603,617 28 November 2023 (28.11.2023) US

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(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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, 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, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, 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, ME, 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))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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))*

(54) Title: HETEROCYCLE FUSED GAMMA-CARBOLINES ACTING ON THE SEROTONINE 5-HT2A RECEPTOR

(57) Abstract: The invention relates to particular substituted heterocycle fused gamma-carbolines, in free, solid, pharmaceutically acceptable salt and/or substantially pure form as described herein, pharmaceutical compositions thereof, and methods of use as non-hallucinogenic biased agonists or antagonists at the serotonin (5-HT_{2A}) receptor, in particularly having agonism biased towards the beta-arrestin signaling pathway. Such compounds are useful for the treatment of mood disorders, general anxiety, social anxiety, depression, anhedonia, and other neuropsychiatric diseases.

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HETEROCYCLE FUSED GAMMA-CARBOLINES ACTING ON THE SEROTONINE 5-HT2A RECEPTOR

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is an international application which claims priority to, and the benefit of, U.S. Provisional Application Ser. No. 63/478,010, filed on Dec. 30, 2022, and U.S. Provisional Application Ser. No. 63/603,617, filed on Nov. 28, 2023, the contents of each of which are hereby incorporated by reference in their entireties.

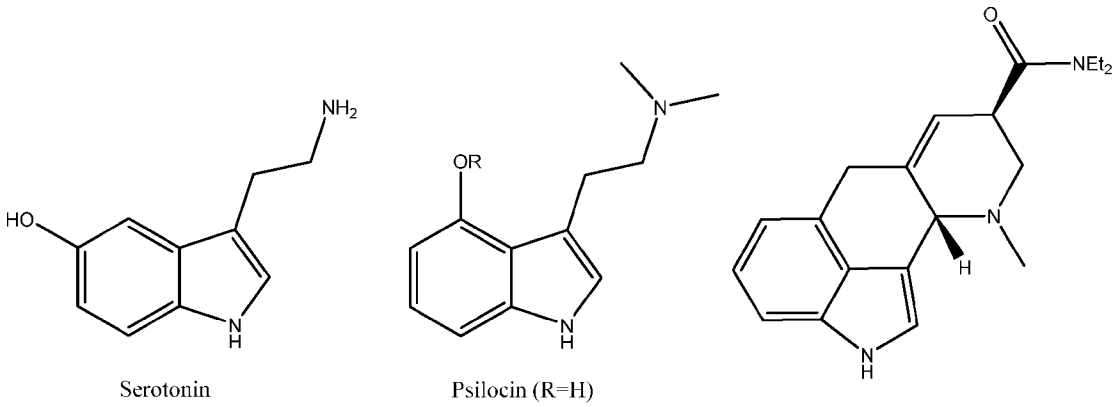
TECHNICAL FIELD

[0001] The invention relates to particular substituted heterocycle fused gamma-carbolines, in free, solid, pharmaceutically acceptable salt and/or substantially pure form as described herein, pharmaceutical compositions thereof, and methods of use as non-hallucinogenic biased agonists or antagonists at the serotonin (5-HT_{2A}) receptor, in particularly having agonism biased towards the beta-arrestin signaling pathway, or as serotonin (5-HT_{2A}) receptor antagonists. Such compounds may be useful for the treatment of mood disorders, general anxiety, social anxiety, depression, schizophrenia, anhedonia, and other neuropsychiatric diseases.

BACKGROUND

[0002] Serotonin, also known as 5-hydroxytryptamine (5-HT), is a neurotransmitter widely distributed in the brain. The dysregulation of serotonergic signaling in the brain has been implicated in the pathogenesis of several neuropsychiatric diseases. Drugs that directly or indirectly target 5-HT, such as 5-HT_2 receptor agonists and selective serotonin reuptake inhibitors, are widely used in psychiatry, finding use in the treatment of numerous mood disorders as well as in the treatment of psychosis. However, strong 5-HT_2 agonists tend to cause hallucinations, which is a dangerous side effect. Serotonergic psychedelic hallucinogens are powerful psychoactive substances that alter both perception and mood, and they may be useful in restoring function to dysregulated serotonergic networks in the brain. There have been studies suggesting that the classic hallucinogenic psychedelic serotonin agonists, such as LSD (D-lysergic acid diethylamide) and psilocybin (via its active metabolite psilocin) could be very effective in the treatment of numerous neuropsychiatric disorders, especially depression, but these drugs are not feasible in practice because of their hallucinogenic side effects. The hallucinogenic psychedelics can cause overwhelming distress (i.e., “bad trips”) or prolonged or

intermittent psychoses, can promote self-harm or harm to others, and are prone to abuse and dependence. In addition, it has been reported that serotonergic agents having 5-HT_{2B} agonist activity may cause valvular heart disease and/or pulmonary arterial hypertension. Therefore, there has been an effort to develop novel compounds having a pharmacological profile for treatment of mood and other CNS disorders, similar to the hallucinogenic psychedelics, but without the hallucinations, abuse liability, or valvular heart disease risk.

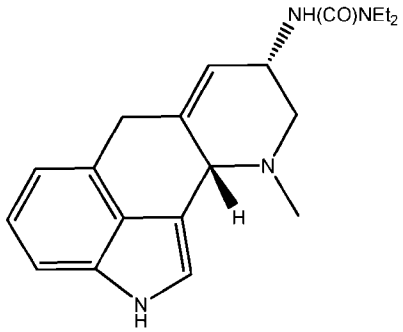


Serotonin

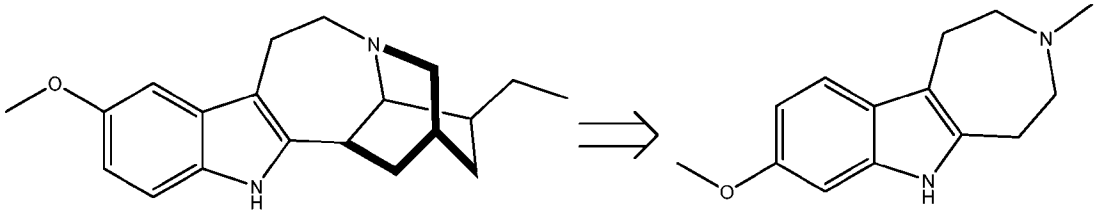
Psilocin (R=H)
Psilocybin (R=PO_3H_2)

LSD

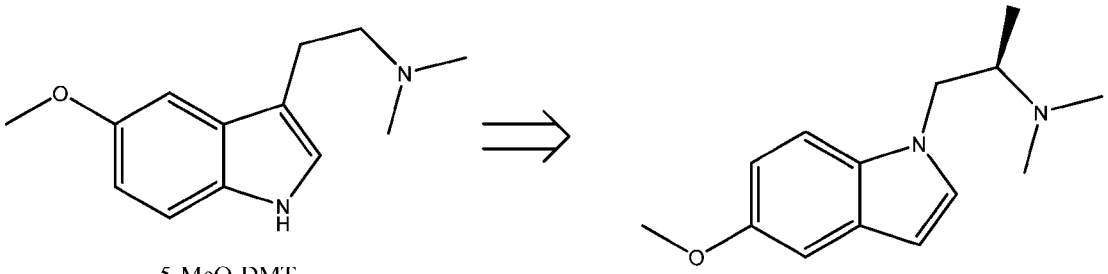
[0003] One well-known non-hallucinogenic psychedelic analog is lisuride, developed in the 1970's, which has been used for the treatment of Parkinson's disease and migraine attacks. Two non-hallucinogenic psychedelic analogs have been recently described as having anti-depressant like behavior. Cameron et al. generated the novel compound tabernanthalog by modifying the skeletal core of the natural hallucinogenic psychedelic ibogaine. *Nature*, 589:474-79 (2021). *Cell*, 184:2779-92.e18 (2021). Similarly, based on the well-known hallucinogenic psychedelic 5-methoxy-dimethyltryptamine, Dong et al. arrived at the novel analog AAZ-A-154. However, neither of these groups developed any structure-activity guidance for these compounds, and it thus remained unclear how to rationally design non-hallucinogenic psychedelic analogs.



Lisuride



Ibogaine Tabernanthalog



5-MeO-DMT AAZ-A-154

[0004] There are seven families of serotonin receptors, numbered 5-HT_1 to 5-HT_7. Except for 5-HT3, a ligand gated ion channel, all of the serotonin receptors have long been known to be G-protein coupled receptors (GPCRs). GPCRs have an intracellular domain which is bound to a heterotrimeric G protein. The G protein consists of alpha-, beta-, and gamma-subunits in a complex. The G-protein heterotrimer is normally in an inactive state, bound to a guanosine diphosphate ligand. Agonist binding to a GPCR causes a conformational change in the protein's intracellular domain which allows it to catalyze the exchange of the bound GDP for a GTP molecule (guanosine triphosphate). This results in activation of the G-protein and its dissociation from the GPCR's intracellular domain. In particular, the G-protein alpha subunit (G-alpha) dissociates and diffuses into the cytosol. There are numerous types of G-alpha proteins which differ in their functional effects. Some G-alpha proteins, including G_i, G_o, and G_s, regulate levels of the cytosolic second messenger cAMP (cyclic adenosine monophosphate), by activating or inactivating adenylyl cyclase enzymes. The G-alpha-q variant (G_q) operates by activating phospholipase C enzyme, which cleaves phosphatidylinositol diphosphate (PIP_2) to form the two second messengers inositol triphosphate (IP_3) and diacylglycerol (DAG). IP3 stimulates calcium release from intracellular storage locations, resulting in the activation of various calcium-dependent kinases, and DAG stimulates protein kinase C (PKC) activation. Because G-proteins are abundant soluble cytosolic proteins, an agonist-activated GPCR which has activated and released its G-protein may bind to another GDP-bound heterotrimer, thus activating and releasing a second GTP-bound G-alpha subunit, and so on, until the receptor is deactivated.

[0005] GPCRs are deactivated in a two-step process. First, they are phosphorylated by a family of enzymes called G receptor kinases (GRKs). This greatly reduces the affinity of the GPCR's active site for G-protein. In the second step, beta-arrestin proteins can competitively bind to the active site of the phosphorylated GPCR, resulting in complete inhibition of G-protein binding. The arrestin-GPCR complex then targets the inactivated receptor for either recycling or degradation within the cell.

[0006] The beta-arrestin proteins were originally thought to only play a role in inactivating and targeting the inactivated GPCR for recycling or degradation. However, in the last few years, it has become increasingly apparent that beta-arrestin proteins also play a novel role in G-protein independent signaling mechanisms. Apparently, the GPCR-arrestin complex created following agonist-induced receptor activation and deactivation may serve as a scaffold which can attract many other proteins to form large multi-protein complexes. The complexes can then cause the activation of a variety of kinases involved in cell signaling, including Src, ERKs, and MAPKs. For example, some signaling cascades, such as the MAPK cascade, require two kinase proteins to approach each other closely so that one may phosphorylate the other. Arrestin complexes may facilitate such phosphorylation by binding to both kinase proteins at the same time. Therefore, beta-arrestin signaling provides an alternative mechanism for GPCR signal transduction that does not rely on G-protein-induced signaling cascades and second messengers.

[0007] Signaling bias is the concept that some ligands will bind to a GPCR in such a manner as to bias the receptor towards or away from one of the two signaling pathway: G-protein mediated signaling and beta-arrestin mediated signaling. Several examples of such biased GPCR ligands have been discovered, and it creates the potential for functionally selective receptor agonism. For example, the mu-opioid receptor (MOR) is a GPCR coupled to the G_i-type alpha subunit, so that agonist binding results in inhibition of adenylate cyclase activity and a reduction in cytosolic cAMP levels. It is found that this G-protein mediated pathway is responsible for morphine and other opioid drugs' analgesic activity. However, it is beta-arrestin recruitment to the receptor that is the cause of the major opioid side effects, respiratory depression and inhibition of gastrointestinal motility. Various MOR ligands have been discovered which show bias towards the G-protein signaling and away from the beta-arrestin signaling, resulting in enhanced analgesic efficacy with a reduced side effect profile. This can either reflect a higher

efficacy for agonism via one pathway or the other, or even agonism of one pathway and antagonism of the other pathway.

[0008] While the 5-HT_1, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 receptors are coupled to the cAMP-regulating G proteins, the 5-HT_2 family of receptors are GPCRs coupled to Gq proteins, thus resulting in a classic signaling cascade mediated by the phosphatidylinositol pathway. It has also been found that the 5-HT_2 receptors are also capable of activating a beta-arrestin signaling cascade as well. It is believed that serotonin agonists must agonize both the G-protein signaling pathway and the beta-arrestin signaling pathway of the 5-HT_{2A} receptor in order to cause hallucinations, while agonists which selectively agonize the beta-arrestin pathway without agonizing the G-protein coupled pathway may provide relief of mood disorders, anxiety, and other CNS disorders without hallucinogenic side effects.

[0009] For example, Cao et al. recently studied the binding of numerous compounds, including serotonin, psilocin, LSD, the non-hallucinogenic psychedelic analog lisuride, and lumateperone, to the 5-HT_{2A} receptor using high-resolution X-ray crystallography. *Science*, 375:403-11 (2022). They identified a new binding mode for serotonin and psilocin. Traditionally, LSD, lisuride, serotonin and psilocin were known to bind in the so-called "orthostatic binding pocket (OBP)." In this binding mode, the polycyclic core of LSD and lisuride binds low in the OBP, while the side chains of LSD and lisuride protrude into the so-called "extended-binding pocket (EBP)." In contrast, the indole core of serotonin and psilocin sit higher in the OBP, closer to the EBP, but without significant protrusion into the EBP.

[00010] Surprisingly, Cao et al. discovered that serotonin and psilocin have a second binding mode which is flipped so that the indole core sits in the EBP with only minimal presence in the upper part of the OBP. Cao further generated data suggesting that this second binding mode is responsible for increased beta-arrestin recruitment by the receptor, thus explaining the existence of biased serotonin receptor agonism. They also presented evidence that the G_q-mediated signaling is responsible for the hallucinogenic effects of the traditional psychedelics, and that ligands which are biased towards beta-arrestin recruitment may provide the therapeutic benefits of the psychedelics, such as antidepressant action, without hallucinogenic side effects.

[00011] Substituted heterocycle fused gamma-carbolines are known to be agonists or antagonists of 5-HT_2 receptors, particularly 5-HT_{2A} receptors, and are useful in treating central nervous system disorders. These compounds have been generally disclosed in U.S. Pat. No.

6,548,493; 7,238,690; 6,552,017; 6,713,471; 7,183,282; U.S. RE 39.680, and U.S. RE 39,679. U.S. Patent 8,309,722, and U.S. Patent 7,081,455, disclose methods of making such substituted heterocycle fused gamma-carbolines and uses of these gamma-carbolines as serotonin agonists and antagonists useful for the control and prevention of central nervous system disorders such as addictive behavior and sleep disorders.

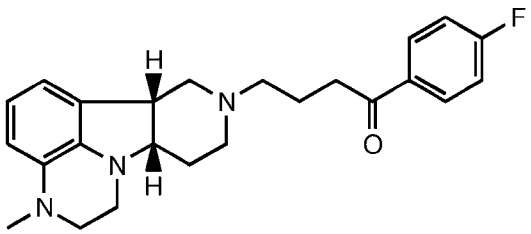
[00012] In addition, U.S. Patent 8,598,119 discloses use of particular substituted heterocycle fused gamma-carbolines for the treatment of a combination of psychosis and depressive disorders as well as sleep, depressive and/or mood disorders in patients with psychosis or Parkinson's disease. In addition to disorders associated with psychosis and/or depression, this patent application discloses and claims use of these compounds at a low dose to selectively antagonize 5-HT_{2A} receptors without affecting or minimally affecting dopamine D_2 receptors, thereby useful for the treatment of sleep disorders without the side effects associated with high occupancy of the dopamine D_2 pathways or side effects of other pathways (e.g., $GABA_A$ receptors) associated with conventional sedative-hypnotic agents (e.g., benzodiazepines). U.S. Patent 8,648,077 discloses methods of preparing toluenesulfonic acid addition salt crystals of these substituted heterocycle fused gamma-carbolines.

[00013] US 2021/006009 discloses evidence showing that the aforementioned substituted fused heterocycle gamma carbolines may operate, in part, through glutamate (NMDA and AMPA receptor) receptor activation leading to enhanced mTOR1 signaling, in a manner similar to that of ketamine. Ketamine is a selective NMDA receptor antagonist. Ketamine acts through a system that is unrelated to the common psychogenic monoamines (serotonin, norepinephrine and dopamine), and this may be a major reason for its much more rapid effects. Ketamine directly antagonizes extrasynaptic glutamatergic NMDA receptors, which also decreases GABAergic inhibition resulting in indirect activation of AMPA-type glutamate receptors. The downstream effects of AMPA receptor activation involve increase levels of brain-derived neurotrophic factor (BDNF) and activation of mTORC1 kinase pathways. Like ketamine, recent evidence suggests that compounds related to those of the present disclosure enhance both NMDA and AMPA-induced currents in rat medial prefrontal cortex pyramidal neurons via activation of D1 receptors, and that this is associated with increased mTORC1 signaling.

[00014] U.S. 10,245,260 discloses novel oxo-metabolites of the substituted heterocycle fused gamma-carbolines disclosed in the above-mentioned publications. These new oxo-metabolites

retain much of the unique pharmacologic activity of the parent compounds, including serotonin receptor inhibition, SERT inhibition, and dopamine receptor modulation. However, these oxo-metabolites were found to unexpectedly also show significant activity at mu-opioid receptors. Analogs of these novel compounds have also been disclosed, for example, in publications U.S. 10, 906,906 and U.S. 10,961,245.

[00015] One such substituted heterocycle fused gamma-carboline of the aforementioned art is lumateperone shown below,



Formula A

with the chemical name (4-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-lH-pyrido[3',4':4,5]pyrrolo[l,2,3-de]quinoxalin-8(7H)-yl)-l-(4-fluorophenyl)-l-butanone). It is known to be an extremely potent serotonin receptor (5-HT_{2A}) antagonist, as well as a modulator of dopamine receptor (D1 and/or D2) signaling, and a serotonin transporter (SERT) antagonist, and it is useful in treating a variety of central nervous system disorders. It has also been known as ITI-007.

[00016] Lumateperone *antagonizes* the serotonin-2A (5-HT_{2A}) receptor, and/or modulates dopamine receptor signaling at the level of key intracellular phosphoproteins. This compound is principally known to be useful for the treatment of positive and negative symptoms of schizophrenia, depression (especially acute depression and bipolar depression), anxiety and traumatic disorders (including acute anxiety and post-traumatic stress disorder), and dementias (including Alzheimer's disease and the symptoms associated therewith). Lumateperone's effect as an anti-depressant is tied to its antagonism at the 5-HT_{2A} receptor and its inhibition of the serotonin transporter (SERT), pharmacological features which it shares with the SARI class of antidepressants (Serotonin Antagonist and Reuptake Inhibitor), which includes trazodone, nefazodone, lorpiprazole, and mepiprazole.

[00017] At dopamine D2 receptors, lumateperone has dual properties and acts as both a post-synaptic antagonist and a pre-synaptic partial agonist of the D2 receptor. It also stimulates phosphorylation of glutamatergic NMDA NR2B, or GluN2B, receptors in a mesolimbic specific manner. It is believed that this regional selectivity in the brain areas is thought to mediate the

efficacy of antipsychotic drugs, together with the serotonergic, glutamatergic, and dopaminergic interactions, may result in antipsychotic efficacy for positive, negative, affective and cognitive symptoms associated with schizophrenia. The compound also exhibits serotonin reuptake inhibition, providing antidepressant activity for the treatment of schizoaffective disorder, co-morbid depression, and/or as a stand-alone treatment for major depressive disorder. Lumateperone is also useful for the treatment of bipolar disorder and other psychiatric and neurodegenerative disorders, particularly behavioral disturbances associated with dementia, autism and other CNS diseases. These features may be able to improve the quality of life of patients with schizophrenia and enhance social function to allow them to more fully integrate into their families and their workplace.

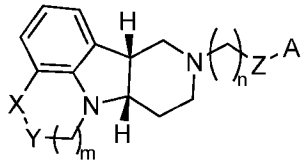
[00018] Lumateperone tosylate (Caplyta®) is currently approved in the United States for the treatment of schizophrenia and bipolar depression. It is currently in clinical trials and development for additional indications, including major depressive disorder (MDD).

[00019] The functional effects of lumateperone on the beta-arrestin recruitment and G_q-mediated signaling pathways induced by binding to the 5-HT_{2A} receptor have not been previously disclosed. The present inventors have found that lumateperone is a potent *antagonist* of 5-HT_{2A} receptors in both the beta-arrestin and G_q functional assays.

[00020] There remains a need for new compounds with efficacy in treating neuropsychiatric disorders, especially depression, anxiety, and schizophrenia. It would be particularly beneficial to have compounds with strong biased agonism (e.g., full agonism or partial agonism) towards beta-arrestin recruitment at the 5-HT_{2A} receptor in order to provide a non-hallucinogenic anti-depressant or anxiolytic effect.

BRIEF SUMMARY

[00021] In a first aspect, the present disclosure relates to a compound (Compound I) of Formula I:



Formula I

wherein:

X is S, S(O), $S(O)_2$, O, CH_2, CHR^b, $C(R^b)_2$, NH, $N(R^a)$ (e.g., $N(CH_3)$), N-C(O)-R^a, N-C(O)-O-R^a, N-C(O)-O-CH_2-O-R^a, N-CH_2-O-C(O)-R^a, $N^+(=O^-)$, a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane), or a spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane), wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is optionally substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;
Y is CH_2, CHR^c, -C(O)-, $C(R^c)_2$, a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane), or a spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane), wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is optionally substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;
Z is a bond, -S-, S(O), $S(O)_2$, -O-, -NH, $N(R^d)$, -C(O)-, -C(OH)-, -C(OC_{1-6}alkyl), -C(=N-OH)-, -C(=N-OC_{1-6}alkyl)-, a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane), a spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane), or -O$(CH_2)_p$O- wherein p is 2, 3, or 4 (e.g., p is 2), wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is optionally substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;
A is H, C_{3-6}cycloalkyl (e.g., cyclopropyl or cyclohexyl), aryl (e.g., phenyl), or heteroaryl, wherein said cycloalkyl, aryl, or heteroaryl is substituted by 0-5 groups R;
each R is independently selected from aryl (e.g., phenyl), aryloxy (e.g., phenoxy), heteroaryl (e.g., pyridyl), C_{1-6}alkyl (e.g., methyl, ethyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkylsulfonyl (e.g., methylsulfonyl), C_{1-6}alkoxy (e.g., methoxy, ethoxy), C_{1-6}alkylthio (e.g., methylthio), halo (e.g., F), cyano, C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), or hydroxy, wherein each of said aryl, heteroaryl, alkyl, haloalkyl, alkylsulfonyl, alkoxy, alkylthio, cycloalkyl, or cycloalkoxy is optionally further substituted by one or more groups selected from aryl (optionally substituted with halo), halo, C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkylsulfonyl (e.g., methylsulfonyl), C_{1-6}alkoxy (e.g., methoxy), C_{1-}

$_{6}$alkylthio (e.g., methylthio), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), amino, C_{1-6}alkylamino (e.g., methylamino), di(C_{1-6}alkyl)amino (e.g., dimethylamino), (C_{1-6}alkyl)(C_{1-6}alkyl)amino (e.g., methylethylamino), and hydroxy;

R^a and R^d, are each independently selected from C_{1-20}alkyl (e.g., methyl or tert-butyl), and C_{1-2}alkylaryl (e.g., benzyl or phenethyl);

R^b and R^c are each independently selected from C_{1-6}alkyl (e.g., methyl, ethyl, tert-butyl), C_{1-6}alkoxy, C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and C_{1-2}alkylaryl (e.g., benzyl or phenethyl);

m is 1 or 2;

n is 1, 2, 3, 4, or 5;

in free or salt form (e.g., pharmaceutically acceptable salt form);

provided that n is not 3 when Z is -C(O)-, X is CH_2 or O, and m is 2; and

provided that n is not 3 when Z is -C(O)-, X is CH_2, and m is 1; and

provided that n is not 3 when Z is -C(O)- or -O-, X is NH or N(R^a), and m is 1; and provided that n is not 3 when Z is O, X is NCH_3, Y is -C(O)-, and m is 1.

[00022] The present disclosure further provides additional embodiments of first aspect, including:

1.1 Compound I, wherein X is S, S(O), or $S(O)_2$;

1.2 Compound I, wherein X is O;

1.3 Compound I, wherein X is CH_2, CHR^b, or $C(R^b)_2$;

1.4 Compound 1.3, wherein R^b is independently C_{1-6}alkyl (e.g., methyl);

1.5 Compound I, wherein X is CH_2;

1.6 Compound I, wherein X is NH;

1.7 Compound I, wherein X is N(R^a);

1.8 Compound I, wherein X is N-C(O)-R^a;

1.9 Compound I, wherein X is N-C(O)-O-R^a;

1.10 Compound I, wherein X is N-C(O)-O-CH_2-O-R^a;

1.11 Compound I, wherein X is N-CH_2-O-C(O)-R^a;

1.12 Compound I, or any of 1.7-1.11, wherein R^a is C_{1-2}alkylaryl (e.g., benzyl or phenethyl);

1.13 Compound I, or any of 1.7-1.11, wherein R^a is C_{1-20}alkyl (e.g., methyl or tert-butyl);

1.14 Compound I, or any of 1.7-1.11, wherein R^a is C_{10-20}alkyl (e.g., decyl or dodecyl);

1.15 Compound I, or any of 1.7-1.11, wherein R^a is C_{1-15}alkyl (e.g., hexyl or octyl);

1.16 Compound I, or any of 1.7-1.11, wherein R^a is C_{7-15}alkyl (e.g., heptyl or nonyl);

1.17 Compound I, or any of 1.7-1.11, wherein R^a is C_{1-6}alkyl (e.g., butyl or hexyl);

1.18 Compound I, or any of 1.7-1.11, wherein R^a is C_{1-4}alkyl (e.g., n-butyl or tert-butyl);

1.19 Compound I, or any of 1.7-1.11, wherein R^a is C_{1-3}alkyl (e.g., propyl or isopropyl);

1.20 Compound I, or any of 1.7-1.11, wherein R^a is C_{1-2}alkyl (e.g., methyl or ethyl);

1.21 Compound I, or any of 1.7-1.11, wherein X is $N(CH_3)$;

1.22 Compound I, wherein X is a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane);

1.23 Compound 1.22, wherein the spiro-joined C_{3-6}cycloalkyl is selected from cyclopropane, cyclobutane, cyclopentane, and cyclohexane;

1.24 Compound 1.22, wherein the spiro-joined C_{3-6}cycloalkyl is cyclopropane;

1.25 Compound I, wherein X is spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane);

1.26 Compound 1.25, wherein the spiro-joined 3-6-membered heterocycloalkyl is selected from aziridine, azetidine, oxetane, pyrrolidine, tetrahydrofuran, piperidine, tetrahydropyran, piperazine, and morpholine;

1.27 Compound 1.25, wherein the spiro-joined 3-6-membered heterocycloalkyl is selected from aziridine;

1.28 Compound I, or any of 1.22-1.27, wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is unsubstituted;

1.29 Compound I, or any of 1.22-1.27, wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;

1.30 Compound I, or any of 1.1-1.29, wherein Y is CH_2;

1.31 Compound I, or any of 1.1-1.29, wherein Y is -C(O)-;

1.32 Compound I, or any of 1.1-1.29, wherein Y is CHR^c or $C(R^c)_2$;

1.33 Compound 1.32, wherein each R^c is independently C_{1-6}alkyl;

1.34 Compound 1.32, wherein each R^c is independently selected from methyl, ethyl and propyl;

1.35 Compound I, or any of 1.1-1.29, wherein Y is a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane);

1.36 Compound 1.35, wherein the spiro-joined C_{3-6}cycloalkyl is selected from cyclopropane, cyclobutane, cyclopentane, and cyclohexane;

1.37 Compound 1.35, wherein the spiro-joined C_{3-6}cycloalkyl is cyclopropane;

1.38 Compound I, or any of 1.1-1.29, wherein Y is spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane);

1.39 Compound 1.38, wherein the spiro-joined 3-6-membered heterocycloalkyl is selected from aziridine, azetidine, oxetane, pyrrolidine, tetrahydrofuran, piperidine, tetrahydropyran, piperazine, and morpholine;

1.40 Compound 1.39, wherein the spiro-joined 3-6-membered heterocycloalkyl is aziridine;

1.41 Compound I, or any of 1.35-1.40, wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is unsubstituted;

1.42 Compound I, or any of 1.35-1.40, wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;

1.43 Compound I, or any of 1.1-1.42, wherein Z is a bond;

1.44 Compound I, or any of 1.1-1.42, wherein Z is S, S(O), or $S(O)_2$;

1.45 Compound I, or any of 1.1-1.42, wherein Z is O;

1.46 Compound I, or any of 1.1-1.42, wherein Z is NH;

1.47 Compound I, or any of 1.1-1.42, wherein Z is $N(R^a)$, e.g., $N(CH_3)$;

1.48 Compound I, or any of 1.1-1.42, wherein Z is -C(O)-;

1.49 Compound I, or any of 1.1-1.42, wherein Z is -C(OH)-, -C(OC_{1-6}alkyl), -C(=N-OH)-, -C(=N-OC_{1-6}alkyl)-, optionally wherein said C_{1-6}alkyl is methyl;

1.50 Compound I, or any of 1.1-1.42, wherein Z is a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane);

1.51 Compound 1.50, wherein the spiro-joined C_{3-6}cycloalkyl is selected from cyclopropane, cyclobutane, cyclopentane, and cyclohexane;

1.52 Compound 1.50, wherein the spiro-joined C_{3-6}cycloalkyl is cyclopropane

1.53 Compound I, or any of 1.1-1.42, wherein Z is spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane);

1.54 Compound 1.53, wherein the spiro-joined 3-6-membered heterocycloalkyl is selected from aziridine, azetidine, oxetane, pyrrolidine, tetrahydrofuran, piperidine, tetrahydropyran, piperazine, and morpholine;

1.55 Compound 1.53, wherein the spiro-joined 3-6-membered heterocycloalkyl is aziridine;

1.56 Compound I, or any of 1.49-1.55, wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is unsubstituted;

1.57 Compound I, or any of 1.49-1.55, wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;

1.58 Compound I, or any of 1.1-1.57, wherein A is a 6-10 membered aryl ring, e.g., selected from phenyl and naphthyl, substituted by 0-5 groups R;

1.59 Compound I, or any of 1.1-1.57, wherein A is a 5-10 membered heteroaryl ring, substituted by 0-5 groups R;

1.60 Compound 1.59, wherein A is selected from furan, thiophene (e.g., thiophen-2-yl), pyrrole, oxazole, thiazole, imidazole, isoxazole, isothiazole, pyrazole, pyridine (e.g., pyrid-4-yl), 2-oxopyridine (e.g., 2-oxopyridin-1(2H)-yl), pyrimidine, pyridazine, pyrazine, benzofuran (e.g., benzofuran-4-yl, or benzofuran-7-yl, or 2-methylbenzofuran-4-yl), dihydrobenzofuran (e.g., 2,3-dihydrobenzofuran-7-yl), benzothiophene, indole (e.g., indol-1-yl, indol-3-yl, or

indol-5-yl), benzoxazole, benzothiazole, benzimidazole (e.g., benzo[d]imidazol-1-yl), benzisoxazole (e.g., benzo[d]isoxazol-3-yl, or benzo[d]isoxazol-4-yl), benzisothiazole (e.g., benzo[d]isothiazol-3-yl), benzotriazole (e.g., benzo[d][1,2,3-triazol-1-yl), indazole (e.g., indazol-1-yl, indazol-3-yl, or indazol-7-yl), quinoline (e.g., quinolin-8-yl), isoquinoline (e.g., isoquinolin-7-yl), quinazoline (e.g., quinazolin-7-yl), and quinoxaline (e.g., quinoxalin-5-yl);

1.61 Compound 1.60, wherein A is substituted by 0 groups R;

1.62 Compound 1.60, wherein A is substituted by 1 group R;

1.63 Compound 1.60, wherein A is substituted by 2 groups R;

1.64 Compound 1.58, wherein A is a phenyl ring, substituted by 0-5 groups R;

1.65 Compound 1.64, wherein there is one group R;

1.66 Compound 1.65, wherein the group R is positioned at the para position of the phenyl ring;

1.67 Compound 1.65, wherein the group R is positioned at the meta position of the phenyl ring;

1.68 Compound 1.65, wherein the group R is positioned at the ortho position of the phenyl ring;

1.69 Compound 1.64, wherein there are two groups R;

1.70 Compound 1.69, wherein the groups R are positioned at the ortho and para positions of the phenyl ring;

1.71 Compound 1.69, wherein the groups R are positioned at the meta and para positions of the phenyl ring;

1.72 Compound 1.69, wherein the groups R are positioned at the ortho and meta positions on the same side of the phenyl ring;

1.73 Compound 1.69, wherein the groups R are positioned at the ortho and meta positions on opposite sides of the phenyl ring;

1.74 Compound 1.69, wherein the groups R are positioned at the two ortho positions of the phenyl ring;

1.75 Compound 1.69, wherein the groups R are positioned at the two meta positions of the phenyl ring;

1.76 Compound 1.64, wherein there are three groups R;

1.77 Compound 1.76, wherein the groups R are positioned at the two ortho positions and the para position of the phenyl ring;

1.78 Compound 1.64, wherein there are four groups R;

1.79 Compound 1.64, wherein there are five groups R;

1.80 Compound I, or any of 1.1-1.79, wherein each group R is independently selected from methyl, ethyl, trifluoromethyl, methoxy, ethoxy, F, Cl, cyano, hydroxy, 2-methoxyethoxy, methylsulfonyl, methylthio, cyclopropoxy, cyclopropylmethoxy, methylamino, 4-fluorophenoxy, and (4-fluorobenzyl)oxy;

1.81 Compound I, or any of 1.1-1.80, wherein A is selected from the group consisting of: phenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 2-methylphenyl, 2-ethylphenyl, 3-ethylphenyl, 4-ethylphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-fluorophenyl, 3-chloro-4-fluorophenyl, 2-cyano-4-fluorophenyl, 3-cyano-4-fluorophenyl, 2-methyl-4-fluorophenyl, 3-methyl-4-fluorophenyl, 2-methoxy-4-fluorophenyl, 2-methoxy-5-fluorophenyl, 2-fluoro-4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 2-hydroxyphenyl, 2,5-dimethoxyphenyl, 2-trifluoromethyoxyphenyl, 3-trifluoromethylphenyl, 2-(methylsulfonyl)phenyl, 3-(methylthio)phenyl, 4-(methoxyethoxy)phenyl, 4-(4-fluorobenzyloxy)phenyl, 4-(4-fluorophenoxy)phenyl, 3-cyclopropoxyphenyl, 3-(cyclopropylmethoxy)phenyl, and 2-(methylamino)phenyl;

1.82 Compound I, or any of 1.1-1.80, wherein A is selected from the group consisting of: pyrid-4-yl, thiophen-2-yl, indol-1-yl, indol-3-yl, 5-fluoroindol-3-yl, indazol-1-yl, indazol-3-yl, indazol-7-yl, benzofuran-4-yl, benzofuran-7-yl, 2,3-dihydrobenzofuran-7-yl, 2-methylbenzofuran-7-yl, benzo[d]isoxazol-3-yl, benzo[d]isoxazol-4-yl, benzo[d]isoxazol-7-yl, 6-fluorobenzo[d]isoxazol-3-yl, benzo[d]isothiazol-3-yl, benzo[d]imidazole-1-yl, benzo[d][1,2,3]triazol-1-yl, isoquinolin-7-yl, quinolin-8-yl, quinoxaline-5-yl, quinazolin-7-yl, and 2-oxopyridin-1(2H)-yl;

1.83 Compound I, or any of 1.1-1.80, wherein A is selected from the group consisting of: phenyl, 2-ethylphenyl, 4-fluorophenyl, 2-methoxyphenyl, 3-methoxyphenyl, benzofuran-7-yl, benzo[d]isoxazol-3-yl, and benzo[d]isothiazol-3-yl;

1.84 Compound I, or any of 1.1-1.83, wherein m is 1;

1.85 Compound I, or any of 1.1-1.83, wherein m is 2;

1.86 Compound I, or any of 1.1-1.85, wherein n is 2;

1.87 Compound I, or any of 1.1-1.85, wherein n is 3;

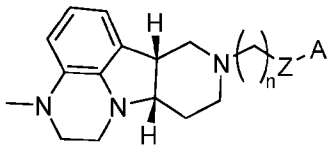
1.88 Compound I, or any of 1.1-1.85, wherein n is 4;

1.89 Compound I, or any of 1.1-1.85, wherein n is 5;

1.90 Compound I, or any of 1.1-1.89, wherein X is S, O, CH_2, NH, $N(CH_3)$, or spiro-joined cyclopropyl; Y is CH_2, C(O), or spiro-joined cyclopropyl, and Z is a bond, -O-, -C(O)-, $-O(CH_2)_2O-$, or $-C(=NOCH_3)-$;

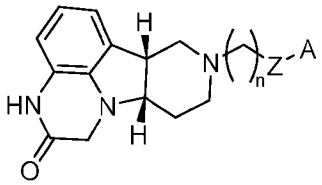
1.91 Compound I, or any of 1.1-1.89, wherein X is $N(CH_3)$ or spiro-joined cyclopropyl; Y is CH_2, C(O), or spiro-joined cyclopropyl, and Z is a bond, -O-, or -C(O)-;

1.92 Compound I, or any of 1.1-1.91, wherein the compound of Formula I is a compound of Formula Ia:



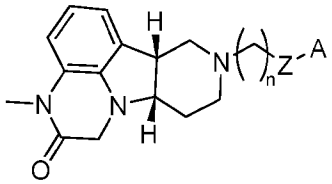
wherein n, Z, and A are defined as in any preceding embodiment;

1.93 Compound I, or any of 1.1-1.91, wherein the compound of Formula I is a compound of Formula Ib:



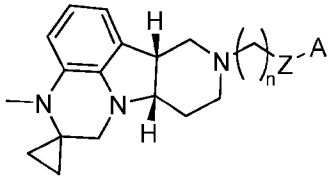
wherein n, Z, and A are defined as in any preceding embodiment;

1.94 Compound I, or any of 1.1-1.91, wherein the compound of Formula I is a compound of Formula Ic:



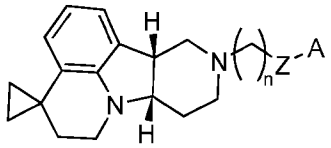
wherein n, Z, and A are defined as in any preceding embodiment;

1.95 Compound I, or any of 1.1-1.91, wherein the compound of Formula I is a compound of Formula Id:



wherein n, Z, and A are defined as in any preceding embodiment;

1.96 Compound I, or any of 1.1-1.91, wherein the compound of Formula I is a compound of Formula Ie:



wherein n, Z, and A are defined as in any preceding embodiment;

1.97 Compound I, or any of 1.1-1.96, wherein n is 4 and Z is a bond;

1.98 Compound I, or any of 1.1-1.96, wherein n is 3 and Z is -O- or -C(O)-;

1.99 Compound I, or any of 1.1-1.96, wherein n is 3 and Z is a bond;

1.100 Compound I, or any of 1.1-1.96, wherein n is 2 and Z is -O- or -C(O)-;

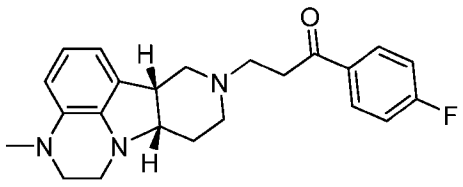
1.101 Compound I, or any of 1.1-1.96, wherein n is 2 and Z is a bond;

1.102 Compound I, or any of 1.1-1.96, wherein n is 1 and Z is -O- or -C(O)-;

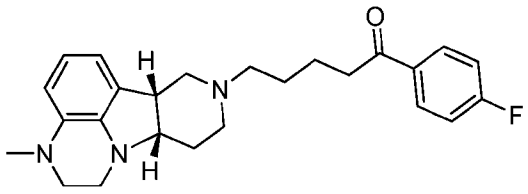
1.103 Compound I, or any of 1.1-1.96, wherein n is 1 and Z is a bond;

1.104 Compound I, or any of 1.1-1.103, wherein A is H or C_{3-6}cycloalkyl (e.g., cyclopropyl or cyclohexyl), Z is a bond or -C(O)-, and n is 1, 2, or 3;

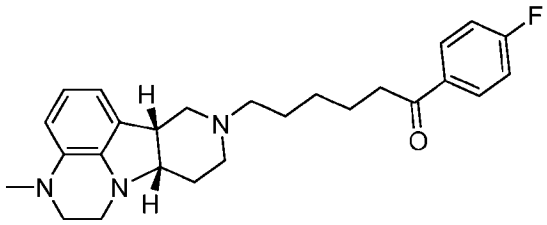
1.105 Compound I, or any of 1.1-1.103, wherein the compound is selected from the group consisting of:



,



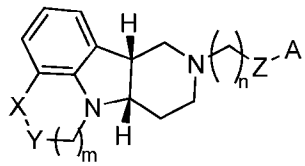
, and



;

each independently in free or pharmaceutically acceptable salt or form;

1.106 Compound I, or any of 1.1-1.105, wherein the compound is the compound of any one of Examples 1 to 180, or is selected from the group consisting of:



Formula I,

wherein the variables are defined as provided any of the following embodiments:

X	Y	m	n	Z	A
-N(CH_3)-	-CH_2-	1	3	-O-	2-CN-4-F-phenyl
-N(CH_3)-	-CH_2-	1	4	-C(O)-	4-F-phenyl
-N(CH_3)-	-CH_2-	1	2	-C(O)-	4-F-phenyl
-N(CH_3)-	Cyp	1	3	-C(O)-	4-F-phenyl
-N(CH_3)-	-CH_2-	1	5	-C(O)-	4-F-phenyl
-N(CH_3)-	-CH_2-	1	3	-C(O)-	4-($CH_3OCH_2CH_2O$)-phenyl
Cyp	-CH_2-	1	3	-C(O)-	4-F-phenyl
Cyp	-CH_2-	1	3	-O-	4-F-phenyl
-NH-	-C(O)-	1	3	-O-	3-Me-4-F-phenyl
-NH-	-C(O)-	1	3	-O-	3-Cl-4-F-phenyl
-NH-	-C(O)-	1	3	-O-	3-CN-4-F-phenyl
-N(CH_3)-	-CH_2-	1	2	-O(CH_2)$_2$O-	4-F-phenyl

-N(CH_3)-	-CH_2-	1	3	-C(O)-	4-((4-F-benzyl)oxy)
-N(CH_3)-	Cyp	1	2	-C(O)-	4-F-phenyl
-N(CH_3)-	Cyp	1	2	-O-	4-F-phenyl
-N(CH_3)-	Cyp	1	2	-C(O)-	2-Me-4-F-phenyl
-N(CH_3)-	Cyp	1	2	-O-	2-Me-4-F-phenyl
-NH-	-C(O)-	1	2	-O-	4-F-phenyl
-N(CH_3)-	Cyp	1	3	bond	3-Cl-phenyl
-N(CH_3)-	Cyp	1	3	bond	3-MeO-phenyl
-N(CH_3)-	Cyp	1	3	bond	3-CF_3-phenyl
-N(CH_3)-	Cyp	1	3	bond	2-Cl-phenyl
-N(CH_3)-	Cyp	1	3	bond	2-Me-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-Cl-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-MeO-phenyl
-N(CH_3)-	-CH_2-	1	2	-O-	4-F-phenyl
-N(CH_3)-	-CH_2-	1	2	-O-	2-MeO-4-F-phenyl
-N(CH_3)-	-CH_2-	1	3	bond	2-MeO-phenyl
-N(CH_3)-	-CH_2-	1	3	bond	3-MeO-phenyl
-N(CH_3)-	-CH_2-	1	3	bond	3-Cl-phenyl
-N(CH_3)-	-CH_2-	1	3	bond	2-Cl-phenyl
-N(CH_3)-	-CH_2-	1	3	bond	3-CF_3-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-Cl-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-MeO-phenyl
-N(CH_3)-	-CH_2-	1	3	bond	2-Me-phenyl
-CH_2-	-CH_2-	2	2	-C(O)-	4-F-phenyl
-CH_2-	-CH_2-	2	2	-O-	4-F-phenyl
-CH_2-	-CH_2-	2	2	bond	4-F-phenyl
-N(CH_3)-	Cyp	1	3	bond	2-MeO-phenyl
-N(CH_3)-	Cyp	1	2	bond	benzo[d]isoxazol-3-yl
-N(CH_3)-	-CH_2-	1	2	-C(O)-	2-Me-4-F-phenyl
-O-	-CH_2-	2	2	-O-	4-F-phenyl

-O-	-CH_2-	2	2	-C(O)-	4-F-phenyl
-S-	-CH_2-	2	2	-C(O)-	4-F-phenyl
-CH_2-	-CH_2-	1	2	-C(O)-	4-F-phenyl
-S-	-CH_2-	1	2	-C(O)-	4-F-phenyl
-NH-	Cyp	1	2	-O-	4-F-phenyl
-NH-	Cyp	1	2	-O-	2-Me-4-F-phenyl
-NH-	Cyp	1	2	-C(O)-	4-F-phenyl
-NH-	Cyp	1	2	-C(O)-	2-Me-4-F-phenyl
Cyp	-CH_2-	1	2	-O-	4-F-phenyl
Cyp	-CH_2-	1	2	-O-	2-Me-4-F-phenyl
Cyp	-CH_2-	1	2	-C(O)-	4-F-phenyl
Cyp	-CH_2-	1	2	-C(O)-	2-Me-4-F-phenyl
-NH-	-C(O)-	1	2	-C(O)-	4-F-phenyl
-NH-	-C(O)-	1	2	-C(O)-	2-Me-4-F-phenyl
-NH-	-C(O)-	1	2	-C(O)-	2-F-4-Me-phenyl
-CH_2-	-CH_2-	2	3	bond	2-MeO-phenyl
-CH_2-	-CH_2-	2	3	bond	2-HO-phenyl
-CH_2-	-CH_2-	2	3	bond	2-Cl-phenyl
-CH_2-	-CH_2-	2	2	bond	2-Cl-phenyl
-CH_2-	-CH_2-	2	3	bond	3-MeO-phenyl
-CH_2-	-CH_2-	2	3	bond	3-CF_3-phenyl
-CH_2-	-CH_2-	2	3	bond	3-Cl-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]isoxazol-3-yl
-N(CH_3)-	Cyp	1	2	bond	6-F-benzo[d]isoxazol-3-yl
-N(CH_3)-	-CH_2-	1	2	bond	6-F-benzo[d]isoxazol-3-yl
Cyp	-CH_2-	1	3	-O-	2-Me-4-F-phenyl
-N(CH_3)-	-CH_2-	1	3	-C(O)-	4-(4-F-PhO)-phenyl
Cyp	-CH_2-	1	2	bond	2-MeO-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	3-MeO-phenyl
Cyp	-CH_2-	1	2	bond	benzo[d]isoxazol-3-yl

-N(CH_3)-	Cyp	1	4	bond	2-CN-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-CN-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-CN-phenyl
-N(CH_3)-	-CH_2-	1	3	bond	2-CN-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-oxopyridin-1(2H)-yl
-N(CH_3)-	-CH_2-	1	2	bond	2-MeO-4-F-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-MeO-4-F-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-CF_3O-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-Et-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	4-MeO-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	3-CN-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	4-CN-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	5-F-indol-3-yl
-N(CH_3)-	-CH_2-	1	3	-C(O)-	2-MeO-phenyl
-N(CH_3)-	-C(O)-	1	2	-O-	4-F-phenyl
-N(CH_3)-	-C(O)-	1	2	bond	2-MeO-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-HO-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	2-MeO-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-EtO-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	benzofuran-7-yl
-N(CH_3)-	-CH_2-	1	3	-O-	2-MeO-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]isothiazol-3-yl
-N(CH_3)-	-CH_2-	1	2	bond	2,5-di-MeO-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	4-Et-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	indol-3-yl
-N(CH_3)-	Cyp	1	2	bond	2-Et-phenyl
-N(CH_3)-	Cyp	1	2	bond	3-MeO-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	phenyl
-N(CH_3)-	-CH_2-	1	1	bond	3-MeO-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	3-Et-phenyl

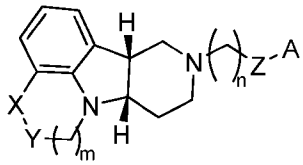
-N(CH_3)-	-CH_2-	1	1	bond	4-MeO-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	2-Et-phenyl
-N^+(=O)$^-$-	Cyp	1	2	-O-	4-F-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-$MeSO_2$-phenyl
-N(CH_3)-	Cyp	1	2	bond	benzo[d]isothiazol-3-yl
-N(CH_3)-	-CH_2-	1	1	bond	cyclohexyl
-N(CH_3)-	-CH_2-	1	2	bond	2-MeO-5-F-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	3-Et-Phenyl
-N(CH_3)-	-CH_2-	1	2	bond	3-EtO-phenyl
-N(CH_3)-	Cyp	1	2	bond	benzofuran-7-yl
-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]imidazole-1-yl
-N(CH_3)-	-CH_2-	1	2	bond	benzo[d][1,2,3]triazol-1-yl
-N(CH_3)-	-CH_2-	1	2	bond	indazol-3-yl
-NH-	-C(O)-	1	2	bond	benzo[d]isothiazol-3-yl
-N(CH_3)-	-C(O)-	1	2	bond	benzo[d]isothiazol-3-yl
-N(CH_3)-	Cyp	1	1	bond	2-MeO-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	benzo[d]isoxazol-3-yl
-N(CH_3)-	-CH_2-	1	1	bond	benzofuran-7-yl
-N(CH_3)-	-CH_2-	1	1	bond	benzo[d]isothiazol-3-yl
-N(CH_3)-	-CH_2-	1	1	bond	quinolin-8-yl
-N(CH_3)-	-CH_2-	1	1	bond	benzo[d]oxazol-7-yl
-N(CH_3)-	-CH_2-	1	1	bond	2,3-dihydrobenzofuran-7-yl
-N(CH_3)-	-CH_2-	1	2	-O-	2-CN-4-F-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	indazol-1-yl
-N(CH_3)-	-C(O)-	1	2	-C(O)-	4-F-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	quinoxalin-5-yl
-N(CH_3)-	-CH_2-	1	1	-C(O)-	4-F-Phenyl
-N(CH_3)-	-CH_2-	1	2	-C(=NOMe)	4-F-Ph
-N(CH_3)-	-CH_2-	1	3	-C(O)-	phenyl
-N(CH_3)-	-CH_2-	1	2	-C(=NOMe)	phenyl

-N(CH_3)-	-C(O)-	1	2	-C(O)-	phenyl
-N(CH_3)-	-CH_2-	1	2	-C(O)-	thiophen-2-yl
-N(CH_3)-	-CH_2-	1	1	bond	3-(O-cyclopropyl)phenyl
-N(CH_3)-	-CH_2-	1	1	bond	3-(OCH_2-cyclopropyl)phenyl
-N(CH_3)-	-C(O)-	1	2	bond	2-MeO-phenyl
-N(CH_3)-	-C(O)-	1	2	bond	3-MeO-phenyl
-N(CH_3)-	-C(O)-	1	2	bond	benzo[d]isoxazol-3-yl
-N(CH_3)-	-CH_2-	1	1	bond	3-MeS-phenyl
-N(CH_3)-	Cyp	1	2	-C(O)-	phenyl
-N(CH_3)-	Cyp	1	3	-C(OH)-	4-F-phenyl
-N(CH_3)-	Cyp	1	3	-C(OH)-	phenyl
-N(CH_3)-	Cyp	1	3	-C(OMe)-	4-F-phenyl
-N(CH_3)-	Cyp	1	3	-C(OMe)-	phenyl
-N(CH_3)-	-CH_2-	1	2	bond	2-(MeNH)-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-HO-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-MeO-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-EtO-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-CF_3O-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-$MeSO_2$-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-(MeNH)-phenyl
-N(CH_3)-	Cyp	1	2	bond	3-CN-phenyl
-N(CH_3)-	Cyp	1	2	bond	4-MeO-phenyl
-N(CH_3)-	Cyp	1	2	bond	4-CN-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	quinazolin-7-yl
-N(CH_3)-	-CH_2-	1	1	bond	isoquinolin-7-yl
-N(CH_3)-	-CH_2-	1	1	bond	benzo[d]isoxazol-4-yl
-N(CH_3)-	-CH_2-	1	1	bond	benzofuran-4-yl
-N(CH_3)-	-CH_2-	1	1	bond	2-Me-benzofuran-7-yl
-N(CH_3)-	-CH_2-	1	2	bond	3-MeS-phenyl
-N(CH_3)-	-CH_2-	1	2	bond	3-(O-Cyclopropyl)phenyl

-N(CH_3)-	-CH_2-	1	2	bond	3-(OCH_2-Cyclopropyl)phenyl
-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]isoxazol-4-yl
-N(CH_3)-	-CH_2-	1	2	bond	benzofuran-4-yl
-N(CH_3)-	-CH_2-	1	2	bond	2-Me-benzofuran-7-yl
-N(CH_3)-	Cyp	1	2	bond	indazol-7-yl
-N(CH_3)-	Cyp	1	2	bond	quinolin-8-yl
-N(CH_3)-	Cyp	1	2	bond	pyrid-4-yl
-N(CH_3)-	-CH_2-	1	2	bond	quinolin-8-yl
-N(CH_3)-	-CH_2-	1	2	bond	indol-1-yl
-N(CH_3)-	-CH_2-	1	2	bond	pyrid-4-yl
-N(CH_3)-	Cyp	1	1	bond	3-Et-phenyl
-N(CH_3)-	Cyp	1	2	-O-	3-CN-4-F-phenyl
-N(CH_3)-	-CH_2-	1	1	bond	H
-N(CH_3)-	-CH_2-	1	2	bond	H
-N(CH_3)-	-CH_2-	1	3	bond	H
-N(CH_3)-	-CH_2-	1	1	bond	Cyclopentyl
-N(CH_3)-	-CH_2-	1	1	bond	Cyclobutyl
-N(CH_3)-	-CH_2-	1	1	bond	Cyclopropyl

each independently in free or pharmaceutically acceptable salt or form, wherein Cyp refers to a spiro-joined cyclopropyl ring;

1.107 Compound I, or any of 1.1-1.105, wherein the compound is selected from the group consisting of:



Formula I,

wherein the variables are defined as provided any of the following embodiments:

X	Y	m	n	Z	A
-N(CH_3)-	-CH_2-	1	2	-C(O)-	4-F-phenyl
-N(CH_3)-	Cyp	1	3	-C(O)-	4-F-phenyl

-N(CH_3)-	Cyp	1	2	-C(O)-	4-F-phenyl
-N(CH_3)-	Cyp	1	2	-O-	4-F-phenyl
-N(CH_3)-	Cyp	1	2	bond	2-MeO-phenyl
-N(CH_3)-	Cyp	1	2	bond	benzo[d]isoxazol-3-yl
-N(CH_3)-	-CH_2-	1	2	bond	3-MeO-phenyl
Cyp	-CH_2-	1	2	bond	benzo[d]isoxazol-3-yl
-N(CH_3)-	-CH_2-	1	2	bond	benzofuran-7-yl
-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]isothiazol-3-yl
-N(CH_3)-	Cyp	1	2	bond	2-Et-phenyl
-N(CH_3)-	Cyp	1	2	bond	3-MeO-phenyl
-N(CH_3)-	Cyp	1	2	bond	benzo[d]isothiazol-3-yl
-N(CH_3)-	Cyp	1	2	bond	benzofuran-7-yl
-N(CH_3)-	-C(O)-	1	2	bond	benzo[d]isothiazol-3-yl
-N(CH_3)-	Cyp	1	1	bond	2-MeO-phenyl
-N(CH_3)-	-C(O)-	1	2	-C(O)-	4-F-phenyl
-N(CH_3)-	-C(O)-	1	2	bond	benzo[d]isoxazol-3-yl
-N(CH_3)-	Cyp	1	2	-C(O)-	Phenyl
-N(CH_3)-	Cyp	1	1	Bond	3-Et-phenyl

;

1.108 Compound I, or any of 1.1-1.107, in free form;

1.109 Compound I, or any of 1.1-1.107, in salt form, e.g., pharmaceutically acceptable salt form;

1.110 Compound I, or any of 1.1-1.107, wherein the compound is in acid addition salt form, for example, hydrochloric or toluenesulfonic acid salt form;

1.111 Compound I, or any of 1.1-1.10, in substantially pure diastereomeric form (i.e., substantially free from other diastereomers);

1.112 Compound I or any of 1.1-1.110, having a diastereomeric excess of greater than 70%, preferably greater than 80%, more preferably greater than 90% and most preferably greater than 95%;

1.113 Compound I or any of 1.1-1.112, in solid form, e.g., in crystal form;

1.114 Compound I or any of 1.1-1.113, in isolated or purified form (e.g., in at least 90% pure form, or at least 95% or at least 98% or at least 99%).

1.115 Compound I or any of 1.1-1.114, wherein the compound has 5-HT_{2A} receptor binding affinity of at least 60% at 100 nM concentration, e.g., at least 70%, or at least 75%, or at least 80%, or at least 85%, or at least 90%, or at least 95%, or at least 98%, at 100 nM concentration;

1.116 Compound I or any of 1.1-1.115, wherein the compound has a 5-HT_{2A} receptor dissociation constant (K_d) of less than 250 nM, or less than 100 nM, or less than 70 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, or less than 10 nM;

1.117 Compound I or any of 1.1-1.116, wherein the compound is an agonist of beta-arrestin signaling via the 5-HT_{2A} receptor, e.g., a partial agonist or a full agonist;

1.118 Compound 1.116, wherein the compound is a partial agonist of beta-arrestin signaling having an E_{max} of less than 90%, or less than 80%, or less than 70%, or less than 60%, or less than 50%, or less than 40%, or less than 30%, or less than 20%, or less than 10%, relative to a full agonist (e.g., alpha-methylserotonin);

1.119 Compound 1.117 or 1.118, wherein the compound has an EC_{50} for 5-HT_{2A} receptor beta-arrestin agonism of less than 500 nM, or less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 70 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, or less than 10 nM;

1.120 Compound 1.117, 1.118 or 1.119, wherein the compound has a beta-arrestin signaling relative intrinsic activity (RA_i) of less than 1.0 compared to the reference compound alpha-methylserotonin, e.g., a relative intrinsic activity of less than 0.8, or less than 0.6, or less than 0.5, or less than 0.4, or less than 0.3, or less than 0.2, or less than 0.1, or 0.1 to 0.8, or 0.2 to 0.8, or 0.4 to 0.8, or 0.5 to 0.8, or 0.2 to 0.6, or 0.2 to 0.5, or 0.2 to 0.4, or 0.5 to 1.0, or 0.5 to 0.9, or 0.5 to 0.8, or 0.6 to 0.9, or 0.6 to 0.8;

1.121 Compound 1.117, 1.118, or 1.119, wherein the compound has a beta-arrestin signaling relative intrinsic activity (RA_i) of greater than 1.0 compared to the

reference compound alpha-methylserotonin, e.g., a relative intrinsic activity of 1.0 to 1.2, or 1.0 to 1.4, or 1.0 to 1.6;

1.122 Compound I or any of 1.1-1.116, wherein the compound is an antagonist of beta-arrestin signaling via the 5-HT_{2A} receptor;

1.123 Compound 1.122, wherein the compound has an IC_{50} for 5-HT_{2A} receptor beta-arrestin antagonism of less than 300 nM, or less than 200 nM, or less than 100 nM, or less than 70 nM, or less than 60 nM, or less than 50 nM, or less than 40 nM, or less than 30 nM, or less than 20 nM, or less than 10 nM;

1.124 Compound I or any of 1.1-1.116, wherein the compound is not an antagonist of beta-arrestin signaling via the 5-HT_{2A} receptor;

1.125 Compound 1.124, wherein the compound has an IC_{50} for 5-HT_{2A} receptor beta-arrestin antagonism of greater than 10 nM, or greater than 50 nM, or greater than 100 nM, or greater than 250 nM, or greater than 500 nM, or greater than 1000 nM, or greater than 5000 nM, or greater than 10,000 nM;

1.126 Compound I or any of 1.1-1.125, wherein the compound is not an agonist of G-q signaling via the 5-HT_{2A} receptor, or is a weak agonist thereof;

1.127 Compound 1.126, wherein the compound is a partial agonist of G-q signaling having an E_{max} of less than 90%, or less than 80%, or less than 70%, or less than 60%, or less than 50%, or less than 40%, or less than 30%, or less than 20%, or less than 10%, relative to a full agonist (e.g., alpha-methylserotonin), preferably an E_{max} of less than 50% or less than 30% or less than 10%;

1.128 Compound 1.125 or 1.126, wherein the compound has an EC_{50} for 5-HT_{2A} receptor G-q agonism of greater than 10 nM, or greater than 25 nM, or greater than 50 nM, or greater than 100 nM, or greater than 150 nM, or greater than 200 nM, or greater than 500 nM, or greater than 1000 nM, or greater than 2000 nM, or greater than 5000 nM, or greater than 10,000 nM;

1.129 Compound 1.125, 1.126 or 1.127, wherein the compound has a G-q signaling relative intrinsic activity (RA_i) of less than 1.0 compared to the reference compound alpha-methylserotonin, e.g., a relative intrinsic activity of less than 0.8, or less than 0.6, or less than 0.5, or less than 0.4, or less than 0.3, or less than 0.2, or less than 0.1, or 0.1 to 0.8, or 0.2 to 0.8, or 0.4 to 0.8, or 0.5 to 0.8, or 0.2 to

0.6, or 0.2 to 0.5, or 0.2 to 0.4, or 0.5 to 1.0, or 0.5 to 0.9, or 0.5 to 0.8, or 0.6 to 0.9, or 0.6 to 0.8;

1.130 Compound I or any of 1.1-1.129, wherein the compound is an antagonist of G-q signaling via the 5-HT_{2A} receptor;

1.131 Compound 1.130, wherein the compound has an IC_{50} for 5-HT_{2A} receptor G-q antagonism of less than 10 nM, or less than 25 nM, or less than 50 nM, or less than 100 nM, or less than 150 nM, or less than 200 nM, or less than 500 nM;

1.132 Compound I or any of 1.1-1.131, wherein the compound has a bias ratio (beta-arrestin/G-q) for agonism 5-HT_{2A} receptor of at least 2, or at least 5, or at least 10, or at least 25, or at least 50, or at least 100, or at least 150, or at least 200 or at least 500, or at least 1000, or at least 10,000, or undefined (i.e., where the compound has any degree of beta-arrestin agonism and zero G-q agonism);

1.133 Compound I or any of 1.1-1.132, wherein the compound is an antagonist or agonist of the D1 and/or D2 dopamine receptor (e.g., having at least 70% receptor affinity at 100 nM concentration or an IC50 of less than 100 nM);

1.134 Compound I or any of 1.1-1.132, wherein the compound is not active at the D1 and/or D2 dopamine receptor (e.g., having less than 50% receptor affinity at 100 nM concentration and/or an EC_{50} or IC_{50} of more than 500 nM);

1.135 Compound I or any of 1.1-1.134, wherein the compound is an antagonist of the serotonin transporter (e.g., having at least 70% receptor binding affinity at 100 nM concentration or an IC_{50} of less than 100 nM);

1.136 Compound I or any of 1.1-1.134, wherein the compound is not active at the serotonin transporter (e.g., having less than 50% receptor binding affinity at 100 nM concentration and/or an EC_{50} or IC_{50} of more than 500 nM);

1.137 Compound I or any of 1.1-1.136, wherein the compound is an agonist, antagonist, or partial agonist of the mu-opioid receptor (e.g., having at least 70% receptor binding affinity at 100 nM concentration or an EC_{50} or IC_{50} of less than 100 nM);

1.138 Compound I or any of 1.1-1.136, wherein the compound is not active at the mu-opioid receptor (e.g., having at less than 50% receptor binding affinity at 100 nM concentration and/or an EC_{50} or IC_{50} of more than 500 nM);

1.139 Compound I, or any of 1.1-1.138, wherein the compound is non-hallucinogenic, e.g., at therapeutic doses for the treatment of a neuropsychiatric disorder described herein (e.g., depression, anxiety, etc.) the compound does not cause visual or auditory hallucinations, visual distortions (such as drifting, morphing, breathing or melting of objects and surfaces in the field of view), detachment from reality, dissociation, delirium, undesired altered states of consciousness;

1.140 Compound I, or any of 1.1-1.139, wherein the compound does not stimulate head twitch response in an animal test model, or is antagonist of DOI-induced head twitch response;

1.141 Compound I, or any of 1.1-1.140, wherein the compound is effective in a murine model of depression (tail suspension or forced swim test);

1.142 Compound I, or any of 1.1-1.141, wherein the compound is effective in an animal model of social anxiety disorder or anhedonia;

1.143 Compound I, or any of 1.1-1.142, wherein the compound does not have 5-HT_{2B} agonist activity (e.g., an EC50 of greater than 100 nM, or greater than 500 nM, or greater than 1000 nM, or greater than 10,000 nM);

1.144 Compound I, or any of 1.1-1.143, wherein the compound has 5-HT_{2B} antagonist activity (e.g., an IC50 of less than 1000 nM, or less than 500 nM, or less than 250 nM, or less than 100 nM, or less than 50 nM, or less than 25 nM, or less than 15 nM);

1.145 Compound I, or any of 1.1-1.144, wherein the compound has 5-HT_{2c} agonist activity (e.g., an EC50 of less than 1000 nM, or less than 500 nM, or less than 250 nM, or less than 100 nM, or less than 50 nM, or less than 25 nM, or less than 15 nM);

1.146 Compound I, or any of 1.1-1.144, wherein the compound does not have 5-HT_{2C} antagonist activity (e.g., an IC50 of greater than 100 nM, or greater than 500 nM, or greater than 1000 nM, or greater than 10,000 nM);

1.147 Compound I, or any of 1.1-1.146, wherein the compound binds to the alpha-1A adrenergic receptor (e.g., with a binding affinity Ki of less than 1000 nM, or less than 500 nM, or less than 250 nM, or less than 200 nM, or less than 150 nM, or less than 100 nM, or less than 50 nM, or less than 25 nM);

1.148 Compound I, or any of 1.1-1.147, wherein the compound does not cause psychoses (e.g., prolonged or intermittent psychoses);

1.149 Compound I, or any of 1.1-1.148, wherein the compound does not promote self-harm or harm to others in the patient;

1.150 Compound I, or any of 1.1-1.149, wherein the compound does not cause heart valvulopathy or pulmonary arterial hypertension, e.g., wherein the compound is safe to administer to a patient having cardiac comorbidities;

1.151 Compound I, or any of 1.1-1.150, wherein the compound does not cause abuse or dependence (e.g., physical or psychological dependence);

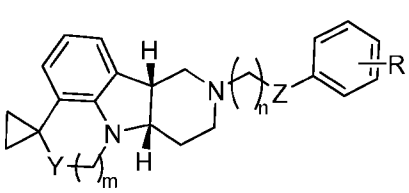
1.152 Compound I, or any of 1.1-1.151, wherein the compound is functionally inactive at one or more of the following receptors and ion channels: adenosine A2A, alpha-1A adrenergic, alpha-2A adrenergic, beta-1 adrenergic, beta-2 adrenergic, GABA-A benzodiazepine site (BZD, central), CB1 cannabinoid, CB2 cannabinoid, cholecystokinin CCK1, endothelin-A (ETA), NMDA, histamine H1, histamine H2, MAO-A, muscarinic M1, muscarinic M2, muscarinic M3, nicotinic acetylcholine (neuronal alpha-4-beta-2), delta opioid, kappa opioid, mu opioid, serotonin-1A, serotonin-1B, serotonin-3, glucocorticoid (GR), androgen (AR), vasopressin V1A, cardiac calcium channel (dihydropyridine site), hERG potassium channel, voltage-gated potassium channel K_V, sodium channel (site 2), norepinephrine transporter, dopamine transporter, and/or serotonin transporter;

1.153 Compound 1.152, wherein the compound has an in vitro receptor activity (for agonism or antagonism) of less than 60% inhibition of radioligand binding (e.g., at 100 nM test concentration) for any one or more of said receptor or ion channels, e.g., less than 50%, less than 40%, less than 30%, less than 20%, or less than 10%;

1.154 Compound I, or any of 1.1-1.153, wherein the compound is orally bioavailable (e.g., oral bioavailability of at least 10%, or at least 15%, or at least 20%, or at least 30%, or at least 40%).

[00023] As used herein, the term "spiro-joined" is meant to clarify that the stated C_{3-6}cycloalkyl group or 3-6-membered heterocycloalkyl is present in a spiro-junction, meaning that one atom of said cyclic group is an atom of the ring to which the group is attached. For example,

the follow are examples of compounds of Formula I having spiro-joined cyclic groups within the scope of the present disclosure: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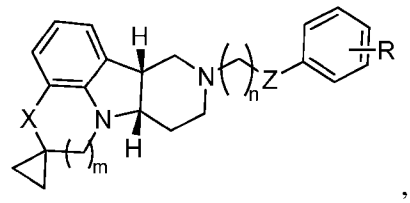
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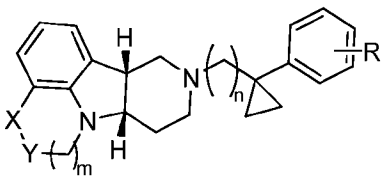
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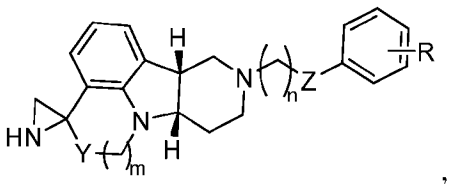
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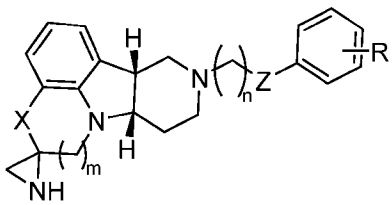
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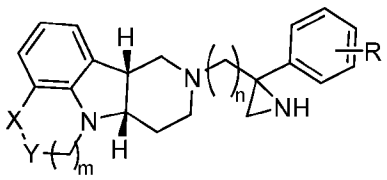
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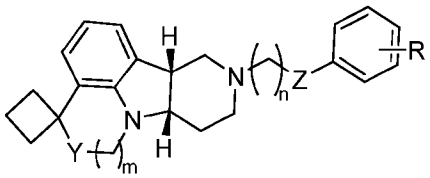
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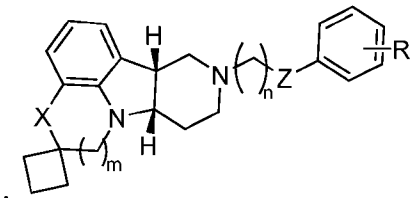
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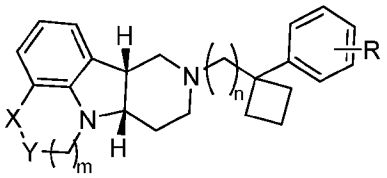
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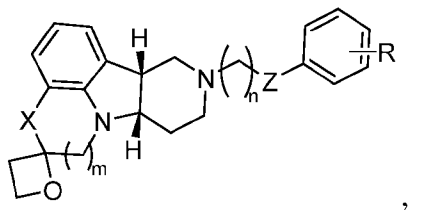
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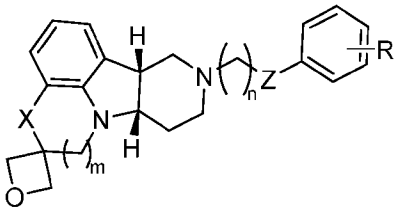
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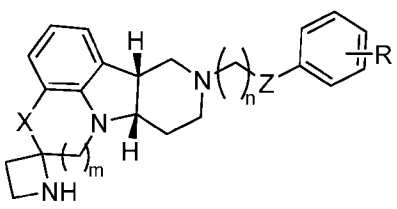
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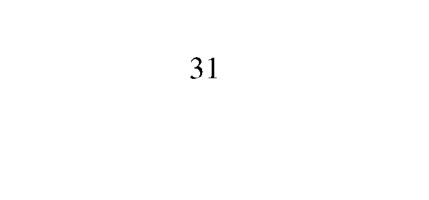
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In each of the above examples, the cyclopropane, cyclobutane, aziridine, azetidine, or oxetane, may be replaced by any other C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl, including, but not limited to, cyclopentane, cyclohexane, tetrahydrofuran, tetrahydropyran, pyrrolidine, piperidine, piperazine, or morpholine.

[00024] As used hereinbelow, the "Compound of the Invention" refers to a Compound of Formula I or any of 1.1-1.154.

[00025] In a second aspect, the present disclosure provides a pharmaceutical composition (Pharmaceutical Composition 1) comprising Compound of the Invention, e.g., in admixture with a pharmaceutically acceptable diluent or carrier. In a particular embodiment, the Compound of the Invention is in pharmaceutically acceptable salt form. In some embodiments, the pharmaceutical composition is in the form of a tablet or capsule, e.g., for gastroenteric absorption (i.e., absorption through the stomach and/or large and small intestines). In some embodiments, the pharmaceutical composition is an oral transmucosal composition, e.g., an orally dissolving tablet, wafer, film, gel or spray. For example, the composition may be a rapidly-dissolving sublingual or buccal tablet, wafer, film, or gel. In some embodiments, the pharmaceutical composition is formulated for intranasal or intrapulmonary administration (e.g., as an aerosol, mist, or powder for inhalation). In some embodiments, the pharmaceutical composition is formulated for intravenous, intrathecal, intramuscular, subcutaneous or intraperitoneal injection. In particular, pharmaceutical compositions for intramuscular or subcutaneous injection may be in the form of long-acting injectable compositions or depot compositions, e.g., providing for sustained or delayed release of the Compound of the Invention into the blood stream and body tissues. Alternatively, particularly as formulated for intravenous, intrathecal, intraperitoneal, or subcutaneous injection, the composition may be an immediate-acting composition, e.g., providing immediate release into the body fluids of the majority or entirety of the dose.

[00026] In a further embodiment, the Pharmaceutical Compositions of the present disclosure, are for a sustained or delayed release formulation (Pharmaceutical Composition 1-A), e.g., a depot formulation. In some embodiments, the Compound of the Invention is provided, preferably in free or pharmaceutically acceptable salt form, in admixture with a pharmaceutically acceptable diluent or carrier, in the form of an injectable depot, which provides sustained or delayed release of the compound.

[00027] In a particular embodiment, the Pharmaceutical Composition 1-A comprises a Compound of the Invention, in free base or pharmaceutically acceptable salt form, optionally in crystal form, wherein the compound has been milled to, or the compound crystallized to, microparticle or nanoparticle size, e.g., particles or crystals having a volume-based particle size (e.g., diameter or Dv50) of 0.5 to 100 microns, for example, for example, 5-30 microns, 10-20 microns, 20-100 microns, 20-50 microns or 30-50 microns. Such particles or crystals may be combined with a suitable pharmaceutically acceptable diluent or carrier, for example water, to form a depot formulation for injection. For example, the depot formulation may be formulated for intramuscular or subcutaneous injection with a dosage of drug suitable for 4 to 6 weeks of treatment. In some embodiments, the particles or crystals have a surface area of 0.1 to 5 m^2/g, for example, 0.5 to 3.3 m^2/g or from 0.8 to 1.2 m^2/g.

[00028] In another embodiment, the present disclosure provides a Pharmaceutical Composition 1-B, which is Pharmaceutical Composition 1, wherein Compound of the Invention, is in a polymeric matrix. In one embodiment, the Compound of the present disclosure is dispersed or dissolved within the polymeric matrix. In a further embodiment, the polymeric matrix comprises standard polymers used in depot formulations such as polymers selected from a polyester of a hydroxy fatty acid and derivatives thereof, or a polymer of an alkyl alpha-cyanoacrylate, a polyalkylene oxalate, a polyortho ester, a polycarbonate, a polyortho-carbonate, a polyamino acid, a hyaluronic acid ester, and mixtures thereof. In a further embodiment, the polymer is selected from a group consisting of polylactide, poly d,l-lactide, poly glycolide, PLGA 50:50, PLGA 85:15 and PLGA 90:10 polymer. In another embodiment, the polymer is selected form poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxanone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mono- and distearate, and the like. In a preferred embodiment, the polymeric matrix comprises poly(d,l-lactide-co-glycolide).

[00029] The Pharmaceutical Composition 1-B is particularly useful for sustained or delayed release, wherein the Compound of the present disclosure is released upon degradation of the polymeric matrix. These Compositions may be formulated for controlled- and/or sustained-release of the Compounds of the present disclosure (e.g., as a depot composition) over a period

of up to 180 days, e.g., from about 14 to about 30 to about 180 days. For example, the polymeric matrix may degrade and release the Compounds of the present disclosure over a period of about 30, about 60 or about 90 days. In another example, the polymeric matrix may degrade and release the Compounds of the present disclosure over a period of about 120, or about 180 days.

[00030] In still another embodiment, the Pharmaceutical Composition 1 or 1-A or 1-B may be formulated for administration by injection, for example, as a sterile solution.

[00031] In another embodiment, the present disclosure provides a Pharmaceutical Composition (Pharmaceutical Composition 1-C) comprising a Compound of the Invention as hereinbefore described, in an osmotic controlled release oral delivery system (OROS), which is described in US 2001/0036472 and US 2009/0202631, the contents of each of which applications are incorporated by reference in their entirety. Therefore in one embodiment, the present disclosure provides a pharmaceutical composition or device comprising (a) a gelatin capsule containing a Compound of any of Formulae I et seq. in free or pharmaceutically acceptable salt form, optionally in admixture with a pharmaceutically acceptable diluent or carrier; (b) a multilayer wall superposed on the gelatin capsule comprising, in outward order from the capsule: (i) a barrier layer, (ii) an expandable layer, and (iii) a semipermeable layer; and (c) and orifice formed or formable through the wall (Pharmaceutical Composition P.1).

[00032] In another embodiment, the invention provides a pharmaceutical composition comprising a gelatin capsule containing a liquid, the Compound of the Invention in free or pharmaceutically acceptable salt form, optionally in admixture with a pharmaceutically acceptable diluent or carrier, the gelatin capsule being surrounded by a composite wall comprising a barrier layer contacting the external surface of the gelatin capsule, an expandable layer contacting the barrier layer, a semi-permeable layer encompassing the expandable layer, and an exit orifice formed or formable in the wall (Pharmaceutical Composition P.2).

[00033] In still another embodiment, the invention provides a composition comprising a gelatin capsule containing a liquid, the Compound of the Invention in free or pharmaceutically acceptable salt form, optionally in admixture with a pharmaceutically acceptable diluent or carrier , the gelatin capsule being surrounded by a composite wall comprising a barrier layer contacting the external surface of the gelatin capsule, an expandable layer contacting the barrier layer, a semipermeable layer encompassing the expandable layer, and an exit orifice formed or

formable in the wall, wherein the barrier layer forms a seal between the expandable layer and the environment at the exit orifice (Pharmaceutical Composition P.3).

[00034] In still another embodiment, the invention provides a composition comprising a gelatin capsule containing a liquid, the Compound of the Invention in free or pharmaceutically acceptable salt form, optionally in admixture with a pharmaceutically acceptable diluent or carrier, the gelatin capsule being surrounded by a barrier layer contacting the external surface of the gelatin capsule, an expandable layer contacting a portion of the barrier layer, a semi-permeable layer encompassing at least the expandable layer, and an exit orifice formed or formable in the dosage form extending from the external surface of the gelatin capsule to the environment of use (Pharmaceutical Composition P.4). The expandable layer may be formed in one or more discrete sections, such as for example, two sections located on opposing sides or ends of the gelatin capsule.

[00035] In a particular embodiment, the Compound of the Invention in the Osmotic-controlled Release Oral Delivery System (i.e., in Composition P.1-P.4) is in a liquid formulation, which formulation may be neat, liquid active agent, liquid active agent in a solution, suspension, emulsion or self-emulsifying composition or the like.

[00036] Further information on Osmotic-controlled Release Oral Delivery System composition including characteristics of the gelatin capsule, barrier layer, an expandable layer, a semi-permeable layer; and orifice may be found in US 2001/0036472, the contents of which are incorporated by reference in their entirety.

[00037] Other Osmotic-controlled Release Oral Delivery System for the Compound of Formulas I et seq. or the Pharmaceutical Composition of the present disclosure may be found in US 2009/0202631, the contents of which are incorporated by reference in their entirety. Therefore, in another embodiment, the invention provides a composition or device comprising (a) two or more layers, said two or more layers comprising a first layer and a second layer, said first layer comprises the Compound of the Invention in free or pharmaceutically acceptable salt form, optionally in admixture with a pharmaceutically acceptable diluent or carrier, said second layer comprises a polymer; (b) an outer wall surrounding said two or more layers; and (c) an orifice in said outer wall (Pharmaceutical Composition P.5).

[00038] Pharmaceutical Composition P.5 preferably utilizes a semi-permeable membrane surrounding a three-layer-core: in these embodiments, the first layer is referred to as a first drug

layer and contains low amounts of drug (e.g., the Compound of the Invention) and an osmotic agent such as salt, the middle layer referred to as the second drug layer contains higher amounts of drug, excipients and no salt; and the third layer referred to as the push layer contains osmotic agents and no drug (Pharmaceutical Composition P.6). At least one orifice is drilled through the membrane on the first drug layer end of the capsule-shaped tablet.

[00039] Pharmaceutical Composition P.5 or P.6 may comprise a membrane defining a compartment, the membrane surrounding an inner protective subcoat, at least one exit orifice formed or formable therein and at least a portion of the membrane being semi-permeable; an expandable layer located within the compartment remote from the exit orifice and in fluid communication with the semi-permeable portion of the membrane; a first drug layer located adjacent the exit orifice; and a second drug layer located within the compartment between the first drug layer and the expandable layer, the drug layers comprising the Compound of the Invention in free or pharmaceutically acceptable salt thereof (Pharmaceutical Composition P.7). Depending upon the relative viscosity of the first drug layer and second drug layer, different release profiles are obtained. It is imperative to identify the optimum viscosity for each layer. In the present invention, viscosity is modulated by addition of salt, sodium chloride. The delivery Profile from the core is dependent on the weight, formulation and thickness of each of the drug layers.

[00040] In a particular embodiment, the invention provides Pharmaceutical Composition P.7 wherein the first drug layer comprises salt and the second drug layer contains no salt. Pharmaceutical Composition P.5-P.7 may optionally comprise a flow-promoting layer between the membrane and the drug layers.

[00041] Pharmaceutical Compositions P.1-P.7 will generally be referred to as Osmotic-controlled Release Oral Delivery System Composition.

[00042] In a third aspect, the invention provides a method (Method 1) for the treatment or prophylaxis of a central nervous system disorder, or more than one central nervous system disorder, the method comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of the Invention (e.g., a Compound of Formula I), wherein the Compound of the Invention is a biased agonist of the 5-HT_{2A} receptor. In further embodiments of Method 1, the present disclosure provides:

1.1 Method 1, wherein the Compound of the invention is a Compound of Formula I, in free form;

1.2 Method 1, wherein the Compound of the invention is a Compound of Formula I, in pharmaceutically acceptable salt form;

1.3 Method 1.2, wherein the pharmaceutically acceptable salt form is a toluenesulfonic acid addition salt.

1.4 Any of Methods 1 or 1.1-1.3, wherein the Compound of the Invention is administered in the form of a pharmaceutical composition comprising Compound of the Invention in admixture with a pharmaceutically acceptable diluent or carrier (e.g., Pharmaceutical Composition I or any of 1-A, 1-B, 1-C, or P.1 to P.7);

1.5 Method 1.4, wherein the pharmaceutical composition is a Pharmaceutical Composition 1-A, 1-B or 1-C;

1.6 Method 1.4, wherein the pharmaceutical composition is any of the Pharmaceutical Compositions P.1 to P.7;

1.7 Method 1 or any of Methods 1.1-1.6, wherein the central nervous system disorder is a disorder which is susceptible to treatment by agonism of the beta-arrestin signaling pathway and/or agonism or antagonism of the G-q signaling pathway, mediated by the 5-HT_{2A} receptor;

1.8 Method 1 or any of Methods 1.1-1.7, wherein the central nervous system disorder is a disorder involving, mediated by, or affected (directly or indirectly) by, the serotonin 5-HT_{2A} receptor, the dopamine D1 receptor, and/or D2 receptor systems, and/or the serotonin reuptake transporter (SERT) pathways, and/or the mu-opioid receptor pathway;

1.9 Method 1, or any of 1.1-1.7, wherein the central nervous system disorder is a disorder involving, mediated by, or affected (directly or indirectly) by, the serotonin 5-HT_{2A} receptor, the serotonin reuptake transporter (SERT), but not the dopamine D1 receptor or D2 receptor systems, and not the mu-opioid receptor pathway;

1.10 Method 1, or any of 1.1-1.7, wherein the central nervous system disorder is a disorder not involving, mediated by, or affected (directly or indirectly) by, one or

more of the dopamine D1 receptor, dopamine D2 receptor, serotonin reuptake transporter (SERT), or mu-opioid receptor pathway;

1.11 Method 1, or any of 1.1-1.7, wherein the central nervous system disorder is a disorder involving, mediated by, or affected (directly or indirectly) by, the serotonin 5-HT_{2A} receptor;

1.12 Method 1, or any of 1.1-1.11, wherein central nervous system disorder is a disorder involving, mediated by, or affected (directly or indirectly) by, signaling via the beta-arrestin signaling pathway of the serotonin 5-HT_{2A} receptor;

1.13 Method 1 or any of Methods 1.1-1.12, wherein the central nervous system disorder is a disorder selected from a group consisting of anxiety (including general anxiety, social anxiety, and panic disorders), and depression (for example refractory depression and major depressive disorder, bipolar depression);

1.14 Method 1 or any of Methods 1.1-1.13, wherein the central nervous system disorder is anxiety, such as general anxiety, social anxiety, and panic disorders;

1.15 Method 1 or any of Methods 1.1-1.13, wherein the central nervous system disorder is depression, such as refractory depression, major depressive disorder, and bipolar depression, and/or anhedonia;

1.16 Method 1, or any of 1.1-1.15, wherein the patient suffers from any combination of the disorders recited in Methods 1.7-1.15;

1.17 Method 1, or any of 1.1-1.15, wherein the method is a method for the treatment or prophylaxis of any combination of the disorders recited in Methods 1.7-1.15;

1.18 Method 1 or any of Methods 1.1-1.17, wherein said patient is not responsive to or is unable to tolerate the side effects of conventional anti-depressant agents;

1.19 Method 1 or any of Methods 1.1-1.18, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline;

1.20 Method 1 or any of Methods 1.1-1.19, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, sibutramine, duloxetine, atomoxetine, desvenlafaxine, milnacipran, and levomilnacipran;

1.21 Method 1 or any of Methods 1.1-1.20, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with conventional anxiolytic agents, such as lorazepam, diazepam, alprazolam, and buspirone;

1.22 Any of the foregoing methods, wherein the therapeutically effective amount of the Compound of the Invention (e.g., the Compound of Formula I) is 1 mg-1000mg, preferably 2.5mg-50mg, or for a long-acting formulation, 25mg-1500mg, for example, 50mg to 500mg, or 250mg to 1000mg, or 250mg to 750mg, or 75mg to 300mg;

1.23 Method 1.22, wherein the therapeutically effective amount is 1 mg-100mg per day, preferably 2.5mg-50mg per day.

1.24 Method 1.22, wherein the therapeutically effective amount of the Compound of the Invention is 1 mg-1000mg, for example 2.5mg-50mg, or for a long-acting formulation, 25mg-1500mg, for example, 50mg to 500mg, or 250mg to 1000mg, or 250mg to 750mg, or 75mg to 300mg;

1.25 Method 1.22, where therapeutically in the effective amount of the Compound of the Invention is 1 mg-100mg per day, for example 2.5mg-50mg per day;

1.26 Method 1.22, wherein the therapeutically effective amount of the Compound of the Invention is 1 mg-5mg, preferably 2.5-5mg, per day;

1.27 Method 1.22, wherein the therapeutically effective amount of the Compound of the Invention is 2.5mg or 5mg, per day;

1.28 Method 1 or any of 1.1-1.27, wherein the pharmaceutical composition is a sustained release or delayed release formulation, e.g., according to Pharmaceutical Composition 1-A as described herein;

1.29 Method 1 or any of 1.1-1.28, wherein the pharmaceutical composition comprises the Compound of the Invention in a polymeric matrix, e.g., according to Pharmaceutical Composition 1-B as described herein;

1.30 Method 1 or any of 1.1-1.29, wherein the pharmaceutical composition is in the form of a tablet or capsule;

1.31 Method 1 or any of 1.1-1.30, wherein the pharmaceutical composition is formulated for oral, sublingual, or buccal administration;

1.32 Method 1 or any of 1.1-1.31, wherein the pharmaceutical composition is a rapidly-dissolving oral tablet (e.g., a rapidly dissolving sublingual tablet);

1.33 Method 1 or any of 1.1-1.32, wherein the pharmaceutical composition is formulated for intranasal or intrapulmonary administration (e.g., as an aerosol, mist, or powder for inhalation);

1.34 Method 1 or any of 1.1-1.33, wherein the pharmaceutical composition is formulated for administration by injection, for example, as a sterile aqueous solution;

1.35 Method 1.34, wherein the pharmaceutical composition is formulated for intravenous, intrathecal, intramuscular, subcutaneous or intraperitoneal injection

1.36 Any of Method 1 or 1.1-1.35, wherein the method further comprises the concurrent administration of one or more other therapeutic agents, e.g., administered simultaneously, separately or sequentially;

1.37 Method 1.36, wherein the additional therapeutic agent is an anti-depressant agent, optionally wherein the anti-depressant agent is selected from amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine sulfate, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine, ketamine, and esketamine;

1.38 Method 1.36, wherein the additional therapeutic agent is an anxiolytic agent, optionally selected from lorazepam, diazepam, alprazolam, and buspirone;

1.39 Method 1, or any of 1.1-1.38, wherein the method does not cause psychoses (e.g., prolonged or intermittent psychoses);

1.40 Method 1, or any of 1.1-1.39, wherein the method does not promote self-harm or harm to others in the patient;

1.41 Method 1, or any of 1.1-1.40, wherein the method does not cause heart valvulopathy or pulmonary arterial hypertension, e.g., wherein the method is safe for treatment of a patient having cardiac comorbidities;

1.42 Method 1, or any of 1.1-1.41, wherein the method does not cause abuse or dependence (e.g., physical or psychological dependence);

1.43 Method 1, or any of 1.1-1.42, wherein the patient suffers from or has previously diagnosed with hallucinogen persisting perception disorder (HPPD);

1.44 Method 1, or any of 1.1-1.43, wherein the patient suffers from or has previously diagnosed with psychosis (e.g., schizophrenia).

[00043] In a fourth aspect, the invention provides a method (Method 2) for the treatment or prophylaxis of a central nervous system disorder, or more than one central nervous system disorder, the method comprising administering to a patient in need thereof a therapeutically effective amount of a Compound of the Invention (e.g., a Compound of Formula I), wherein the Compound of the Invention is an antagonist of the 5-HT_{2A} receptor. In particular embodiments, Method 2 comprises administering:

2.1 Method 2, wherein the Compound of the invention is a Compound of Formula I, in free form;

2.2 Method 2, wherein the Compound of the invention is a Compound of Formula I, in pharmaceutically acceptable salt form;

2.3 Method 2.2, wherein the pharmaceutically acceptable salt form is a toluenesulfonic acid addition salt.

2.4 Any of Methods 2 or 2.1-2.3, wherein the Compound of the Invention is administered in the form of a pharmaceutical composition comprising Compound of the Invention in admixture with a pharmaceutically acceptable diluent or carrier (e.g., Pharmaceutical Composition I or any of 1-A, 1-B, 1-C, or P.1 to P.7);

2.5 Method 2.4, wherein the pharmaceutical composition is a Pharmaceutical Composition 1-A, 1-B or 1-C;

2.6 Method 2.4, wherein the pharmaceutical composition is any of the Pharmaceutical Compositions P.1 to P.7;

2.7 Method 2 or any of Methods 2.1-2.6, wherein the central nervous system disorder is a disorder which is susceptible to treatment by antagonism of the 5-HT_{2A} receptor, e.g., antagonism of the beta-arrestin signaling pathway and antagonism of the G-q signaling pathway, mediated by the 5-HT_{2A} receptor;

2.8 Method 2 or any of Methods 2.1-2.7, wherein the central nervous system disorder is a disorder involving, mediated by, or affected (directly or indirectly) by, the

serotonin 5-HT_{2A} receptor, dopamine D1 receptor, and/or D2 receptor systems, and/or the serotonin reuptake transporter (SERT) pathways, and/or the mu-opioid receptor pathway;

2.9 Method 2, or any of 2.1-2.7, wherein the central nervous system disorder is a disorder involving, mediated by, or affected (directly or indirectly) by, the serotonin 5-HT_{2A} receptor or serotonin reuptake transporter (SERT), but not the dopamine D1 receptor or D2 receptor systems, and not the mu-opioid receptor pathway;

2.10 Method 2, or any of 2.1-2.7, wherein the central nervous system disorder is a disorder involving, mediated by, or affected (directly or indirectly) by, the serotonin 5-HT_{2A} receptor or serotonin reuptake transporter (SERT), but not the mu-opioid receptor pathway;

2.11 Method 2, or any of 2.1-2.7, wherein the central nervous system disorder is a disorder involving, mediated by, or affected (directly or indirectly) by, the serotonin 5-HT_{2A} receptor;

2.12 Method 2 or any of Methods 2.1-2.12, wherein the central nervous system disorder is a disorder selected from a group consisting of anxiety, depression, psychosis, schizophrenia, sleep disorders, impulse control disorder, post-traumatic stress disorder, intermittent explosive disorder, and dementia;

2.13 Method 2 or any of Methods 2.1-2.13, wherein the central nervous system disorder is anxiety, such as general anxiety, social anxiety, and panic disorders;

2.14 Method 2 or any of Methods 2.1-2.13, wherein the central nervous system disorder is depression, such as refractory depression, major depressive disorder, and bipolar depression;

2.15 Method 2 or any of Methods 2.1-2.13, wherein the central nervous system disorder is psychosis, e.g., schizophrenia;

2.16 Method 2.16, wherein the method is effective to treat the positive and/or negative symptoms of schizophrenia;

2.17 Method 2, or any of 2.1-2.16, wherein the patient suffers from any combination of the disorders recited in Methods 2.7-2.16;

2.18 Method 2, or any of 2.1-2.46, wherein the method is a method for the treatment or prophylaxis of any combination of the disorders recited in Methods 2.7-2.16;

2.19 Method 2 or any of Methods 2.1-2.18, wherein said patient is not responsive to or is unable to tolerate the side effects of conventional antipsychotic drugs, e.g., chlorpromazine, haloperidol, droperidol, fluphenazine, loxapine, mesoridazine molindone, perphenazine, pimozide, prochlorperazine promazine, thioridazine, thiothixene, trifluoperazine, brexpiprazole, cariprazine, asenapine, lurasidone, clozapine, aripiprazole, olanzapine, quetiapine, risperidone and ziprasidone;

2.20 Method 2 or any of Methods 2.1-2.19, wherein said patient is not responsive to or is unable to tolerate the side effects of conventional anti-depressant agents;

2.21 Method 2 or any of Methods 2.1-2.20, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with selective serotonin reuptake inhibitors (SSRIs), such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline;

2.22 Method 2 or any of Methods 2.1-2.21, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, sibutramine, duloxetine, atomoxetine, desvenlafaxine, milnacipran, and levomilnacipran;

2.23 Method 2 or any of Methods 2.1-2.22, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with conventional anxiolytic agents, such as lorazepam, diazepam, alprazolam, and buspirone;

2.24 Method 2 or any of Methods 2.1-2.23, wherein said patient is not responsive to or cannot tolerate the side effects from, treatment with antipsychotic agents, such as clomipramine, risperidone, quetiapine and olanzapine;

2.25 Any of the foregoing methods, wherein the therapeutically effective amount of the Compound of the Invention (e.g., the Compound of Formula I) is 1 mg-1000mg, preferably 2.5mg-50mg, or for a long-acting formulation, 25mg-1500mg, for example, 50mg to 500mg, or 250mg to 1000mg, or 250mg to 750mg, or 75mg to 300mg;

2.26 Method 2.26, wherein the therapeutically effective amount is 1 mg-100mg per day, preferably 2.5mg-50mg per day.

2.27 Method 2.26, wherein the therapeutically effective amount of the Compound of the Invention is 1 mg-1000mg, for example 2.5mg-50mg, or for a long-acting formulation, 25mg-1500mg, for example, 50mg to 500mg, or 250mg to 1000mg, or 250mg to 750mg, or 75mg to 300mg;

2.28 Method 2.26, wherein the therapeutically effective amount of the Compound of the Invention is 1 mg-100mg per day, for example 2.5mg-50mg per day;

2.29 Method 2.26, wherein the therapeutically effective amount of the Compound of the Invention is 1 mg-5mg, preferably 2.5-5mg, per day;

2.30 Method 2.26, wherein the therapeutically effective amount of the Compound of the Invention is 2.5mg or 5mg, per day;

2.31 Method 2 or any of Methods 2.1-2.30, wherein the pharmaceutical composition is a sustained release or delayed release formulation, e.g., according to Pharmaceutical Composition 1-A as described herein;

2.32 Method 2 or any of Methods 2.1-2.30, wherein the pharmaceutical composition comprises the Compound of the Invention in a polymeric matrix, e.g., according to Pharmaceutical Composition 1-B as described herein;

2.33 Method 2 or any of Methods 2.1-2.32, wherein the pharmaceutical composition is in the form of a tablet or capsule;

2.34 Method 2 or any of Methods 2.1-2.33, wherein the pharmaceutical composition is formulated for oral, sublingual, or buccal administration;

2.35 Method 2 or any of Methods 2.1-2.34, wherein the pharmaceutical composition is a rapidly-dissolving oral tablet (e.g., a rapidly dissolving sublingual tablet);

2.36 Method 2 or any of Methods 2.1-2.35, wherein the pharmaceutical composition is formulated for intranasal or intrapulmonary administration (e.g., as an aerosol, mist, or powder for inhalation);

2.37 Method 2 or any of Methods 2.1-2.36, wherein the pharmaceutical composition is formulated for administration by injection, for example, as a sterile aqueous solution;

2.38 Method 2.37, wherein the pharmaceutical composition is formulated for intravenous, intrathecal, intramuscular, subcutaneous or intraperitoneal injection

2.39 Method 2 or any of Methods 2.1-2.38, wherein the method further comprises the concurrent administration of one or more other therapeutic agents, e.g., administered simultaneously, separately or sequentially;

2.40 Method 2.39, wherein the additional therapeutic agent is an antipsychotic agent, optionally wherein the antipsychotic agent is selected from a group consisting of chlorpromazine, haloperidol, droperidol, fluphenazine, loxapine, mesoridazine, molindone, perphenazine, pimozide, prochlorperazine promazine, thioridazine, thiothixene, trifluoperazine, brexpiprazole, cariprazine, asenapine, lurasidone, clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone and paliperidone;

2.41 Method 2.39, wherein the additional therapeutic agent is an anti-depressant agent, optionally wherein the anti-depressant agent is selected from amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, duloxetine, escitalopram, fluoxetine, fluvoxamine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine sulfate, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, venlafaxine, ketamine, and esketamine;

2.42 Method 2.39, wherein the additional therapeutic agent is an atypical antipsychotic agent, optionally wherein the agent is selected from a group consisting of brexpiprazole, cariprazine, asenapine, lurasidone, clozapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, and paliperidone;

2.43 Method 2.39, wherein the additional therapeutic agent is an atypical stimulant, optionally selected from modafinil, adrafinil, and armodafinil;

2.44 Method 2.39, wherein the additional therapeutic agent is an anti-Parkinson's agent, optionally selected from L- dopa, co-careldopa, duodopa, stalevo, Symmetrel, benztropine, biperiden, bromocriptine, entacapone, pergolide, pramipexole, procyclidine, ropinirole, selegiline and tolcapone;

2.45 Method 2.39 wherein the additional therapeutic agent is an anxiolytic agent, optionally selected from lorazepam, diazepam, alprazolam, and buspirone;

2.46 Method 2, or any of 2.1-2.45, wherein the method does not cause psychoses (e.g., prolonged or intermittent psychoses);

2.47 Method 2, or any of 2.1-2.46, wherein the method does not promote self-harm or harm to others in the patient;

2.48 Method 2, or any of 2.1-2.47, wherein the method does not cause heart valvulopathy or pulmonary arterial hypertension, e.g., wherein the method is safe for treatment of a patient having cardiac comorbidities;

2.49 Method 2, or any of 2.1-2.48, wherein the method does not cause abuse or dependence (e.g., physical or psychological dependence.

[00044] In some embodiments of the methods described hereinbelow, the Pharmaceutical Composition comprising a Compound of the Invention may be administered for controlled- and/or sustained-release of the Compounds of the Invention over a period of from about 14 days, about 30 to about 180 days, preferably over the period of about 30, about 60 or about 90 days. Controlled- and/or sustained-release is particularly useful for circumventing premature discontinuation of therapy, particularly for antipsychotic drug therapy where non-compliance or non-adherence to medication regimes is a common occurrence.

[00045] In some embodiments of the methods described hereinbelow, the Pharmaceutical Composition comprising a Compound of the Invention may be a Depot Composition of the present disclosure which is administered for controlled- and/or sustained-release of the Compounds of the Invention over a period of time.

[00046] The Compounds of the present disclosure (i.e., Compounds of the Invention) and the Pharmaceutical Compositions of the present disclosure may be used in combination with a second therapeutic agent, particularly at lower dosages than when the individual agents are used as a monotherapy so as to enhance the therapeutic activities of the combined agents without causing the undesirable side effects commonly occur in conventional monotherapy. Therefore, the Compounds of the present disclosure may be simultaneously, sequentially, or contemporaneously administered with other therapeutic agents as described hereinabove, such as opiate, opioid, analgesic, anti-depressant, anti-psychotic, other hypnotic agents, and/or agents use to treat Parkinson's disease or mood disorders.

[00047] In any of the embodiments of Method 1 et seq. or Method 2 et seq. wherein the Compound of the present disclosure is administered along with one or more second therapeutic agents, the one or more second therapeutic agents may be administered as a part of the pharmaceutical composition comprising the Compound of the present disclosure. Alternatively,

the one or more second therapeutic agents may be administered in separate pharmaceutical compositions (such as pills, tablets, capsules and injections) administered simultaneously, sequentially or separately from the administration of the Compound of the present disclosure.

[00048] In some further embodiments of the present disclosure, the Pharmaceutical Compositions of the present disclosure may be used in combination with a second therapeutic agent, particularly at lower dosages than when the individual agents are used as a monotherapy so as to enhance the therapeutic activities of the combined agents without causing the undesirable side effects, wherein the second therapeutic agent is an opioid antagonist or inverse agonist (e.g., naloxone). The Compounds of the present disclosure may be simultaneously, sequentially, or contemporaneously administered with such opioid antagonists or opioid inverse agonists.

[00049] In a fifth aspect, the present disclosure provides use of a Compound of the Invention, in the manufacture of a medicament for use according to Method 1 or any of Methods 1.1-1.42 or Method 2 or any of Methods 2.1-2.49. In another embodiment, the present disclosure provides a Compound of the Invention, for use in the treatment of a disease or disorder according to Method 1 or any of Methods 1.1-1.42 or Method 2 or any of Methods 2.1-2.49.

DETAILED DESCRIPTION

[00050] The term "biased agonist" as used herein, is used in reference to a compound having activity at the serotonin 5-HT_{2A} receptor with either partial or full agonism for beta-arrestin signaling via the receptor, but with either antagonism or weak partial agonism for G-q mediated signaling. A useful measure of bias is the "bias ratio", which is calculated as the ratio of the intrinsic relative activity (RA_i) for beta-arrestin signaling over the RA_i for G-q signaling. A non-biased agonist has a bias ratio of 1.0. A biased agonist has a non-zero bias ratio. In some embodiments, compounds of the present disclosure are preferably biased towards beta-arrestin signaling, and thus have a bias ratio greater than 1.0. More preferably, the bias ratio towards beta-arrestin signaling is greater than 10, or greater than 100, or greater than 1000, or 10,000 or more.

[00051] As used herein, the term "partial agonist" is understood to refer to a compound having agonism to any extent that is lesser than that of a reference standard full agonist. For example, the reference compound for 5-HT_{2A} receptor agonism is alpha-methylserotonin. A

compound which has a maximum efficacy (E_{max}) that is less than 100% of the maximum efficacy for alpha-methylserotonin is a partial agonist.

[00052] The term "hallucinogen" refers to a compound which causes hallucinogenic symptoms, which are any one or more symptoms selected from visual hallucinations, auditory hallucinations, visual distortions (such as drifting, morphing, breathing or melting of objects and surfaces in the field of view), detachment from reality, dissociation, delirium, and undesired altered states of consciousness. A compound of the present disclosure is considered "non-hallucinogenic" if at doses which are therapeutically effective for the treatment of neuropsychiatric disorders described herein (e.g., depression, anxiety, etc.) the compound does not cause hallucinogenic symptoms.

[00053] It is understood that the terms "opiate" and "opioid" are distinct, in that "opiate" refers to natural products derived from the opium poppy, such as morphine, codeine and heroin, but "opioid" refers to these natural compounds as well as semi-synthetic and synthetic derivatives thereof, such as fentanyl and its analogs.

[00054] "Alkyl" as used herein is a saturated or unsaturated hydrocarbon moiety, e.g., one to twenty-one carbon atoms in length, unless indicated otherwise; any such alkyl may be linear or branched (e.g., n-butyl or tert-butyl), preferably linear, unless otherwise specified. For example, "C_{1-21} alkyl" denotes alkyl having 1 to 21 carbon atoms. In one embodiment, alkyl is optionally substituted with one or more hydroxy or C_{1-22}alkoxy (e.g., ethoxy) groups. In another embodiment, alkyl contains 1 to 21 carbon atoms, preferably straight chain and optionally saturated or unsaturated, for example in some embodiments wherein R_1 is an alkyl chain containing 1 to 21 carbon atoms, preferably 6-15 carbon atoms, 16-21 carbon atoms, e.g., so that together with the -C(O)- to which it attaches, e.g., when cleaved from the compound of Formula I, forms the residue of a natural or unnatural, saturated or unsaturated fatty acid.

[00055] The term "pharmaceutically acceptable diluent or carrier" is intended to mean diluents and carriers that are useful in pharmaceutical preparations, and that are free of substances that are allergenic, pyrogenic or pathogenic, and that are known to potentially cause or promote illness. Pharmaceutically acceptable diluents or carriers thus exclude bodily fluids such as example blood, urine, spinal fluid, saliva, and the like, as well as their constituent components such as blood cells and circulating proteins. Suitable pharmaceutically acceptable diluents and carriers can be found in any of several well-known treatises on pharmaceutical

formulations, for example Anderson, Philip O.; Knoben, James E.; Troutman, William G, eds., Handbook of Clinical Drug Data, Tenth Edition, McGraw-Hill, 2002; Pratt and Taylor, eds., Principles of Drug Action, Third Edition, Churchill Livingston, New York, 1990; Katzung, ed., Basic and Clinical Pharmacology, Ninth Edition, McGraw Hill, 20037ybg; Goodman and Gilman, eds., The Pharmacological Basis of Therapeutics, Tenth Edition, McGraw Hill, 2001; Remington's Pharmaceutical Sciences, 20th Ed., Lippincott Williams & Wilkins., 2000; and Martindale, The Extra Pharmacopoeia, Thirty-Second Edition (The Pharmaceutical Press, London, 1999); all of which are incorporated by reference herein in their entirety.

[00056] The terms "purified," "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g., from a reaction mixture), or natural source or combination thereof. Thus, the term "purified," "in purified form" or "in isolated and purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan (e.g., chromatography, recrystallization, LC-MS and LC-MS/MS techniques and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

[00057] Unless otherwise indicated, the Compounds of the Invention may exist in free base form or in salt form, such as a pharmaceutically acceptable salt form, e.g., as acid addition salts. An acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric acid or toluenesulfonic acid. In addition, a salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, or a salt with an organic base which affords a physiologically-acceptable cation. In a particular embodiment, the salt of a Compound of the Invention is a toluenesulfonic acid addition salt or the hydrochloric acid addition salt.

[00058] The Compounds of the Invention are intended for use as pharmaceuticals, therefore pharmaceutically acceptable salts are preferred. Salts which are unsuitable for pharmaceutical uses may be useful, for example, for the isolation or purification of free Compounds of the Invention, and are therefore also included within the scope of the compounds of the present disclosure.

[00059] The Compounds of the Invention may comprise one or more chiral carbon atoms. The compounds thus exist in individual isomeric, e.g., enantiomeric or diastereomeric form or as mixtures of individual forms, e.g., racemic/diastereomeric mixtures. Any isomer may be present in which the asymmetric center is in the (*R*)-, (*S*)-, or (*R,S*)- configuration. The invention is to be understood as embracing both individual optically active isomers as well as mixtures (e.g., racemic/diastereomeric mixtures) thereof. Accordingly, the Compounds of the Invention may be a racemic mixture or it may be predominantly, e.g., in pure, or substantially pure, isomeric form, e.g., greater than 70% enantiomeric/diastereomeric excess ("ee"), preferably greater than 80% ee, more preferably greater than 90% ee, most preferably greater than 95% ee. The purification of said isomers and the separation of said isomeric mixtures may be accomplished by standard techniques known in the art (e.g., column chromatography, preparative TLC, preparative HPLC, simulated moving bed and the like).

[00060] Geometric isomers by nature of substituents about a double bond or a ring may be present in cis (*Z*) or trans (*E*) form, and both isomeric forms are encompassed within the scope of this invention.

[00061] It is also intended that the compounds of the present disclosure encompass their stable and unstable isotopes. Stable isotopes are nonradioactive isotopes which contain one additional neutron compared to the abundant nuclides of the same species (i.e., element). It is expected that the activity of compounds comprising such isotopes would be retained, and such compound would also have utility for measuring pharmacokinetics of the non-isotopic analogs. For example, the hydrogen atom at a certain position on the compounds of the disclosure may be replaced with deuterium (a stable isotope which is non-radioactive). Examples of known stable isotopes include, but not limited to, deuterium (^{2}H or D), ^{13}C, ^{15}N, ^{18}O. Alternatively, unstable isotopes, which are radioactive isotopes which contain additional neutrons compared to the abundant nuclides of the same species (i.e., element), e.g., ^{123}I, ^{131}I, ^{125}I, ^{14}C, ^{18}F, may replace the corresponding abundant species of I, C and F. Another example of useful isotope of the compound of the invention is the ^{14}C isotope. These radio isotopes are useful for radio-imaging and/or pharmacokinetic studies of the compounds of the invention. In addition, the substitution of atoms of having the natural isotopic distributing with heavier isotopes can result in desirable change in pharmacokinetic rates when these substitutions are made at metabolically liable sites.

For example, the incorporation of deuterium (^2H) in place of hydrogen can slow metabolic degradation when the position of the hydrogen is a site of enzymatic or metabolic activity.

[00062] Compounds of the Invention may be included as a depot formulation, e.g., by dispersing, dissolving or encapsulating the Compounds of the Invention in a polymeric matrix as described hereinbefore, such that the Compound is continually released as the polymer degrades over time. The release of the Compounds of the Invention from the polymeric matrix provides for the controlled- and/or delayed- and/or sustained-release of the Compounds, e.g., from the pharmaceutical depot composition, into a subject, for example a warm-blooded animal such as man, to which the pharmaceutical depot is administered. Thus, the pharmaceutical depot delivers the Compounds of the Invention to the subject at concentrations effective for treatment of the particular disease or medical condition over a sustained period of time, e.g., 14-180 days, preferably about 30, about 60 or about 90 days.

[00063] Polymers useful for the polymeric matrix in the Composition of the Invention (e.g., Depot composition of the Invention) may include a polyester of a hydroxyfatty acid and derivatives thereof or other agents such as polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, poly-beta.-hydroxybutyric acid, epsilon.-capro-lactone ring opening polymer, lactic acid-glycolic acid copolymer, 2-hydroxybutyric acid-glycolic acid copolymer, polylactic acid-polyethylene glycol copolymer or polyglycolic acid-polyethylene glycol copolymer), a polymer of an alkyl alpha-cyanoacrylate (for example poly(butyl 2-cyanoacrylate)), a polyalkylene oxalate (for example polytrimethylene oxalate or polytetramethylene oxalate), a polyortho ester, a polycarbonate (for example polyethylene carbonate or polyethylene-propylene carbonate), a polyortho-carbonate, a polyamino acid (for example poly-gamma.-L-alanine, poly-.gamma.-benzyl-L-glutamic acid or poly-y-methyl-L-glutamic acid), a hyaluronic acid ester, and the like, and one or more of these polymers can be used.

[00064] If the polymers are copolymers, they may be any of random, block and/or graft copolymers. When the above alpha-hydroxycarboxylic acids, hydroxydicarboxylic acids and hydroxytricarboxylic acids have optical activity in their molecules, any one of D-isomers, L-isomers and/or DL-isomers may be used. Among others, alpha-hydroxycarboxylic acid polymer (preferably lactic acid-glycolic acid polymer), its ester, poly-alpha-cyanoacrylic acid esters, etc. may be used, and lactic acid-glycolic acid copolymer (also referred to as poly(lactide-alpha-glycolide) or poly(lactic-co-glycolic acid), and hereinafter referred to as PLGA) are preferred.

Thus, in one aspect the polymer useful for the polymeric matrix is PLGA. As used herein, the term PLGA includes polymers of lactic acid (also referred to as polylactide, poly(lactic acid), or PLA). Most preferably, the polymer is the biodegradable poly(d,l-lactide-co-glycolide) polymer.

[00065] In a preferred embodiment, the polymeric matrix of the invention is a biocompatible and biodegradable polymeric material. The term "biocompatible" is defined as a polymeric material that is not toxic, is not carcinogenic, and does not significantly induce inflammation in body tissues. The matrix material should be biodegradable wherein the polymeric material should degrade by bodily processes to products readily disposable by the body and should not accumulate in the body. The products of the biodegradation should also be biocompatible with the body in that the polymeric matrix is biocompatible with the body. Particular useful examples of polymeric matrix materials include poly(glycolic acid), poly-D,L-lactic acid, poly-L-lactic acid, copolymers of the foregoing, poly(aliphatic carboxylic acids), copolyoxalates, polycaprolactone, polydioxanone, poly(ortho carbonates), poly(acetals), poly(lactic acid-caprolactone), polyorthoesters, poly(glycolic acid-caprolactone), polyanhydrides, and natural polymers including albumin, casein, and waxes, such as, glycerol mono- and distearate, and the like. The preferred polymer for use in the practice of this invention is dl(polylactide-co-glycolide). It is preferred that the molar ratio of lactide to glycolide in such a copolymer be in the range of from about 75:25 to 50:50.

[00066] Useful PLGA polymers may have a weight-average molecular weight of from about 5,000 to 500,000 Daltons, preferably about 150,000 Daltons. Dependent on the rate of degradation to be achieved, different molecular weight of polymers may be used. For a diffusional mechanism of drug release, the polymer should remain intact until all of the drug is released from the polymeric matrix and then degrade. The drug can also be released from the polymeric matrix as the polymeric excipient bioerodes.

The PLGA may be prepared by any conventional method, or may be commercially available. For example, PLGA can be produced by ring-opening polymerization with a suitable catalyst from cyclic lactide, glycolide, etc. (see EP-0058481B2; Effects of polymerization variables on PLGA properties: molecular weight, composition and chain structure).

[00067] It is believed that PLGA is biodegradable by means of the degradation of the entire solid polymer composition, due to the break-down of hydrolysable and enzymatically cleavable ester linkages under biological conditions (for example in the presence of water and biological

enzymes found in tissues of warm-blooded animals such as humans) to form lactic acid and glycolic acid. Both lactic acid and glycolic acid are water-soluble, non-toxic products of normal metabolism, which may further biodegrade to form carbon dioxide and water. In other words, PLGA is believed to degrade by means of hydrolysis of its ester groups in the presence of water, for example in the body of a warm-blooded animal such as man, to produce lactic acid and glycolic acid and create the acidic microclimate. Lactic and glycolic acid are by-products of various metabolic pathways in the body of a warm-blooded animal such as man under normal physiological conditions and therefore are well tolerated and produce minimal systemic toxicity.

[00068] In another embodiment, the polymeric matrix useful for the invention may comprise a star polymer wherein the structure of the polyester is star-shaped. These polyesters have a single polyol residue as a central moiety surrounded by acid residue chains. The polyol moiety may be, e. g., glucose or, e. g., mannitol. These esters are known and described in GB 2,145,422 and in U. S. Patent No. 5,538,739, the contents of which are incorporated by reference.

[00069] The star polymers may be prepared using polyhydroxy compounds, e. g., polyol, e.g., glucose or mannitol as the initiator. The polyol contains at least 3 hydroxy groups and has a molecular weight of up to about 20,000 Daltons, with at least 1, preferably at least 2, e.g., as a mean 3 of the hydroxy groups of the polyol being in the form of ester groups, which contain polylactide or co-polylactide chains. The branched polyesters, e.g., poly (d, l-lactide-co-glycolide) have a central glucose moiety having rays of linear polylactide chains.

[00070] The depot compositions of the invention (long-acting injectable compositions having a Compound of the Invention in a polymeric matrix) as hereinbefore described may comprise the polymer in the form of microparticles or nanoparticles, or in a liquid form, with the Compounds of the Invention dispersed or encapsulated therein. "Microparticles" is meant solid particles that contain the Compounds of the Invention either in solution or in solid form wherein such compound is dispersed or dissolved within the polymer that serves as the matrix of the particle. By an appropriate selection of polymeric materials, a microparticle formulation can be made in which the resulting microparticles exhibit both diffusional release and biodegradation release properties.

[00071] When the polymer is in the form of microparticles, the microparticles may be prepared using any appropriate method, such as by a solvent evaporation or solvent extraction method. For example, in the solvent evaporation method, the Compounds of the Invention and

the polymer may be dissolved in a volatile organic solvent (for example a ketone such as acetone, a halogenated hydrocarbon such as chloroform or methylene chloride, a halogenated aromatic hydrocarbon, a cyclic ether such as dioxane, an ester such as ethyl acetate, a nitrile such as acetonitrile, or an alcohol such as ethanol) and dispersed in an aqueous phase containing a suitable emulsion stabilizer (for example polyvinyl alcohol, PVA). The organic solvent is then evaporated to provide microparticles with the Compounds of the Invention encapsulated therein. In the solvent extraction method, the Compounds of the Invention and polymer may be dissolved in a polar solvent (such as acetonitrile, dichloromethane, methanol, ethyl acetate or methyl formate) and then dispersed in an aqueous phase (such as a water/PVA solution). An emulsion is produced to provide microparticles with the Compounds of the Invention encapsulated therein. Spray drying is an alternative manufacturing technique for preparing the microparticles.

[00072] Another method for preparing the microparticles of the invention is also described in both U.S. Pat. No. 4,389,330 and U.S. Pat. No. 4,530,840.

[00073] The microparticle of the present invention can be prepared by any method capable of producing microparticles in a size range acceptable for use in an injectable composition. One preferred method of preparation is that described in U.S. Pat. No. 4,389,330. In this method the active agent is dissolved or dispersed in an appropriate solvent. To the agent-containing medium is added the polymeric matrix material in an amount relative to the active ingredient that provides a product having the desired loading of active agent. Optionally, all of the ingredients of the microparticle product can be blended in the solvent medium together.

[00074] Solvents for making such compositions comprising the Compounds of the Invention and the polymeric matrix material that can be employed in the practice of the present invention include organic solvents, such as acetone; halogenated hydrocarbons, such as chloroform, methylene chloride, and the like; aromatic hydrocarbon compounds; halogenated aromatic hydrocarbon compounds; cyclic ethers; alcohols, such as, benzyl alcohol; ethyl acetate; and the like. In one embodiment, the solvent for use in the practice of the present invention may be a mixture of benzyl alcohol and ethyl acetate. Further information for the preparation of microparticles useful for the invention can be found in U.S. Patent Publication Number 2008/0069885, the contents of which are incorporated herein by reference in their entirety.

[00075] The amount of the Compounds of the present disclosure incorporated in the microparticles usually ranges from about 1 wt. % to about 90 wt. %, preferably 30 to 50 wt. %,

more preferably 35 to 40 wt. %. By weight % is meant parts of the Compounds of the present disclosure per total weight of microparticle.

[00076] The pharmaceutical depot compositions may comprise a pharmaceutically-acceptable diluent or carrier, such as a water miscible diluent or carrier.

[00077] Details of Osmotic-controlled Release Oral Delivery System composition may be found in EP 1 539 115 (U.S. Pub. No. 2009/0202631) and WO 2000/35419 (US 2001/0036472), the contents of each of which are incorporated by reference in their entirety.

[00078] A "therapeutically effective amount" is any amount of the Compounds of the invention (for example as contained in the pharmaceutical depot) which, when administered to a subject suffering from a disease or disorder, is effective to cause a reduction, remission, or regression of the disease or disorder over the period of time as intended for the treatment.

[00079] Dosages employed in practicing the present invention will of course vary depending, e.g., on the particular disease or condition to be treated, the particular Compound of the Invention used, the mode of administration, and the therapy desired. Unless otherwise indicated, an amount of the Compound of the Invention for administration (whether administered as a free base or as a salt form) refers to or is based on the amount of the Compound of the Invention in free base form (i.e., the calculation of the amount is based on the free base amount).

[00080] Compounds of the Invention may be administered by any satisfactory route, including orally, parenterally (intravenously, intramuscular, intranasal, pulmonary or subcutaneous) or transdermally. In certain embodiments, the Compounds of the Invention, e.g., in depot formulation, is preferably administered parenterally, e.g., by injection, for example, intramuscular or subcutaneous injection.

[00081] In general, satisfactory results for the methods of treatment disclosed herein, or use of the Compounds of the Invention as hereinbefore described, as set forth above are indicated to be obtained on oral administration at dosages of the order from about 1 mg to 100 mg once daily, preferably 2.5 mg-50 mg, e.g., 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg or 50 mg, once daily, preferably via oral administration.

[00082] For some disease treatments, lower doses are satisfactory, particularly for sleep disorder treatment, such as from about 2.5mg-5mg, e.g., 2.5mg, 3mg, 4mg or 5mg, of a Compound of the Invention, in free or pharmaceutically acceptable salt form, once daily, preferably via oral administration.

[00083] Satisfactory results for methods of treatment involving co-administration of a second therapeutic agent may be obtained at doses of less than 100mg, preferably less than 50mg, e.g., less than 40mg, less than 30mg, less than 20mg, less than 10mg, less than 5mg, less than 2.5mg, once daily.

[00084] For treatment of the disorders disclosed herein wherein the depot composition is used to achieve longer duration of action, the dosages will be higher relative to the shorter action composition, e.g., higher than 1-100mg, e.g., 25mg, 50mg, 100mg, 500mg, 1,000mg, or greater than 1000mg. Duration of action of the Compounds of the present disclosure may be controlled by manipulation of the polymer composition, i.e., the polymer:drug ratio and microparticle size. Wherein the composition of the invention is a depot composition, administration by injection is preferred.

[00085] The pharmaceutically acceptable salts of the Compounds of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free base forms of these compounds with a stoichiometric amount of the appropriate acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Further details for the preparation of these salts, e.g., toluenesulfonic salt in amorphous or crystal form, may be found in U.S. 8,309,722, 8.648,077, 9,199,995, and 9,586,960.

[00086] Pharmaceutical compositions comprising Compounds of the present disclosure may be prepared using conventional diluents or excipients (an example include, but is not limited to sesame oil) and techniques known in the galenic art. Thus, oral dosage forms may include tablets, capsules, solutions, suspensions and the like.

[00087] The term "concurrently" when referring to a therapeutic use means administration of two or more active ingredients to a patient as part of a regimen for the treatment of a disease or disorder, whether the two or more active agents are given at the same or different times or whether given by the same or different routes of administrations. Concurrent administration of the two or more active ingredients may be at different times on the same day, or on different dates or at different frequencies.

[00088] The term "simultaneously" when referring to a therapeutic use means administration of two or more active ingredients at or about the same time by the same route of administration.

[00089] The term "separately" when referring to a therapeutic use means administration of two or more active ingredients at or about the same time by different route of administration

Methods of Making the Compounds of the Invention:

[00090] The Compound of Formula A, and methods for its synthesis, including the synthesis of intermediates used in the synthetic schemes described below, have been disclosed in, for example, U.S. 10,245,260, and US 2022/0041600, and US 2022/0064166, the contents of which are hereby incorporated by reference in their entireties.

[00091] The synthesis of similar fused gamma-carbolines has been disclosed in, for example, U.S. 8,309,722, U.S. 8,993,572, US 2017/0183350, WO 2018/126140 and WO 2018/126143, the contents of each of which are incorporated by reference in their entireties. Compounds of the present disclosure can be prepared using similar procedures.

[00092] Other Compounds of the present disclosure came be made by analogous procedures known to those skilled in the art.

[00093] Isolation or purification of the diastereomers of the Compounds of the Invention may be achieved by conventional methods known in the art, e.g., column purification, preparative thin layer chromatography, preparative HPLC, crystallization, trituration, simulated moving beds and the like.

[00094] Salts of the Compounds of the present disclosure may be prepared as similarly described in U.S. Pat. No. 6,548,493; 7,238,690; 6,552,017; 6,713,471; 7,183,282, 8,648,077; 9,199,995; 9,586,860; U.S. RE39680; and U.S. RE39679, the contents of each of which are incorporated by reference in their entirety.

[00095] Diastereomers of prepared compounds can be separated by, for example, HPLC using CHIRALPAK® AY-H, 5μ, 30x250mm at room temperature and eluted with 10% ethanol / 90% hexane / 0.1% dimethylethylamine. Peaks can be detected at 230 nm to produce 98-99.9%ee of the diastereomer.

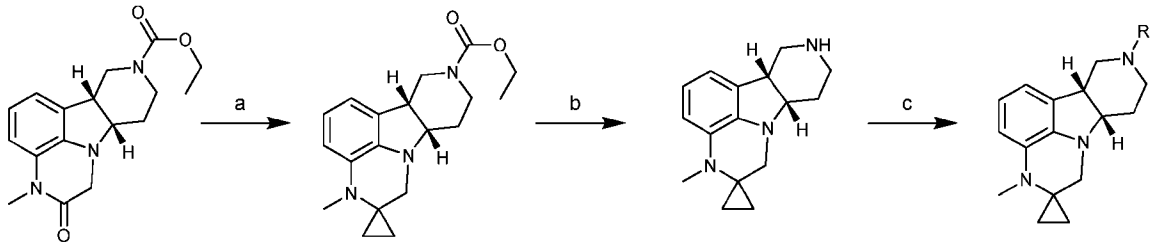
EXAMPLES

[00096] Method for the synthesis of the compounds of the present disclosure are known in the art. In particular, methods for synthesis of the tetracyclic core structure, and for various modifications and variations of the pendant side chain on the piperidine ring have been

published. For example, see Li, et al., *Journal of Medicinal Chemistry* 57:2670-2682 (2014), U.S. 6,713,471, U.S. 6,552,017, U.S. 7,071,186, U.S. 8,309,722, U.S., 9,708,322, U.S. 10,245,260, U.S. 10,688,097, U.S. 10,961,245, U.S. 10,906,906, U.S. 11,427,587, U.S. 11,453,670, and US 2022/0048910, the contents of each of which are hereby incorporated by reference in their entireties.

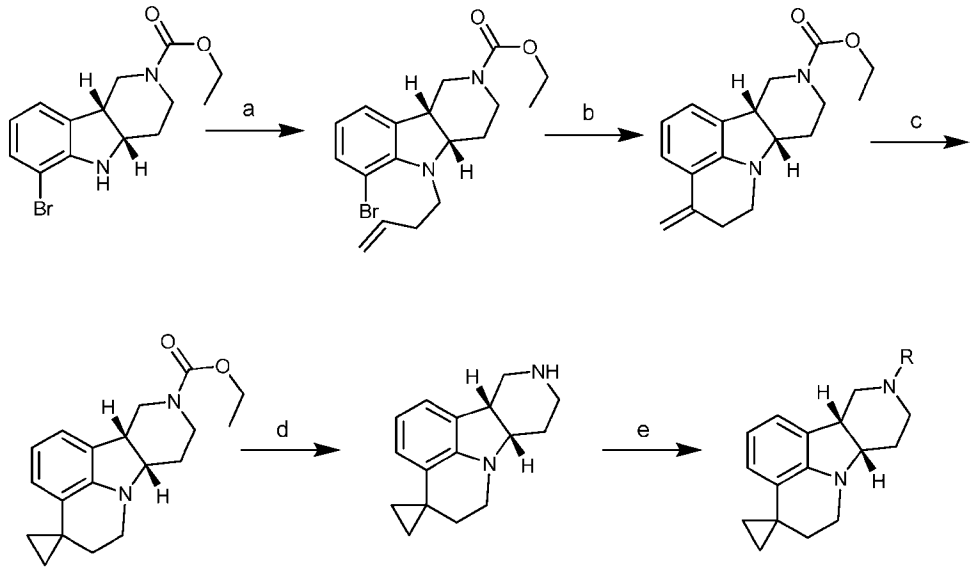
[00097] Compounds of the present disclosure may be prepared according to the following general schemes:

[00098] Scheme 1



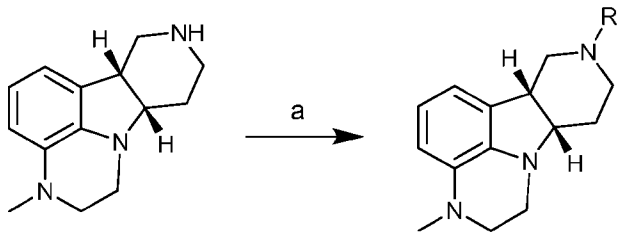
Typical reagents and conditions: (a) ethylmagnesium bromide, titanium isopropoxide, THF, 25 °C; (b) sat. KOH in 90% EtOH solution, 100 °C; (c) RX, KI, DIPEA, DMF, 75 °C.

[00099] Scheme 2

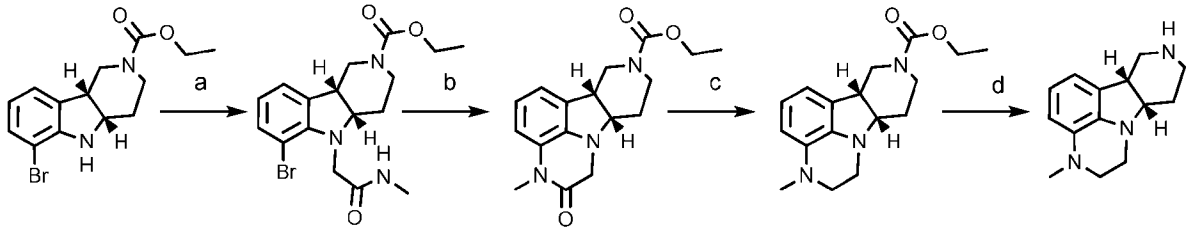


Typical reagents and conditions: (a) 4-bromo-1-butene, DIPEA, KI, dioxane, 110 °C; (b) DBU, $Pd(OAc)_2$, tricyclohexylphosphine, DMF, 140 °C; (c) $ZnEt_2$, CH_2I_2, CH_2Cl_2, 0 °C; (d) sat. KOH in 90% EtOH solution, 100 °C; (e) RX, KI, DIPEA, DMF, 75 °C.

[000100] Scheme 3

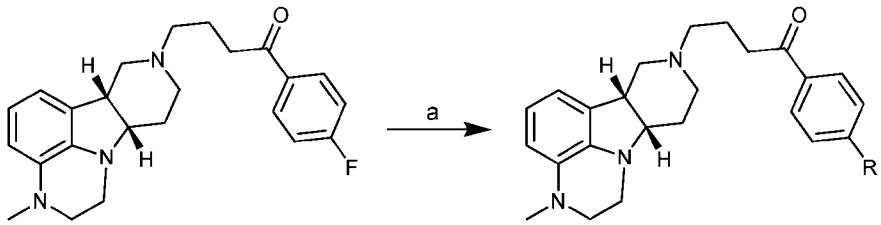


Typical reagents and conditions: (a) RX, DIPEA, KI, 18-crown-6, dioxane, 95 °C, or RX, K_2CO_3, dioxane, 60 °C. The tetracyclic starting material can be made according to known methods, for example, according to the following **Scheme 3-A**:



Typical reagents and conditions: (a) N-methyl chloroacetamide, DIPEA, KI, dioxane, reflux, 48 h; (b) CuI, K_2CO_3, DMEDA, dioxane, reflux, 24 h; (c) BH_3-THF, THF, 60 °C, 20 h; (d) KOH, n-BuOH, 120 °C, 3 h.

[000101] **Scheme 4**



Typical reagents and conditions: (a) ROH, Triton B, KOH, 18-crown-6, 150 °C.

[000102] According to the above general schemes, the following compounds of Examples 1 to 180 are, or will be, synthesized and characterized:

Ex.	X	Y	m	n	Z	A
1	-N(CH_3)-	-CH_2-	1	3	-O-	2-CN-4-F-phenyl
2	-N(CH_3)-	-CH_2-	1	4	-C(O)-	4-F-phenyl
3	-N(CH_3)-	-CH_2-	1	2	-C(O)-	4-F-phenyl

4	-N(CH_3)-	Cyp	1	3	-C(O)-	4-F-phenyl
5	-N(CH_3)-	-CH_2-	1	5	-C(O)-	4-F-phenyl
6	-N(CH_3)-	-CH_2-	1	3	-C(O)-	4-($CH_3OCH_2CH_2O$)-phenyl
7	Cyp	-CH_2-	1	3	-C(O)-	4-F-phenyl
8	Cyp	-CH_2-	1	3	-O-	4-F-phenyl
9	-NH-	-C(O)-	1	3	-O-	3-Me-4-F-phenyl
10	-NH-	-C(O)-	1	3	-O-	3-Cl-4-F-phenyl
11	-NH-	-C(O)-	1	3	-O-	3-CN-4-F-phenyl
12	-N(CH_3)-	-CH_2-	1	2	-$O(CH_2)_2O$-	4-F-phenyl
13	-N(CH_3)-	-CH_2-	1	3	-C(O)-	4-((4-F-benzyl)oxy)
14	-N(CH_3)-	Cyp	1	2	-C(O)-	4-F-phenyl
15	-N(CH_3)-	Cyp	1	2	-O-	4-F-phenyl
16	-N(CH_3)-	Cyp	1	2	-C(O)-	2-Me-4-F-phenyl
17	-N(CH_3)-	Cyp	1	2	-O-	2-Me-4-F-phenyl
18	-NH-	-C(O)-	1	2	-O-	4-F-phenyl
19	-N(CH_3)-	Cyp	1	3	bond	3-Cl-phenyl
20	-N(CH_3)-	Cyp	1	3	bond	3-MeO-phenyl
21	-N(CH_3)-	Cyp	1	3	bond	3-CF_3-phenyl
22	-N(CH_3)-	Cyp	1	3	bond	2-Cl-phenyl
23	-N(CH_3)-	Cyp	1	3	bond	2-Me-phenyl
24	-N(CH_3)-	Cyp	1	2	bond	2-Cl-phenyl
25	-N(CH_3)-	Cyp	1	2	bond	2-MeO-phenyl
26	-N(CH_3)-	-CH_2-	1	2	-O-	4-F-phenyl
27	-N(CH_3)-	-CH_2-	1	2	-O-	2-MeO-4-F-phenyl
28	-N(CH_3)-	-CH_2-	1	3	bond	2-MeO-phenyl
29	-N(CH_3)-	-CH_2-	1	3	bond	3-MeO-phenyl
30	-N(CH_3)-	-CH_2-	1	3	bond	3-Cl-phenyl
31	-N(CH_3)-	-CH_2-	1	3	bond	2-Cl-phenyl
32	-N(CH_3)-	-CH_2-	1	3	bond	3-CF_3-phenyl
33	-N(CH_3)-	-CH_2-	1	2	bond	2-Cl-phenyl

34	-N(CH_3)-	-CH_2-	1	2	bond	2-MeO-phenyl
35	-N(CH_3)-	-CH_2-	1	3	bond	2-Me-phenyl
36	-CH_2-	-CH_2-	2	2	-C(O)-	4-F-phenyl
37	-CH_2-	-CH_2-	2	2	-O-	4-F-phenyl
38	-CH_2-	-CH_2-	2	2	bond	4-F-phenyl
39	-N(CH_3)-	Cyp	1	3	bond	2-MeO-phenyl
40	-N(CH_3)-	Cyp	1	2	bond	benzo[d]isoxazol-3-yl
41	-N(CH_3)-	-CH_2-	1	2	-C(O)-	2-Me-4-F-phenyl
42	-O-	-CH_2-	2	2	-O-	4-F-phenyl
43	-O-	-CH_2-	2	2	-C(O)-	4-F-phenyl
44	-S-	-CH_2-	2	2	-C(O)-	4-F-phenyl
45	-CH_2-	-CH_2-	1	2	-C(O)-	4-F-phenyl
46	-S-	-CH_2-	1	2	-C(O)-	4-F-phenyl
47	-NH-	Cyp	1	2	-O-	4-F-phenyl
48	-NH-	Cyp	1	2	-O-	2-Me-4-F-phenyl
49	-NH-	Cyp	1	2	-C(O)-	4-F-phenyl
50	-NH-	Cyp	1	2	-C(O)-	2-Me-4-F-phenyl
51	Cyp	-CH_2-	1	2	-O-	4-F-phenyl
52	Cyp	-CH_2-	1	2	-O-	2-Me-4-F-phenyl
53	Cyp	-CH_2-	1	2	-C(O)-	4-F-phenyl
54	Cyp	-CH_2-	1	2	-C(O)-	2-Me-4-F-phenyl
55	-NH-	-C(O)-	1	2	-C(O)-	4-F-phenyl
56	-NH-	-C(O)-	1	2	-C(O)-	2-Me-4-F-phenyl
57	-NH-	-C(O)-	1	2	-C(O)-	2-F-4-Me-phenyl
58	-CH_2-	-CH_2-	2	3	bond	2-MeO-phenyl
59	-CH_2-	-CH_2-	2	3	bond	2-HO-phenyl
60	-CH_2-	-CH_2-	2	3	bond	2-Cl-phenyl
61	-CH_2-	-CH_2-	2	2	bond	2-Cl-phenyl
62	-CH_2-	-CH_2-	2	3	bond	3-MeO-phenyl
63	-CH_2-	-CH_2-	2	3	bond	3-CF_3-phenyl

64	-CH_2-	-CH_2-	2	3	bond	3-Cl-phenyl
65	-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]isoxazol-3-yl
66	-N(CH_3)-	Cyp	1	2	bond	6-F-benzo[d]isoxazol-3-yl
67	-N(CH_3)-	-CH_2-	1	2	bond	6-F-benzo[d]isoxazol-3-yl
68	Cyp	-CH_2-	1	3	-O-	2-Me-4-F-phenyl
69	-N(CH_3)-	-CH_2-	1	3	-C(O)-	4-(4-F-PhO)-phenyl
70	Cyp	-CH_2-	1	2	bond	2-MeO-phenyl
71	-N(CH_3)-	-CH_2-	1	2	bond	3-MeO-phenyl
72	Cyp	-CH_2-	1	2	bond	benzo[d]isoxazol-3-yl
73	-N(CH_3)-	Cyp	1	4	bond	2-CN-phenyl
74	-N(CH_3)-	Cyp	1	2	bond	2-CN-phenyl
75	-N(CH_3)-	-CH_2-	1	2	bond	2-CN-phenyl
76	-N(CH_3)-	-CH_2-	1	3	bond	2-CN-phenyl
77	-N(CH_3)-	-CH_2-	1	2	bond	2-oxopyridin-1(2H)-yl
78	-N(CH_3)-	-CH_2-	1	2	bond	2-MeO-4-F-phenyl
79	-N(CH_3)-	Cyp	1	2	bond	2-MeO-4-F-phenyl
80	-N(CH_3)-	-CH_2-	1	2	bond	2-CF_3O-phenyl
81	-N(CH_3)-	-CH_2-	1	2	bond	2-Et-phenyl
82	-N(CH_3)-	-CH_2-	1	2	bond	4-MeO-phenyl
83	-N(CH_3)-	-CH_2-	1	2	bond	3-CN-phenyl
84	-N(CH_3)-	-CH_2-	1	2	bond	4-CN-phenyl
85	-N(CH_3)-	-CH_2-	1	2	bond	5-F-indol-3-yl
86	-N(CH_3)-	-CH_2-	1	3	-C(O)-	2-MeO-phenyl
87	-N(CH_3)-	-C(O)-	1	2	-O-	4-F-phenyl
88	-N(CH_3)-	-C(O)-	1	2	bond	2-MeO-phenyl
89	-N(CH_3)-	-CH_2-	1	2	bond	2-HO-phenyl
90	-N(CH_3)-	-CH_2-	1	1	bond	2-MeO-phenyl
91	-N(CH_3)-	-CH_2-	1	2	bond	2-EtO-phenyl
92	-N(CH_3)-	-CH_2-	1	2	bond	benzofuran-7-yl
93	-N(CH_3)-	-CH_2-	1	3	-O-	2-MeO-phenyl

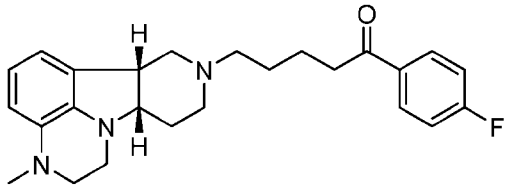
94	-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]isothiazol-3-yl
95	-N(CH_3)-	-CH_2-	1	2	bond	2,5-di-MeO-phenyl
96	-N(CH_3)-	-CH_2-	1	1	bond	4-Et-phenyl
97	-N(CH_3)-	-CH_2-	1	2	bond	indol-3-yl
98	-N(CH_3)-	Cyp	1	2	bond	2-Et-phenyl
99	-N(CH_3)-	Cyp	1	2	bond	3-MeO-phenyl
100	-N(CH_3)-	-CH_2-	1	1	bond	phenyl
101	-N(CH_3)-	-CH_2-	1	1	bond	3-MeO-phenyl
102	-N(CH_3)-	-CH_2-	1	1	bond	3-Et-phenyl
103	-N(CH_3)-	-CH_2-	1	1	bond	4-MeO-phenyl
104	-N(CH_3)-	-CH_2-	1	1	bond	2-Et-phenyl
105	-N^+(=O)$^-$-	Cyp	1	2	-O-	4-F-phenyl
106	-N(CH_3)-	-CH_2-	1	2	bond	2-$MeSO_2$-phenyl
107	-N(CH_3)-	Cyp	1	2	bond	benzo[d]isothiazol-3-yl
108	-N(CH_3)-	-CH_2-	1	1	bond	cyclohexyl
109	-N(CH_3)-	-CH_2-	1	2	bond	2-MeO-5-F-phenyl
110	-N(CH_3)-	-CH_2-	1	2	bond	3-Et-Phenyl
111	-N(CH_3)-	-CH_2-	1	2	bond	3-EtO-phenyl
112	-N(CH_3)-	Cyp	1	2	bond	benzofuran-7-yl
113	-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]imidazole-1-yl
114	-N(CH_3)-	-CH_2-	1	2	bond	benzo[d][1,2,3]triazol-1-yl
115	-N(CH_3)-	-CH_2-	1	2	bond	indazol-3-yl
116	-NH-	-C(O)-	1	2	bond	benzo[d]isothiazol-3-yl
117	-N(CH_3)-	-C(O)-	1	2	bond	benzo[d]isothiazol-3-yl
118	-N(CH_3)-	Cyp	1	1	bond	2-MeO-phenyl
119	-N(CH_3)-	-CH_2-	1	1	bond	benzo[d]isoxazol-3-yl
120	-N(CH_3)-	-CH_2-	1	1	bond	benzofuran-7-yl
121	-N(CH_3)-	-CH_2-	1	1	bond	benzo[d]isothiazol-3-yl
122	-N(CH_3)-	-CH_2-	1	1	bond	quinolin-8-yl
123	-N(CH_3)-	-CH_2-	1	1	bond	benzo[d]oxazol-7-yl

124	-N(CH_3)-	-CH_2-	1	1	bond	2,3-dihydrobenzofuran-7-yl
125	-N(CH_3)-	-CH_2-	1	2	-O-	2-CN-4-F-phenyl
126	-N(CH_3)-	-CH_2-	1	2	bond	indazol-1-yl
127	-N(CH_3)-	-C(O)-	1	2	-C(O)-	4-F-phenyl
128	-N(CH_3)-	-CH_2-	1	1	bond	quinoxalin-5-yl
129	-N(CH_3)-	-CH_2-	1	1	-C(O)-	4-F-Phenyl
130	-N(CH_3)-	-CH_2-	1	2	-C(=NOMe)	4-F-Ph
131	-N(CH_3)-	-CH_2-	1	3	-C(O)-	phenyl
132	-N(CH_3)-	-CH_2-	1	2	-C(=NOMe)	phenyl
133	-N(CH_3)-	-C(O)-	1	2	-C(O)-	phenyl
134	-N(CH_3)-	-CH_2-	1	2	-C(O)-	thiophen-2-yl
135	-N(CH_3)-	-CH_2-	1	1	bond	3-(O-cyclopropyl)phenyl
136	-N(CH_3)-	-CH_2-	1	1	bond	3-(OCH_2-cyclopropyl)phenyl
137	-N(CH_3)-	-C(O)-	1	2	bond	2-MeO-phenyl
138	-N(CH_3)-	-C(O)-	1	2	bond	3-MeO-phenyl
139	-N(CH_3)-	-C(O)-	1	2	bond	benzo[d]isoxazol-3-yl
140	-N(CH_3)-	-CH_2-	1	1	bond	3-MeS-phenyl
141	-N(CH_3)-	Cyp	1	2	-C(O)-	phenyl
142	-N(CH_3)-	Cyp	1	3	-C(OH)-	4-F-phenyl
143	-N(CH_3)-	Cyp	1	3	-C(OH)-	phenyl
144	-N(CH_3)-	Cyp	1	3	-C(OMe)-	4-F-phenyl
145	-N(CH_3)-	Cyp	1	3	-C(OMe)-	phenyl
146	-N(CH_3)-	-CH_2-	1	2	bond	2-(MeNH)-phenyl
147	-N(CH_3)-	Cyp	1	2	bond	2-HO-phenyl
148	-N(CH_3)-	Cyp	1	2	bond	2-MeO-phenyl
149	-N(CH_3)-	Cyp	1	2	bond	2-EtO-phenyl
150	-N(CH_3)-	Cyp	1	2	bond	2-CF_3O-phenyl
151	-N(CH_3)-	Cyp	1	2	bond	2-$MeSO_2$-phenyl
152	-N(CH_3)-	Cyp	1	2	bond	2-(MeNH)-phenyl
153	-N(CH_3)-	Cyp	1	2	bond	3-CN-phenyl

154	-N(CH_3)-	Cyp	1	2	bond	4-MeO-phenyl
155	-N(CH_3)-	Cyp	1	2	bond	4-CN-phenyl
156	-N(CH_3)-	-CH_2-	1	1	bond	quinazolin-7-yl
157	-N(CH_3)-	-CH_2-	1	1	bond	isoquinolyn-7-yl
158	-N(CH_3)-	-CH_2-	1	1	bond	benzo[d]isoxazol-4-yl
159	-N(CH_3)-	-CH_2-	1	1	bond	benzofuran-4-yl
160	-N(CH_3)-	-CH_2-	1	1	bond	2-Me-benzofuran-7-yl
161	-N(CH_3)-	-CH_2-	1	2	bond	3-MeS-phenyl
162	-N(CH_3)-	-CH_2-	1	2	bond	3-(O-Cyclopropyl)phenyl
163	-N(CH_3)-	-CH_2-	1	2	bond	3-(OCH_2-Cyclopropyl)phenyl
164	-N(CH_3)-	-CH_2-	1	2	bond	benzo[d]isoxazol-4-yl
165	-N(CH_3)-	-CH_2-	1	2	bond	benzofuran-4-yl
166	-N(CH_3)-	-CH_2-	1	2	bond	2-Me-benzofuran-7-yl)
167	-N(CH_3)-	Cyp	1	2	bond	indazol-7-yl
168	-N(CH_3)-	Cyp	1	2	bond	quinolin-8-yl
169	-N(CH_3)-	Cyp	1	2	bond	pyrid-4-yl
170	-N(CH_3)-	-CH_2-	1	2	bond	quinolin-8-yl
171	-N(CH_3)-	-CH_2-	1	2	bond	indol-1-yl
172	-N(CH_3)-	-CH_2-	1	2	bond	pyrid-4-yl
173	-N(CH_3)-	Cyp	1	1	bond	3-Et-phenyl
174	-N(CH_3)-	Cyp	1	2	-O-	3-CN-4-F-phenyl
175	-N(CH_3)-	-CH_2-	1	1	bond	H
176	-N(CH_3)-	-CH_2-	1	2	bond	H
177	-N(CH_3)-	-CH_2-	1	3	bond	H
178	-N(CH_3)-	-CH_2-	1	1	bond	Cyclopentyl
179	-N(CH_3)-	-CH_2-	1	1	bond	Cyclobutyl
180	-N(CH_3)-	-CH_2-	1	1	bond	Cyclopropyl

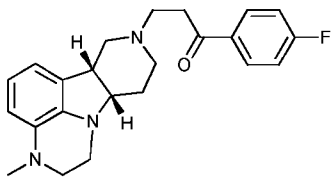
Representative synthetic Examples follow.

[000103] Example 2. 1-(4-fluorophenyl)-5-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)pentan-1-one



[000104] The synthesis method is analogous to Example 71, with 5-chloro-1-(4-fluorophenyl)-1-pentanone added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 17% isolated yield. ^{1}H NMR (500 MHz, DMSO) δ 8.10 – 8.01 (m, 2H), 7.40 – 7.28 (m, 2H), 6.53 – 6.46 (m, 1H), 6.43 – 6.38 (m, 1H), 6.32 (dd, J = 7.9, 1.0 Hz, 1H), 3.43 (ddd, J = 11.5, 9.7, 3.0 Hz, 1H), 3.26 (dt, J = 11.4, 2.9 Hz, 3H), 3.10 (ddd, J = 6.8, 4.3, 2.4 Hz, 1H), 3.02 (dd, J = 7.8, 6.7 Hz, 2H), 2.78 (s, 3H), 2.74 (ddd, J = 11.3, 6.2, 1.7 Hz, 1H), 2.68 (td, J = 9.9, 2.8 Hz, 1H), 2.54 (t, J = 11.5 Hz, 1H), 2.35 – 2.15 (m, 2H), 2.07 (td, J = 11.5, 2.9 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.80 – 1.69 (m, 2H), 1.62 (p, J = 7.3 Hz, 2H), 1.54 – 1.41 (m, 2H). HRMS (ESI) m/z calcd. for $C_{25}H_{30}FN_3O$ $[M+H]^+$: 408.2446; found: 408.2446.

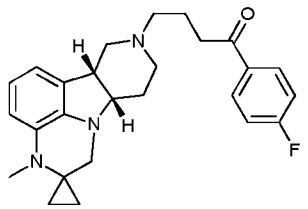
[000105] Example 3. 1-(4-fluorophenyl)-3-((6bR,10aS)-3-methyl-2,3,6b,7,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(9H)-yl)propan-1-one.



[000106] To a degassed solution of 2-((6bR,10aS)-3-methyl-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)ethan-1-ol hydrogen chloride (3.0 g, 11.3 mmol) in anhydrous dioxane (20mL) is added N, N-diisopropylethylamine (3.0 g, 22.6 mmol), 3-chloro-1-(4-fluorophenyl)propan-1-one (2.3g, 12.4 mmol), potassium iodide (2.3 g, 13.6 mmol) and a catalytic amount of 18-crown-6 under argon. The resulting mixture is heated to 95 °C and stirred for 6.5 hours. After cooling to room temperature, the solvent is removed, and the residue is suspended in ethyl acetate (50 mL) and water (50 mL). The aqueous phase is separated and extracted twice with ethyl acetate (30 mL). The combined organic phase is dried over $MgSO_4$ and concentrated. The residue is purified by silica gel column chromatography using a gradient of 0 – 20% mixed solvents [ethyl acetate/methanol/7N NH_3 in methanol (10 : 1 : 0.1 v/v)] in ethyl acetate to obtain the title product as a brown solid (0.8 g, yield 16%). MS (ESI)

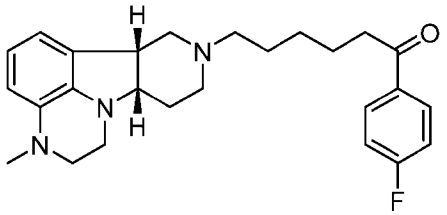
m/z 380.2 $[M+1]^+$. ^1H NMR (500 MHz, DMSO) δ 9.15 (s, 1H), 8.19 – 8.07 (m, 2H), 7.42 (t, J = 8.8 Hz, 2H), 6.62 (t, J = 7.7 Hz, 1H), 6.50 (d, J = 7.3 Hz, 1H), 6.44 (d, J = 7.9 Hz, 1H), 3.68 – 3.57 (m, 3H), 3.53 – 3.41 (m, 5H), 3.35 (q, J = 2.6 Hz, 1H), 3.23 (d, J = 5.8 Hz, 1H), 3.14 (q, J = 13.1 Hz, 1H), 2.82 (s, 4H), 2.76 – 2.61 (m, 2H), 2.29 (d, J = 15.5 Hz, 1H), 2.07 (t, J = 14.8 Hz, 1H).

[000107] Example 4. 1-(4-fluorophenyl)-4-((6b'R,10a'S)-3'-methyl-6b',7',10',10a'-tetrahydrospiro[cyclopropane-1,2'-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxalin]-8'(1'H,3'H,9'H)-yl)butan-1-one.



[000108] The synthesis method is analogous to the synthesis of compound of Example 15 according to Scheme 1, wherein 4-chloro-1-(4-fluorophenyl)butan-1-one is added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 13% isolated yield. MS (ESI) m/z 420.3 $[M+1]^+$. ^1H NMR (500 MHz, DMSO) δ 8.09 – 7.99 (m, 2H), 7.40 – 7.28 (m, 2H), 6.56 – 6.51 (m, 2H), 6.48 (dd, J = 6.6, 2.5 Hz, 1H), 3.11 (ddd, J = 6.8, 4.3, 2.6 Hz, 1H), 3.00 (t, J = 6.9 Hz, 2H), 2.91 (dt, J = 10.3, 6.3 Hz, 1H), 2.74 (dd, J = 11.4, 6.3 Hz, 1H), 2.69 (dd, J = 10.0, 2.0 Hz, 1H), 2.58 (s, 3H), 2.56 – 2.53 (m, 2H), 2.39 – 2.20 (m, 2H), 2.18 – 2.07 (m, 1H), 1.88 (t, J = 10.9 Hz, 1H), 1.83 – 1.74 (m, 3H), 1.70 – 1.56 (m, 1H), 1.24 (s, 1H), 1.11 – 1.00 (m, 1H), 0.79 – 0.62 (m, 1H), 0.41 (ddd, J = 9.8, 6.3, 4.1 Hz, 1H).

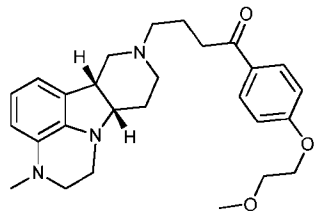
[000109] Example 5. 1-(4-fluorophenyl)-6-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)hexan-1-one



[000110] The synthesis method is analogous to Example 71, with 6-chloro-1-(4-fluorophenyl)-1-hexanone added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 11% isolated yield. ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 6.87 – 6.77 (m, 2H), 6.75 – 6.71 (m, 1H), 6.70 – 6.66 (m, 2H), 6.64 (dd, J = 7.9, 1.2 Hz, 1H), 3.99 (t, J = 5.8 Hz, 2H), 3.57 (dt, J =

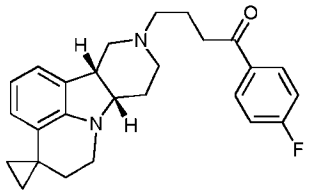
12.1, 6.3 Hz, 1H), 3.45 (ddd, *J* = 11.9, 6.4, 2.0 Hz, 1H), 3.39 – 3.26 (m, 2H), 3.18 – 2.99 (m, 2H), 2.92 (dd, *J* = 9.9, 2.2 Hz, 1H), 2.90 – 2.79 (m, 1H), 2.71 (s, 3H), 2.54 (t, *J* = 11.7 Hz, 1H), 2.48 – 2.39 (m, 1H), 2.37 (d, *J* = 10.0 Hz, 1H), 2.32 – 2.23 (m, 2H), 2.18 (d, *J* = 3.4 Hz, 2H), 2.04 (dq, *J* = 15.5, 2.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.43, 157.18 (d, *J* = 240Hz), 152.75, 140.19, 136.76, 128.88, 120.84, 117.59 (d, *J* = 25.2Hz), 115.89, 115.07, 112.60 (d, *J* = 25.2Hz), 111.92(d, *J* = 10.1Hz), 66.07, 63.03, 54.93, 53.74, 48.58, 47.96, 41.94, 39.39, 38.17, 24.69, 22.63, 16.46, 14.55, 9.94. HRMS (ESI) m/z calcd. for $C_{26}H_{32}FN_3O$ $[M+H]^+$: 422.2602; found: 422.2602.

[000111] Example 6. 1-(4-(2-methoxyethoxy)phenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,7,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(9H)-yl)butan-1-one.



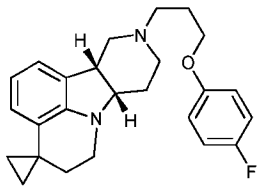
[000112] A mixture of 2-methoxyethan-1-ol (1.5 mL), 1-(4-fluorophenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,9, 10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(7H)-yl)butan-1-one (0.5 g, 1.3 mmol), N,N,N-trimethyl-1-phenylmethanaminium hydroxide (0.3 g, 1.7 mmol), and 85% KOH (0.1g, 1.5 mmol) is microwave heated at 150 °C for 3 hours under argon. After cooling to room temperature, the reaction mixture is evaporated to dryness. The residue is adjusted to pH 9 by adding aqueous NH_4Cl with agitation, and the resulting suspension is then extracted with dichloromethane three times (3 ×10 mL). The combined organic phase is dried over $MgSO_4$ and concentrated. The residue is purified by silica gel column chromatography using a gradient of 0 – 40% mixed solvents [dichloromethane /methanol/ 7N NH_3 in methanol (10 : 1 : 0.1 v/v)] in dichloromethane. The title product is obtained as a brown solid (0.4 g, yield 35%). MS (ESI) m/z 450.3 $[M+1]^+$.^{1}H NMR (500 MHz, MeOD) δ 8.05 – 7.95 (m, 2H), 7.09 – 6.99 (m, 2H), 6.61 (t, J = 7.7 Hz, 1H), 6.50 (d, J = 7.3 Hz, 1H), 6.43 (dd, J = 8.0, 0.9 Hz, 1H), 4.27 – 4.17 (m, 2H), 3.81 – 3.75 (m, 2H), 3.52 (ddd, J = 11.8, 10.1, 3.2 Hz, 1H), 3.44 (s, 3H), 3.38 (t, J = 3.0 Hz, 1H), 3.31 (d, J = 3.0 Hz, 2H), 3.29 (t, J = 2.9 Hz, 1H), 3.15 (ddd, J = 6.5, 4.2, 2.2 Hz, 1H), 3.08 (dt, J = 10.8, 6.3 Hz, 1H), 2.85 (s, 4H), 2.77 (td, J = 10.0, 2.8 Hz, 2H), 2.51 – 2.37 (m, 2H), 2.32 (td, J = 11.9, 3.0 Hz, 1H), 2.04 – 1.86 (m, 5H).

[000113] Example 7. 1-(4-fluorophenyl)-4-((7a'S,11a'R)-5',6',8',9',11',11a'-hexahydrospiro[cyclopropane-1,4'-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinolin]-10'(7a'H)-yl)butan-1-one.



[000114] The synthesis method is analogous to the synthesis of the compound of Example 8 according to Scheme 2 wherein 4-chloro-1-(4-fluorophenyl)butan-1-one is added in Step E instead of 1-(3-chloropropoxy)-4-fluorobenzene. 21% isolated yield. MS (ESI) m/z 405.31 $[M + H]^+$.

[000115] Example 8. (7a'S,11a'R)-10'-(3-(4-fluorophenoxy)propyl)-5',6',7a',8',9',10',11',11a'-octahydrospiro[cyclopropane-1,4'-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline].



[000116] Step A: (4aS,9bR)-ethyl 6-bromo-5-(but-3-en-1-yl)-3,4,4a,5-tetrahydro-1H-pyrido[4,3-b]indole-2(9bH)-carboxylate. A mixture of ethyl (4a*S*,9b*R*)-6-bromo-1,3,4,4a,5,9b-hexahydro-2*H*-pyrido[4,3-*b*]indole-2-carboxylate (6.51 g, 20.0 mmol), 4-bromo-1-butene (4.05 g, 30.0 mmol), DIPEA (5.17 g, 40.0 mmol), and KI (4.98 g, 30.0 mmol) in anhydrous dioxane (17 mL) is heated under an argon atmosphere at 110 °C for 48 hours. The reaction is cooled to room temperature and the solvent is removed under reduced pressure. The residue is suspended in DCM (200 mL) and washed with water (100 mL). The DCM phase is separated, dried over K_2CO_3, and concentrated to give a brown oil. This oil product is purified by silica gel column chromatography using a gradient of 0 – 70% ethyl acetate in hexane as an eluent. The title compound is obtained as a brown oil (3.6 g, 48% yield). MS (ESI) m/z 379.16 $[M + H]^+$.

[000117] Step B: ethyl (6bR,10aS)-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate. To a degassed solution of (4aS,9bR)-ethyl 6-bromo-5-(but-3-en-1-yl)-3,4,4a,5-tetrahydro-1H-pyrido[4,3-b]indole-2(9bH)-

carboxylate (850 mg, 2.24 mmol), K_2CO_3 (1.1 mg, 7.92 mmol), and tricyclohexylphosphine (59 mg, 0.21 mmol) in DMF (6 mL) is added $Pd(OAc)_2$ (24 mg, 0.11 mmol) under an argon atmosphere. The resulting mixture is stirred at 140 °C for 3 hours. After evaporation of the reaction solvent, the residue is purified by flash column chromatography on silica gel using a gradient of 0 – 30% ethyl acetate in hexane as an eluent. The title compound is obtained as a beige solid (200 mg, 30% yield). MS (ESI) m/z 299.13 $[M + H]^+$.

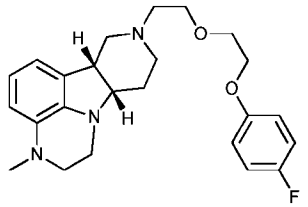
[000118] Step C: (7a'S,11a'R)-ethyl 5',6',8',9',11',11a'-hexahydrospiro[cyclopropane-1,4'-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline]-10'(7a'H)-carboxylate. CH_2I_2 (600 mg, 2.23 mmol) is added dropwise to a stirred solution of $ZnEt_2$ (1.5 M in toluene, 0.7 mL, 1.1 mmol) in dichloromethane (0.5 mL) at 0 °C under an argon atmosphere, and the mixture is stirred at 0 °C for 50 minutes. A solution of ethyl (6bR,10aS)-2-oxo-2,3,6b,9,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(7H)-carboxylate (165 mg, 0.553 mmol) in dichloromethane (0.5 mL) is added, and the resulting mixture is stirred at 0 °C for 4 hours. The reaction is then quenched with saturated NH_4Cl (0.5 mL) and neutralized with saturated $NaHCO_3$ (10 mL). The resulting solution is extracted with dichloromethane (20 mL) and the organic layer is evaporated to dryness. The residue is purified by silica gel column chromatography using a gradient of 0 – 100% of a mixture of ethyl acetate: methanol: 7 N NH_3 in methanol (10 : 1 : 0.1 v/v/v) in ethyl acetate as an eluent. The title compound is obtained as a beige solid (75 mg, 43% yield). MS (ESI) m/z 313.14 $[M + H]^+$.

[000119] Step D: (7a'S,11a'R)-5',6',7a',8',9',10',11',11a'-octahydrospiro[cyclopropane-1,4'-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline]. (7a'S,11a'R)-ethyl 5',6',8',9',11',11a'-hexahydrospiro[cyclopropane-1,4'-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline]-10'(7a'H)-carboxylate (70 g, 0.224 mmol) is suspended in saturated KOH in 90% EtOH solution (0.7 mL) at room temperature and microwave heated at 100 °C with stirring for 4 hours. The reaction is cooled to room temperature and ethyl acetate (20 mL) is added. The mixture is washed with water (10 mL), followed by brine (10 mL). The ethyl acetate phase is separated, dried over K_2CO_3 and concentrated. The residue is further dried over high vacuum to give the title compound as a beige solid (70 mg, yield > 100%). This crude product is used directly in the next step without any further purification. MS (ESI) m/z 241.17 $[M + H]^+$.

[000120] Step E: (7a'S,11a'R)-10'-(3-(4-fluorophenoxy)propyl)-5',6',7a',8',9',10',11',11a'-octahydrospiro[cyclopropane-1,4'-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline]. A mixture of

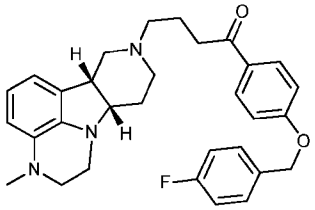
(7a'S,11a'R)-5',6',7a',8',9',10',11',11a'-octahydrospiro[cyclopropane-1,4'-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline] (20 mg, 0.083 mmol), 1-(3-chloropropoxy)-4-fluorobenzene (30 mg, 0.16 mmol) and KI (32 mg, 0.2 mmol) in DMF (0.4 mL) is bubbled with argon for 3 min, and then DIPEA (0.35 mL, 0.2 mmol) is added. The mixture is stirred at 75 °C for 2 hours, and then cooled to room temperature. The solvent is removed, and the residue is dissolved in DCM (5 mL) and washed with water (2 mL). The DCM phase is dried over K_2CO_3, and filtered, and the filtrate is concentrated. The residue is purified by HPLC to provide the final compound as a light orange oil (8 mg, 25% yield). MS (ESI) m/z 393.29 $[M + H]^+$.

[000121] Example 12. (6bR,10aS)-8-(2-(2-(4-fluorophenoxy)ethoxy)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline.



[000122] The synthesis method is analogous to the synthesis of the compound of Example 3 according to Scheme 3 wherein 1-(2-(2-chloroethoxy)ethoxy)-4-fluorobenzene is added instead of 3-chloro-1-(4-fluorophenyl)propan-1-one. 19% isolated yield. MS (ESI) m/z 412.2 $[M+1]^+$.

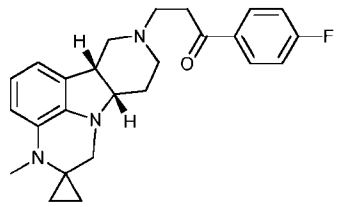
[000123] Example 13. 1-(4-((4-fluorobenzyl)oxy)phenyl)-4-((6bR,10aS)-3-methyl-2,3,6b,7,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin-8(9H)-yl)butan-1-one.



[000124] The synthesis method is analogous to the synthesis of the compound of Example 6 according to Scheme 4 wherein (4-fluorophenyl)methanol is added instead of 2-methoxyethan-1-ol. 68 % isolated yield. MS (ESI) m/z 500.3 $[M+1]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.95 (m, 2H), 7.47 – 7.39 (m, 2H), 7.15 – 7.07 (m, 2H), 7.04 – 6.98 (m, 2H), 6.67 (t, J = 7.6 Hz, 1H), 6.53 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 7.9, 0.9 Hz, 1H), 3.62 (ddd, J = 11.3, 9.8, 2.8 Hz, 1H), 3.31 (ddt, J = 18.9, 11.3, 2.9 Hz, 2H), 3.25 – 3.19 (m, 1H), 3.12 (s, 1H), 3.02 – 2.94 (m,

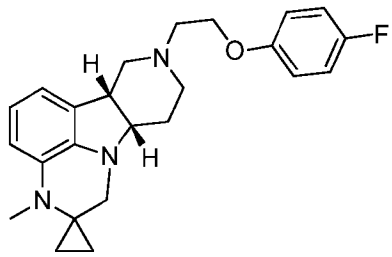
2H), 2.89 (s, 3H), 2.84 (td, J = 9.8, 2.7 Hz, 2H), 2.69 (s, 1H), 2.42 (s, 2H), 2.27 (s, 1H), 1.95 (d, J = 25.3 Hz, 6H), 1.28 (s, 1H), 0.93 – 0.83 (m, 1H).

[000125] Example 14. 1-(4-fluorophenyl)-3-((6b'R,10a'S)-3'-methyl-6b',7',10',10a'-tetrahydrospiro[cyclopropane-1,2'-pyrido[3',4':4,5]-pyrrolo[1,2,3-de]quinoxalin]-8'(1'H,3'H,9'H)-yl)propan-1-one.



[000126] The synthesis method is analogous to the synthesis of compound of Example 15 according to Scheme 1, wherein 3-chloro-1-(4-fluorophenyl)propan-1-one is added in Step C, instead of 1-(2-bromoethoxy)-4-fluorobenzene. 63% isolated yield. MS (ESI) m/z 406.32 [M + H]$^+$. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.9, 5.4 Hz, 2H), 7.13 (dd, J = 8.6, 8.6 Hz, 2H), 6.67 (d, J = 5.9 Hz, 2H), 6.61 (dd, J = 5.8, 3.2 Hz, 1H), 3.35 – 3.26 (m, 1H), 3.17 (s, 3H), 2.90 (t, J = 5.7 Hz, 2H), 2.87 – 2.81 (m, 2H), 2.70 (s, 3H), 2.69 – 2.63 (m, 1H), 2.42 (d, J = 9.9 Hz, 2H), 2.21 (t, J = 11.1 Hz, 1H), 1.96 – 1.85 (m, 2H), 1.26 (t, J = 7.1 Hz, 1H), 1.14 – 1.05 (m, 1H), 0.89 – 0.81 (m, 1H), 0.75 – 0.67 (m, 1H), 0.55 – 0.46 (m, 1H).

[000127] Example 15. (6b'R,10a'S)-8'-(2-(4-fluorophenoxy)ethyl)-3'-methyl-1',3',6b',7',8',9',10',10a'-octahydrospiro-[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].



[000128] Step A: (6b'R,10a'S)-ethyl 3'-methyl-3',6b',7',9',10',10a'-hexahydrospiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline]-8'(1'H)-carboxylate. Ethylmagnesium bromide (3.0 M in Et_2O, 13.6 mL, 10 mmol) is added dropwise to a vigorously stirred solution of (6bR,10aS)-ethyl 3-methyl-2-oxo-2,3,6b,7,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(9H)-carboxylate (4.29 g, 13.6 mmol) and titanium isopropoxide (6.1 mL, 20.6 mmol) in THF (40 mL). The solution is stirred at room

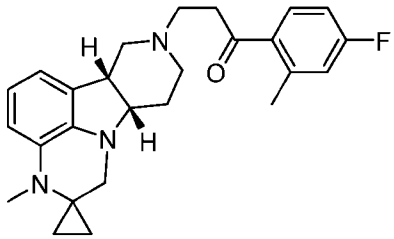
temperature for 24 hours and then quenched with saturated NH_4Cl (15 mL). The solvent is removed under reduced pressure and the residue is suspended in DCM (200 mL) and washed with water (100 mL). The DCM phase is separated, dried over K_2CO_3, and concentrated to give a brown oil. This crude oil is purified by silica gel column chromatography using a gradient of 0 – 100% ethyl acetate in hexane as an eluent. The title compound is obtained as a light brown solid (3.12 g, 70% yield). MS (ESI) m/z 328.16 $[M + H]^+$.

[000129] Step B: (6b'R,10a'S)-3'-methyl-1',3',6b',7',8',9',10',10a'-octahydrospiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline]. (6b'R,10a'S)-ethyl 3'-methyl-3',6b',7',9',10',10a'-hexahydrospiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline]-8'(1'H)-carboxylate (1.71 g, 5.22 mmol) is suspended in saturated KOH in 90% EtOH solution (17 mL) at room temperature and the reaction is microwave heated at 100 °C with stirring for 4 hours. The reaction is cooled to room temperature and then ethyl acetate (200 mL) is added. The mixture is washed with water (100 mL), followed by brine (100 mL). The ethyl acetate phase is separated, dried over K_2CO_3 and concentrated. The residue is further dried over high vacuum to give the title compound as a beige solid (1.0 g, 72% yield). This crude product is used directly in the next step without any further purification. MS (ESI) m/z 256.17 $[M + H]^+$.

[000130] Step C: (6b'R,10a'S)-8'-(2-(4-fluorophenoxy)ethyl)-3'-methyl-1',3',6b',7',8',9',10',10a'-octahydrospiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline]. A mixture of (6b'R,10a'S)-3'-methyl-1',3',6b',7',8',9',10',10a'-octahydrospiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline] (300 mg, 1.18 mmol), 1-(2-bromoethoxy)-4-fluorobenzene (309 mg, 1.41 mmol), and KI (195 mg, 1.18 mmol) in DMF (3 mL) is bubbled with argon for 3 minutes, and then DIPEA (0.41 mL, 2.35 mmol) is added. The mixture is stirred at 75 °C for 2 h, and then cooled to room temperature. The solvent is removed, and the residue is dissolved in DCM (30 mL) and washed with water (20 mL). The DCM phase is dried over K_2CO_3, and filtered, and the filtrate is concentrated. The obtained product is purified by silica gel column chromatography using a gradient of 0 – 100% ethyl acetate in hexane as an eluent. The final compound is obtained as a light brown oil (338 mg, 73% yield). MS (ESI) m/z 394.25 $[M + H]^+$. ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (dd, J = 9.2, 8.2 Hz, 2H), 6.89 – 6.82 (m, 2H), 6.70 – 6.65 (m, 2H), 6.64 – 6.59 (m, 1H), 4.08 (s, 2H), 3.34 – 3.27 (m, 1H), 3.22 (s, 1H), 2.96 (s, 1H), 2.89 – 2.82 (m, 1H), 2.79 (s, 3H), 2.70 (s, 3H), 2.42 (d, J = 9.9

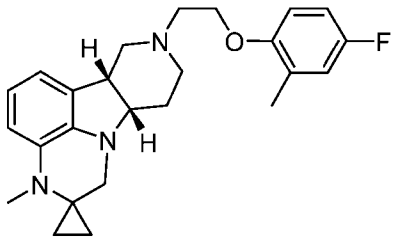
Hz, 2H), 2.25 (t, J = 10.3 Hz, 1H), 2.01 – 1.86 (m, 2H), 1.61 (s, 1H), 1.16 – 1.05 (m, 1H), 0.90 – 0.83 (m, 1H), 0.76 – 0.67 (m, 1H), 0.56 – 0.47 (m, 1H).

[000131] Example 16. 1-(4-fluoro-2-methylphenyl)-3-((6b'R,10a'S)-3'-methyl-6b',9',10',10a'-tetrahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxalin]-8'(7'H)-yl)propan-1-one.



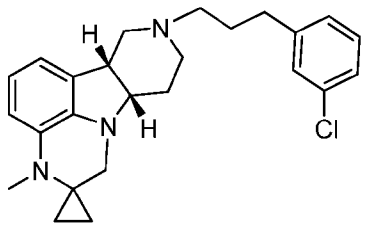
[000132] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1 wherein 3-chloro-1-(o-tolyl)propan-1-one was added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 30% isolated yield. MS (ESI) m/z 394.28 $[M + H]^+$.

[000133] Example 17. (6b'R,10a'S)-8'-(2-(4-fluoro-2-methylphenoxy)ethyl)-3'-methyl-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].



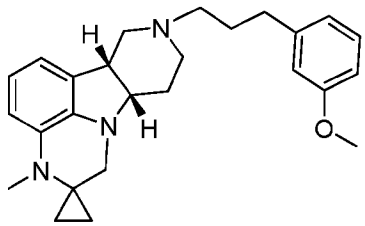
[000134] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1, wherein 1-(2-chloroethoxy)-2-methylbenzene is added in Step C, instead of 1-(2-bromoethoxy)-4-fluorobenzene. 33% isolated yield. MS (ESI) m/z 408.33 $[M + H]^+$.

[000135] Example 19. (6b'R,10a'S)-8'-(3-(3-chlorophenyl)propyl)-3'-methyl-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].



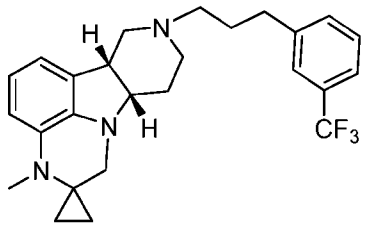
[000136] The synthesis method is analogous to the synthesis of compound of Example 15 according to Scheme 1 wherein 1-(3-bromopropyl)-3-chlorobenzene is added in Step C, instead of 1-(2-bromoethoxy)-4-fluorobenzene. 70% isolated yield. MS (ESI) m/z 408.29 $[M + H]^+$.

[000137] **Example 20. (6b'R,10a'S)-8'-(3-(3-methoxyphenyl)propyl)-3'-methyl-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].**



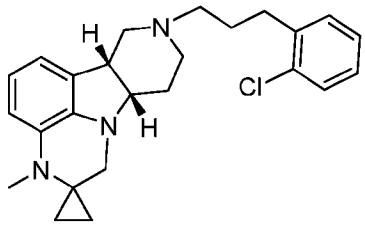
[000138] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1 wherein 1-(3-bromopropyl)-3- methoxybenzene is added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 70% isolated yield. MS (ESI) m/z 404.35 $[M + H]^+$.

[000139] **Example 21. (6b'R,10a'S)-3'-methyl-8'-(3-(3-(trifluoromethyl)phenyl)propyl)-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].**



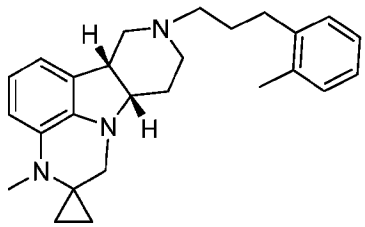
[000140] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1 wherein 1-(3-bromopropyl)-3-(trifluoromethyl)benzene is added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 58% isolated yield. MS (ESI) m/z 442.28 $[M + H]^+$.

[000141] Example 22. (6b'R,10a'S)-8'-(3-(2-chlorophenyl)propyl)-3'-methyl-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].



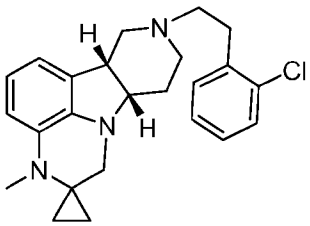
[000142] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1 wherein 1-(3-bromopropyl)-2-chlorobenzene is added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 80% isolated yield. MS (ESI) m/z 408.29 $[M + H]^+$.

[000143] Example 23. (6b'R,10a'S)-3'-methyl-8'-(3-(o-tolyl)propyl)-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].



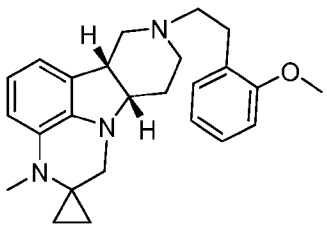
[000144] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1 wherein 1-(3-bromopropyl)-2-methylbenzene is added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 79% isolated yield. MS (ESI) m/z 388.35 $[M + H]^+$.

[000145] Example 24 (6b'R,10a'S)-8'-(2-chlorophenethyl)-3'-methyl-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].



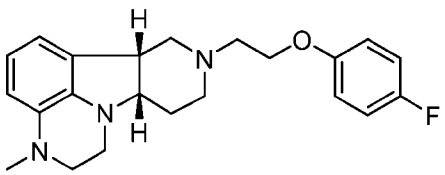
[000146] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1 wherein 1-(2-bromoethyl)-2-chlorobenzene is added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 39% isolated yield. MS (ESI) m/z 394.27 $[M + H]^+$.

[000147] **Example 25. (6b'R,10a'S)-8'-(2-methoxyphenethyl)-3'-methyl-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].**



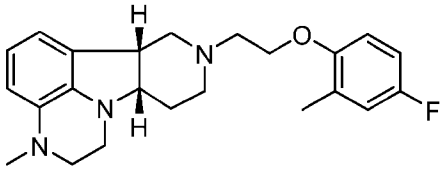
[000148] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1 wherein 1-(2-bromoethyl)-2-methoxybenzene is added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 66% isolated yield. MS (ESI) m/z 390.32 $[M + H]^+$.

[000149] **Example 26. (6b*R*,10a*S*)-8-(2-(4-fluorophenoxy)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline**



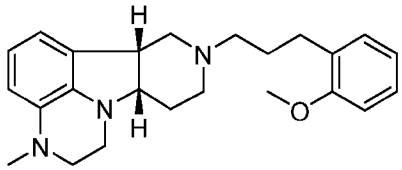
[000150] The synthesis method is analogous to Example 71, with 1-(2-bromoethoxy)-4-fluorobenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 75% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 – 6.92 (m, 2H), 6.89 – 6.79 (m, 2H), 6.66 (t, J = 7.6 Hz, 1H), 6.52 (d, J = 7.3 Hz, 1H), 6.41 (d, J = 7.8 Hz, 1H), 4.07 (td, J = 6.0, 1.2 Hz, 2H), 3.61 (ddd, J = 11.2, 9.9, 3.0 Hz, 1H), 3.32 (dt, J = 9.9, 2.9 Hz, 1H), 3.27 (dt, J = 11.3, 2.9 Hz, 1H), 3.25 – 3.16 (m, 2H), 2.95 (ddd, J = 11.3, 6.0, 1.9 Hz, 1H), 2.87 (s, 3H), 2.85 – 2.81 (m, 1H), 2.81 – 2.69 (m, 3H), 2.41 (dt, J = 11.2, 7.9 Hz, 1H), 2.12 (t, J = 11.0 Hz, 1H), 1.96 (dt, J = 7.3, 4.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4 (d, J = 239.4 Hz), 155.1, 138.1, 135.1, 130.1, 120.5, 115.9 (d, J = 37.8Hz), 115.8, 112.8, 109.1, 66.8, 64.5, 57.5, 57.0, 50.8, 49.6, 44.5, 41.8, 37.7, 25.1. HRMS (ESI) m/z calcd. for $C_{22}H_{26}N_3OF$ $[M+H]^+$: 368.2133; found: 368.2138.

[000151] Example 27. (6b*R*,10a*S*)-8-(2-(4-fluoro-2-methylphenoxy)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000152] The synthesis method is analogous to Example 71, with 1-(2-chloroethoxy)-4-fluoro-2-methylbenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 50% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 – 6.82 (m, 1H), 6.73 (dd, J = 8.9, 4.6 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 6.52 (dd, J = 7.4, 0.9 Hz, 1H), 6.41 (dd, J = 7.9, 0.9 Hz, 1H), 4.08 (td, J = 5.9, 1.2 Hz, 2H), 3.62 (ddd, J = 11.3, 10.0, 3.0 Hz, 1H), 3.32 (dt, J = 10.0, 2.9 Hz, 1H), 3.27 (dt, J = 11.3, 2.9 Hz, 1H), 3.25 – 3.14 (m, 2H), 3.03 – 2.95 (m, 1H), 2.87 (s, 2H), 2.86 – 2.74 (m, 3H), 2.56 – 2.36 (m, 1H), 2.20 (s, 2H), 2.16 (t, J = 11.1 Hz, 1H), 2.01 – 1.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1 (d, J = 239.4 Hz), 153.3, 138.1, 135.1, 130.1, 128.9 (d, J = 2.5 Hz), 120.5, 117.4 (d, J = 25.2 Hz), 112.8, 112.4 (d, J = 25.2 Hz), 112.2 (d, J = 12.6 Hz), 109.0, 67.4, 64.4, 57.6, 57.1, 50.8, 49.7, 44.5, 41.9, 37.7, 25.2, 16.6. HRMS (ESI) m/z calcd. for $C_{23}H_{28}N_3OF$ $[M+H]^+$: 382.2289; found: 382.2292.

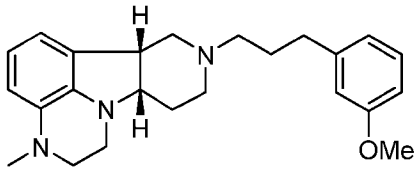
[000153] Example 28. (6b*R*,10a*S*)-8-(3-(2-methoxyphenyl)propyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000154] The synthesis method is analogous to Example 71, with 1-(3-chloropropyl)-2-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 69% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.07 (m, 2H), 6.94 – 6.78 (m, 2H), 6.65 (t, J = 7.6 Hz, 1H), 6.52 (dd, J = 7.5, 0.9 Hz, 1H), 6.40 (dd, J = 8.1, 0.9 Hz, 1H), 3.81 (s, 3H), 3.60 (ddd, J = 11.2, 9.9, 3.0 Hz, 1H), 3.31 (dt, J = 10.0, 2.9 Hz, 1H), 3.26 (dt, J = 11.3, 2.9 Hz, 1H), 3.24 – 3.21 (m, 1H), 3.20 – 3.13 (m, 1H), 2.96 – 2.88 (m, 1H), 2.87 (s, 3H), 2.83 (td, J = 9.9, 2.9 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.65 – 2.56 (m, 2H), 2.51 – 2.32 (m, 2H), 2.28 – 2.19 (m, 1H), 2.09 – 1.89 (m, 3H), 1.86 – 1.69 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 138.2, 135.1, 130.8, 130.3, 129.9, 127.1, 120.4, 120.4, 112.8, 110.3, 109.0, 64.8, 58.7, 56.5, 55.3, 50.8, 49.2, 44.5,

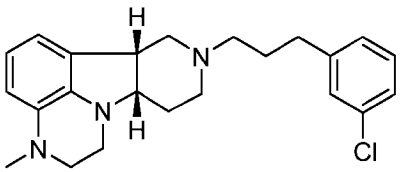
41.9, 37.7, 28.4, 27.2, 25.2. HRMS (ESI) m/z calcd. For $C_{24}H_{31}N_3O$ $[M+H]^+$: 378.2540; found: 378.2533.

[000155] Example 29. (6b*R*,10a*S*)-8-(3-(3-methoxyphenyl)propyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000156] The synthesis method is analogous to Example 71, with 1-(3-bromopropyl)-3-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 73% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (td, J = 7.7, 0.7 Hz, 1H), 6.78 (d, J = 1.2 Hz, 1H), 6.76 – 6.70 (m, 2H), 6.65 (t, J = 7.6 Hz, 1H), 6.52 (d, J = 1.0 Hz, 1H), 6.40 (dd, J = 7.9, 0.9 Hz, 1H), 3.80 (s, 3H), 3.69 – 3.48 (m, 1H), 3.31 (dt, J = 9.9, 2.9 Hz, 1H), 3.26 (dt, J = 11.3, 2.9 Hz, 1H), 3.26 – 3.19 (m, 1H), 3.20 – 3.13 (m, 1H), 2.90 – 2.87 (m, 1H), 2.87 (s, 3H), 2.82 (td, J = 9.9, 2.8 Hz, 1H), 2.73 – 2.64 (m, 1H), 2.61 (t, J = 6.8 Hz, 2H), 2.48 – 2.29 (m, 2H), 2.28 – 2.18 (m, 1H), 2.14 – 1.91 (m, 3H), 1.85 – 1.74 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 144.1, 138.1, 135.1, 130.3, 129.4, 121.0, 120.4, 114.3, 112.8, 111.2, 109.0, 64.7, 58.4, 56.5, 55.3, 50.8, 49.2, 44.5, 41.9, 37.7, 34.0, 28.7, 25.2. HRMS (ESI) m/z calcd. for $C_{24}H_{31}N_3O$ [M+H]+: 378.2540; found: 378.2529.

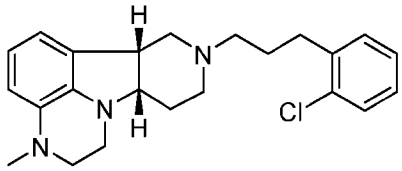
[000157] Example 30. (6b*R*,10a*S*)-8-(3-(3-chlorophenyl)propyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000158] The synthesis method is analogous to Example 71, with 1-(3-bromopropyl)-3-chlorobenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 72% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H), 7.17 – 7.12 (m, 1H), 7.10 – 7.01 (m, 1H), 6.65 (t, J = 7.6 Hz, 1H), 6.52 (dd, J = 7.4, 0.9 Hz, 1H), 6.41 (dd, J = 7.9, 0.9 Hz, 1H), 3.68 – 3.53 (m, 1H), 3.31 (dt, J = 9.9, 2.9 Hz, 1H), 3.27 (dt, J = 11.3, 2.9 Hz, 1H), 3.25 – 3.21 (m, 1H), 3.20 – 3.12 (m, 1H), 2.87 (s, 3H), 2.86 – 2.75 (m, 1H), 2.72 – 2.52 (m, 3H), 2.42 – 2.27 (m, 2H), 2.28 – 2.17 (m, 1H), 2.15 – 1.88 (m, 3H), 1.85 – 1.75 (m, 2H). ^{13}C NMR (126 MHz,

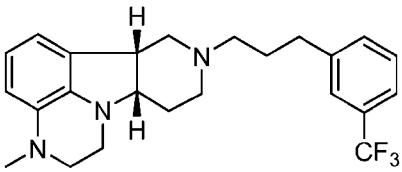
$CDCl_3$) δ 144.5, 138.1, 135.1, 134.2, 130.2, 129.7, 128.7, 126.7, 126.0, 120.4, 112.8, 109.0, 64.7, 58.1, 56.5, 50.8, 49.2, 44.5, 41.9, 37.7, 33.6, 28.6, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{28}ClN_3$ $[M+H]^+$: 382.2045; found: 382.2037.

[000159] Example 31. (6b*R*,10a*S*)-8-(3-(2-chlorophenyl)propyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000160] The synthesis method is analogous to Example 71, with 1-(3-bromopropyl)-2-chlorobenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 75% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, J = 7.8, 1.4 Hz, 1H), 7.22 (dd, J = 7.5, 1.9 Hz, 1H), 7.17 (td, J = 7.4, 1.4 Hz, 1H), 7.12 (td, J = 7.6, 1.9 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 6.52 (dd, J = 7.4, 0.9 Hz, 1H), 6.40 (dd, J = 7.9, 1.0 Hz, 1H), 3.66 – 3.54 (m, 1H), 3.31 (dt, J = 9.9, 2.9 Hz, 1H), 3.27 (dt, J = 11.3, 2.9 Hz, 1H), 3.25 – 3.20 (m, 1H), 3.20 – 3.12 (m, 1H), 2.92 – 2.88 (m, 1H), 2.87 (s, 3H), 2.83 (td, J = 9.9, 2.9 Hz, 1H), 2.79 – 2.71 (m, 2H), 2.71 – 2.63 (m, 1H), 2.53 – 2.31 (m, 2H), 2.30 – 2.17 (m, 1H), 2.12 – 1.91 (m, 3H), 1.88 – 1.75 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 138.1, 135.1, 134.1, 130.5, 130.3, 129.6, 127.4, 126.8, 120.4, 112.8, 109.0, 64.8, 58.3, 56.5, 50.8, 49.2, 44.5, 41.9, 37.7, 31.7, 27.2, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{28}ClN_3$ $[M+H]^+$: 382.2045; found: 382.2038.

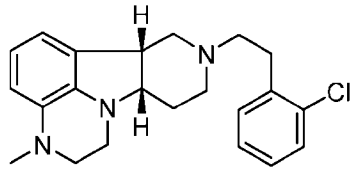
[000161] Example 32. (6b*R*,10a*S*)-3-methyl-8-(3-(3-(trifluoromethyl)phenyl)propyl)-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000162] The synthesis method is analogous to Example 71, with 1-(3-bromopropyl)-3-(trifluoromethyl)benzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 88% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 2H), 7.41 – 7.30 (m, 2H), 6.65 (t, J = 7.6 Hz, 1H), 6.52 (dd, J = 7.3, 0.9 Hz, 1H), 6.41 (dd, J = 8.0, 0.9 Hz, 1H), 3.67 – 3.54 (m, 1H), 3.31 (dt, J = 9.9, 3.0 Hz, 1H), 3.27 (dt, J = 11.3, 2.9 Hz, 1H), 3.25 – 3.20 (m, 1H), 3.20 – 3.12 (m, 1H), 2.87 (s, 3H), 2.86 – 2.79 (m, 2H), 2.70 (t, J = 6.8 Hz, 2H), 2.67 – 2.61 (m, 1H), 2.44 –

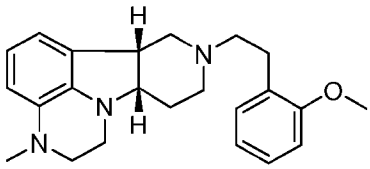
2.30 (m, 2H), 2.24 (td, J = 10.9, 4.5 Hz, 1H), 2.11 – 1.90 (m, 3H), 1.85 (p, J = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 138.1, 135.1, 132.0, 130.7 (q, J = 32.8), 130.2, 128.8, 125.3 (q, J = 3.8 Hz), 124.4 (q, J = 277.2 Hz), 122.8 (q, J = 3.8 Hz), 120.4, 112.8, 109.0, 64.7, 57.9, 56.5, 50.8, 49.2, 44.5, 41.9, 37.7, 33.7, 28.6, 25.2. HRMS (ESI) m/z calcd. for $C_{24}H_{28}F_3N_3$ $[M+H]^+$: 416.2308; found: 416.2298.

[000163] Example 33. (6b*R*,10a*S*)-8-(2-chlorophenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000164] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-2-chlorobenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 46% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, J = 7.7, 1.5 Hz, 1H), 7.23 (dd, J = 7.5, 1.9 Hz, 1H), 7.18 (td, J = 7.4, 1.5 Hz, 1H), 7.13 (td, J = 7.5, 1.9 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.55 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 8.0, 0.9 Hz, 1H), 3.68 – 3.55 (m, 1H), 3.33 (dt, J = 10.0, 3.0 Hz, 1H), 3.30 – 3.15 (m, 3H), 3.10 – 2.91 (m, 3H), 2.87 (s, 3H), 2.84 (td, J = 10.0, 2.9 Hz, 1H), 2.80 – 2.73 (m, 1H), 2.69 – 2.49 (m, 2H), 2.44 – 2.30 (m, 1H), 2.10 (t, J = 11.1 Hz, 1H), 2.04 – 1.92 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 138.2, 135.1, 134.2, 131.0, 130.2, 129.6, 127.6, 127.0, 120.4, 112.9, 109.1, 64.7, 58.7, 56.4, 50.8, 49.1, 44.5, 42.0, 37.7, 31.4, 25.2. HRMS (ESI) m/z calcd. for $C_{22}H_{26}ClN_3$ $[M+H]^+$: 368.1888; found: 368.1879.

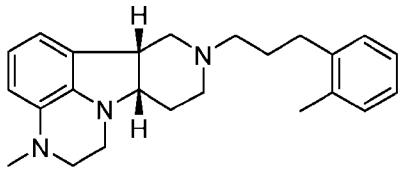
[000165] Example 34. (6b*R*,10a*S*)-8-(2-methoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000166] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-2-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 88% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (td, J = 7.8, 1.7 Hz, 1H), 7.14 (dd, J = 7.4, 1.8 Hz, 1H), 6.87 (td, J = 7.4, 1.1 Hz, 1H), 6.83 (dd, J = 8.2, 1.1 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.56 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 8.0, 0.9 Hz, 1H), 3.80 (s, 3H), 3.71 – 3.53 (m, 1H), 3.33

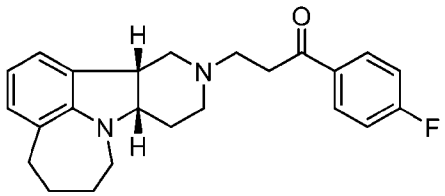
(dt, J = 10.0, 2.9 Hz, 1H), 3.31 – 3.15 (m, 3H), 3.11 – 2.98 (m, 1H), 2.88 (s, 3H), 2.87 – 2.71 (m, 4H), 2.71 – 2.48 (m, 2H), 2.44 – 2.29 (m, 1H), 2.06 (t, J = 10.7 Hz, 1H), 2.02 – 1.92 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 138.2, 135.1, 130.4, 130.4, 129.0, 127.4, 120.5, 120.4, 112.9, 110.4, 109.0, 64.8, 59.1, 56.4, 55.4, 50.8, 49.1, 44.5, 42.0, 37.7, 28.1, 25.3. HRMS (ESI) m/z calcd. for $C_{23}H_{29}N_3O$ $[M+H]^+$: 364.2383; found: 364.2375.

[000167] Example 35. (6b*R*,10a*S*)-3-methyl-8-(3-(o-tolyl)propyl)-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000168] The synthesis method is analogous to Example 71, with 1-(3-bromopropyl)-2-methylbenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 81% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 7.01 (m, 4H), 6.65 (t, J = 7.6 Hz, 1H), 6.52 (dd, J = 7.3, 0.9 Hz, 1H), 6.41 (dd, J = 7.9, 0.9 Hz, 1H), 3.68 – 3.51 (m, 1H), 3.32 (dt, J = 9.9, 2.9 Hz, 1H), 3.27 (dt, J = 11.3, 2.9 Hz, 1H), 3.25 – 3.21 (m, 1H), 3.20 – 3.13 (m, 1H), 2.96 – 2.88 (m, 1H), 2.87 (s, 3H), 2.83 (td, J = 9.9, 2.8 Hz, 1H), 2.73 – 2.66 (m, 1H), 2.68 – 2.57 (m, 2H), 2.51 – 2.34 (m, 2H), 2.31 (s, 3H), 2.28 – 2.19 (m, 1H), 2.07 – 1.90 (m, 3H), 1.85 – 1.70 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 138.1, 136.0, 135.1, 130.3, 128.9, 126.0, 126.0, 120.4, 112.8, 109.0, 64.7, 58.7, 56.6, 50.8, 49.2, 44.5, 41.9, 37.7, 31.2, 27.7, 25.2, 19.4. HRMS (ESI) m/z calcd. for $C_{24}H_{31}N_3$ $[M+H]^+$: 362.2591; found: 362.2582.

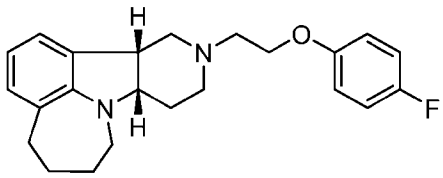
[000169] Example 36. 1-(4-fluorophenyl)-3-((8a*S*,12a*R*)-4,5,6,7,9,10,12,12a-octahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indol-11(8a*H*)-yl)propan-1-one



[000170] The synthesis method is analogous to Example 71, with 3-chloro-1-(4-fluorophenyl)propan-1-one and (8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole used in Step D. 46% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 – 7.86 (m, 1H), 7.19 – 7.05 (m, 1H), 6.92 (ddd, J = 12.4, 7.4, 1.3 Hz, 1H), 6.68 (t, J = 7.4 Hz, 0H), 3.32 – 3.22 (m, 2H), 3.21 – 3.18 (m, 1H), 3.17 – 3.10 (m, 1H), 2.94 – 2.87 (m, 1H), 2.86 – 2.73

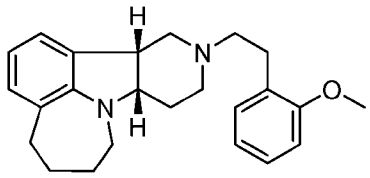
(m, 3H), 2.73 – 2.61 (m, 2H), 2.49 (td, *J* = 12.1, 2.0 Hz, 1H), 2.37 (td, *J* = 11.8, 2.9 Hz, 1H), 2.15 – 1.95 (m, 3H), 1.94 – 1.84 (m, 2H), 1.81 – 1.71 (m, 1H), 1.67 – 1.49 (m, 1H). 13C NMR (126 MHz, CDCl3) δ 197.8, 165.9 (d, J = 252 Hz), 152.9, 133.6 (d, J = 2.5 Hz), 133.4, 130.9 (d, J = 12.6 Hz), 129.7, 127.4, 121.1, 119.4, 115.8 (d, J = 25.2 Hz), 64.1, 57.4, 53.5, 52.0, 49.4, 41.1, 36.4, 35.4, 30.2, 27.3, 26.0. HRMS (ESI) m/z calcd. for $C_{24}H_{27}FN_2O$ $[M+H]^+$: 379.2180; found: 379.2170.

[000171] Example 37. (8a*S*,12a*R*)-11-(2-(4-fluorophenoxy)ethyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole



[000172] The synthesis method is analogous to Example 71, with 1-(2-bromoethoxy)-4-fluorobenzene and (8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole used in Step D. 72% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 6.88 (m, 4H), 6.88 – 6.77 (m, 2H), 6.69 (t, *J* = 7.3 Hz, 1H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.34 – 3.23 (m, 2H), 3.22 – 3.15 (m, 1H), 2.99 – 2.83 (m, 2H), 2.76 (dq, *J* = 11.8, 5.7 Hz, 3H), 2.65 (ddd, *J* = 14.8, 11.6, 2.3 Hz, 1H), 2.57 – 2.46 (m, 1H), 2.41 (td, *J* = 11.7, 3.2 Hz, 1H), 2.14 – 1.85 (m, 5H), 1.82 – 1.69 (m, 1H), 1.64 – 1.48 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5 (d, *J* = 239.4 Hz), 155.1, 153.0, 133.4, 129.7, 127.4, 121.1, 119.4, 115.9 (d, *J* = 37.8 Hz), 115.8, 66.8, 64.0, 58.0, 57.6, 52.0, 49.9, 41.0, 35.4, 30.2, 27.3, 25.9. HRMS (ESI) m/z calcd. for $C_{23}H_{27}FN_2O$ $[M+H]^+$: 379.2180; found: 379.2171.

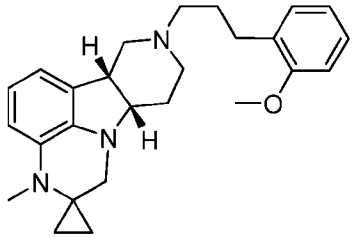
[000173] Example 38. (8a*S*,12a*R*)-11-(2-methoxyphenethyl)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrid[4,3-*b*]indole



[000174] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-2-methoxybenzene and (8a*S*,12a*R*)-4,5,6,7,8a,9,10,11,12,12a-decahydroazepino[3,2,1-*hi*]pyrido[4,3-*b*]indole used in Step D. 83% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (td, *J* = 7.7, 1.8 Hz, 1H), 7.13 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.97 (dd, *J* = 7.3, 1.3 Hz, 1H), 6.92 (dd, *J*

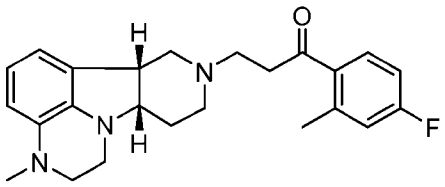
= 7.5, 1.2 Hz, 1H), 6.87 (td, *J* = 7.4, 1.1 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.1 Hz, 1H), 6.70 (t, *J* = 7.4 Hz, 1H), 3.80 (s, 3H), 3.46 – 3.25 (m, 2H), 3.24 – 3.16 (m, 1H), 3.06 – 2.88 (m, 2H), 2.86 – 2.74 (m, 3H), 2.73 – 2.62 (m, 1H), 2.59 – 2.44 (m, 3H), 2.35 (td, *J* = 11.7, 3.2 Hz, 1H), 2.17 – 1.93 (m, 4H), 1.85 (t, *J* = 11.2 Hz, 1H), 1.82 – 1.71 (m, 1H), 1.65 – 1.48 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.7, 153.0, 133.7, 130.4, 129.6, 129.0, 127.4, 127.3, 121.2, 120.5, 119.4, 110.4, 64.3, 59.1, 57.4, 55.4, 52.0, 49.4, 41.2, 35.4, 30.2, 28.2, 27.3, 26.0. HRMS (ESI) m/z calcd. for $C_{24}H_{30}N_2O$ $[M+H]^+$: 363.2431; found: 363.2421.

[000175] Example 39. (6b'R,10a'S)-8'-(3-(2-methoxyphenyl)propyl)-3'-methyl-6b',7',8',9',10',10a'-hexahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline].



[000176] The synthesis method is analogous to the synthesis of the compound of Example 15 according to Scheme 1 wherein 1-(3-chloropropyl)-2-methoxybenzene is added in Step C instead of 1-(2-bromoethoxy)-4-fluorobenzene. 76% isolated yield. MS (ESI) m/z 404.36 $[M + H]^+$.

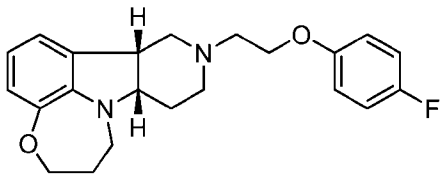
[000177] Example 41. 1-(4-fluoro-2-methylphenyl)-3-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)propan-1-one



[000178] The synthesis method is analogous to Example 71, with 3-chloro-1-(4-fluoro-2-methylphenyl)propan-1-one added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 27% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.60 (m, 1H), 7.05 – 6.82 (m, 2H), 6.76 – 6.58 (m, 1H), 6.50 (dd, *J* = 7.4, 0.9 Hz, 1H), 6.40 (dd, *J* = 8.0, 0.9 Hz, 1H), 3.60 (ddd, *J* = 11.3, 9.9, 2.9 Hz, 1H), 3.43 – 3.24 (m, 2H), 3.23 – 3.17 (m, 1H), 3.17 – 2.99 (m, 3H), 2.87 (s, 3H), 2.86 – 2.70 (m, 4H), 2.69 – 2.61 (m, 1H), 2.50 (s, 3H), 2.33 (td, *J* = 11.6, 3.4 Hz, 1H), 2.04 (t, *J*

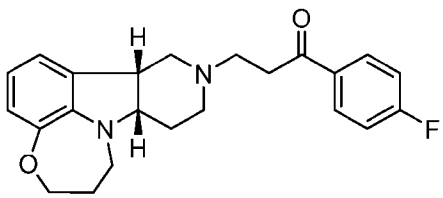
= 11.1 Hz, 1H), 1.99 – 1.80 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.2, 164.0 (d, J = 253.3 Hz), 142.2 (d, J = 8.8 Hz), 138.1, 135.1, 134.3 (d, J = 3.8 Hz), 131.0 (d, J = 8.8 Hz), 130.0, 120.5, 118.8 (d, J = 21.4 Hz), 112.8, 112.6 (d, J = 21.4 Hz), 109.1, 64.6, 56.4, 53.8, 50.8, 49.1, 44.5, 41.9, 39.3, 37.7, 25.2, 21.7. HRMS (ESI) m/z calcd. for $C_{24}H_{28}FN_3O$ $[M+H]^+$: 394.2289; found: 394.2284.

[000179] Example 42. (8a*S*,12a*R*)-11-(2-(4-fluorophenoxy)ethyl)-6,7,8a,9,10,11,12,12a-octahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indole



[000180] The synthesis method is analogous to Example 71, with 1-(2-bromoethoxy)-4-fluorobenzene and (8a*S*,12a*R*)-6,7,8a,9,10,11,12,12a-octahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indole used in Step D. 45% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 – 6.92 (m, 2H), 6.90 – 6.83 (m, 2H), 6.81 – 6.75 (m, 2H), 6.75 – 6.66 (m, 1H), 4.56 – 4.35 (m, 1H), 4.06 (t, J = 5.9 Hz, 1H), 3.94 – 3.69 (m, 1H), 3.44 – 3.34 (m, 0H), 3.34 – 3.28 (m, 1H), 3.27 – 3.22 (m, 1H), 3.03 – 2.84 (m, 1H), 2.84 – 2.64 (m, 3H), 2.62 – 2.49 (m, 1H), 2.40 (td, J = 11.6, 3.3 Hz, 1H), 2.24 – 1.78 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5 (d, J = 239.4 Hz), 155.1, 146.7, 142.9, 135.5, 120.6, 119.6, 117.7, 115.9 (d, J = 37.8 Hz), 115.8, 72.0, 66.8, 64.1, 57.7, 57.5, 50.3, 49.7, 41.5, 31.1, 25.5. HRMS (ESI) m/z calcd. for $C_{22}H_{25}N_2O_2F$ $[M+H]^+$: 369.1973; found: 369.1965.

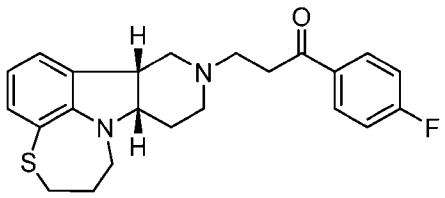
[000181] Example 43. 1-(4-fluorophenyl)-3-((8a*S*,12a*R*)-6,7,9,10,12,12a-hexahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indol-11(8a*H*)-yl)propan-1-one



[000182] The synthesis method is analogous to Example 71, with 3-chloro-1-(4-fluorophenyl)propan-1-one and (8a*S*,12a*R*)-6,7,8a,9,10,11,12,12a-octahydro-5*H*-[1,4]oxazepino[2,3,4-*hi*]pyrido[4,3-*b*]indole used in Step D. 44% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 7.90 (m, 1H), 7.20 – 7.02 (m, 1H), 6.88 – 6.73 (m, 1H), 6.73 – 6.60 (m, 1H), 4.59 – 4.29 (m, 1H), 3.97 – 3.65 (m, 1H), 3.49 – 3.31 (m, 1H), 3.33 – 3.20 (m, 2H), 3.20 –

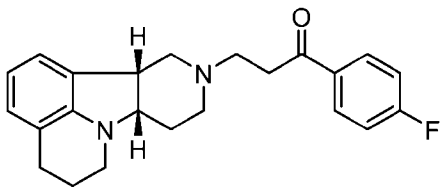
3.06 (m, 2H), 2.93 – 2.73 (m, 3H), 2.72 – 2.64 (m, 1H), 2.61 – 2.48 (m, 1H), 2.46 – 2.31 (m, 1H), 2.18 – 2.00 (m, 3H), 1.95 – 1.81 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 165.9 (d, J = 252 Hz), 146.8, 142.9, 135.5, 133.6 (d, J = 3.8 Hz), 130.9 (d, J = 12.6 Hz), 120.6, 119.6, 117.7, 115.9 (d, J = 12.6 Hz), 72.0, 64.2, 57.1, 53.4, 50.3, 49.2, 41.6, 36.3, 31.1, 25.6. HRMS (ESI) m/z calcd. for $C_{23}H_{25}N_2O_2F$ $[M+H]^+$: 381.1973; found: 381.1967.

[000183] Example 44. 1-(4-fluorophenyl)-3-((8a*S*,12a*R*)-6,7,9,10,12,12a-hexahydro-5*H*-pyrido[4,3-*b*][1,4]thiazepino[2,3,4-*hi*]indol-11(8a*H*)-yl)propan-1-one



[000184] The synthesis method is analogous to Example 71, with 3-chloro-1-(4-fluorophenyl)propan-1-one and (8a*S*,12a*R*)-6,7,8a,9,10,11,12,12a-octahydro-5*H*-pyrido[4,3-*b*][1,4]thiazepino[2,3,4-*hi*]indole used in Step D. 25% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 7.91 (m, 2H), 7.18 – 7.04 (m, 2H), 6.95 (dd, J = 7.8, 1.2 Hz, 1H), 6.89 – 6.82 (m, 1H), 6.68 – 6.52 (m, 1H), 3.88 – 3.73 (m, 1H), 3.67 – 3.48 (m, 1H), 3.33 – 3.24 (m, 1H), 3.20 – 3.11 (m, 3H), 3.09 – 3.03 (m, 1H), 3.00 – 2.90 (m, 1H), 2.87 – 2.73 (m, 3H), 2.69 – 2.63 (m, 1H), 2.37 (td, J = 11.4, 3.3 Hz, 1H), 2.23 – 2.07 (m, 1H), 2.06 – 1.96 (m, 2H), 1.94 – 1.79 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 165.9 (d, J = 252 Hz), 152.3, 133.7, 133.6 (d, J = 2.5 Hz), 130.9 (d, J = 12.6 Hz), 129.0, 121.3, 119.9, 119.8, 115.9 (d, J = 12.6 Hz), 63.9, 56.7, 53.5, 49.3, 47.3, 41.0, 36.4, 32.1, 30.6, 25.8. HRMS (ESI) m/z calcd. for $C_{23}H_{25}N_2OFS$ $[M+H]^+$: 397.1744; found: 397.1738.

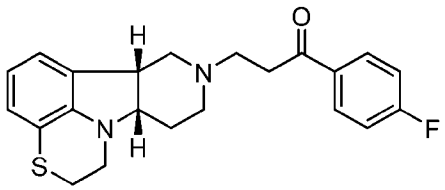
[000185] Example 45. 1-(4-fluorophenyl)-3-((7a*S*,11a*R*)-5,6,8,9,11,11a-hexahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinolin-10(7a*H*)-yl)propan-1-one



[000186] The synthesis method is analogous to Example 71, with 3-chloro-1-(4-fluorophenyl)propan-1-one and (7a*S*,11a*R*)-5,6,7a,8,9,10,11,11a-octahydro-4*H*-pyrido[3',4':4,5]pyrrolo[3,2,1-*ij*]quinoline used in Step D. 30% isolated yield. ^{1}H NMR (500

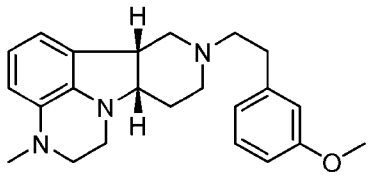
MHz, $CDCl_3$) δ 8.12 – 7.84 (m, 2H), 7.19 – 7.05 (m, 2H), 7.01 – 6.80 (m, 2H), 6.63 (t, J = 7.4 Hz, 1H), 3.43 – 3.23 (m, 2H), 3.21 – 3.09 (m, 3H), 3.01 – 2.75 (m, 3H), 2.75 – 2.61 (m, 3H), 2.53 (td, J = 10.2, 3.6 Hz, 1H), 2.38 (td, J = 11.7, 3.2 Hz, 1H), 2.24 – 2.04 (m, 3H), 2.03 – 1.96 (m, 1H), 1.95 – 1.85 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 165.9 (d, J= 252 Hz), 149.8,133.6 (d, J = 25.2 Hz), 131.0, 130.9 (d, J = 12.6 Hz), 126.9, 121.0, 120.6, 118.7, 115.8 (d, J = 25.2 Hz), 64.0, 56.3, 53.5, 49.1, 44.7, 41.1, 36.4, 25.1, 24.3, 23.2. HRMS (ESI) m/z calcd. for $C_{23}H_{25}N_2OF$ $[M+H]^+$: 365.2024; found: 365.2019.

[000187] Example 46. 1-(4-fluorophenyl)-3-((6b*R*,10a*S*)-1,2,6b,9,10,10a-hexahydropyrido[4,3-*b*][1,4]thiazino[2,3,4-*hi*]indol-8(7*H*)-yl)propan-1-one



[000188] The synthesis method is analogous to Example 71, with 3-chloro-1-(4-fluorophenyl)propan-1-one and (6b*R*,10a*S*)-1,2,6b,7,8,9,10,10a-octahydropyrido[4,3-*b*][1,4]thiazino[2,3,4-*hi*]indole used in Step D. 29% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 – 7.93 (m, 2H), 7.19 – 7.06 (m, 2H), 6.96 – 6.75 (m, 2H), 6.64 (t, J = 7.5 Hz, 1H), 3.68 – 3.54 (m, 1H), 3.53 – 3.44 (m, 1H), 3.38 – 3.32 (m, 1H), 3.23 – 3.12 (m, 3H), 3.09 – 3.03 (m, 1H), 3.01 – 2.90 (m, 1H), 2.89 – 2.74 (m, 3H), 2.71 – 2.57 (m, 1H), 2.33 (td, J = 11.4, 3.3 Hz, 1H), 2.06 (t, J = 11.0 Hz, 1H), 2.01 – 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.7, 165.9 (d, J = 252 Hz), 145.1, 133.6 (d, J = 12.6 Hz), 131.7, 130.9 (d, J = 12.6 Hz), 124.4 (d, J = 12.6 Hz), 119.9, 119.7, 116.3, 115.9 (d, J = 12.6 Hz), 63.6, 56.1, 53.4, 49.0, 43.8, 40.4, 36.3, 27.4, 25.0. HRMS (ESI) m/z calcd. for $C_{22}H_{23}N_2OFS$ $[M+H]^+$: 383.1588; found: 383.1582.

[000189] Example 71. (6b*R*,10a*S*)-8-(3-methoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000190] Step A: (6b*R*,10a*S*)-ethyl 3-methyl-2-oxo-2,3,6b,7,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(9*H*)-carboxylate. A suspension of ethyl (4aS,9bR)-6-bromo-1,3,4,4a,5,9b-hexahydro-2H-pyrido[4,3-b]indole-2-carboxylate (25 g, 76.9

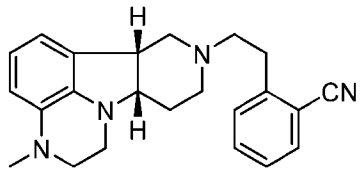
mmol), N-methyl chloroacetamide (12.4 g, 115.3 mmol, 1.5 eq.), potassium iodide (19.2 g, 116 mmol), and diisopropylethylamine (26.6 mL, 153.1 mmol, 2.0 eq.) in dioxane (63 mL) is refluxed for 48 hours. The reaction mixture is then cooled to about 80 °C, and at this temperature copper iodide (2.92 g, 15.4 mmol, 0.2 eq.), potassium carbonate (23.3 g, 168.2 mmol, 2.2 eq.), dimethylethylenediamine (4.96 mL, 46.1 mmol, 0.6 eq.), and additional dioxane (38 mL) are added. The resulting mixture is re-heated to reflux for 24 hours, and then it is cooled to 40 °C. The cooled mixture is poured onto a plug of flash-grade silica gel (63 g) and eluted under vacuum with 6.25 L of ethyl acetate. The eluent is concentrated to a solid residue (320 g), and then redissolved in hot ethanol (80 ml). This mixture is allowed to cool to ambient temperature and stirred overnight, and then cooled to 0-5°C, aged for 1h and filtered. The filtered cake is washed with cold ethanol (15 ml) and allowed to air dry to afford the title compound (17.0 g, 70% yield) as a white solid. ^{1}HNMR (300MHz, $CDCl_3$) 1.28(t, J = 6.9Hz, 3H), 1.86-1.96(m, 2H), 2.72(br, 1H), 3.09-3.48(m, 7H), 3.86-4.21(m, 5H), 6.75(dd, J = 1.2, 7.8Hz, 1H), 6.82(t, J= 7.8Hz, 1H), 6.90(dd, J = 1.2, 7.2Hz, 1H). MS (ESI) m/z 316.2 $[M + H]^+$.

[000191] Step B: (6bR,10aS)-ethyl 3-methyl-2,3,6b,7,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo-[1,2,3-de]quinoxaline-8(9H)-carboxylate. To a suspension of (6bR,10aS)-ethyl 3-methyl-2-oxo-2,3,6b,7,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline-8(9H)-carboxylate (21.8 g, 69.13 mmol) in 50 ml of THF under argon at room temperature is added a 1 M solution of BH_3-THF complex in THF (196 mL, 196.2 mmol, 2.8 eq.) slowly through an addition funnel. The resultant clear solution is stirred at 60 °C for 20 hours and then it is cooled in an ice bath to about 10 °C. To the cooled mixture is added MeOH (33 mL) slowly through an addition funnel while keeping the internal temperature below 25 °C. The resultant mixture is stirred in the ice bath for about 30 minutes, and then it is concentrated in vacuo to afford a yellow paste. The crude paste is then partitioned between EtOAc (218 mL) and water (218 mL). The separated organic layer is dried over (Na_2SO_4), filtered, and concentrated under reduced pressure to afford the title compound (20.76 g, 99% yield) as a yellow liquid. ^{1}HNMR ($CDCI_3$, 300 MHz) δ 1.28 (t, J = 7.0Hz, 3H), 1.79-1.95 (m, 2H), 2.74-2.92 (m, 5H), 3.02-3.22 (m, 2H), 3.22-3.38 (m, 3H), 3.54-3.64 (m, 1H), 3.78-4.24 (m, 4H), 6.41(d, J = 7.8Hz, 1H), 6.54 (d, J = 7.2Hz, 1H), 6.66 (t, J = 7.7Hz, 1H); ^{13}CNMR ($CDCl_3$, 75 MHz) δ 14.9, 24.7, 37.7, 39.9, 41.4, 44.4, 45.8, 50.7, 61.4, 65.0, 109.3, 113.3, 120.6, 128.8, 135.1, 138.2, 155.6.

[000192] Step C: (6b*R*,10a*S*)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo-[1,2,3-*de*]quinoxaline: (6bR,10aS)-ethyl 3-methyl-2,3,6b,7,10,10a-hexahydro-1H-pyrido[3',4':4,5]pyrrolo-[1,2,3-de]quinoxaline-8(9H)-carboxylate (18.5 g, 57 mmol), KOH (12.7 g, 226 mmol), and *n*-butanol (90 mL) are placed in a 300 mL pressure bottle and heated in an oil bath at 120 °C for 3 hours. After *n*-butanol is removed under vacuum, the residue is treated with water (300 mL) and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase is washed with brine (2 × 200 mL), dried over anhydrous Na_2SO_4, and then evaporated to dryness to afford the title compound (11.7 g, 91% yield) as a dense oil, which is used in the next step without further purification.

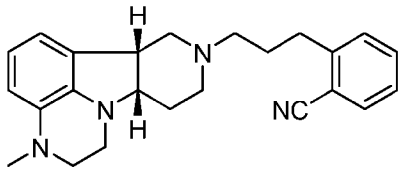
[000193] Step D: (6b*R*,10a*S*)-8-(3-methoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido-[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline**:** A mixture of (6b*R*,10a*S*)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo-[1,2,3-*de*]quinoxaline hydrochloric salt (266 mg, 1.0 mmol), 1-(2-bromoethyl)-3-methoxybenzene (323 mg, 1.5 mmol) and K_2CO_3 (415 mg, 3.0 mmol) in dioxane (1.5 mL) is bubbled with argon for 3 minutes. The resulting mixture is heated to 80 °C and stirred at this temperature for 24 hours. The solvent is removed, and the residue is dissolved in DCM (30 mL) and washed with water (20 mL). The DCM phase is dried over K_2CO_3, filtered, and concentrated. The obtained residue is purified with silica gel column chromatography using a gradient of 0–55% mixture of ethyl acetate: methanol: 7 N NH_3 in methanol (10:1:0.1 v/v/v) in ethyl acetate as an eluent. The title compound is obtained as a light orange oil (200 mg, 55% yield). ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 1H), 6.78 (dt, J = 7.3, 1.2 Hz, 1H), 6.74 (dd, J = 6.5, 1.2 Hz, 2H), 6.67 (t, J = 7.6 Hz, 1H), 6.54 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 7.9, 1.0 Hz, 1H), 3.79 (s, 3H), 3.69 – 3.51 (m, 1H), 3.32 (dt, J = 10.0, 2.9 Hz, 1H), 3.29 – 3.22 (m, 2H), 3.22 – 3.15 (m, 1H), 3.11 – 2.93 (m, 1H), 2.87 (s, 3H), 2.86 – 2.73 (m, 4H), 2.60 (q, J = 11.2 Hz, 2H), 2.35 (s, 1H), 2.22 – 2.02 (m, 1H), 1.98 (s, 2H). ^{13}CNMR (126 MHz, $CDCl_3$) δ 159.8, 142.3, 138.1, 135.2, 130.2, 129.5, 121.3, 120.5, 114.6, 112.8, 111.4, 109.1, 64.7, 60.8, 56.4, 55.3, 50.8, 49.2, 44.5, 41.9, 37.7, 33.8, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{29}N_3O$ $[M+H]^+$: 364.2383; found: 364.2391.

[000194] **Example 75. 2-(2-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]-quinoxalin-8(7*H*)-yl)ethyl)benzonitrile**



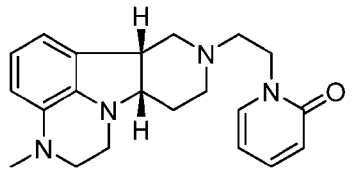
[000195] The synthesis method is analogous to Example 71, with 2-(2-bromoethyl)benzonitrile added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 52% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 7.7, 1.4 Hz, 1H), 7.51 (td, J = 7.6, 1.4 Hz, 1H), 7.34 (dd, J = 7.9, 1.2 Hz, 1H), 7.29 (td, J = 7.6, 1.2 Hz, 1H), 6.66 (t, J = 7.7 Hz, 1H), 6.53 (d, J = 7.3 Hz, 1H), 6.41 (dd, J = 8.0, 0.9 Hz, 1H), 3.69 – 3.49 (m, 1H), 3.44 – 3.21 (m, 3H), 3.20 – 3.13 (m, 1H), 3.13 – 3.01 (m, 2H), 3.00 – 2.90 (m, 1H), 2.87 (s, 3H), 2.85 – 2.73 (m, 1H), 2.73 – 2.59 (m, 2H), 2.41 (td, J = 11.3, 3.8 Hz, 1H), 2.13 (t, J = 11.1 Hz, 1H), 2.00 – 1.86 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 138.2, 135.1, 132.9, 132.9, 130.1, 130.1, 126.7, 120.4, 118.2, 112.9, 112.8, 109.1, 64.6, 59.5, 56.4, 50.8, 48.8, 44.5, 41.9, 37.7, 32.2, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{26}N_4$ $[M+H]^+$: 359.223; found: 359.2226.

[000196] **Example 76. 2-(3-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline-8(7*H*)-yl)propyl)benzonitrile**



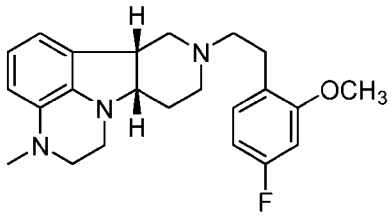
[000197] The synthesis method is analogous to Example 71, with 2-(3-bromopropyl)benzonitrile added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 68% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, J = 7.7, 1.4 Hz, 1H), 7.50 (td, J = 7.7, 1.4 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.31 – 7.26 (m, 1H), 6.64 (t, J = 7.6 Hz, 1H), 6.57 – 6.49 (m, 1H), 6.40 (dd, J = 7.9, 0.9 Hz, 1H), 3.64 – 3.53 (m, 1H), 3.30 (dt, J = 9.9, 2.9 Hz, 1H), 3.26 (dt, J = 11.3, 2.9 Hz, 1H), 3.24 – 3.19 (m, 1H), 3.19 – 3.11 (m, 1H), 2.96 (s, 1H), 2.93 – 2.87 (m, 2H), 2.86 (s, 3H), 2.85 – 2.79 (m, 1H), 2.73 – 2.60 (m, 1H), 2.53 – 2.32 (m, 2H), 2.31 – 2.17 (m, 1H), 2.10 – 1.82 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.5, 138.1, 135.1, 132.9, 132.8, 129.7, 126.5, 120.4, 118.2, 112.8, 112.5, 109.0, 64.7, 57.9, 56.5, 50.8, 49.1, 44.5, 41.9, 37.7, 36.6, 32.5, 28.2, 25.2. HRMS (ESI) m/z calcd. for $C_{24}H_{28}N_4$ $[M+H]^+$: 373.2387; found: 373.2382.

[000198] **Example 77. 1-(2-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)ethyl)pyridin-2(1*H*)-one**



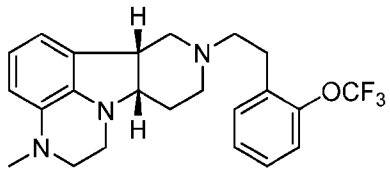
[000199] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)pyridin-2(1*H*)-one added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 9% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (dd, J = 6.9, 2.0 Hz, 1H), 7.31 (ddd, J = 8.9, 6.6, 2.1 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 6.53 (dt, J = 9.1, 1.0 Hz, 1H), 6.48 (d, J = 7.3 Hz, 1H), 6.39 (dd, J = 8.0, 0.9 Hz, 1H), 6.14 (td, J = 6.7, 1.4 Hz, 1H), 3.58 (ddd, J = 12.8, 8.3, 2.3 Hz, 1H), 3.31 – 3.24 (m, 2H), 3.23 – 3.15 (m, 4H), 2.92 (td, J = 11.1, 7.7 Hz, 1H), 2.85 (s, 3H), 2.84 – 2.67 (m, 4H), 2.49 (q, J = 9.5 Hz, 1H), 2.20 (t, J = 11.1 Hz, 1H), 1.94 (dt, J = 7.4, 3.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7, 139.7, 138.6, 137.9, 135.2, 120.80, 120.6, 112.7, 109.2, 105.8, 64.2, 54.7, 50.6, 49.2, 47.1, 44.4, 42.9, 41.5, 37.6, 24.8. HRMS (ESI) m/z calcd. for $C_{21}H_{26}N_4O$ $[M+H]^+$: 351.2179; found: 351.2175.

[000200] **Example 78. (6b*R*,10a*S*)-8-(4-fluoro-2-methoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline**



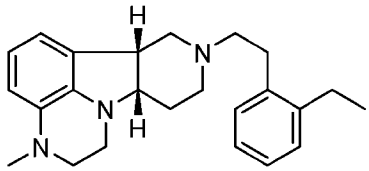
[000201] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-4-fluoro-2-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 65% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 6.94 (m, 1H), 6.66 (dd, J = 7.9, 7.4 Hz, 1H), 6.62 – 6.49 (m, 3H), 6.41 (dd, J = 7.9, 1.0 Hz, 1H), 3.78 (s, 3H), 3.68 – 3.52 (m, 1H), 3.32 (dt, J = 10.1, 2.9 Hz, 1H), 3.29 – 3.12 (m, 3H), 3.11 – 2.97 (m, 1H), 2.87 (s, 3H), 2.86 – 2.72 (m, 4H), 2.63 – 2.42 (m, 2H), 2.40 – 2.26 (m, 1H), 2.04 (t, J = 11.1 Hz, 1H), 2.01 – 1.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, J = 244.4 Hz), 158.5 (d, J = 8.8 Hz), 138.2, 135.3, 130.7 (d, J = 8.8 Hz), 130.1, 124.0, 120.1, 112.9, 109.0, 106.5 (d, J = 21.4 Hz), 98.8 (d, J = 25.2 Hz), 64.8, 59.1, 56.4, 55.6, 50.8, 49.2, 44.5, 42.0, 37.7, 27.6, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{28}N_3OF$ $[M+H]^+$: 382.2289; found: 382.2281.

[000202] Example 80. (6b*R*,10a*S*)-3-methyl-8-(2-(trifluoromethoxy)phenethyl)-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000203] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-2-(trifluoromethoxy)benzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 83% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, J = 7.6, 2.4 Hz, 1H), 7.24 – 7.11 (m, 3H), 6.67 (t, J = 7.6 Hz, 1H), 6.54 (dd, J = 7.3, 1.0 Hz, 1H), 6.42 (dd, J = 7.9, 0.9 Hz, 1H), 3.66 – 3.56 (m, 1H), 3.33 (dt, J = 10.0, 2.9 Hz, 1H), 3.28 (dt, J = 11.4, 2.9 Hz, 1H), 3.25 – 3.23 (m, 2H), 3.23 – 3.17 (m, 1H), 3.02 – 2.93 (m, 1H), 2.92 – 2.88 (m, 2H), 2.88 (s, 3H), 2.84 (td, J = 10.0, 2.9 Hz, 1H), 2.79 – 2.73 (m, 1H), 2.66 – 2.52 (m, 2H), 2.47 – 2.33 (m, 1H), 2.09 (t, J = 11.1 Hz, 1H), 2.03 – 1.89 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 138.2, 135.1, 133.1, 131.3, 130.2, 127.6, 126.9, 120.8 (q, J = 252 Hz), 120.6, 120.5, 112.9, 109.1, 64.7, 59.0, 56.4, 50.8, 49.0, 44.5, 42.0, 37.7, 27.6, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{26}N_3OF_3$ $[M+H]^+$: 418.2101; found: 418.2097. HRMS (ESI) m/z calcd. for $C_{23}H_{26}N_3OF_3$ $[M+H]^+$: 418.2101; found: 418.2097.

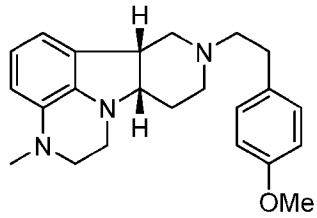
[000204] Example 81. (6b*R*,10a*S*)-8-(2-ethylphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000205] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-2-ethylbenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 64% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.07 (m, 4H), 6.68 (t, J = 7.6 Hz, 1H), 6.56 (d, J = 7.3 Hz, 1H), 6.43 (dd, J = 8.0, 0.9 Hz, 1H), 3.66 – 3.58 (m, 1H), 3.33 (dt, J = 10.0, 2.9 Hz, 1H), 3.31 – 3.15 (m, 3H), 3.10 – 2.97 (m, 1H), 2.88 (s, 3H), 2.87 – 2.81 (m, 3H), 2.81 – 2.76 (m, 1H), 2.66 (q, J = 7.6 Hz, 2H), 2.61 – 2.46 (m, 2H), 2.43 – 2.28 (m, 1H), 2.07 (t, J = 11.0 Hz, 1H), 2.02 – 1.92 (m, 2H), 1.22 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2, 138.2, 138.0, 135.1, 130.2, 129.8, 128.6, 126.5, 126.0, 120.5, 112.9, 109.1, 64.8, 60.6, 56.5, 50.8, 49.3, 44.6,

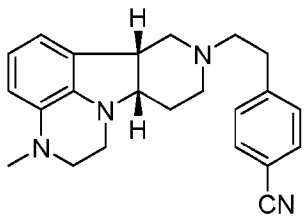
42.0, 37.7, 30.4, 25.7, 25.3, 15.7. HRMS (ESI) m/z calcd. for $C_{24}H_{31}N_3$ $[M+H]^+$: 362.2591; found: 362.2588.

[000206] Example 82. (6b*R*,10a*S*)-8-(4-methoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]-pyrrolo[1,2,3-*de*]quinoxaline



[000207] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-4-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 36% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 – 6.95 (m, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.67 (t, J = 7.6 Hz, 1H), 6.54 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 7.9, 0.9 Hz, 1H), 3.78 (s, 3H), 3.69 – 3.54 (m, 1H), 3.32 (dt, J = 10.0, 3.0 Hz, 1H), 3.30 – 3.17 (m, 3H), 3.12 – 2.95 (m, 1H), 2.88 (s, 3H), 2.86 – 2.71 (m, 4H), 2.71 – 2.48 (m, 2H), 2.44 – 2.26 (m, 1H), 2.06 (t, J = 11.0 Hz, 1H), 2.02 – 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.1, 138.1, 135.2, 132.6, 130.1, 129.7, 120.5, 114.0, 112.8, 109.1, 64.7, 61.1, 56.4, 55.4, 50.8, 49.2, 44.5, 41.9, 37.7, 32.8, 25.1. HRMS (ESI) m/z calcd. for $C_{23}H_{29}N_3O$ $[M+H]^+$: 364.2383; found: 364.2380.

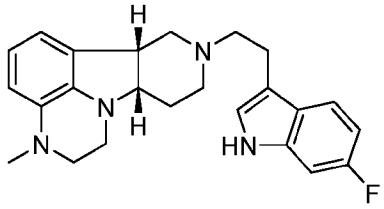
[000208] Example 84. 4-(2-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)ethyl)benzonitrile



[000209] The synthesis method is analogous to Example 71, with 4-(2-bromoethyl)benzonitrile added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 30% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.4 Hz, 2H), 7.39 – 7.27 (m, 2H), 6.66 (t, J = 7.6 Hz, 1H), 6.52 (d, 1H), 6.42 (dd, J = 8.0, 0.9 Hz, 1H), 3.61 (ddd, J = 11.3, 9.8, 2.9 Hz, 1H), 3.32 (dt, J = 9.9, 2.9 Hz, 1H), 3.30 – 3.21 (m, 2H), 3.17 (dt, J = 12.5, 6.3 Hz, 1H), 2.99 – 2.90 (m, 1H), 2.87 (s, 3H), 2.86 – 2.80 (m, 3H), 2.75 – 2.67 (m, 1H), 2.65 – 2.46 (m, 2H), 2.35 (td, J = 11.0, 3.4 Hz, 1H), 2.07 (t, J = 11.1 Hz, 1H), 2.00 – 1.84 (m, 2H). ^{13}C NMR (126 MHz,

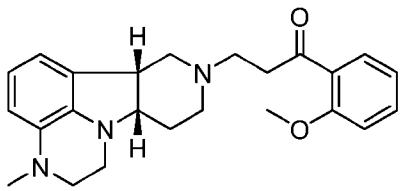
$CDCl_3$) δ 146.5, 138.1, 135.2, 132.3, 130.0, 129.7, 120.5, 119.2, 112.7, 110.1, 109.1, 64.6, 60.0, 56.4, 50.8, 49.2, 44.5, 41.9, 37.7, 33.9, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{26}N_4$ $[M+H]^+$: 359.2230; found: 359.2227.

[000210] Example 85. (6b*R*,10a*S*)-8-(2-(6-fluoro-1*H*-indol-3-yl)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000211] The synthesis method is analogous to Example 71, with 3-(2-bromoethyl)-6-fluoro-1*H*-indole added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 9% isolated yield. ^{1}H NMR (500 MHz, CDCl3) δ 8.05 (d, J = 26.6 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.04 (d, J = 2.3 Hz, 1H), 6.92 (td, J = 9.0, 2.5 Hz, 1H), 6.71 – 6.64 (m, 1H), 6.56 (dd, J = 7.3, 0.9 Hz, 1H), 6.43 (dd, J = 7.9, 0.9 Hz, 1H), 3.62 (ddd, J = 11.4, 9.9, 3.0 Hz, 1H), 3.34 (dt, J = 10.0, 3.0 Hz, 1H), 3.31 – 3.18 (m, 3H), 3.03 (ddd, J = 11.1, 6.1, 1.9 Hz, 1H), 2.98 – 2.90 (m, 3H), 2.88 (s, 3H), 2.85 (td, J = 10.0, 2.9 Hz, 1H), 2.73 – 2.61 (m, 2H), 2.38 (dp, J = 11.1, 7.7 Hz, 1H), 2.10 (dd, J = 11.5, 10.5 Hz, 1H), 2.00 (q, J = 3.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 157.1, 138.4, 135.4, 133.1, 130.4, 123.7, 120.7, 115.1, 113.1, 112.0 (d, J = 8.8 Hz), 110.7 (d, J = 26.5 Hz), 109.4, 104.1 (d, J = 23.9 Hz), 65.0, 59.8, 56.7, 51.1, 49.6, 44.8, 42.5, 38.0, 25.5, 23.3. HRMS (ESI) m/z calcd. for $C_{24}H_{27}N_4F$ $[M+H]^+$: 391.2293; found: 391.2285.

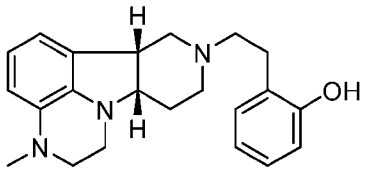
[000212] Example 86. 1-(2-methoxyphenyl)-3-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)propan-1-one



[000213] The synthesis method is analogous to Example 71, with 3-bromo-1-(2-methoxyphenyl)propan-1-one added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 36% isolated yield. ^{1}H NMR (500 MHz, DMSO) δ 7.70 – 7.43 (m, 2H), 7.15 (d, J = 8.3 Hz, 1H), 7.01 (td, J = 7.4, 1.0 Hz, 1H), 6.51 (t, J = 7.6 Hz, 1H), 6.40 (d, J = 7.3 Hz, 1H), 6.36 – 6.27 (m, 1H), 3.87 (s, 3H), 3.57 – 3.38 (m, 1H), 3.36 – 3.21 (m, 3H), 3.16 – 3.03 (m, 3H), 3.03 – 2.94 (m,

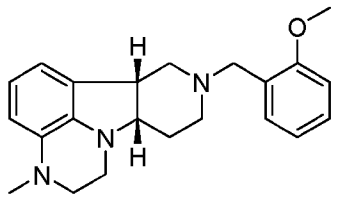
1H), 2.78 (s, 3H), 2.73 – 2.59 (m, 4H), 2.27 – 2.11 (m, 1H), 1.94 – 1.82 (m, 2H), 1.79 – 1.64 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 201.3, 157.8, 137.6, 134.8, 133.4, 129.4, 128.2, 120.4, 119.8, 112.3, 108.6, 63.8, 55.7, 53.0, 49.9, 48.5, 43.8, 40.8, 40.6, 37.1, 24.2. HRMS (ESI) m/z calcd. for $C_{24}H_{29}N_3O_2$ $[M+H]^+$: 392.2333; found: 392.2326.

[000214] Example 89. 2-(2-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quino-xalin-8(7*H*)-yl)ethyl)phenol



[000215] The synthesis method is analogous to Example 71, with 2-(2-bromoethyl)phenol added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 10% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.07 (m, 1H), 6.99 (dd, J = 7.5, 1.7 Hz, 1H), 6.90 (dd, J = 8.0, 1.3 Hz, 1H), 6.75 (td, J = 7.4, 1.3 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.52 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 8.0, 0.9 Hz, 1H), 3.71 – 3.51 (m, 1H), 3.43 – 3.20 (m, 4H), 3.19 – 3.05 (m, 1H), 3.01 – 2.92 (m, 1H), 2.88 (s, 3H), 2.87 – 2.77 (m, 3H), 2.76 – 2.58 (m, 2H), 2.49 (td, J = 11.8, 3.6 Hz, 1H), 2.31 – 1.96 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 137.9, 135.3, 131.0, 129.3, 128.4, 127.9, 120.8, 119.0, 117.8, 112.8, 109.2, 64.3, 59.4, 56.3, 50.7, 49.2, 44.6, 41.4, 37.6, 31.7, 24.7. HRMS (ESI) m/z calcd. for $C_{22}H_{27}N_3O$ $[M+H]^+$: 350.2227; found: 350.2220.

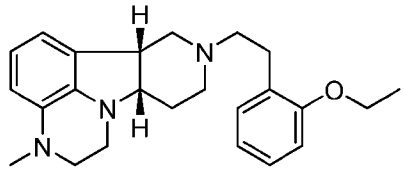
[000216] Example 90. (6b*R*,10a*S*)-8-(2-methoxybenzyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000217] The synthesis method is analogous to Example 71, with 1-(bromomethyl)-2-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 35% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, J = 7.4, 1.8 Hz, 1H), 7.25 – 7.17 (m, 1H), 6.95 (td, J = 7.4, 1.1 Hz, 1H), 6.86 (dd, J = 8.2, 1.1 Hz, 1H), 6.75 – 6.57 (m, 1H), 6.50 (dd, J = 7.3, 1.0 Hz, 1H), 6.40 (dd, J = 7.9, 1.0 Hz, 1H), 3.80 (s, 3H), 3.65 – 3.58 (m, 1H), 3.55 (q, 2H), 3.32 (dt, J = 10.0, 3.0 Hz, 1H), 3.29 – 3.16 (m, 3H), 2.99 – 2.89 (m, 1H), 2.87 (s, 3H), 2.82 (td, J = 9.9, 2.9 Hz, 1H), 2.74 – 2.64 (m, 1H), 2.33 (td, J = 11.1, 4.3 Hz, 1H), 2.06 (t, J = 10.9 Hz, 1H),

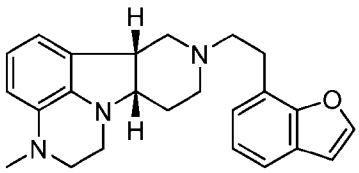
1.97 – 1.83 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 138.2, 135.1, 130.6, 130.4, 128.0, 127.0, 120.5, 120.3, 113.0, 110.6, 108.9, 64.8, 56.6, 56.4, 55.6, 50.8, 49.2, 44.5, 42.0, 37.7, 25.2. HRMS (ESI) m/z calcd. for $C_{22}H_{27}N_3O$ $[M+H]^+$: 350.2227; found: 350.2219.

[000218] Example 91. (6b*R*,10a*S*)-8-(2-ethoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000219] The synthesis method is analogous to Example 71, with 1-(2-chloroethyl)-2-ethoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 78% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.05 (m, 1H), 6.86 (td, J = 7.4, 1.1 Hz, 1H), 6.81 (dd, J = 8.1, 1.1 Hz, 0H), 6.67 (t, 0H), 6.55 (dd, J = 7.4, 0.9 Hz, 0H), 6.42 (dd, J = 7.9, 1.0 Hz, 0H), 4.02 (q, J = 7.0 Hz, 2H), 3.75 – 3.48 (m, 1H), 3.33 (dt, J = 10.1, 2.9 Hz, 1H), 3.30 – 3.15 (m, 3H), 3.10 – 2.95 (m, 1H), 2.88 (s, 3H), 2.87 – 2.78 (m, 4H), 2.76 – 2.51 (m, 2H), 2.49 – 2.22 (m, 1H), 2.08 (t, J = 11.0 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 138.2, 135.1, 130.4, 130.3, 129.1, 127.3, 120.4, 112.9, 111.3, 109.0, 64.8, 63.5, 59.1, 56.5, 50.8, 49.0, 44.6, 42.0, 37.7, 28.1, 25.3, 15.1. HRMS (ESI) m/z calcd. for $C_{24}H_{31}N_3O$ $[M+H]^+$: 378.2540; found: 378.2531.

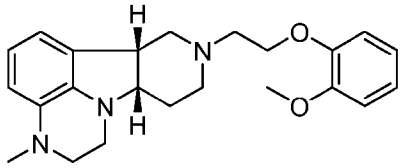
[000220] Example 92. (6b*R*,10a*S*)-8-(2-(benzofuran-7-yl)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000221] The synthesis method is analogous to Example 71, with 7-(2-chloroethyl)benzofuran added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 37% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, J = 2.2 Hz, 1H), 7.44 (dd, J = 7.6, 1.4 Hz, 1H), 7.22 – 7.07 (m, 2H), 6.75 (d, J = 2.2 Hz, 1H), 6.67 (t, J = 7.3 Hz, 1H), 6.56 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 7.9, 0.9 Hz, 1H), 3.62 (ddd, J = 11.4, 10.0, 3.1 Hz, 1H), 3.33 (dt, J = 10.1, 3.0 Hz, 1H), 3.31 – 3.19 (m, 3H), 3.21 – 3.09 (m, 2H), 3.10 – 2.99 (m, 1H), 2.88 (s, 3H), 2.87 – 2.81 (m, 2H), 2.78 – 2.68 (m, 2H), 2.50 – 2.32 (m, 1H), 2.12 (t, J = 11.0 Hz, 1H), 2.06 – 1.91 (m,

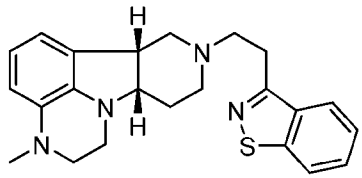
2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 144.7, 138.2, 135.1, 130.3, 127.3, 124.7, 124.3, 123.0, 120.4, 119.2, 112.9, 109.1, 106.9, 64.7, 58.9, 56.4, 50.8, 49.1, 44.5, 42.0, 37.7, 27.8, 25.2. HRMS (ESI) m/z calcd. for $C_{24}H_{27}N_3O$ $[M+H]^+$: 374.2227; found: 374.2236.

[000222] Example 93. (6b*R*,10a*S*)-8-(2-(2-methoxyphenoxy)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000223] The synthesis method is analogous to Example 71, with 1-(2-bromoethoxy)-2-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 32% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 – 6.81 (m, 4H), 6.65 (t, 1H), 6.52 (dd, J = 7.4, 0.9 Hz, 1H), 6.41 (dd, J = 8.1, 0.9 Hz, 1H), 4.18 (t, J = 6.5 Hz, 2H), 3.85 (s, 3H), 3.73 – 3.47 (m, 1H), 3.32 (dt, J = 10.0, 2.9 Hz, 1H), 3.27 (dt, J = 11.3, 2.8 Hz, 1H), 3.24 – 3.17 (m, 2H), 3.07 – 2.92 (m, 1H), 2.87 (s, 3H), 2.86 – 2.75 (m, 4H), 2.56 – 2.32 (m, 1H), 2.15 (t, J = 11.0 Hz, 1H), 2.02 – 1.85 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 148.5, 138.1, 135.1, 130.1, 121.4, 121.0, 120.4, 113.8, 112.9, 112.1, 109.1, 67.1, 64.5, 57.3, 57.0, 56.1, 50.8, 49.6, 44.5, 41.8, 37.7, 25.1. HRMS (ESI) m/z calcd. for $C_{23}H_{29}N_3O_2$ $[M+H]^+$: 380.2333; found: 380.2327.

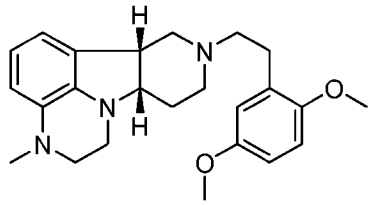
[000224] Example 94. 3-(2-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)ethyl)benzo[*d*]isothiazole



[000225] The synthesis method is analogous to Example 71, with 3-(2-bromoethyl)benzo[*d*]isothiazole added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 67% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.58 – 7.47 (m, 1H), 7.46 – 7.38 (m, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.55 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 8.0, 0.9 Hz, 1H), 3.67 – 3.54 (m, 3H), 3.39 – 3.31 (m, 5H), 3.30 – 3.16 (m, 3H), 3.08 – 2.98 (m, 1H), 2.98 – 2.90 (m, 2H), 2.88 (s, 3H), 2.86 – 2.77 (m, 2H), 2.44 (td, J = 10.9, 4.9 Hz, 1H), 2.16 (t, J = 11.0 Hz, 1H), 2.03 – 1.90 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.1, 152.5, 138.2, 135.1, 134.9, 130.1, 127.7, 124.6, 123.4, 120.5, 120.1,

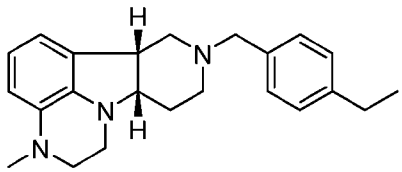
112.9, 109.1, 64.6, 56.8, 56.4, 50.8, 49.2, 44.5, 41.9, 37.7, 29.5, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{26}N_4S$ $[M+H]^+$: 391.1951; found: 391.1960.

[000226] Example 95. (6b*R*,10a*S*)-8-(2,5-dimethoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000227] The synthesis method is analogous to Example 71, with 2-(2-bromoethyl)-1,4-dimethoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 39% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 – 6.73 (m, 2H), 6.71 – 6.63 (m, 2H), 6.55 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 8.0, 0.9 Hz, 1H), 3.75 (d, J = 2.9 Hz, 6H), 3.71 – 3.50 (m, 1H), 3.33 (dt, J = 10.0, 2.9 Hz, 1H), 3.30 – 3.17 (m, 3H), 3.06 – 2.93 (m, 1H), 2.87 (s, 3H), 2.86 – 2.73 (m, 4H), 2.66 – 2.45 (m, 2H), 2.43 – 2.25 (m, 1H), 2.06 (t, J = 11.1 Hz, 1H), 2.01 – 1.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.6, 152.0, 138.2, 135.1, 130.3, 130.3, 120.4, 116.8, 112.9, 111.4, 111.3, 109.0, 64.8, 59.1, 56.4, 56.1, 55.8, 50.8, 49.1, 44.5, 42.0, 37.7, 28.3, 25.3. HRMS (ESI) m/z calcd. for $C_{24}H_{31}N_3O_2$ $[M+H]^+$: 394.2489; found: 394.2484.

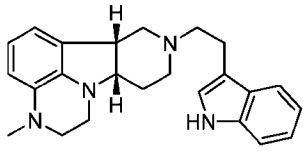
[000228] Example 96. (6b*R*,10a*S*)-8-(4-ethylbenzyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000229] The synthesis method is analogous to Example 71, with 1-(bromomethyl)-4-ethylbenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 30% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.74 – 6.56 (m, 1H), 6.49 (dd, J = 7.4, 0.9 Hz, 1H), 6.41 (dd, J = 7.9, 0.9 Hz, 1H), 3.68 – 3.51 (m, 1H), 3.45 (d, J = 2.4 Hz, 2H), 3.31 (dt, J = 9.9, 3.0 Hz, 1H), 3.29 – 3.21 (m, 2H), 3.20 – 3.13 (m, 1H), 2.87 (s, 3H), 2.86 – 2.79 (m, 2H), 2.65 (q, J = 7.5 Hz, 3H), 2.43 – 2.11 (m, 1H), 1.99 (t, J = 11.2 Hz, 1H), 1.95 – 1.87 (m, 2H), 1.25 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.0, 138.2, 136.0, 135.1, 130.3, 129.3, 127.8, 120.3, 113.0, 109.0, 64.8, 63.2, 56.5, 50.8, 49.1, 44.5,

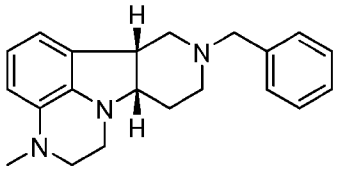
41.9, 37.7, 28.7, 25.2, 15.7. HRMS (ESI) m/z calcd. for $C_{23}H_{29}N_3$ $[M+H]^+$: 348.2434; found: 348.2428.

[000230] Example 97. (6b*R*,10a*S*)-8-(2-(1*H*-indol-3-yl)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000231] The synthesis method is analogous to Example 71, with 3-(2-bromoethyl)-1*H*-indole added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 31% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.74 – 7.48 (m, 1H), 7.40 – 7.30 (m, 1H), 7.23 – 7.15 (m, 1H), 7.13 – 7.07 (m, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 6.57 (dd, J = 7.3, 0.9 Hz, 1H), 6.43 (dd, J = 8.0, 0.9 Hz, 1H), 3.73 – 3.52 (m, 1H), 3.34 (dt, J = 10.1, 2.9 Hz, 1H), 3.31 – 3.19 (m, 3H), 3.12 – 3.03 (m, 1H), 3.00 (t, 2H), 2.88 (s, 3H), 2.87 – 2.79 (m, 2H), 2.78 – 2.58 (m, 2H), 2.45 – 2.31 (m, 1H), 2.24 – 2.07 (m, 1H), 2.03 – 1.96 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 136.4, 135.1, 130.2, 127.7, 122.1, 121.6, 120.5, 119.3, 119.0, 114.7, 112.9, 111.2, 109.1, 64.7, 59.6, 56.5, 50.8, 49.2, 44.5, 41.9, 37.7, 25.2, 23.0. HRMS (ESI) m/z calcd. for $C_{24}H_{28}N_4$ [M+H]+: 373.2387; found: 373.2378.

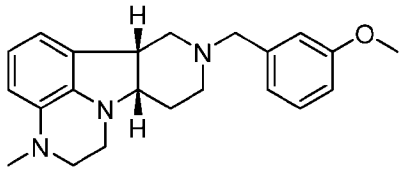
[000232] Example 100. (6b*R*,10a*S*)-8-benzyl-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000233] The synthesis method is analogous to Example 71, with 1-(bromomethyl)benzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 31% isolated yield. ^{1}H NMR (500 MHz, CDCl3) δ 7.39 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 6.75 – 6.58 (m, 1H), 6.48 (dd, J = 7.4, 0.9 Hz, 1H), 6.41 (dd, J = 8.0, 0.9 Hz, 1H), 3.65 – 3.55 (m, 1H), 3.49 (q, J = 3.2 Hz, 2H), 3.32 (dt, J = 9.9, 3.0 Hz, 1H), 3.29 – 3.21 (m, 2H), 3.20 – 3.14 (m, 1H), 2.87 (s, 3H), 2.87 – 2.80 (m, 2H), 2.71 – 2.57 (m, 1H), 2.45 – 2.20 (m, 1H), 2.01 (t, J = 11.1 Hz, 1H), 1.95 – 1.87 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.2, 135.1, 130.3, 129.3, 128.3, 127.0, 120.3,

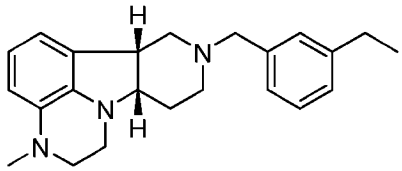
112.9, 109.0, 64.8, 63.5, 56.5, 50.8, 49.2, 44.5, 41.9, 37.7, 25.2. HRMS (ESI) m/z calcd. for $C_{21}H_{25}N_3$ $[M+H]^+$: 320.2121; found: 320.2116.

[000234] Example 101. (6b*R*,10a*S*)-8-(3-methoxybenzyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000235] The synthesis method is analogous to Example 71, with 1-(bromomethyl)-3-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 59% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, J = 8.0 Hz, 1H), 7.02 – 6.87 (m, 2H), 6.83 – 6.76 (m, 1H), 6.64 (t, J = 7.6 Hz, 1H), 6.48 (dd, J = 7.4, 0.9 Hz, 1H), 6.41 (dd, J = 7.9, 0.9 Hz, 1H), 3.82 (s, 3H), 3.66 – 3.56 (m, 1H), 3.46 (s, 2H), 3.32 (dt, J = 9.9, 3.0 Hz, 1H), 3.29 – 3.22 (m, 2H), 3.21 – 3.11 (m, 1H), 2.87 (s, 3H), 2.86 – 2.78 (m, 1H), 2.72 – 2.58 (m, 1H), 2.37 – 2.18 (m, 1H), 2.01 (t, J = 11.1 Hz, 1H), 1.96 – 1.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 140.6, 138.2, 135.1, 130.3, 129.3, 121.6, 120.3, 114.6, 113.0, 112.6, 109.0, 64.8, 63.4, 56.5, 55.3, 50.8, 49.2, 44.5, 41.9, 37.7, 25.2. HRMS (ESI) m/z calcd. for $C_{22}H_{27}N_3O$ $[M+H]^+$: 350.2227; found: 350.222.

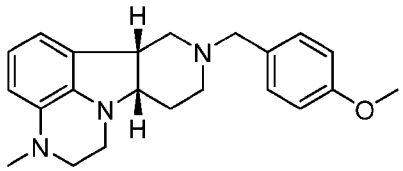
[000236] Example 102. (6b*R*,10a*S*)-8-(3-ethylbenzyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000237] The synthesis method is analogous to Example 71, with 1-(bromomethyl)-3-ethylbenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 64% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, J = 7.5 Hz, 1H), 7.19 – 7.13 (m, 2H), 7.12 – 7.08 (m, 1H), 6.73 – 6.59 (m, 1H), 6.49 (dd, J = 7.4, 1.0 Hz, 1H), 6.41 (dd, J = 8.0, 0.9 Hz, 1H), 3.77 – 3.56 (m, 1H), 3.46 (s, 2H), 3.32 (dt, J = 9.9, 3.0 Hz, 1H), 3.30 – 3.21 (m, 2H), 3.21 – 3.14 (m, 1H), 2.87 (s, 3H), 2.83 (td, J = 9.9, 2.9 Hz, 1H), 2.66 (q, J = 7.6 Hz, 3H), 2.38 – 2.14 (m, 1H), 2.01 (t, J = 11.1 Hz, 1H), 1.95 – 1.89 (m, 2H), 1.25 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 138.8, 138.2, 135.1, 130.3, 128.9, 128.3, 126.7, 126.6, 120.3, 113.0, 109.0, 64.8,

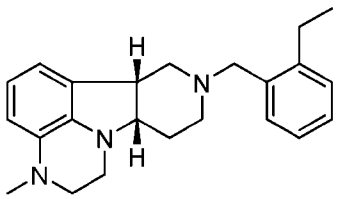
63.6, 56.5, 50.8, 49.2, 44.5, 41.9, 37.7, 28.9, 25.2, 15.7. HRMS (ESI) m/z calcd. for $C_{23}H_{29}N_3$ $[M+H]^+$: 348.2434; found: 348.2428.

[000238] Example 103. (6b*R*,10a*S*)-8-(4-methoxybenzyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000239] The synthesis method is analogous to Example 71, with 1-(bromomethyl)-4-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 61% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H), 6.86 (d, 2H), 6.64 (dd, J = 7.9, 7.3 Hz, 1H), 6.55 – 6.45 (m, 1H), 6.41 (dd, J = 8.0, 0.9 Hz, 1H), 3.81 (s, 3H), 3.61 (ddd, J = 11.3, 9.8, 3.0 Hz, 1H), 3.42 (q, 2H), 3.31 (dt, J = 9.9, 2.9 Hz, 1H), 3.29 – 3.21 (m, 2H), 3.20 – 3.06 (m, 1H), 2.87 (s, 3H), 2.86 – 2.76 (m, 2H), 2.70 – 2.53 (m, 1H), 2.40 – 2.18 (m, 1H), 2.12 – 1.77 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 138.2, 135.1, 130.7, 130.5, 130.3, 120.3, 113.7, 112.9, 109.0, 64.8, 62.8, 56.3, 55.4, 50.8, 49.0, 44.5, 41.9, 37.7, 25.2. HRMS (ESI) m/z calcd. for $C_{22}H_{27}N_3O$ $[M+H]^+$: 350.2227; found: 350.2221.

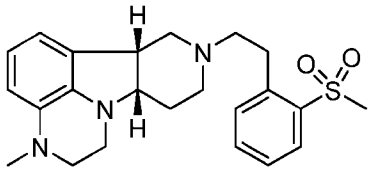
[000240] Example 104. (6b*R*,10a*S*)-8-(2-ethylbenzyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000241] The synthesis method is analogous to Example 71, with 1-(bromomethyl)-2-ethylbenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 76% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 7.4 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.15 (td, J = 7.1, 2.0 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 6.48 (d, J = 7.3 Hz, 1H), 6.41 (dd, J = 7.9, 0.9 Hz, 1H), 3.74 – 3.58 (m, 1H), 3.45 (q, J = 13.2 Hz, 2H), 3.37 – 3.26 (m, 2H), 3.24 – 3.20 (m, 1H), 3.18 – 3.08 (m, 1H), 2.88 (s, 3H), 2.87 – 2.80 (m, 2H), 2.74 (q, J = 7.6 Hz, 2H), 2.66 – 2.61 (m, 1H), 2.29 (td, J = 10.8, 4.6 Hz, 1H), 2.02 (t, J = 11.1 Hz, 1H), 1.97 – 1.82 (m, 2H), 1.22 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 138.2, 136.5, 135.1, 130.4, 130.2, 128.6, 127.2,

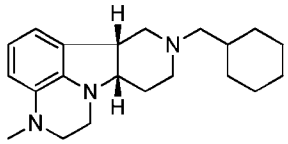
125.5, 120.3, 113.0, 109.0, 64.9, 60.7, 56.7, 50.8, 49.3, 44.5, 42.1, 37.7, 25.6, 25.4, 15.5. HRMS (ESI) m/z calcd. for $C_{23}H_{29}N_3$ $[M+H]^+$: 348.2434; found: 348.2428.

[000242] Example 106. (6b*R*,10a*S*)-3-methyl-8-(2-(methylsulfonyl)phenethyl)-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000243] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-2-(methylsulfonyl)benzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 38% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 – 7.91 (m, 1H), 7.68 – 7.51 (m, 1H), 7.46 – 7.34 (m, 2H), 6.66 (dd, J = 7.9, 7.3 Hz, 1H), 6.53 (dd, J = 7.4, 0.9 Hz, 1H), 6.41 (dd, J = 7.9, 0.9 Hz, 1H), 3.60 (ddd, J = 11.3, 9.9, 3.0 Hz, 1H), 3.32 (dt, J = 10.0, 3.0 Hz, 1H), 3.29 – 3.17 (m, 5H), 3.10 (s, 3H), 3.01 – 2.94 (m, 1H), 2.87 (s, 3H), 2.86 – 2.77 (m, 2H), 2.76 – 2.61 (m, 2H), 2.56 – 2.35 (m, 1H), 2.16 (t, J = 11.0 Hz, 1H), 2.07 – 1.86 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 139.0, 138.1, 135.1, 133.8, 132.5, 130.0, 129.7, 127.1, 120.4, 112.9, 109.1, 64.6, 60.6, 56.4, 50.8, 48.9, 45.0, 44.5, 41.9, 37.7, 30.6, 25.1. HRMS (ESI) m/z calcd. for $C_{23}H_{29}N_3O_2S$ $[M+H]^+$: 412.2053; found: 412.2043.

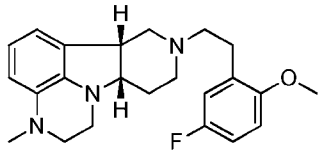
[000244] Example 108. (6b*R*,10a*S*)-8-(cyclohexylmethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000245] The synthesis method is analogous to Example 71, with (iodomethyl)cyclohexane added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 27% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 – 6.61 (m, 1H), 6.52 (dd, J = 7.4, 0.9 Hz, 1H), 6.40 (dd, J = 7.9, 0.9 Hz, 1H), 3.60 (ddd, J = 11.3, 9.8, 3.0 Hz, 1H), 3.31 (dt, J = 10.0, 3.0 Hz, 1H), 3.26 (dt, J = 11.3, 2.9 Hz, 1H), 3.21 (dt, J = 6.5, 3.2 Hz, 1H), 3.19 – 3.12 (m, 1H), 2.87 (s, 3H), 2.85 – 2.78 (m, 2H), 2.67 – 2.56 (m, 1H), 2.27 – 2.12 (m, 1H), 2.13 – 1.99 (m, 2H), 2.02 – 1.86 (m, 3H), 1.83 – 1.63 (m, 5H), 1.59 – 1.43 (m, 1H), 1.37 – 1.05 (m, 3H), 0.99 – 0.77 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.21 135.1, 130.5, 120.3, 112.9, 109.0, 66.1, 64.8, 57.2, 50.8, 49.7, 44.5, 41.9,

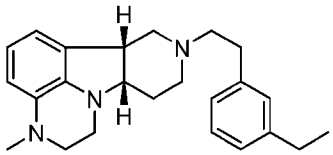
37.7, 35.5, 32.3, 32.3, 29.9, 27.0, 26.4, 25.2. HRMS (ESI) m/z calcd. for $C_{21}H_{31}N_3$ $[M+H]^+$: 326.2591; found: 326.2583.

[000246] Example 109. (6b*R*,10a*S*)-8-(5-fluoro-2-methoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



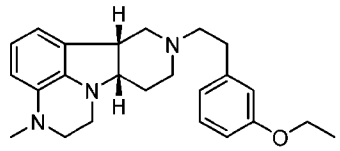
[000247] The synthesis method is analogous to Example 71, with 2-(2-bromoethyl)-4-fluoro-1-methoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 41% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 – 6.81 (m, 2H), 6.74 (dd, J = 8.8, 4.5 Hz, 1H), 6.70 – 6.63 (m, 1H), 6.54 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 7.9, 0.9 Hz, 1H), 3.77 (s, 3H), 3.61 (ddd, J = 11.3, 9.9, 3.0 Hz, 1H), 3.42 – 3.17 (m, 4H), 3.02 (t, J = 8.4 Hz, 1H), 2.87 (s, 3H), 2.86 – 2.78 (m, 4H), 2.60 (p, J = 6.5 Hz, 2H), 2.42 (s, 1H), 2.29 – 1.86 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0 (d, J = 238.14 Hz), 153.8, 138.2, 135.1, 130.8, 130.3, 120.4, 117.0 (d, J = 22.68 Hz), 112.9, 112.9 (d, J = 22.68 Hz), 111.1 (d, J = 7.56 Hz), 109.1, 64.7, 58.7, 56.4, 56.0, 50.8, 49.1, 44.6, 41.9, 37.7, 28.0, 25.2. HRMS (ESI) m/z calcd. for $C_{23}H_{28}N_3OF$ $[M+H]^+$: 382.2289; found: 382.2280.

[000248] Example 110. (6b*R*,10a*S*)-8-(3-ethylphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



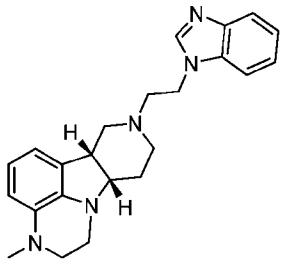
[000249] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-3-ethylbenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 51% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (td, J = 7.4, 0.8 Hz, 1H), 7.10 – 6.96 (m, 3H), 6.67 (t, J = 7.6 Hz, 1H), 6.55 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 8.0, 0.9 Hz, 1H), 3.62 (ddd, J = 11.3, 9.9, 3.0 Hz, 1H), 3.33 (dt, J = 10.0, 2.9 Hz, 1H), 3.30 – 3.19 (m, 3H), 3.11 – 2.99 (m, 1H), 2.88 (s, 3H), 2.87 – 2.77 (m, 4H), 2.76 – 2.49 (m, 4H), 2.48 – 2.28 (m, 1H), 2.23 – 1.87 (m, 3H), 1.23 (t, J = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 140.3, 138.1, 135.2, 130.0, 128.5, 128.5, 126.1, 125.7, 120.5, 112.8, 109.1, 64.6, 60.9, 56.3, 50.8, 49.1, 44.5, 41.7, 37.7, 33.6, 28.9, 25.0, 15.7. HRMS (ESI) m/z calcd. for $C_{24}H_{31}N_3$ $[M+H]^+$: 362.2591; found: 362.2583.

[000250] Example 111. (6b*R*,10a*S*)-8-(3-ethoxyphenethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000251] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-3-ethoxybenzene added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 27% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (td, J = 7.4, 1.3 Hz, 1H), 6.89 – 6.71 (m, 3H), 6.67 (t, J = 7.6 Hz, 1H), 6.54 (dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 7.9, 0.9 Hz, 1H), 4.01 (q, J = 7.0 Hz, 2H), 3.61 (ddd, J = 11.3, 9.9, 3.0 Hz, 1H), 3.43 – 3.21 (m, 4H), 3.14 – 2.98 (m, 1H), 2.87 (s, 3H), 2.87 – 2.76 (m, 4H), 2.73 – 2.53 (m, 2H), 2.42 (t, J = 12.0 Hz, 1H), 2.22 – 1.86 (m, 3H), 1.40 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 141.7, 138.0, 135.2, 129.9, 129.5, 121.1, 120.6, 115.2, 112.8, 112.1, 109.2, 64.5, 63.4, 60.6, 56.1, 50.8, 49.1, 44.5, 41.6, 37.7, 33.5, 24.9, 15.0. HRMS (ESI) m/z calcd. for $C_{24}H_{31}N_3O$ $[M+H]^+$: 378.2540; found: 378.2531.

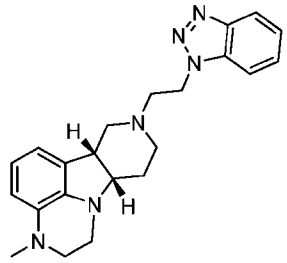
[000252] Example 113. (6b*R*,10a*S*)-8-(2-(1*H*-benzo[d]imidazol-1-yl)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000253] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-1*H*-benzo[*d*]imidazole added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 43% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.86 – 7.74 (m, 1H), 7.61 – 7.41 (m, 1H), 7.41 – 7.27 (m, 2H), 6.69 (t, J = 7.7 Hz, 1H), 6.51 (d, J = 7.4 Hz, 1H), 6.43 (d, J = 8.0 Hz, 1H), 4.68 (ddd, J = 14.3, 8.0, 6.2 Hz, 1H), 4.59 (ddd, J = 14.3, 8.0, 6.0 Hz, 1H), 3.67 – 3.52 (m, 1H), 3.42 (dt, J = 11.9, 6.3 Hz, 1H), 3.34 – 3.23 (m, 3H), 3.20 (ddd, J = 11.6, 6.4, 2.0 Hz, 1H), 3.10 (ddd, J = 13.0, 7.9, 6.2 Hz, 1H), 3.06 – 2.95 (m, 2H), 2.87 (s, 3H), 2.85 – 2.79 (m, 1H), 2.79 – 2.66 (m, 1H), 2.37 (t, J = 11.5 Hz, 1H), 2.33 – 2.18 (m, 1H), 2.08 – 1.97 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.18, 143.23, 142.51, 137.80, 135.67, 133.51, 128.47, 124.24, 123.51, 121.57, 120.40, 113.03, 110.19, 109.89, 77.67, 77.42, 77.16, 63.80, 56.59, 55.68, 50.86, 49.25,

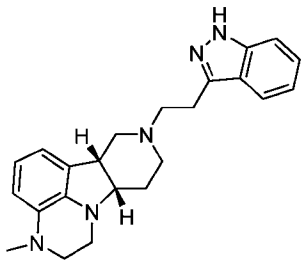
44.76, 41.67, 40.52, 37.87, 23.73. HRMS (ESI) m/z calcd. for $C_{23}H_{27}N_5$ $[M+H]^+$: 374.2339; found: 374.2330.

[000254] Example 114. (6b*R*,10a*S*)-8-(2-(1H-benzo[*d*][1,2,3]triazol-1-yl)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000255] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-1*H*-benzo[*d*][1,2,3]triazole added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 18% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.66 (dt, *J* = 8.4, 1.0 Hz, 1H), 7.51 (ddd, *J* = 8.3, 7.0, 1.0 Hz, 1H), 7.38 (ddd, *J* = 8.2, 6.9, 1.0 Hz, 1H), 6.67 (t, *J* = 7.7 Hz, 1H), 6.49 (dd, *J* = 7.4, 0.9 Hz, 1H), 6.42 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.03 – 4.85 (m, 2H), 3.59 (ddd, *J* = 11.1, 10.0, 3.2 Hz, 1H), 3.31 – 3.20 (m, 4H), 3.20 – 3.07 (m, 3H), 2.98 – 2.89 (m, 1H), 2.87 (s, 3H), 2.85 (s, 1H), 2.62 (td, *J* = 11.9, 3.4 Hz, 1H), 2.30 (t, *J* = 11.1 Hz, 1H), 2.05 (ddt, *J* = 14.8, 12.4, 4.4 Hz, 1H), 1.97 (dt, *J* = 14.8, 2.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.18, 143.23, 142.51, 137.80, 135.67, 133.51, 128.47, 124.24, 123.51, 121.57, 120.40, 113.03, 110.19, 109.89, 77.67, 77.42, 77.16, 63.80, 56.59, 55.68, 50.86, 49.25, 44.76, 41.67, 40.52, 37.87, 23.73. HRMS (ESI) m/z calcd. for C22H26N6 $[M+H]^+$: 375.2292; found: 375.2283.

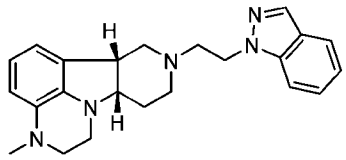
[000256] Example 115. (6b*R*,10a*S*)-8-(2-(1*H*-indazol-3-yl)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000257] The synthesis method is analogous to Example 71, with 3-(2-chloroethyl)-1*H*-indazole added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 16% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.42 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.36 (ddd, *J* = 8.3, 6.8, 1.1 Hz, 1H), 7.14 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.54

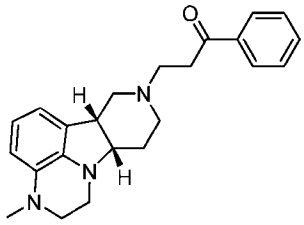
(dd, J = 7.4, 0.9 Hz, 1H), 6.42 (dd, J = 8.0, 0.9 Hz, 1H), 3.62 (ddd, J = 11.3, 10.0, 3.0 Hz, 1H), 3.33 (dt, J = 10.0, 3.0 Hz, 1H), 3.31 – 3.18 (m, 5H), 3.13 – 2.99 (m, 1H), 2.87 (s, 3H), 2.87 – 2.79 (m, 3H), 2.45 (s, 1H), 2.23 – 2.10 (m, 1H), 2.09 – 1.94 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.26, 141.13, 137.87, 134.92, 129.79, 126.65, 122.12, 120.29, 120.25, 120.09, 112.65, 109.72, 108.87, 64.36, 57.48, 56.09, 50.54, 48.81, 44.29, 41.52, 37.44, 24.81, 24.63. HRMS (ESI) m/z calcd. for $C_{23}H_{27}N_5$ $[M+H]^+$: 374.2339; found: 374.2330.

[000258] Example 126. (6bR,10aS)-8-(2-(1H-indazol-1-yl)ethyl)-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1H-pyrido[3',4':4,5]pyrrolo[1,2,3-de]quinoxaline



[000259] The synthesis method is analogous to Example 71, with 1-(2-bromoethyl)-1*H*-indazole added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 25% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 1H), 7.72 (dt, J = 8.1, 1.0 Hz, 1H), 7.45 (dq, J = 8.5, 0.9 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.14 (ddd, J = 8.0, 6.8, 0.9 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 6.50 (dd, J = 7.4, 0.9 Hz, 1H), 6.41 (dd, J = 8.0, 0.9 Hz, 1H), 4.54 (t, J = 7.3 Hz, 2H), 3.64 – 3.54 (m, 1H), 3.28 (ddt, J = 18.6, 11.3, 2.9 Hz, 2H), 3.20 (ddd, J = 6.6, 3.9, 2.5 Hz, 1H), 3.17 – 3.08 (m, 1H), 2.92 – 2.87 (m, 3H), 2.86 (s, 3H), 2.85 – 2.78 (m, 2H), 2.68 (ddt, J = 11.0, 4.7, 2.1 Hz, 1H), 2.40 (td, J = 11.2, 3.9 Hz, 1H), 2.14 (t, J = 11.1 Hz, 1H), 1.91 (q, J = 4.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.48, 137.85, 134.88, 132.91, 129.67, 126.01, 123.87, 120.95, 120.33, 120.21, 112.55, 108.98, 108.82, 64.21, 57.33, 56.52, 50.50, 49.14, 46.86, 44.21, 41.57, 37.42, 24.87. HRMS (ESI) m/z calcd. for $C_{23}H_{27}N_5$ $[M+H]^+$: 374.2339; found: 374.2330.

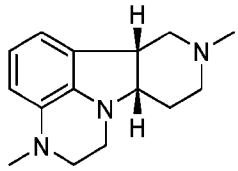
[000260] Example 131. 3-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10a-hexahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8(7*H*)-yl)-1-phenylpropan-1-one



[000261] The synthesis method is analogous to Example 71, with 1-phenylpropan-1-one added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 68% isolated yield. ^{1}H NMR

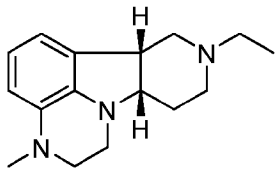
(500 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H), 7.61 – 7.52 (m, 1H), 7.50 – 7.41 (m, 2H), 6.70 – 6.60 (m, 1H), 6.52 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.41 (dd, *J* = 8.0, 0.9 Hz, 1H), 3.61 (ddd, *J* = 11.3, 9.9, 3.0 Hz, 1H), 3.29 (ddt, *J* = 23.4, 11.4, 2.9 Hz, 2H), 3.24 – 3.13 (m, 4H), 2.94 – 2.88 (m, 2H), 2.87 (s, 3H), 2.86 – 2.78 (m, 2H), 2.74 – 2.66 (m, 1H), 2.38 (td, *J* = 11.3, 4.0 Hz, 1H), 2.13 – 2.02 (m, 1H), 2.00 – 1.87 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.19, 137.86, 136.88, 134.88, 132.92, 129.79, 128.48, 127.94, 120.20, 112.56, 108.81, 64.32, 60.26, 56.19, 53.26, 50.52, 48.95, 44.24, 41.64, 37.42, 36.14, 24.94, 14.08. HRMS (ESI) m/z calcd. for $C_{23}H_{27}N_3O$ $[M+H]^+$: 362.2227; found: 362.2223.

[000262] Example 175. (6b*R*,10a*S*)-3,8-dimethyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000263] The synthesis method is analogous to Example 71, with iodomethane added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 31% isolated yield. ^1H NMR (500 MHz, $CDCl_3$) *δ* 6.70 – 6.59 (m, 1H), 6.52 (dd, *J* = 7.4, 0.9 Hz, 1H), 6.41 (dd, *J* = 8.0, 0.9 Hz, 1H), 3.60 (ddd, *J* = 11.3, 9.9, 3.0 Hz, 1H), 3.31 (dt, *J* = 9.9, 3.0 Hz, 1H), 3.27 (dt, *J* = 11.3, 2.9 Hz, 1H), 3.23 – 3.08 (m, 2H), 2.87 (s, 3H), 2.85 – 2.71 (m, 2H), 2.60 (dtd, *J* = 11.2, 3.5, 1.9 Hz, 1H), 2.26 (s, 3H), 2.24 – 2.15 (m, 1H), 2.05 – 1.83 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) *δ* 138.1, 135.1, 130.2, 120.4, 112.8, 109.0, 64.1, 58.6, 51.1, 50.8, 46.7, 44.5, 42.0, 37.7, 25.2. HRMS (ESI) m/z calcd. for $C_{15}H_{21}N_3$ $[M+H]^+$: 244.1808; found: 244.1804.

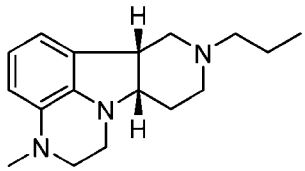
[000264] Example 176. (6b*R*,10a*S*)-8-ethyl-3-methyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000265] The synthesis method is analogous to Example 71, with iodoethane added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 65% isolated yield. ^1H NMR (500 MHz, $CDCl_3$) *δ* 6.68 (t, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 7.4 Hz, 1H), 6.42 (d, *J* = 7.9 Hz, 1H), 3.77 – 3.56 (m, 1H), 3.55 – 3.44 (m, 1H), 3.40 – 3.20 (m, 4H), 3.17 – 3.06 (m, 1H), 2.87 (s, 3H), 2.85 – 2.72

(m, 3H), 2.68 (td, J = 12.5, 3.0 Hz, 1H), 2.52 – 2.33 (m, 1H), 2.27 (t, J = 11.7 Hz, 1H), 2.12 – 1.96 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 135.4, 128.4, 121.2, 112.8, 109.5, 63.7, 53.9, 52.1, 50.6, 47.6, 44.5, 39.9, 37.6, 23.1, 10.2. HRMS (ESI) m/z calcd. for $C_{16}H_{23}N_3$ $[M+H]^+$: 258.1965; found: 258.1960.

[000266] Example 177. (6b*R*,10a*S*)-3-methyl-8-propyl-2,3,6b,7,8,9,10,10a-octahydro-1*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxaline



[000267] The synthesis method is analogous to Example 71, with 1-iodopropane added in Step D instead of 1-(2-bromoethyl)-3-methoxybenzene. 45% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 – 6.61 (m, 1H), 6.52 (dd, J = 7.3, 0.9 Hz, 1H), 6.40 (dd, J = 8.0, 0.9 Hz, 1H), 3.61 (ddd, J = 11.3, 9.9, 3.0 Hz, 1H), 3.31 (dt, J = 10.0, 2.9 Hz, 1H), 3.26 (dt, J = 11.3, 2.9 Hz, 1H), 3.24 – 3.21 (m, 1H), 3.17 (dt, J = 10.9, 6.4 Hz, 1H), 2.94 – 2.87 (m, 1H), 2.82 (td, J = 10.0, 2.9 Hz, 1H), 2.70 – 2.55 (m, 1H), 2.44 – 2.06 (m, 3H), 2.00 – 1.78 (m, 3H), 1.53 (h, J = 7.5 Hz, 2H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 135.1, 130.3, 120.4, 112.9, 109.0, 64.8, 61.1, 56.6, 50.8, 49.2, 44.5, 41.9, 37.7, 25.2, 20.3, 12.2. HRMS (ESI) m/z calcd. for $C_{17}H_{25}N_3$ $[M+H]^+$: 272.2121; found: 272.2116.

[000268] The remaining compounds through Example 180 may be prepared according to analogous procedures.

Example 181: Receptor Binding Profile

[000269] Standard receptor binding to the serotonin, dopamine, and mu-opioid receptors, and to the serotonin transporter, is determined according to literature procedures. For example, the following literature procedures may be used, each of which reference is incorporated herein by reference in their entireties: 5-HT_{2A}: Bryant, H.U. et al. (1996), *Life Sci.,* 15:1259-1268; D2: Hall, D.A. and Strange, P.G. (1997), *Brit. J. Pharmacol.,* 121:731-736; D1: Zhou, Q.Y. et al. (1990), *Nature,* 347:76-80; SERT: Park, Y.M. et al. (1999), *Anal. Biochem.*, 269:94-104; Mu opioid receptor: Wang, J.B. et al. (1994), *FEBS Lett.,* 338:217-222. For example, receptor binding assays can be performed via competitive assay against the agonist radioligand ^{125}I-(+/-)-

DOI, to determine Ki by displacement, using human recombinant HEK-293 cells expressing human 5-HT_{2A}, 5-HT_{2B}, and/or 5-HT_{2C} receptors.

[000270] In general, the results are expressed as a percent of control specific binding:

$$\frac{\text{measured specific binding}}{\text{control specific binding}} \times 100$$

and as a percent inhibition of control specific binding:

$$100 - \left(\frac{\text{measured specific binding}}{\text{control specific binding}} \times 100 \right)$$

obtained in the presence of the test compounds.

[000271] The IC_{50} values (concentration causing a half-maximal inhibition of control specific binding) and Hill coefficients (nH) are determined by non-linear regression analysis of the competition curves generated with mean replicate values using Hill equation curve fitting

$$Y = D + \left[\frac{A-D}{1 + (C/C_{50})^{nH}} \right]$$

where Y = specific binding, A = left asymptote of the curve, D = right asymptote of the curve, C = compound concentration, $C_{50} = IC_{50}$, and nH = slope factor. This analysis was performed using in –house 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) were calculated using the Cheng Prusoff equation:

$$Ki = \frac{IC_{50}}{(1 + L/K_D)}$$

where L = concentration of radioligand in the assay, and K_D = affinity of the radioligand for the receptor. A Scatchard plot is used to determine the K_D.

[000272] The compound of Formula A (ITI-007, lumateperone) is used as a comparison in the assays.

[000273] The following receptor affinity results are obtained (with the Compound of Formula A for comparison):

	Receptor K_i (nM) or maximum binding affinity (%, at 100 nM)

Ex.	5-HT_{2A} (%)	5-HT_{2A} K_i	D1 (%)	D1 K_i	D2 (%)	D2 K_i	SERT (%)	SERT K_i	Mu (%)	Mu K_i
A	97%	0.3	46%	41	83%	49	93%	16	0%	> 10,000
2	76%	33	3%		29%		64%	23	10%	
3	87%	3.4	0%	0	12%		2%	707	0%	
4	97%	0.6	47%	29	79%	15	19%	380	2%	> 10,000
5	76%	53	0%	0	34%		78%	5	0%	
6	27%		0%		0%		97%	4.4	0%	
7	97%	1.7	81%	4.2	47%	34	0%	590	17%	
8	96%	1.6	57%	34	25%	571	0%	8300	34%	
9	68%	34	0%		0%		14%		69%	12
10	65%	42	0%		0%		6%		74%	8.9
11	35%		0%		0%		13%		65%	10
12	40%		0%		0%		16%		7%	
13	97%	18	0%		0%		99%	0.8	0%	
14	88%	12	0%		6%		0%		2%	
15	93%	6.8	0%		14%		0%		7%	
16	97%	3.0	0%		12%		0%		6%	
17	97%	2.4	40%		7%		10%		8%	
19	99%	1.6	2%		21%		9%		5%	
20	98%	5.3	0%		24%		6%		0%	
21	96%	4.9	1%		25%		21%		0%	
22	98%	< 1	16%		18%		1%		22%	
23	94%	2.0	9%		11%		20%		15%	
24	92%	7.4	9%		37%		1%		14%	
25	95%	14	4%		31%		0%		5%	
26	94%	13	5%		31%		10%		4%	
27	92%	1.8	33%		23%		25%		0%	

28	90%	11	0%		40%		38%		0%	
29	93%	1.0	0%		9%		28%		0%	
30	99%	< 1	18%		24%		23%		8%	
31	99%	1.8	14%		29%		14%		9%	
32	95%	3.3	5%		15%		25%		0%	
33	96%	8.4	28%		29%		70%		5%	
34	86%	5.1	6%		40%		52%		0%	
35	97%	8.9	4%		12%		35%		4%	
36	91%		0%		11%		27%		8%	
37	89%		19%		20%		0%		0%	
38	89%	5.8	14%		0%		16%		5%	
39	96%	7.2	17%		30%		24%		14%	
40	87%	10	0%		8%		5%		0%	
41	94%	6.1	4%		0%		11%		0%	
42	66%		0%		11%		3%		0%	
43	49%		0%		5%		0%		0%	
44	93%		0%		12%		2%		3%	
45	90%		0%		16%		0%		5%	
46	93%		0%		24%		28%		9%	
51		7.1								
66	55%									
70		1.9								
71	81%	11	0%		39%		25%		0%	
72		6.9								
73	84%	14	18%		37%		0%		0%	
74	39%	115	17%		42%		0%		0%	
75	44%	37	16%		32%		51%	35	0%	
76	75%	16	24%		53%	39	6%		0%	
77	2%		0%		10%		0%		0%	
78	82%	10	19%		74%	10	40%		0%	

80	54%	42	33%		50%	49	7%		0%	
81	90%	8.4	52%	59	55%	77	32%		17%	
82	54%	53	0%		63%	61	39%		0%	
84	32%		0%		64%	23	68%		0%	
85	59%	35	0%		30%		93%	3.5	12%	
86	82%	26	1%		34%		12%		0%	
87	72%	64	5%		45%		11%		0%	
88	65%	37	18%		0%		8%		0%	
89	79%	31	6%		29%		38%		0%	
90	66%	57	4%		0%		3%		0%	
91	62%	56	9%		25%		0%		0%	
92	98%	2.5	3%		39%		36%		1%	
93	82%	22	18%		42%		30%		0%	
94	96%	3.9	0%		5%		38%		0%	
95	13%		0%		24%		31%		0%	
96	56%	50	0%		0%		0%		0%	
97	68%	58	3%		11%		88%	11.8	0%	
98	93%	8.0	42%		41%		0%		7%	
99	89%	6.8	0%		6%		0%		0%	
100	73%	41	28%		22%		14%		0%	
101	68%	32	0%		0%		12%		0%	
102	76%	9.8	9%		5%		0%		0%	
103	32%		0%		0%		2%		0%	
104	80%	18	5%		5%		6%		0%	
106	14%		1%		12%		16%		0%	
107	97%	1.4	3%		29%		0%		9%	
108	15%		0%		37%		0%		1%	
109	70%	19	26%		67%	24	67%	13	0%	
110	93%	3.8	10%	57%	57%	42	22%		7%	
111	73%	36	0%		25%		29%		2%	

113	4%		1%		0%		0%		0%	
114	0%		0%		0%		0%		0%	
115	30%		10%		49%	81	64%	27	6%	
126	55%	19	5%		0%		2%		0%	
129	88%	12	7%		0%		0%		0%	
131	89%		6%		25%		0%		3%	
175	62%	61	9%		0%		4%		0%	
176	39%		0%		0%		11%		0%	
177	42%		13%		0%		7%		0%	

[000274] As shown, many of the compounds of the present disclosure show significantly more receptor selectivity than the reference compound of Formula A. For example, the compounds of Examples 14, 15, and 16 show little D1, D2, or Mu receptor affinity, but retain strong affinity at the serotonin 2A receptor.

[000275] Selected compounds are also tested in receptor binding assays for the 5-HT_{2B}, and/or 5-HT_{2C} receptors. Some results are shown in the following table:

Ex.	5-HT_{2A} (%)	5-HT_{2A} K_i	5-HT_{2B} (%)	5-HT_{2B} K_i	5-HT_{2C} (%)	5-HT_{2C} K_i
3	87%	3.4	73%	6.9	95%	2.6
14	88%	12	76%	14	97%	2.5
15	93%	6.8	71%	10	68%	26
25	95%	14	87%	4.9	63%	30
40	87%	10	80%	4.8	81%	21
51	87%	7.1	57%	30	43%	97
66	70%	55	0%	434	17%	296
70	95%	1.9	87%	8.5	75%	36
72	92%	6.9	96%	1.7	80%	20

[000276] Selected compounds are also tested in receptor functional assays for the 5-HT_{2B} and 5-HT_{2C} receptors as agonists (EC_{50}) or antagonists (IC_{50}). Some results are shown in the following table:

Ex.	5-HT_{2B}		5-HT_{2C}
	EC_{50} (nM)	IC_{50} (nM)	EC_{50} (nM)
3	> 10,000	25	15
14	> 10,000	20	7
15	> 10,000	54	1500
25	> 10,000	15	127
40	> 10,000	14	40
51	> 10,000	11.9	322
70	> 10,000	36	87
72	> 10,000	14	34

[000277] Some compounds are additionally tested in a receptor profiling panel consisting agonist and/or antagonist radioligand binding assays. Assays are conducted using a 100 nM concentration of the test compound. Compound binding is calculated as a percent inhibition of the binding of the specific radioligand for the receptor (or ion channel) tested, which can be an agonist or antagonist. The following receptors and ion channels are included in the panel:

Receptor or Ion Channel	Reference Ligand
adenosine A2A	NECA (agonist)
alpha-1A adrenergic	WB 4101 (antagonist)
alpha-2A adrenergic	Yohimbine (antagonist)
beta-1 adrenergic	Atenolol (agonist)
beta-2 adrenergic	ICI 118551 (antagonist)
GABA-A benzodiazepine site (BZD central)	Diazepam (agonist)
CB1 cannabinoid	CP 55940 (agonist)
CB2 cannabinoid	WIN 55212-2 (agonist)
cholecystokinin CCK1	CCK-8s (agonist)
dopamine D1	SCH 23390 (antagonist)
dopamine D2S	7-Hydroxy-DPAT (agonist)
endothelin-A (ETA)	Endothelin-1 (agonist)

NMDA	CGS 19755 (antagonist)
histamine H1	Pyrilamine (antagonist)
histamine H2	Cimetidine (antagonist)
MAO-A	Clorgyline (antagonist)
muscarinic M1	Pirenzepine (antagonist)
muscarinic M2	Methoctramine (antagonist)
muscarinic M3	4-DAMP (antagonist)
nicotinic acetylcholine (neuronal alpha-4-beta-2)	Nicotine (agonist)
delta opioid	DPDPE (agonist)
kappa opioid	U50488 (agonist)
mu opioid	DAMGO (agonist)
serotonin-1A	8-Hydroxy-DPAT (agonist)
serotonin-1B	Serotonine (antagonist)
serotonin-2A	DOI (agonist)
serotonin-2B	DOI (agonist)
serotonin-3	MDL 72222 (antagonist)
glucocorticoid (GR)	Dexamethasone (agonist)
androgen (AR)	Testosterone (agonist)
vasopressin V1A	$[d(CH_2)_5{}^1,Tyr(Me)_2]$-AVP (agonist)
cardiac calcium channel (dihydropyridine site)	Nitrendipine (antagonist)
hERG potassium channel	Terfenadine
voltage-gated potassium channel K_V	Alpha-dendrotoxin (antagonist)
sodium channel (site 2)	Veratridine (antagonist)
norepinephrine transporter	Protriptyline (antagonist)
dopamine transporter	BTCP (antagonist)
serotonin transporter	Imipramine (antagonist)

It is unexpectedly found that the compounds of the present disclosure have high selectivity with few off-target interactions. For example, the compounds interact significantly (> 45% inhibition) only with the following receptors: alpha-1A (e.g., 40-80% inhibition), serotonin-2A (e.g., 50-

100% inhibition), and serotonin-2B (50-100% inhibition), with insignificant activity (< 40% inhibition) at other receptors which are commonly associated with side effects, such as the serotonin-1A, serotonin-1B, serotonin-3, muscarinic, other adrenergic, and histamine receptors.

[000278] These results are particularly surprising because it is found that compounds having a tetracyclic core corresponding to, or related to, that of the instantly disclosed compounds, but without the side chain (i.e., compounds of Formula I wherein n is 0 and Z-A is H) have significant activity in the receptor assays for serotonin-1A (> 70% inhibition), serotonin-1B (> 50% inhibition), serotonin-2A (> 70% inhibition), and serotonin-2B (> 80% inhibition).

[000279] **Example 182: Biased Agonism/Antagonism**

[000280] *G-q Signaling Agonism/Antagonism at the 5-HT$_{2A}$ Receptor.* Selected compounds are submitted to 5-HT$_{2A}$ agonist and antagonist assays for G-q recruitment. Alpha-methylserotonin is used as the reference control for agonist assays, and altanserin is used as the control for antagonist assays.

[000281] Agonist Assay: CHO-K1 cells expressing human 5-HT$_{2A}$ (ES-313-AF) are obtained from PerkinElmer and used according to the supplier's recommendations. Frozen cells are thawed in a water bath at 37 °C, and then are resuspended in 10 mL Ham's F-12 medium containing 10% FBS. Cells are recovered by centrifugation at 150g for 5 minutes and are then resuspended in pre-warmed assay buffer (DMEM/HAM's F-12 with HEPES) at 3x10^5 cells/L in a Falcon tube. Under sterile conditions, Coelenterazine H is added to a final concentration of 5 µM to the cell suspension. The Falcon tube is wrapped in aluminum foil and placed on a rotating wheel (about 45° angle and 7 rpm/min speed) for 4 hours at room temperature. Cells are then diluted to 1x10^5 cells/mL in assay buffer and transferred to a beaker wrapped in aluminum foil on a magnetic stirrer. After 1 hour of incubation, 50 µL of cells (5,000 cells/well) are injected into 50 µL of the test compound at increasing concentrations in the wells of a 96-well white plate. Light emission is recorded for 20 seconds immediately with FLUOstar Omega luminescence detector (BMG LABTECH). Digitonin at a final concentration of 50 µM in assay buffer is used as a positive control to measure the receptor independent cellular calcium response. Curve fitting was performed using GraphPad Prism and EC_{50} values are determined using a 4-parameter logistic fit, and maximum response (E_{max}) values are calculated by subtracting the bottom value from the top value of the dose-response curve.

[000282] Antagonist Assay: 50 µL of cells (5,000 cells/well) are mixed with 50 µL of the test compound at increasing concentrations in the wells of a 96-well white plate, and then the plates are incubated 15 minutes at room temperature. Thereafter, 50 µL of alpha-methylserotonin (final assay concentration corresponding to its measured EC_{80}) is injected and the light emission is recorded for 20 seconds immediately with FLUOstar Omega luminescence detector (BMG LABTECH). Curve fitting is performed using Prism and IC_{50} values are determined using a 4-parameter logistic fit. For the antagonists, the apparent dissociation constants (K_B) are calculated using the modified Cheng Prusoff equation—$K_B = IC_{50} / (1+(A/EC_{50A}))$ – where A is the concentration of the reference agonist alpha-methylserotonin, and EC_{50A} is the EC_{50} value of the reference agonist alpha-methylserotonin.

[000283] *Beta-arrestin Signaling Agonism/Antagonism at the 5-HT_{2A} Receptor.* Selected compounds are submitted to 5-HT_{2A} agonist and antagonist assays for beta-arrestin recruitment. Alpha-methylserotonin is used as the reference control for agonist assays, and altanserin is used as the control for antagonist assays.

[000284] Agonist Assay: U2OS cells expressing human 5-HT_{2A} receptor (93-0401E3CP19L) are obtained from Eurofins DiscoverX and used according to the supplier's recommendations. Frozen cells are thawed in a water bath at 37 °C, and then mixed with 0.5 mL of pre-warmed Cell Plating Reagent. Cells are pipetted up and down gently several times to ensure even distribution before transfer to 11.5 mL of pre-warmed Cell Plating Reagent and poured into a disposable reagent reservoir. 100 µL of cells are plated into each well of the 96-well tissue culture plate, and the plates are incubated for 24 hours at 37 °C (5% CO_2). 10 µL of the test compound at increasing concentrations is added into the cells in the 96-well plate, and then the plates are incubated for 3 hours at room temperature. After addition of 55 µL of prepared detection reagent and a further 1-hour incubation, the samples are read on an Envision luminescence plate reader. All assay points are determined in duplicate and the data is presented as average values. Curve fitting is performed using Prism software (Graphpad), EC_{50} values are determined using a 4-parameter logistic fit, and maximum response (E_{max}) values are calculated by subtracting the bottom value from the top value of the dose-response curve.

[000285] Antagonist Assay: 5 µL of the test compound at increasing concentrations is added into the cells in the 96-well plate, and the plates are incubated for 30 minutes at 37 °C (5% CO_2). Thereafter 5 µL of α-methylserotonin (final assay concentration Thereafter, 50 µL of

alpha-methylserotonin (final assay concentration corresponding to its measured EC_{80}) is added and the plates are incubated for 3 hours at room temperature. After addition of 55 µL of prepared detection reagent and a further 1-hour incubation, the samples are read on an Envision luminescence plate reader. All assay points are determined in duplicate and the data is presented as average values. Curve fitting is performed using Prism software (Graphpad), EC_{50} values are determined using a 4-parameter logistic fit. For the antagonists, the apparent dissociation constants (K_B) are calculated using the modified Cheng Prusoff equation—$K_B = IC_{50} / (1+(A/EC_{50A}))$ – where A is the concentration of the reference agonist alpha-methylserotonin, and EC_{50A} is the EC_{50} value of the reference agonist alpha-methylserotonin.

[000286] For both the G-q signaling agonism assay and the beta-arrestin signaling agonism assay, the EC_{50} (effective concentration for 50% activation), and the E_{max} (maximum activation) are determined.

[000287] The maximum efficacy (E_{max}) for the compound is calculated as a percentage of the maximal signaling activity induced by the compound compared to that induced by the full agonist alpha-methylserotonin. This is an indication of the compound's intrinsic activity. Any degree of maximal activity less than that of the full agonist reference indicates that the test compound is a partial agonist.

[000288] Like intrinsic activity (E_{max}), intrinsic relative activity (RA_i) is another way to quantify the partial versus full agonism of receptor activity, but it also takes into account the efficacy of the compound. It is calculated using the following formula:

$$RA_i = \frac{E_{max\text{-}B} EC_{50\text{-}A}}{E_{max\text{-}A} EC_{50\text{-}B}}$$

[000289] *Bias Score.* Bias score (or bias ratio) is calculated as the ratio of the intrinsic relative activity (RA_i) for agonism of beta-arrestin signaling over the intrinsic relative activity (RA_i) for agonism of G-q signaling.

[000290] The results are shown in the table below (RA_i = Intrinsic Relative Activity, compared to the positive controls methylserotonin or altanserin):

	Beta-Arrestin Signaling				G-q Signaling				Bias Score
Ex.	Agonism			Antag.	Agonism			Antag.	
	EC_{50} (nM)	E_{max}	RA_i	IC_{50} (nM)	EC_{50} (nM)	E_{max}	RA_i	IC_{50} (nM)	

A	> 10,000	0%		1.24	> 10,000	0%		2.34	
2	> 10,000	0%		298	> 10,000	0%		179	
3	71	55%	0.65	> 10,000	1108	45%	0.004	233	181
4	> 10,000	0%		4.11	> 10,000	0%		5	
5	> 10,000	0%		417	> 10,000	0%		282	
13	> 10,000	0%		253	> 10,000	0%		184	
14	154	69%	0.38	> 10,000	1744	40%	0.004	229	89
15	22	23%	0.88	399	> 10,000	0%	0.000	152	$>10^3$
16	11	21%	1.52	641	708	57%	0.015	59	104
17	> 10,000	0%		221	> 10,000	0%		92	
19	> 10,000	0%		72	> 10,000	0%		22	
20	> 10,000	0%		195					
21	> 10,000	0%		196	> 10,000	0%		71	
22	> 10,000	0%		49					
23	> 10,000	0%		116	> 10,000	0%		64	
24	> 10,000	0%		313	> 10,000	0%		326	
25	68	47%	0.57	1339	> 10,000	0%		746	$>10^3$
26	15.6	16%	0.86	515	> 10,000	0%		197	$>10^3$
27	> 10,000	0%		159					
28	> 10,000	0%		184					
29	> 10,000	0%		129					
30	> 10,000	0%		46					
31	> 10,000	0%		22					
32	> 10,000	0%		110					
33	> 10,000	0%		125					
34	46	25%	0.47	416	> 10,000	0%		325	$>10^3$
35	> 10,000	0%		73					
36	36	54%	1.3	6299					
37	30	15%	0.42	425					
38	40	21%	0.46	496					

39	16	12%	0.61	372	> 10,000	0%		84	$>10^3$
40	111	72%	0.54	> 10,000	> 10,000	0%	0	1443	$>10^3$
41	26.5	16%	0.51	1072					
42	> 10,000	0%		516					
43	84	22%	0.23	2119					
44	27	42%	1.33	4638					
45	3276	52%	1.25	> 10,000					
46	33	49%	1.28	9527					
51	30	30%	0.86	1723	> 10,000	0%		880	$>10^3$
66	2226	55%		> 10,000	> 10,000	0%		2307	$>10^3$
70	28	42%	1.3	569	> 10,000	0%		405	$>10^3$
71	30	33%	0.95	654	> 10,000	0%		151	$>10^3$
72	25	70%	2.4	> 10,000	> 10,000	0%		665	$>10^3$
73	> 10,000	0%		199					
74	> 10,000	0%		1151					
75	> 10,000	0%		529					
76	> 10,000	0%		284					
77	4154	29%	0.01	2112					
78	> 10,000	0%		159					
79	> 10,000	0%		373					
80	> 10,000	0%		526					
81	16	31%	1.7	196					
82	> 10,000	0%		525					
84	> 10,000	0%		846					
85	> 10,000	0%		795					
86	37	25%	0.57	2203					
87	61	29%	0.41	1053					
88	266	17%	0.05	876					
89	17	10%	0.52	144					
90	61	32%	0.45	968					

91	123	24%	0.17	978					
92	6	30%	4.0	42	> 10,000	0%		62	$>10^3$
93	> 10,000	0%		260					
94	5	45%	7.2	210	> 10,000	0%		73	$>10^3$
95	> 10,000	0%		6253					
96	118	35%	0.25	1537					
97	> 10,000	0%		491					
98	33	47%	1.2	1632	> 10,000	0%		274	$>10^3$
99	26	54%	1.79	597	> 10,000	0%		310	$>10^3$
100	65	36%	0.48	581					
101	58	56%	0.83	> 10,000					
102	68	41%	0.51	4141					
103	190	52%	0.23	> 10,000					
104	32	15%	0.40	588					
106	> 10,000	0%		2924					
107	14	62%	3.7	> 10,000	> 10,000	0%		64	$>10^3$
108	390	11%	0.02	2876					
109	88	24%	0.23	1082					
110	13	20%	1.3	764					
111	55	24%	0.38	766					
112	13	31%	2.1	> 10,000	> 10,000	0%		99	$>10^3$
113	> 10,000	0%		> 10,000					
114	787	19%	0.02	> 10,000					
115	> 10,000	0%		2499					
116	18	9%	0.43	348					
117	12	34%		859	> 10,000	0%			$>10^3$
118	59	60%	0.87	> 10,000	> 10,000	0%		266	$>10^3$
119	> 10,000	0%		359					
120	83	65%	0.67	> 10,000					
121	> 10,000	0%		131					

122	581	56%	0.08	> 10,000					
123	869	31%	0.03	> 10,000					
124	255	36%	0.12	1801					
125	17	8%	0.34	239					
126	69	18	0.23	1038					
127	69	50%	0.62	> 10,000	4065	19%	0.001	168	491
128	916	9%	0.01	5403					
129	> 10,000	0%		81					
130	> 10,000	0%		2513					
131	26	58%	1.9	> 10,000	> 10,000	0%			$>10^3$
132	> 10,000	0%		3780					
133	40	65%	1.4	> 10,000	2392	24%	0.003	148	529
134	17	67%	3.5	> 10,000	> 10,000	0%		105	$>10^3$
135	47	16%	0.30	1147					
136	101	13%	0.11	3489					
137	16	19%	1.1	531	> 10,000	0%			$>10^3$
138	46	38%	0.70	2179	> 10,000	0%		1241	$>10^3$
139	90	56%	0.54	> 10,000	> 10,000	0%		1567	$>10^3$
140	49	34%	0.60	2619	> 10,000	0%		476	$>10^3$
141	24	89%	3.2	> 10,000	778	55%	0.02	45	169
160	83	46%	0.48	> 10,000	> 10,000	0%		587	$>10^3$
165	27	21%	0.66	423	> 10,000	0%		268	$>10^3$
166	12	29%	2.0	489	> 10,000	0%		154	$>10^3$
173	36	40%	0.97	3654	> 10,000	0%		249	$>10^3$
174	> 10,000	0%		11	> 10,000	0%		11	
175	37	27%	0.62	3160					
176	506	70%	0.18	> 10,000					
177	35	23%	0.57	3031					

[000291] The compounds of Examples 2, 4, and 5 are each strong (full) antagonists of the G-q signaling pathway, with the compound of Example 4 having comparable antagonist activity to the non-biased reference compound of Formula A. Preferably, for non-hallucinogenic activity, compounds should have either antagonistic activity at the G-q signaling pathway, or partial agonist activity with low intrinsic efficacy. Full agonist activity at the G-q signaling pathway (i.e., high intrinsic activity) is believed to cause hallucinogenic side effects.

[000292] For maximum effectiveness, the compounds of the present disclosure are preferably agonists of beta-arrestin mediated signaling, either as partial agonists or as full agonists. Thus, in combination with the lack of agonist activity at the G-q pathway, they should be strongly biased towards beta-arrestin signaling. The compounds of Examples 2, 4, and 5, however, are antagonists of beta-arrestin signaling. The compound of Example 4, for example, much like the compound of Formula A, has equivalent strong antagonistic activity at both G-q and beta-arrestin signaling pathways. Thus, while it could be a potent antidepressant, antipsychotic, like lumateperone (ITI-007), it would not display the unique hallmarks of the psychedelic antidepressant family.

[000293] In contrast, the compounds of Examples 14, 15, and 16 in particular show partial agonist activity in the beta-arrestin assay and significant bias towards beta-arrestin mediated agonism, especially the compound of Example 15, which has zero G-q mediated agonist activity. The compounds of Examples 24, 25, and 40, also show zero G-q mediated agonist activity, but while the compound of Example 24 is a beta-arrestin antagonist, the compounds of Examples 25 and 40 are beta-arrestin partial agonists.

[000294] The results together show a wide variety of functional activity profiles for the compounds according to the present disclosure, which will provide them each with the potential for varying uses and secondary effect or side effect profiles.

[000295] The data further shows a trend that compound having a 2 or 3-atom side chain linker preferentially active the beta-arrestin signaling pathway, with varying levels of intrinsic activity. For example, compounds wherein n is 2 or 3, and Z is a bond, or compounds wherein n is 1 or 2 and Z is a group one-atom across (e.g., a -C(O)-, -O-, or a carbonyl equivalent group). For some embodiments, the side chain linker is preferably 3 atoms in length, thus wherein n is 3 and Z is a bond, or n is 2 and Z is a group one-atom across.

[000296] For example, comparison of the results for the homologous compounds of Examples 2, 3, 4, and 129, and the reference Compound A, each having Z= -C(O)- with n of 1-5, suggests that having a linker that is shorter or longer may reduce or eliminate beta-arrestin agonist activity (n=1, 3, 4, 5), compared to a linker of optimal length (n =2). Indeed, in this series, even though all compounds bind strongly to the 5-HT_{2A} receptor as antagonists (Ki = 0.5-53 nM), only the compound of Example 3 shows beta-arrestin agonist activity but Gq antagonist activity. In contrast, the Compound A, wherein n = 3, is a potent beta-arrestin signaling antagonist, rather than an agonist, as well as a Gq signaling antagonist.

[000297] The data also suggests that the substituent pattern around the A ring may impact binding modes of the compounds to the 5-HT_{2A} receptor, as can the connecting group Z. For some series of compounds agonist versus antagonist binding may depend on the choice of group Z or on the presence or absence of electron-donating or electron-withdrawing groups on the ring A. This permits one to tune the desired activity of the molecule by optimizing these various groups, achieving either strong agonism and/or strong antagonism in the signaling pathways, including mixed agonist/antagonist activities for beta-arrestin signaling (e.g., the compound of Example 34. The data suggests that small electron-donating groups on ring A may promote agonistic beta-arrestin activity, while larger groups or electron-withdrawing groups on ring A may abolish agonistic beta arrestin activity.

[000298] While the compounds of the present disclosure provide a range of related receptor binding activities, it should be noted that the desirable antidepressant, anxiolytic, and other CNS therapeutic properties of the hallucinogenic psychedelics is presently believed to be associated with beta-arrestin signaling at the 5-HT2A receptor, it cannot yet be ruled that some degree of Gq signaling is also desirable. While strong Gq signaling results in hallucinogenic effects, it remains possible that there is a degree of Gq signaling that may be beneficial to the therapeutic use of the present compounds without causing an undue risk of hallucinatory behavior. Indeed, in patients without a history of psychosis or hallucinogen persisting perception disorder (HPPD), higher levels of Gq signaling may be permissible, whereas in patients with such history, a compound that is more completely devoid of Gq signaling may be optimal.

[000299] **Example 183: *In Vivo* Characterization**

[000300] Selected compounds (test compounds) are submitted to rodent functional model assays to determine *in vivo* efficacy.

[000301] *Head Twitch Assay.* The stereotyped head twitch response induced by 5-HT_{2A} agonists is used as a behavioral proxy for hallucinations. See Halberstadt, et al., Neuropharmacology, 167, 107933 (2020). The head-twitch response is an indicator of hallucinogenic potency of a compound in humans and occurs nearly immediately after the administration of a classical psychedelic in rodents. By definition, a head-twitch is a rapid movement of the head from one side to the other. Head twitch is used to evaluate the potential hallucinogenic liability of compounds (at up to 10 mg/kg) relative to the positive control DOI (2.5 mg/kg). Male C57bl/6 mice (9 weeks of age) are administered test compounds and vehicle via subcutaneous (SC) injection. Mice receiving the positive control DOI receive an intraperitoneal (IP) injection. At 30 minutes post-treatment, the number of head twitch responses is recorded by a blinded observer for 5 minutes.

[000302] *Open Field Test of Anxiety-Like Behaviors.* Adult mice are habituated to the test room for one hour, and then administered a SC injection of test compound (1, 3, or 10 mg/kg) or methylcellulose vehicle, in the hind flank. For testing, animals are placed in one of four arenas in a square apparatus measuring 500 cm x 500 cm for 15 minutes. Sessions are filmed using Anymaze software (Stoelting Co, IL), using a camera mounted to the ceiling. Locomotor activity is measured by the software within the pre-defined arena. An additional center arena is pre-defined for each zone, all with an area of 100 cm x 100 cm.

[000303] *Rat Social Interaction Test.* Test compound (0.3, 1.0, 3 and 3.0 mg/kg, or alternatively, 1, 3, and 10 mg/kg) or vehicle (0.5% aqueous CMC) is injected SC 30 minutes before behavioral testing. During the testing phase, a pair of rats (Sprague-Dawley males) receiving the same treatment are placed in a white Plexiglass open field arena and are allowed to interact for 6 minutes. Social interactions include sniffing the other rat, grooming the other rat, climbing over, under or around the other rat, following the other rat, and exploring the ano-genital area of the other rat. The time the rats spend interacting with each other during the 6-minute test is recorded by a trained observer. Chlordiazepoxide (IP, 5 mg/kg) is used as a positive control.

[000304] *mTOR signaling in the pre-frontal cortex (PFC).* Male adult mice are injected SC with either test compound (1 mg/kg) or vehicle. At 24 hours post-injection, samples from the

PFC region of the brain are collected, and a synaptoneurosome-enriched fraction is collected and prepared for Western blotting., Quantitative analysis of phospho (p) protein immunoblots are determined relative to total levels of each protein. Change in the amount of phosphorylated ERK, Akt, mTOR, and P70S6K proteins, in the PFC are determined relative to vehicle-treated mice, as previously described (Dutheil, et al., *J. Neuroscience*, 43(5):863-77, 2023).

[000305] It is found that compounds according to the disclosure (e.g., Examples 3, 14, 15, 25, 40, 69, 70, 71, 72, 92, 98, 99, 107, 112, 117, 118) elicit non-hallucinogenic activity, increase social interaction, and/or reduce measures of anxiety in test animals. For example, unlike the serotonergic psychedelic DOI, even high doses of a test compound up to 10 mg/kg does not elicit hallucinogenic behavior, as shown by a rate of head twitch comparable to control (e.g., < 10 head twitches per 5 minutes, or less than 5 head twitches or less than 1 head twitch (mean results)) and substantially less than that induced by DOI ($p < 0.0001$). Test compounds also show a dose dependent increase in social interaction between rats, and the data show that even the lowest test dose of 0.3 mg/kg is effective. In the open-field test, the test compounds are found to dose dependently reduce anxiety-like behaviors, including time in the center arena and number of entries into the center arena, without altering levels of locomotor activity or immobility. The lowest dose tested, 1 mg/kg, is found to be effective. These results demonstrate functional anxiolytic activity.

[000306] The test compounds are also found to stimulate mTOR signaling in the mouse medial PFC, as demonstrated by increases in p-ERK, p-mTOR, and p-P70s6k in the tested brain regions. The mTOR signaling pathway has been shown to contribute to neuroplasticity and enhanced cognitive function and it is altered in brain regions associated with major depressive disorder. Rapid-acting antidepressants have been reported to stimulate this pathway in the prefrontal cortex.

[000307] **Example 184: Pharmacokinetic evaluation**

[000308] Compounds according to the present disclosure are submitted to a standard testing protocol for oral pharmacokinetics in Sprague-Dawley rats (males, 200-400 g). Test compounds are administered to rats either IV at 1 mg/kg or PO at 10 mg/kg, using a 0.05M citrate phosphate buffer as vehicle. Other potential vehicles include PEG-400 and aqueous 10% Trapposol/1% Tween 80, depending on compound solubility. In some studies, a third arm may utilize subcutaneous dosing (e.g., SC at 1 mg/kg). Plasma samples are collected at 2, 5, 15, and 30

minutes, and 1, 2, 4, 8, and 24 hours, post-dosing. After processing, plasma samples are analyzed for the presence of the test compound, and for some cases, for the presence of major expected metabolites (e.g., N-des-methyl metabolite). Time to maximum concentration (Tmax), maximal plasma concentration (Cmax), and area-under-the-curve (AUC) are calculated from the data. Comparison between the AUC values for oral versus IV dosing provides the oral bioavailability of the test compound.

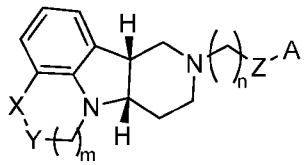
[000309] Compounds tested include Examples 40, 99, 107, 112, 117, and 118. The compounds are found to have acceptable oral bioavailability.

[000310] The forgoing examples are merely exemplary and are not meant to limit the scope of the present disclosure in any way.

CLAIMS

What is claimed:

1. A compound of a Formula I



Formula I

wherein:

X is S, S(O), $S(O)_2$, O, CH_2, CHR^b, $C(R^b)_2$, NH, $N(R^a)$ (e.g., $N(CH_3)$), N-C(O)-R^a, N-C(O)-O-R^a, N-C(O)-O-CH_2-O-R^a, N-CH_2-O-C(O)-R^a, $N^+(=O^-)$, a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane), or a spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane), wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is optionally substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;

Y is CH_2, CHR^c, -C(O)-, $C(R^c)_2$, a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane), or a spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane), wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is optionally substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;

Z is a bond, -S-, S(O), $S(O)_2$, -O-, -NH, $N(R^d)$, -C(O)-, -C(OH)-, -C(OC_{1-6}alkyl), -C(=N-OH)-, -C(=N-OC_{1-6}alkyl)-, a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane), a spiro-joined 3-6-membered heterocycloalkyl (e.g., aziridine or oxetane), or -O$(CH_2)_p$O- wherein p is 2, 3, or 4 (e.g., p is 2), wherein said spiro-joined C_{3-6}cycloalkyl or 3-6-membered heterocycloalkyl is optionally substituted by one or more groups selected from C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkoxy (e.g., methoxy), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and hydroxy;

A is H, a C_{3-6}cycloalkyl (e.g., cyclopropyl or cyclohexyl), aryl (e.g., phenyl), or heteroaryl, wherein said cycloalkyl, aryl, or heteroaryl is substituted by 0-5 groups R;

each R is independently selected from aryl (e.g., phenyl), aryloxy (e.g., phenoxy), heteroaryl (e.g., pyridyl), C_{1-6}alkyl (e.g., methyl, ethyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkylsulfonyl (e.g., methylsulfonyl), C_{1-6}alkoxy (e.g., methoxy, ethoxy), C_{1-6}alkylthio (e.g., methylthio), halo (e.g., F), cyano, C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), or hydroxy, wherein each of said aryl, heteroaryl, alkyl, haloalkyl, alkylsulfonyl, alkoxy, alkylthio, cycloalkyl, or cycloalkoxy is optionally further substituted by one or more groups selected from aryl (optionally substituted with halo), halo, C_{1-6}alkyl (e.g., methyl), haloC_{1-6}alkyl (e.g., trifluoromethyl), C_{1-6}alkylsulfonyl (e.g., methylsulfonyl), C_{1-6}alkoxy (e.g., methoxy), C_{1-6}alkylthio (e.g., methylthio), C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), amino, C_{1-6}alkylamino (e.g., methylamino), di(C_{1-6}alkyl)amino (e.g., dimethylamino), (C_{1-6}alkyl)(C_{1-6}alkyl)amino (e.g., methylethylamino), and hydroxy;

R^a and R^d, are each independently selected from C_{1-20}alkyl (e.g., methyl or tert-butyl), and C_{1-2}alkylaryl (e.g., benzyl or phenethyl);

R^b and R^c are each independently selected from C_{1-6}alkyl (e.g., methyl, ethyl, tert-butyl), C_{1-6}alkoxy, C_{3-6}cycloalkyl (e.g., cyclopropyl), C_{3-6}cycloalkoxy (e.g., cyclopropoxy), and C_{1-2}alkylaryl (e.g., benzyl or phenethyl);

m is 1 or 2;

n is 1, 2, 3, 4, or 5;

in free or salt form (e.g., pharmaceutically acceptable salt form);

provided that n is not 3 when Z is -C(O)-, X is CH_2 or O, and m is 2; and

provided that n is not 3 when Z is -C(O)-, X is CH_2, and m is 1; and

provided that n is not 3 when Z is -C(O)- or -O-, X is NH or N(R^a), and m is 1;

and provided that n is not 3 when Z is O, X is NCH_3, Y is -C(O)-, and m is 1.

2. The compound according to claim 1, wherein X is NH or N(R^a) (e.g., N(CH_3)).
3. The compound according to claim 1, wherein X is S, S(O), $S(O)_2$, or O.
4. The compound according to claim 1, wherein X is a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane).
5. The compound according to any of claims 1-4, wherein Y is CH_2 or -C(O)-.

6. The compound according to any of claims 1-4, wherein Y is a spiro-joined C_{3-6}cycloalkyl (e.g., cyclopropane).
7. The compound according to any of claims 1-6, wherein Z is a bond, CH_2, -C(O)-, or -O-.
8. The compound according to any of claims 1-7, wherein A is a 6-10 membered aryl ring, e.g., selected from phenyl and naphthyl, substituted by 0-5 groups R.
9. The compound according to any of claims 1-7, wherein A is a 5-10 membered heteroaryl ring, substituted by 0-5 groups R.
10. The compound according to any one of claims 1-7, wherein A is selected from furan, thiophene (e.g., thiophen-2-yl), pyrrole, oxazole, thiazole, imidazole, isoxazole, isothiazole, pyrazole, pyridine (e.g., pyrid-4-yl), 2-oxopyridine (e.g., 2-oxopyridin-1(2H)-yl), pyrimidine, pyridazine, pyrazine, benzofuran (e.g., benzofuran-4-yl, or benzofuran-7-yl, or 2-methylbenzofuran-4-yl), dihydrobenzofuran (e.g., 2,3-dihydrobenzofuran-7-yl), benzothiophene, indole (e.g., indol-1-yl, indol-3-yl, or indol-5-yl), benzoxazole, benzothiazole, benzimidazole (e.g., benzo[d]imidazol-1-yl), benzisoxazole (e.g., benzo[d]isoxazol-3-yl, or benzo[d]isoxazol-4-yl), benzisothiazole (e.g., benzo[d]isothiazol-3-yl), benzotriazole (e.g., benzo[d][1,2,3-triazol-1-yl), indazole (e.g., indazol-1-yl, indazol-3-yl, or indazol-7-yl), quinoline (e.g., quinolin-8-yl), isoquinoline (e.g., isoquinolin-7-yl), quinazoline (e.g., quinazolin-7-yl), and quinoxaline (e.g., quinoxalin-5-yl), each substituted by 0-5 groups R.
11. The compound according to any of claims 1-7, wherein A is phenyl substituted by 0-5 group R wherein each group R is independently selected from methyl, trifluoromethyl, methoxy, F, Cl, cyano, hydroxy, 2-methoxyethoxy, and (4-fluorobenzyl)oxy.
12. The compound according to any of claims 1-11, wherein the compound is selected from any one of the compounds of Examples 1 to 180.
13. The compound according to any of claims 1-12, in pharmaceutically acceptable salt form.
14. The compound according to any one of claims 1-13, wherein the compound is an agonist of beta-arrestin signaling via the 5-HT_{2A} receptor.
15. The compound according to any one of claims 1-13, wherein the compound is an antagonist of beta-arrestin signaling via the 5-HT_{2A} receptor.

16. The compound according to any one of claims 1-15, wherein the compound is not an agonist or antagonist of G-q signaling via the 5-HT_{2A} receptor, or is a weak agonist or antagonist thereof.
17. The compound according to any one of claims 1-16, wherein the compound has a bias ratio (beta-arrestin/G-q) for agonism or antagonism 5-HT_{2A} receptor of the of at least 2, or at least 5, or at least 10, or at least 25, or at least 50, or at least 100, or at least 150, or at least 200.
18. A pharmaceutical composition comprising a compound according to any one of claims 1-17, in free or pharmaceutically acceptable salt form (e.g., pharmaceutically acceptable salt form), in admixture with a pharmaceutically acceptable diluent or carrier.
19. A method for the treatment or prophylaxis of a central nervous system disorder, comprising administering to a patient in need thereof a compound according to any one of claims 1-17, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 18.
20. Use of a compound according to any of claims 1-17, in free or pharmaceutically acceptable salt form, or a pharmaceutical composition according to claim 18, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for the treatment or prophylaxis of a central nervous system disorder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/086562

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4985 A61P25/18 A61P25/22 A61P25/24 C07D487/16
ADD.

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)
A61P C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2022/372035 A1 (LI PENG [US] ET AL) 24 November 2022 (2022-11-24) claim 14 paragraph [[0241]] page 2: compounds of formula A and B	1,2,5, 7-20
X	US 2022/296591 A1 (LI PENG [US] ET AL) 22 September 2022 (2022-09-22) claim 1, par [0011]: formula (I) paragraph [0313] examples	1,2,5, 7-20
X	WO 2020/154519 A2 (INTRA CELLULAR THERAPIES INC [US]) 30 July 2020 (2020-07-30) paragraph [0045] claim 1	1,2,5, 7-20

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[X] Further documents are listed in the continuation of Box C.

[X] 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

"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
12 April 2024	18/06/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Panday, Narendra

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/165755 A1 (INTRA-CELLULAR THERAPIES INC [US]) 28 September 2017 (2017-09-28) claims, examples page 4: formula Q-2	1,2,5, 7-20
X,P	CN 117 069 720 A (SHANGHAI YISHI PHARMACEUTICAL TECH CO LTD) 17 November 2023 (2023-11-17) paragraph [0064] - paragraph [0068] paragraph [0173] paragraph [0229] - paragraph [0230] paragraph [0249] - paragraph [0251] page [0013] & DATABASE CAPLUS [Online] Chemical Abstract Service, Columbus, Ohio, US; 16 May 2023 (2023-05-16), Song Yunlong ET AL: "Preparation of quinoxaline derivative and application as 5-HT2A receptoragonist", XP093136355, retrieved from STN Database accession no. 2023:2377458 abstract depicted compounds	1,2,5, 7-20
X,P	CN 116 444 520 A (UNIV SHANGHAI TECH ET AL.) 18 July 2023 (2023-07-18) paragraph [0060] - paragraph [0061] paragraph [0062]; compounds I-28, I-29 claim 8 & DATABASE CAPLUS [Online] Chemical Abstract Service, Columbus, Ohio, US; 18 July 2023 (2023-07-18), Cheng Jianjun ET AL: "Preparation of cyclopiperidine compounds as 5-HT2A receptor for depressiontreatment", XP093136359, retrieved from STN Database accession no. 2023:1474543 abstract depicted compounds	1,2,5, 7-20
X	US 2013/202692 A1 (MATES SHARON [US] ET AL) 8 August 2013 (2013-08-08) paragraph [0312] Claims 1, with X = NH, NMe and Y = CH(OH) (first possibility)	1,2,5, 7-11, 13-20

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICES, COLUMBUS OHIO; 8 August 2013 (2013-08-08), Mates Sharon ET AL: "Organic compounds", XP093136380, Database accession no. 2016:2120038 abstract RN1345667-47-1, RN1345667-48-2, 1345667-49-3, 1345667-50-6 -----	
X	PENG LI ET AL: "Discovery of a Tetracyclic Quinoxaline Derivative as a Potent and Orally Active Multifunctional Drug Candidate for the Treatment of Neuropsychiatric and Neurological Disorders", JOURNAL OF MEDICINAL CHEMISTRY, vol. 57, no. 6, 5 March 2014 (2014-03-05), pages 2670-2682, XP055545362, US ISSN: 0022-2623, DOI: 10.1021/jm401958n page 2673; table 2; compounds 43, 44, 45, 47 -----	1,2,5, 7-11, 13-20

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INTERNATIONAL SEARCH REPORT

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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.:
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 additional sheet

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 an 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, 2, 5, 7-20(all partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2, 5, 7-20(all partially)

   Compound of formula (I) with X = N, Y = CH2, pharmaceutical composition comprising it, medical uses involving it.

   ---

2. claims: 1, 2, 5, 7-20(all partially)

   Compound of formula (I) with X = N, Y = CO, pharmaceutical composition comprising it, medical uses involving it.

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3. claims: 1, 2, 6-20(all partially)

   Compound of formula (I) with X = N, Y = spiro-joined C3-6 Cycloalkyl, pharmaceutical composition comprising it, medical uses involving it.

   ---

4. claims: 1, 2, 7-20(all partially)

   Compound of formula (I) with X = N, Y = possibilities indicated in claim 1, not being as in inventions 1-3, pharmaceutical composition comprising it, medical uses involving it.

   ---

5. claims: 1, 3, 5-20(all partially)

   Compound of formula (I) with X = S, SO, SO2, pharmaceutical composition comprising it, medical uses involving it.

   ---

6. claims: 1, 3, 5-20(all partially)

   Compound of formula (I) with X = O, pharmaceutical composition comprising it, medical uses involving it.

   ---

7. claims: 4(completely); 1, 5-20(partially)

   Compound of formula (I) with X = C (optionally substituted as according to the possibilities for X in claim 1) , pharmaceutical composition comprising it, medical uses involving it.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2023/086562

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Information on patent family members

International application No
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