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(54) **INDOLE DERIVATIVES AS SEROTONERGIC AGENTS USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO**

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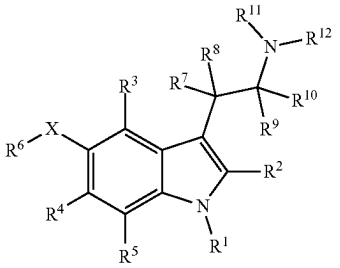
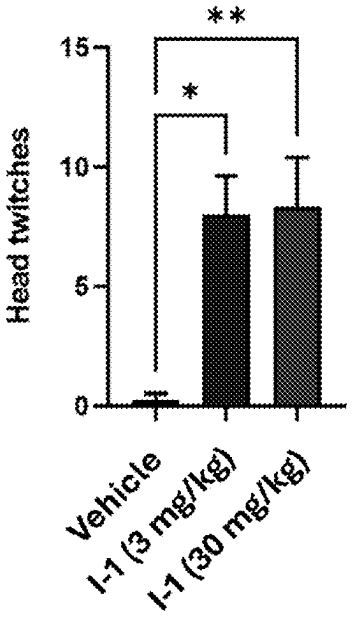
(57) **ABSTRACT**

The present disclosure relates to indole derivatives of general Formula (I), to processes for their preparation, to compositions including them and to their use in activation of a serotonin receptors in a cell, as well as to treating diseases, disorders, or conditions by activation of a serotonin receptors in a cell. The diseases, disorders, or conditions include, for example, psychosis, mental illnesses, and central nervous system (CNS) disorders.

Formula (I)





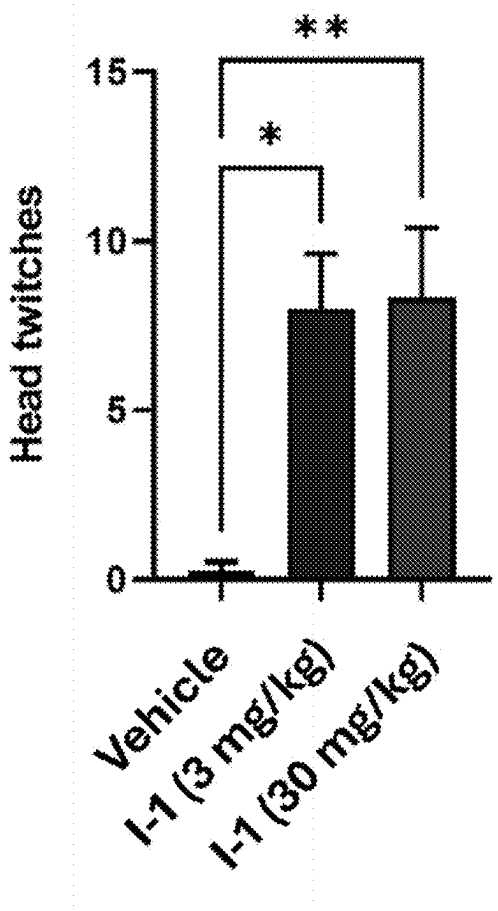


Figure 1

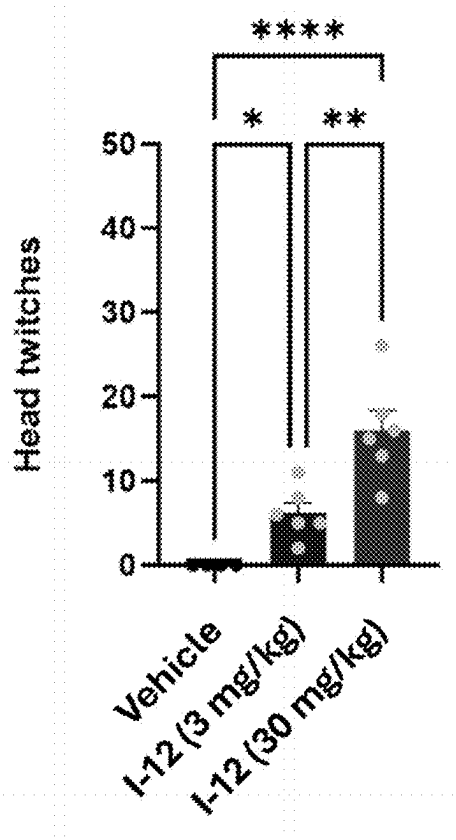


Figure 2

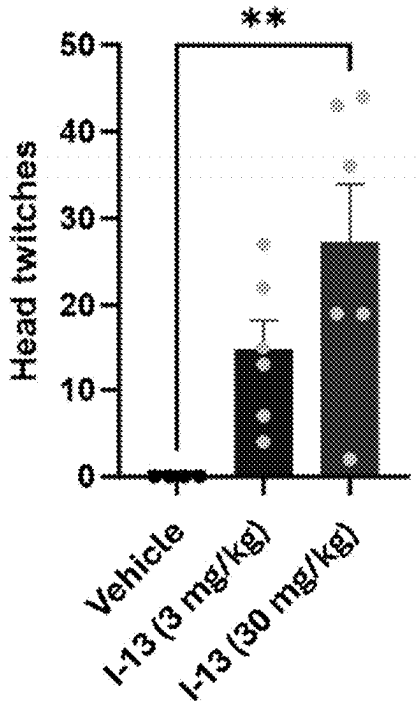


Figure 3

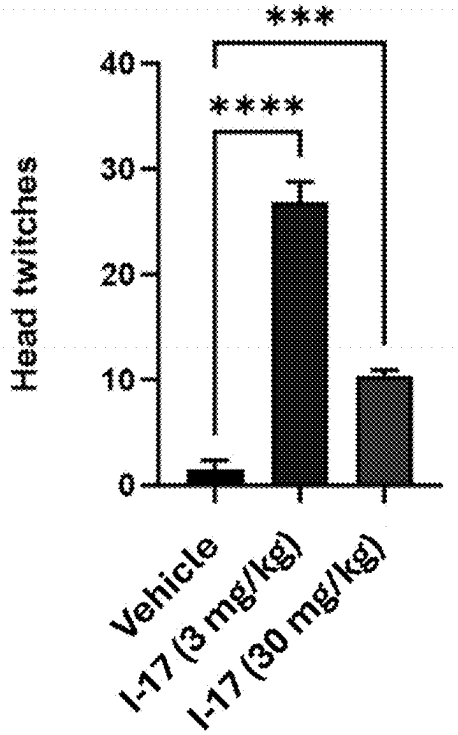


Figure 4

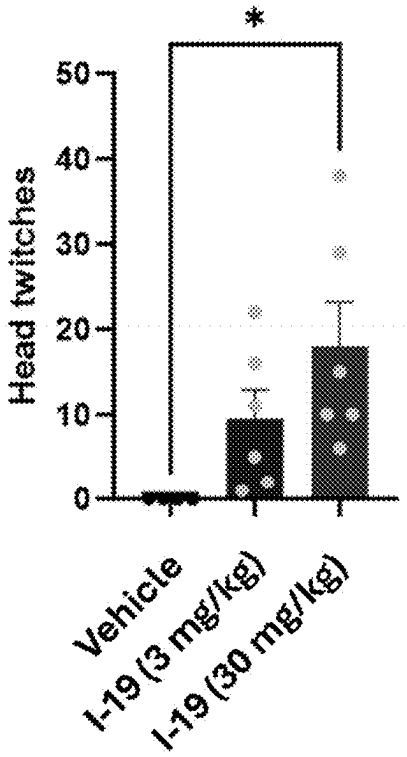


Figure 5

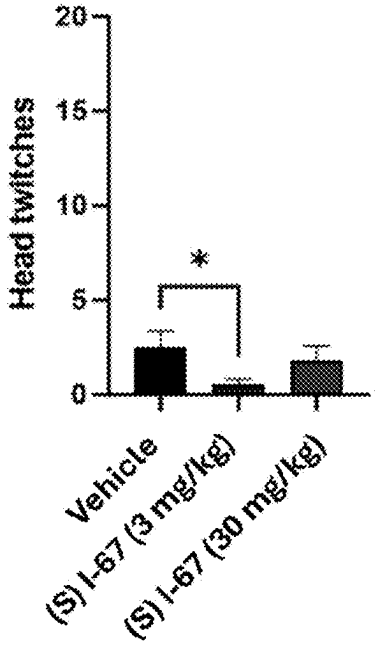


Figure 6

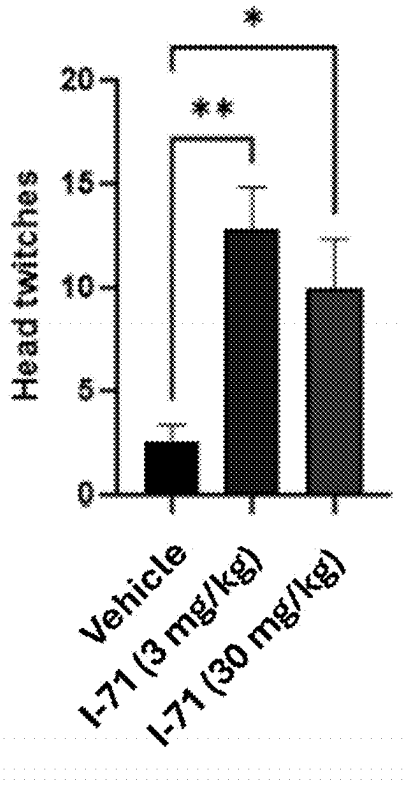


Figure 7

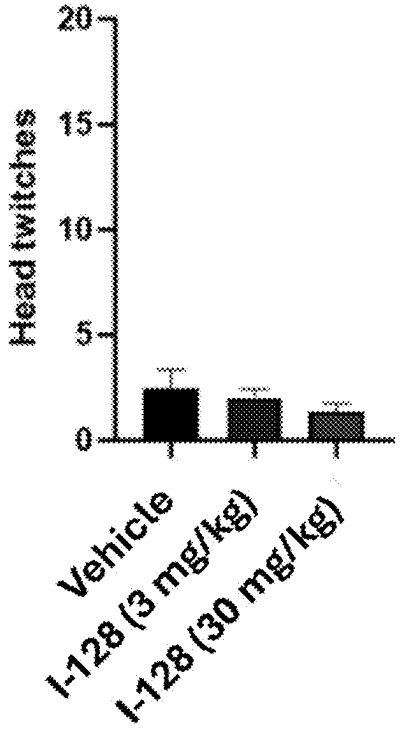


Figure 8

INDOLE DERIVATIVES AS SEROTONERGIC AGENTS USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO

CROSS-REFERENCE TO RELATED APPLICATIONS AND CLAIMS OF PRIORITY

[0001] This application is a continuation application of International Application No. PCT/IB2024/000642 filed on Nov. 12, 2024, which claims the benefit of priority of U.S. Provisional Application No. 63/598,671 filed on Nov. 14, 2023, and U.S. Provisional Application No. 63/598,711 filed on Nov. 14, 2023, the complete disclosures of all of which are incorporated herein by reference and priority of each being claimed.

FIELD

[0002] The disclosure relates to indole derivatives of general Formula (I) for the treatment of different conditions that are treated by activation of serotonin receptors or receptor subtypes, for example, mental illnesses and neurological disease, in the fields of psychiatry, neurobiology, and pharmacotherapy. The present disclosure further comprises methods for making the compounds of Formula (I) and corresponding intermediates.

BACKGROUND

[0003] Mental health disorders, or mental illness, refer to a wide range of disorders that include, but are not limited to, depressive disorders, anxiety and panic disorders, schizophrenia, eating disorders, substance misuse disorders, post-traumatic stress disorder, attention deficit/hyperactivity disorder and obsessive-compulsive disorder. Many mental health disorders, as well as neurological disorders, are impacted by alterations, dysfunction, degeneration, and/or damage to the brain's serotonergic system, which may explain, in part, common endophenotypes and comorbidities among neuropsychiatric and neurological diseases.

[0004] The field of psychedelic neuroscience has witnessed a recent renaissance following a decade of restricted research due to the evolving legal status of psychedelics. Psychedelics (serotonergic hallucinogens) are powerful psychoactive substances that alter perception and mood and affect numerous cognitive processes. Today there is a consensus that psychedelics are agonists or partial agonists at serotonin 5-hydroxytryptamine 2A (5-HT_{2A}) receptors.

[0005] Psychedelics have both rapid onset and persisting effects long after their acute effects, which includes changes in mood and brain function. Long lasting effects may result from their unique receptor affinities, which affect neurotransmission via neuromodulatory systems that serve to modulate brain activity, i.e., neuroplasticity, and promote cell survival, are neuroprotective, and modulate brain neuroimmune systems. The mechanisms which lead to these long-term neuromodulatory changes may be linked to epigenetic modifications, gene expression changes and modulation of pre- and post-synaptic receptor densities. These previously under-researched, psychedelic drugs may potentially provide the next generation of neurotherapeutics, where treatment resistant psychiatric and neurological diseases, e.g., depression, post-traumatic stress disorder, dementia, and addiction, may become treatable with attenuated pharmacological risk profiles.

[0006] Although there is a general perception that psychedelic drugs are dangerous, from a physiologic safety standpoint, they are one of the safest known classes of central nervous system (CNS) drugs. Preliminary data show that psychedelic administration in humans results in a unique profile of effects and potential adverse reactions that need to be appropriately addressed to maximize safety. The primary safety concerns are largely psychologic, rather than physiologic, in nature. Somatic effects vary but are relatively insignificant, even at doses that elicit powerful psychologic effects. Psilocybin, when administered in a controlled setting, has frequently been reported to cause transient, delayed headache, with incidence, duration, and severity increased in a dose-related manner [Johnson et al., Drug Alcohol Depend (2012) 123(1-3):132-140]. It has been found that repeated administration of psychedelics leads to a very rapid development of tolerance known as tachyphylaxis, a phenomenon believed to be mediated, in part, by 5-HT_{2A} receptors. In fact, several studies have shown that rapid tolerance to psychedelics correlates with downregulation of 5-HT_{2A} receptors. For example, daily LSD administration selectively decreased 5-HT_2 receptor density in the rat brain [Buckholtz et al., Eur. J. Pharmacol. 1990, 109:421-425. 1985; Buckholtz et al., Life Sci. 1985, 42:2439-2445].

[0007] Classic psychedelics and dissociative psychedelics are known to have rapid onset antidepressant and anti-addictive effects, unlike any currently available treatment. Randomized clinical control studies have confirmed antidepressant and anxiolytic effects of classic psychedelics in humans.

[0008] Psilocybin (4-phosphoryloxy-N,N-dimethyltrypatmine) has the chemical formula $C_{12}H_{17}N_2O_4P$. It is a tryptamine-based prodrug and is one of the major psychoactive constituents in mushrooms of the psilocybe species. It was first isolated from psilocybe mushrooms by Hofmann in 1957, later synthesized by him in 1958 [Passie et al., Addict Biol., 2002, 7(4):357-364], and was used in psychiatric, psychological research and in psychotherapy during the early to mid-1960s up until its controlled drug scheduling in 1970 in the United States, and up until the 1980s in Germany [Passie 2005; Passie et al., Addict Biol., 2002, 7(4):357-364]. Research into the effects of psilocybin resumed in the mid-1990s, and it is currently the preferred compound for use in studies of the effects of serotonergic hallucinogens [Carter et al., J. Cogn. Neurosci., 2005 17(10):1497-1508; Gouzoulis-Mayfrank et al., Neuropsychopharmacology 1999, 20(6):565-581; Hasler et al, Psychopharmacology (Berl) 2004, 172(2):145-156], likely because it has a shorter duration of action and suffers from less notoriety than LSD. Like other members of this class, psilocybin induces sometimes profound changes in perception, cognition, and emotion, including emotional lability.

[0009] In humans as well as other mammals, psilocybin is transformed into the active metabolite psilocin, or the 4-hydroxy-N,N-dimethyltryptamine parent compound. It is likely that psilocin partially or wholly produces most of the subjective and physiological effects of psilocybin in humans and non-human animals. Recently, human psilocybin research confirmed the 5-HT_{2A} activity of psilocybin via the parent psilocin, and provides some support for indirect effects on dopamine through 5-HT_{2A} activity and possible activity at other serotonin receptors. In fact, the most consistent finding for involvement of other receptors in the actions of psychedelics is the 5-HT_{1A} receptor. That is

particularly true for tryptamines and LSD, which generally have significant affinity and functional potency at this receptor. It is known that 5-HT_{1A} receptors are colocalized with 5-HT_{2A} receptors on cortical pyramidal cells [Martin-Ruiz et al., J Neurosci. 2001, 21(24):9856-986], where the two receptor types have opposing functional effects [Araneda et al., Neuroscience 1991, 40(2):399-412].

[0010] Although the exact role of the 5-HT_{2A} receptor, and other 5-HT_2 receptor family members, is not well understood with respect to the amygdala, it is evident that the 5-HT_{2A} receptor plays an important role in emotional responses and is an important target to be considered in the actions of 5-HT_{2A} agonist psychedelics. In fact, a majority of known 5-HT_{2A} agonists produce hallucinogenic effects in humans, and rodents generalize from one 5-HT_{2A} agonist to others, as between psilocybin and LSD [Aghajanian et al., Eur J Pharmacol., 1999, 367(2-3):197-206; Nichols at al., J Neurochem., 2004, 90(3):576-584]. Psilocybin has a stronger affinity for the human 5-HT_{2A} receptor than for the rat receptor and it has a lower K(i) for both 5-HT_{2A} and 5-HT_{2C} receptors than LSD. Moreover, results from a series of drug-discrimination studies in rats found that 5-HT_{2A} antagonists, but not 5-HT_{1A} antagonists, prevented rats from recognizing psilocybin [Winter et al., Pharmacol Biochem Behav., 2007, 87(4):472-480]. Daily doses of LSD and psilocybin reduce 5-HT_2 receptor density in rat brain.

[0011] Today, psilocybin is one of the most widely used psychedelics in human studies due to its relative safety, moderately long active duration, and good absorption in subjects. There remains strong research and therapeutic potential for psilocybin as recent studies have shown varying degrees of success in neurotic disorders, alcoholism, depression associated with major depressive disorder, treatment resistant depression and in terminally ill cancer patients, obsessive compulsive disorder, addiction, anxiety, post-traumatic stress disorder, and even cluster headaches.

[0012] Recent developments include several double-blind placebo-controlled phase 2 studies of psilocybin-assisted psychotherapy in patients with treatment resistant depression, major depressive disorder, and cancer-related psychosocial distress that demonstrate unprecedented positive relief of anxiety and depression. Two recent small pilot studies of psilocybin-assisted psychotherapy also have shown positive benefit in treating both alcohol and nicotine addiction. Recently, blood oxygen level-dependent functional magnetic resonance imaging (fMRI) and magnetoencephalography (ME G) have been employed for in vivo brain imaging in humans after administration of a psychedelic, and results indicate that intravenously administered psilocybin and LSD produce decreases in oscillatory power in areas of the brain's default mode network [Nichols D E. Pharmacol Rev., 2016, 68(2):264-355].

[0013] Preliminary studies using positron emission tomography (PET) showed that psilocybin ingestion (15 or 20 mg orally) increased absolute metabolic rate of glucose in frontal, and to a lesser extent in other, cortical regions as well as in striatal and limbic subcortical structures in healthy participants, suggesting that some of the key behavioral effects of psilocybin involve the frontal cortex [Gouzoulis-Mayfrank et al., Neuropsychopharmacology, 1999, 20(6): 565-581; Vollenweider et al., Brain Res. Bull. 2001, 56(5): 495-507]. Although 5-HT_{2A} agonism is widely recognized as the primary action of classic psychedelic agents, psilocybin has less affinity for a wide range of other pre- and post-synaptic serotonin and dopamine receptors, as well as the serotonin reuptake transporter [Tyls et al., Eur. Neuropsychopharmacol., 2014, 24(3):342-356]. Psilocybin activates 5-HT_{1A} receptors, which may contribute to antidepressant/anti-anxiety effects.

[0014] Depression and anxiety are two of the most common psychiatric disorders worldwide. Depression is a multifaceted condition characterized by episodes of mood disturbances alongside other symptoms such as anhedonia, psychomotor complaints, feelings of guilt, attentional deficits, and suicidal tendencies, all of which can range in severity. Similarly, anxiety disorders are a collective of etiologically complex disorders characterized by intense psychosocial distress and other symptoms depending on the subtype. Anxiety associated with life-threatening disease is the only anxiety subtype that has been studied in terms of psychedelic-assisted therapy. Pharmacological and psychosocial interventions are commonly used to manage this type of anxiety, but their efficacy is mixed and limited such that they often fail to provide satisfactory emotional relief. Recent interest into the use of psychedelic-assisted therapy may represent a promising alternative for patients with depression and anxiety that are ineffectively managed by conventional methods.

[0015] Generally, the psychedelic treatment model consists of administering the orally-active drug to induce a mystical experience lasting approximately 4-9 h depending on the psychedelic [Halberstadt, Behav Brain Res., 2015, 277:99-120; Nichols, Pharmacol. Rev., 2016, 68(2): 264-355]. This enables participants to work through and integrate difficult feelings and situations, leading to enduring antidepressant and anxiolytic effects. Classical psychedelics like psilocybin and LSD are being studied as potential candidates. In one study with classical psychedelics for the treatment of depression and anxiety associated with life-threatening disease, it was found that, in a supportive setting, psilocybin and LSD consistently produced significant and sustained anti-depressant and anxiolytic effects.

[0016] Psychedelic treatment is generally well-tolerated with few if any persisting adverse effects. Regarding the mechanisms of action of psychedelics, they mediate their main therapeutic effects biochemically via serotonin receptor agonism, and psychologically by generating meaningful psycho-spiritual experiences that contribute to mental flexibility. Given the limited success rates of current treatments for anxiety and mood disorders, and considering the high morbidity associated with these conditions, there is potential for psychedelics to provide symptom relief in patients inadequately managed by conventional methods.

[0017] Further emerging clinical research and evidence suggest psychedelic-assisted therapy also shows potential as an alternative treatment for refractory substance use disorders and mental health conditions, and thus may be an important tool in a crisis where existing approaches have yielded limited success [dos Santos et al., Ther Adv Psychopharmacol., 2016, 6(3):193-213]. Similarly encouraging are findings from a recent pilot study of psilocybin-assisted therapy for tobacco use disorder, demonstrating abstinence rates of 80% at six months follow-up and 67% at 12 months follow-up [Johnson et al., https://www.ncbi.nlm.nih.gov/pubmed/27441452, J Drug Alcohol Abuse, 2017, 43(1):55-60; Johnson et al., Psychopharmacol. 2014, 28(11):983-992]; such rates are considerably higher than any documented in the tobacco cessation literature. Notably,

mystical-type experiences generated from the psilocybin sessions were significantly correlated with positive treatment outcomes. These results coincide with bourgeoning evidence from recent clinical trials lending support to the effectiveness of psilocybin-assisted therapy for treatment-resistant depression and end-of-life anxiety [Carhart-Harris et al., Neuropsychopharmacology, 2017, 42(11):2105-2113]. Research on the potential benefits of psychedelic-assisted therapy for opioid use disorder (OUD) is beginning to emerge, and accumulating evidence supports a need to advance this line of investigation. Available evidence from earlier randomized clinical trials suggests a promising role for treating OUD: higher rates of abstinence were observed among participants receiving high dose LSD and ketamine-assisted therapies for heroin addiction compared to controls at long-term follow-up. Recently, a large United States population study among 44,000 individuals found that psychedelic use was associated with 40% reduced risk of opioid abuse and 27% reduced risk of opioid dependence in the following year, as defined by DSM-IV criteria [Pisano et al., J Psychopharmacol., 2017, 31(5):606-613]. Similarly, a protective moderating effect of psychedelic use was found on the relationship between prescription opioid use and suicide risk among marginalized women [Argento et al., J Psychopharmacol., 2018, 32(12):1385-1391]. Despite the promise of these preliminary findings with classical psychedelic agents, further research is warranted to determine how psychedelics may ameliorate the opioid crisis response. Meanwhile, growing evidence on the safety and efficacy of psilocybin for the treatment of mental and substance use disorders should help to motivate further clinical investigation into its use as a novel intervention for OUD.

[0018] Regular doses of psychedelics also ameliorate sleep disturbances, which are highly prevalent in depressed patients with more than 80% of depressed patients having complaints of poor sleep quality. The sleep symptoms are often unresolved by first-line treatment and are associated with a greater risk of relapse and recurrence. Interestingly, sleep problems often appear before other depression symptoms, and subjective sleep quality worsens before the onset of an episode in recurrent depression. Two other studies assessing electroencephalographic (EEG) brain activity during sleep showed that psychedelics, such as LSD, positively affect sleep patterns. It further was suggested that a single dose of a psychedelic causes a reset of the biological clock underlying sleep/wake cycles and thereby enhances cognitive-emotional processes in depressed people but also improves feelings of well-being and enhances mood in healthy individuals [Kuypers, Medical Hypotheses, 2019, 125:21-24].

[0019] In a systematic meta-analysis of clinical trials from 1960-2018 researching the therapeutic use of psychedelic treatment in patients with serious or terminal illnesses and related psychiatric illness, it was found that psychedelic therapy (mostly with LSD) may improve cancer-related depression, anxiety, and fear of death. Four randomized controlled clinical trials were published between 2011 and 2016, mostly with psilocybin treatment, that demonstrated psychedelic-assisted treatment can produce rapid, robust, and sustained improvements in cancer-related psychological and existential distress. [Ross S, Int Rev Psychiatry, 2018, 30(4):317-330]. Many patients facing cancer or other life-threatening illnesses experience significant existential distress related to loss of meaning or purpose in life, which can be associated with hopelessness, demoralization, powerlessness, perceived burdensomeness, and a desire for hastened death. Those features are also often at the core of clinically significant anxiety and depression, and they can substantially diminish quality of life in this patient population. The alleviation of these core features of existential distress should be among the central aims of palliative care. Accordingly, several manualized psychotherapies for cancer-related existential distress have been developed in recent years, with an emphasis on dignity and meaning-making. However, there are currently no pharmacologic interventions for existential distress per se, and available pharmacologic treatments for depressive symptoms in patients with cancer have not demonstrated superiority over placebo. There remains a need for additional effective treatments for those conditions [Rosenbaum et al., Curr. Oncol., 2019, 26(4): 225-226].

[0020] Recently, there has been growing interest in a new dosing paradigm for psychedelics, such as psilocybin and LSD, referred to colloquially as microdosing. Under this paradigm, sub-perceptive doses of the serotonergic hallucinogens, approximately 10% or less of the full dose, are taken on a more consistent basis of once each day, every other day, or every three days, or a permutation of the same. Not only is this dosing paradigm more consistent with current standards in pharmacological care, but it may be particularly beneficial for certain conditions, such as Alzheimer's disease, other neurodegenerative diseases, attention deficit disorder, attention deficit hyperactivity disorder, and for certain patient populations such as elderly, juvenile, and patients that are fearful of or opposed to psychedelic assisted therapy. Moreover, this approach may be particularly well suited for managing cognitive deficits and preventing neurodegeneration. For example, subpopulations of low attentive and low motivated rats demonstrate improved performance on the 5-choice serial reaction time and progressive ratio tasks, respectively, following doses of psilocybin below the threshold for eliciting the classical wet dog shake behavioral response associated with hallucinogenic doses (Blumstock et al., WO 2020/157569 A1). Similarly, treatment of patients with hallucinogenic doses of 5-HT_{2A} agonists is associated with increased BDNF and activation of the mTOR pathway, which are thought to promote neuroplasticity and are hypothesized to serve as molecular targets for the treatment of dementias and other neurodegenerative disorders (Ly et al., Cell Rep., 2018, 23(11):3170-3182). Additionally, several groups have demonstrated that low, non-hallucinogenic and non-psychomimetic, doses of 5-HT_{2A} agonists also show similar neuroprotective and increased neuroplasticity effects (neuroplastogens) and reduced neuroinflammation, which could be beneficial in treatment of both neurodegenerative and neurodevelopmental diseases and chronic disorders (Manfredi et al., WO 2020/181194, Flanagan et al., Int. Rev. Psychiatry, 2018, 13:1-13; Nichols et al., 2016, Psychedelics as medicines; an emerging new paradigm). This repeated, lower dose paradigm may extend the utility of these compounds to additional indications and may prove useful for wellness applications.

[0021] Psychosis is often referred to as an abnormal state of mind that is characterized by hallucinatory experiences, delusional thinking, and disordered thoughts. Moreover, this state is accompanied by impairments in social cognition, inappropriate emotional expressions, and bizarre behavior. Most often, psychosis develops as part of a psychiatric disorder, of which it represents an integral part of schizo-

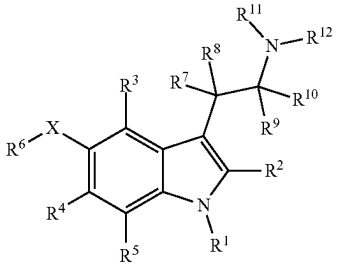
phrenia. It corresponds to the most florid phase of the illness. The very first manifestation of psychosis in a patient (i.e., in vivo) is referred to as first-episode psychosis. It reflects a critical transitional stage toward the chronic establishment of the disease, that is presumably mediated by progressive structural and functional abnormalities seen in diagnosed patients. [ACS Chem. Neurosci., 2018, 9, 2241-2251]. Anecdotal evidence suggests that low, non-hallucinogenic doses (microdosing) of psychedelics that are administered regularly can reduce symptoms of schizophrenia and psychosis.

SUMMARY

[0022] This Summary is provided to introduce a selection of representative concepts in a simplified form, which representative concepts are further described below in the Detailed Description. This Summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

[0023] The present disclosure includes compounds having the general structural formula (I):

Formula (I)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0024] wherein:

[0025] X is absent or selected from O, S, S(O), and SO_2;

[0026] R^1 is selected from H, C_1-C_6alkyl, C_1-C_6alkyleneP(O)$(OR^{13})_2$, C_1-C_6alkyleneOP(O)$(OR^{13})_2$C(O)R^{13}, CO_2R^{13}, C(O)N$(R^{13})_2$, S(O)R^{13}, and SO_2R^{13};

[0027] R^2 is selected from H, halo, and C_1-C_6alkyl;

[0028] R^3, R^4, and R^5 are independently selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

[0029] R^6 is selected from H, C_1-C_{10}alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC$_3$-C_7cycloalkyl, C_1-C_6alkyleneC$_3$-C_{10}heterocycloalkyl, C_1-C_6alkyleneC$_6$-C_{10}aryl, and C_1-C_6alkyleneC$_5$-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15};

[0030] R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_6alkyl;

[0031] R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC$_3$-C_7cycloalkyl, C_1-C_6alkyleneC$_3$-C_{10}heterocycloalkyl, C_1-C_6alkyleneC$_6$-C_{10}aryl, and C_1-C_6alkyleneC$_5$-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and C(O)R^{17}; or

[0032] R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl;

[0033] Z is selected from O, C(O), NR^{19}C(O), NR^{18}C(O)O, C(O)NR^{19}, OC(O)NR^{19}, and NR^{19};

[0034] Z' is selected from O, C(O), NR^{20}C(O), NR^{20}C(O)O, C(O)NR^{20}, OC(O)NR^{20}, and NR^{20};

[0035] R^{13}, R^1, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H and C_1-C_6alkyl;

[0036] R^{14} and R^{16} are independently selected from H, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and C(O)C_1-C_4alkyl; and

[0037] available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof,

[0038] provided when X is O, R^1 is H, CH_3 or CD_3, R^2, R^3, R^4, R^1, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl, then R^{11} and R^{12} are not H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl;

[0039] provided when X is O, R^1, R^2, R^3, R^4, R^1, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is CH_3 or CHF_2, then R^{11} and R^{12} are not CH_3 or CD_3; and provided when X is absent and R^6 is H, then at least one of R^{11} and R^{12} is not H or C_1-C_6alkyl.

[0040] In some embodiments, provided (1) when X is absent, then R^6 is not H, D, or halogen, and (2) when X is O, S, S(O), or SO_2, then at least one of R^{11} and R^{12} is not selected from H, D, halogen, C_1-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, and C_1-C_6deuterohaloalkyl.

[0041] In some embodiments, provided (1) when X is absent, then R^6 is not H, D, or halogen, and (2) when X is O, S, S(O), or SO_2, then neither R^{11} nor R^{12} is selected from H, D, halogen, C_1-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, and C_1-C_6deuterohaloalkyl.

[0042] In some embodiments, provided X is absent, then R^6 is not H, D, or halogen.

[0043] In some embodiments, including embodiments in which X is O, S, S(O), or SO_2, at least one of R^{11} and R^{12} is not selected from H, D, halogen, C_1-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, and C_1-C_6deuterohaloalkyl.

[0044] In some embodiments, including embodiments in which X is O, S, S(O), or SO_2, neither R^{11} nor R^{12} is H, D, halogen, C_1-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, or C_1-C_6deuterohaloalkyl.

[0045] In a further embodiment, the compounds of the disclosure are used as medicaments. Accordingly, the disclosure also includes a compound of the disclosure for use as a medicament.

[0046] The present disclosure includes a method for activating a serotonin receptor in a cell, either in a biological sample or in a patient, comprising administering an effective amount of one or more compounds of the disclosure to the cell.

[0047] The present disclosure also includes a method of treating psychosis or psychotic symptoms comprising administering a therapeutically effective amount of one or more compounds of the disclosure to a subject in need thereof.

[0048] The present disclosure also includes a method of treating a mental illness comprising administering a therapeutically effective amount of one or more compounds of the disclosure to a subject in need thereof.

[0049] The disclosure additionally provides a process for the preparation of compounds of the disclosure. General and specific processes are discussed in more detail below and set forth in the examples below.

[0050] This disclosure further provides intermediates for the compounds disclosed herein, methods of making the intermediates, and methods for making the compounds from the intermediates.

[0051] Other features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating embodiments of the disclosure, are given by way of illustration only and the scope of the claims should not be limited by these embodiments but should be given the broadest interpretation consistent with the description as a whole.

BRIEF DESCRIPTION OF THE DRAWINGS

[0052] The embodiments of the disclosure will now be described in greater detail with reference to the attached drawings, which are incorporated herein by reference and in which:

[0053] FIGS. **1** to **5** are graphs showing the effect of various doses (i.e., 3 mg/kg and 30 mg/kg) of exemplary compounds of Formula (I), specifically I-1, I-12, I-13, I-17, and I-19, respectively, on head-twitch response (HTR) in male C57BL6 mice. The mice were treated with compound I-1, I-12, I-13, I-17, or I-19 (3 mg/kg, 20 mg/kg, SC) by SC route and the total number of head twitches were recorded over a 20 min period. Data are expressed as mean±S E M. The induction of head twitches elicited by 5-HT_{2A} receptor agonists is believed to represent a behavioral proxy of their psychedelic effects; and

[0054] FIGS. **6** to **8** are bar graphs showing the effect of various doses (3 mg/kg and 30 mg/kg) of exemplary compounds of Formula (I), specifically (S) I-67, I-71, and I-128, respectively, on head-twitch response (HTR) in male C57BL6 mice. The mice were treated with exemplary compound (S) I-67, I-71, or I-128 (3 mg/kg, 30 mg/kg, SC) by SC route (N=6 mice/dose), and the total number of head twitches were recorded over a 20 min period. Induction of head twitches elicited by 5-HT_{2A} receptor agonists is believed to represent a behavioral proxy of their psychedelic effects. Data presented as mean±S.E.M. Analyzed using one-way ANOVA with Fishers post-hoc LSD. *$p<0.05$, **$p<0.01$, *$p<0.0001$ #Acute effects of test compounds (20-minute post SC. dosing).

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

I. Definitions

[0055] Unless otherwise indicated, the definitions and embodiments described in this and other sections are intended to be applicable to all embodiments and aspects of the present disclosure herein described for which they are suitable as would be understood by a person skilled in the art.

[0056] The term "compound(s) of the disclosure" or "compound(s) of the present disclosure" and the like, as used herein, refers to a compound Formula (I) (including Formula (I-A), (I-B), (I-C), (I-D), (I-E), (I-F), (I-G), (I-H), (I-I), and (I-J) that fall within the scope of Formula (I)) and includes pharmaceutically acceptable salts, solvates, and/or prodrugs thereof.

[0057] The term "composition(s) of the disclosure" or "composition(s) of the present disclosure" and the like, as used herein, refers to a composition, such a pharmaceutical composition, comprising one or more compounds of the disclosure.

[0058] The term "and/or," as used herein, means that the listed items are present, or used, individually or in combination. In effect, this term means that "at least one of" or "one or more" of the listed items is used or present. The term "and/or" with respect to pharmaceutically acceptable salts and/or solvates thereof means that the compounds of the disclosure exist as individual salts and solvates, as well as a combination of, for example, a salt of a solvate of a compound of the disclosure. As used herein, the term "and/or" means either or both (or any combination or all of the terms or expressed referred to), e.g., "A, B, and/or C" encompasses A alone, B alone, C alone, A and B, A and C, B and C, and A, B, and C.

[0059] As used in the present disclosure, the singular forms "a," "an," and "the" include plural references unless the content clearly dictates otherwise. For example, an embodiment including "a compound" should be understood to present certain aspects with one compound, or two or more additional compounds. It will be understood by those with skill in the art that if a specific number of an introduced claim element is intended, such intent will be explicitly recited in the claim, and in the absence of such recitation no such limitation is present. For a non-limiting example, as an aid to understanding, the appended claims contain usage of the introductory phrases "at least one" and "one or more" to introduce claim elements. However, the use of such phrases should not be construed to imply that the introduction of a claim element by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim element to embodiments containing only one such element, even when the same claim includes the introductory phrase "one or more" or "at least one" and indefinite articles such as "a" or "an"; the same holds true for the use in the claims of definite articles.

[0060] As used in this disclosure and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of

including, such as "include" and "includes") or "containing" (and any form of containing, such as "contain" and "contains"), are inclusive or open-ended and do not exclude additional, unrecited elements or process steps.

[0061] The term "consisting" and its derivatives, as used herein, are intended to be closed terms that specify the presence of the stated features, elements, components, groups, integers and/or steps and also exclude the presence of other unstated features, elements, components, groups, integers, and/or steps.

[0062] The term "consisting essentially of," as used herein, is intended to specify the presence of the stated features, elements, components, groups, integers, and/or steps as well as those that do not materially affect the basic and novel characteristic(s) of these features, elements, components, groups, integers, and/or steps.

[0063] In embodiments comprising an "additional" or "second" component, such as an additional or second compound, the second component, as used herein, is chemically different from the other components or first component. A "third" component is different from the other, first and second components and further enumerated or "additional" components are similarly different. "First," "second," "third," etc. in this context is not meant to imply an order or sequence, other than the order in which the terms appear in the claims, unless the claims clearly indicate otherwise.

[0064] The term "suitable," as used herein, means that the selection of the particular compound or conditions would depend on the specific synthetic manipulation to be performed, the identity of the molecule(s) to be transformed and/or the specific use for the compound, but the selection would be well within the skill of a person trained in the art. All process/method steps described herein are to be conducted under conditions sufficient to provide the product shown. A person skilled in the art would understand that all reaction conditions, including, for example, reaction solvent, reaction time, reaction temperature, reaction pressure, reactant ratio and whether or not the reaction should be performed under an anhydrous or inert atmosphere, can be varied to optimize the yield of the desired product and it is within their skill to do so.

[0065] The terms "about," "substantially," and "approximately," as used herein, mean a reasonable amount of deviation of the modified term such that the end result is not significantly changed. These terms of degree should be construed as including a deviation of at least 5% of the modified term if this deviation would not negate the meaning of the word it modifies or unless the context suggests otherwise to a person skilled in the art.

[0066] The present description refers to a number of chemical terms and abbreviations used by those skilled in the art. Nevertheless, definitions of selected terms are provided for clarity and consistency.

[0067] The term "alkyl" as used herein, whether it is used alone or as part of another group, means straight or branched chain, saturated alkyl groups. The number of carbon atoms that are possible in the referenced alkyl group are indicated by the prefix "C_{n1}-C_{n2}." Thus, for example, the term "C_1-C_6alkyl" (or "C_{1-6}alkyl") means an alkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms and includes, for example, any of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec-, and tert-butyl, n- and iso-propyl, ethyl, and methyl. As another example, "C_1-C_4alkyl" refers to n-, iso-, sec- and tert-butyl, n- and isopropyl, ethyl, and methyl.

[0068] The term "alkenyl" whether it is used alone or as part of another group, means straight or branched chain, unsaturated alkyl groups containing at least one double bond. The number of carbon atoms that are possible in the referenced alkenyl group are indicated by the prefix "C_{n1}-C_{n2}." For example, the term C_2-C_6alkenyl (or C_{2-6}alkenyl) means an alkenyl group having 2, 3, 4, 5, or 6 carbon atoms.

[0069] The term "alkynyl" as used herein, whether it is used alone or as part of another group, means straight or branched chain, unsaturated alkyl groups containing at least one triple bond. The number of carbon atoms that are possible in the referenced alkynyl group are indicated by the prefix "C_{n1}-C_{n2}." For example, the term C_2-C_6alkynyl (or C_{2-6}alkynyl) means an alkynyl group having 2, 3, 4, 5, or 6 carbon atoms.

[0070] The term "cycloalkyl," as used herein, whether it is used alone or as part of another group, means a saturated carbocyclic group containing one or more rings. The number of carbon atoms that are possible in the referenced cycloalkyl group are indicated by the numerical prefix "C_{n1}-C_{n2}." For example, the term C_{3-7}cycloalkyl (or C_{3-7}cycloalkyl) means a cycloalkyl group having 3, 4, 5, 6, or 7 carbon atoms.

[0071] The term "heterocycloalkyl" as used herein, whether it is used alone or as part of another group, refers to cyclic groups containing at least one non-aromatic ring in which one or more of the atoms are a heteromoiety selected from O, S, and N, including oxidized or substituted versions thereof (e.g., S(O) and SO_2), and the remaining atoms are C. Heterocycloalkyl groups are either saturated or unsaturated (i.e., contain one or more double bonds) and/or optionally comprise one or more C═O groups (i.e., one or more carbon atoms in the ring is oxidized to C═O). W hen a heterocycloalkyl group contains the prefix C_{n1}-C_{n2} this prefix indicates the number of carbon atoms in the corresponding carbocyclic group, in which one or more, suitably 1 to 5, of the ring atoms is replaced with a heteromoiety as selected from O, S, and N including oxidized or substituted versions thereof, and the remaining atoms are C. Heterocycloalkyl groups may also be preceded by "n1- to n2-membered" which refers to the total number of atoms in the group. Heterocycloalkyl groups are optionally benzofused.

[0072] The term "aryl," as used herein, whether it is used alone or as part of another group, refers to carbocyclic groups containing at least one aromatic ring.

[0073] The term "heteroaryl," as used herein, whether it is used alone or as part of another group, refers to cyclic groups containing at least one heteroaromatic ring in which one or more of the atoms are a heteromoiety selected from O, S, and N, including oxidized or substituted versions thereof (e.g., S(O) and SO_2), and the remaining atoms are C. When a heteroaryl group contains the prefix C_{n1-n2} this prefix indicates the number of carbon atoms in the corresponding carbocyclic group, in which one or more, suitably 1 to 5, of the ring atoms is replaced with a heteroatom as defined above. Heteroaryl groups may also be preceded by "n1- to n2-membered" which refers to the total number of atoms in the group. Heteroaryl groups are optionally benzofused.

[0074] All cyclic groups, including aryl, heteroaryl, heterocycloalkyl, and cycloalkyl groups, contain one or more than one ring (i.e., are polycyclic). When a cyclic group contains more than one ring, the rings may be fused, bridged, spirofused, or linked by a bond.

[0075] The term "benzofused," as used herein, refers to a polycyclic group in which a benzene ring is fused with another ring.

[0076] A first ring being "fused" with a second ring means the first ring and the second ring share two adjacent atoms there between.

[0077] A first ring being "bridged" with a second ring means the first ring and the second ring share two non-adjacent atoms there between.

[0078] A first ring being "spirofused" with a second ring means the first ring and the second ring share one atom there between.

[0079] The term "halogen" (or "halo") whether it is used alone or as part of another group, refers to a halogen atom and includes fluoro, chloro, bromo, and iodo.

[0080] The term "haloalkyl," as used herein, refers to an alkyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a halogen. Thus, for example, "C_{1-6}haloalkyl" (or "C_1-C_6haloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more halogen substituents.

[0081] As used herein, the term "haloalkenyl" refers to an alkenyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a halogen. Thus, for example, "C_{2-6}haloalkenyl" (or "C_1-C_6haloalkenyl") refers to a C_2 to C_6 linear or branched alkenyl group as defined above with one or more halogen substituents.

[0082] As used herein, the term "haloalkynyl" refers to an alkynyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a halogen. Thus, for example, "C_{2-6}haloalkynyl" (or "C_1-C_6haloalkynyl") refers to a C_2 to C_6 linear or branched alkynyl group as defined above with one or more halogen substituents.

[0083] The term "deuteroalkyl," as used herein, refers to an alkyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium. Thus, for example, "C_1-6deuteroalkyl" (or "C_1-C_6deuteroalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more deuterium substituents.

[0084] The term "deuteroalkenyl," as used herein, refers to an alkenyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium. Thus, for example, "C_{2-6}deuteroalkenyl" (or "C_2-C_6deuteroalkenyl") refers to a C_2 to C_6 linear or branched alkenyl group as defined above with one or more deuterium substituents.

[0085] The term "deuteroalkynyl," as used herein, refers to an alkynyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium. Thus, for example, "C_{2-6}deuteroalkynyl" (or "C_2-C_6deuteroalkynyl") refers to a C_2 to C_6 linear or branched alkynyl group as defined above with one or more deuterium substituents.

[0086] The term "fluoroalkyl," as used herein, refers to an alkyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a fluorine. Thus, for example, "C_{1-6}fluoroalkyl" (or "C_1-C_6fluoroalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more fluorine substituents.

[0087] The term "fluoroalkenyl," as used herein, refers to an alkenyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a fluorine. Thus, for example, "C_{2-6}fluoroalkenyl" (or "C_2-C_6fluoroalkenyl") refers to a C_2 to C_6 linear or branched alkenyl group as defined above with one or more fluorine substituents.

[0088] The term "fluoroalkynyl," as used herein, refers to an alkynyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a fluorine. Thus, for example, "C_{2-6}fluoroalkynyl" (or "C_2-C_6fluoroalkynyl") refers to a C_2 to C_6 linear or branched alkynyl group as defined above with one or more fluorine substituents.

[0089] The term "deuterohaloalkyl," as used herein, refers to an alkyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium and one or more of the available hydrogen atoms have been independently replaced with a halogen. Thus, for example, "C_{1-6}deuterohaloalkyl" (or "C_1-C_6deuterohaloalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more deuterium substituents and one or more halogen substituents.

[0090] The term "deuterohaloalkenyl," as used herein, refers to an alkenyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium and one or more of the available hydrogen atoms have been independently replaced with a halogen. Thus, for example, "C_{2-6}deuterohaloalkenyl" (or "C_2-C_6deuterohaloalkenyl") refers to a C_2 to C_6 linear or branched alkenyl group as defined above with one or more deuterium substituents and one or more halogen substituents.

[0091] The term "deuterohaloalkynyl," as used herein, refers to an alkynyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium and one or more of the available hydrogen atoms have been independently replaced with a halogen. Thus, for example, "C_{2-6}deuterohaloalkynyl" (or "C_1-C_6deuterohaloalkynyl") refers to a C_2 to C_6 linear or branched alkynyl group as defined above with one or more deuterium substituents and one or more halogen substituents.

[0092] The term "deuterofluoroalkyl," as used herein, refers to an alkyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium and one or more of the available hydrogen atoms have been independently replaced with a fluorine. Thus, for example, "C_{1-6}deuterofluoroalkyl" (or "C_1-C_6deuterofluoroalkyl") refers to a C_1 to C_6 linear or branched alkyl group as defined above with one or more deuterium substituents and one or more fluorine substituents.

[0093] The term "deuterofluoroalkenyl," as used herein, refers to an alkenyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium and one or more of the available hydrogen atoms have been independently replaced with a fluorine. Thus, for example, "C_{2-6}deuterofluoroalkenyl" (or "C_1-C_6deuterofluoroalkenyl") refers to a C_2 to C_6 linear or branched alkenyl group as defined above with one or more deuterium substituents and one or more fluorine substituents.

[0094] The term "deuterofluoroalkynyl," as used herein, refers to an alkynyl group as defined above in which one or more of the available hydrogen atoms have been independently replaced with a deuterium and one or more of the available hydrogen atoms have been independently replaced with a fluorine. Thus, for example, "C_{2-6}deuterofluoroalkynyl" (or "C_2-C_6deuterofluoroalkynyl") refers to a C_2 to C_6 linear or branched alkynyl group as defined above with one or more deuterium substituents and one or more fluorine substituents.

[0095] The suffix "ene" at the end of a group (for example "alkylene" or "alkenylene") means that the group is bivalent, that is that it is bonded to two variables each on a different end of or location on the group.

[0096] The term "optionally substituted," as used herein, means that the subject group is unsubstituted or substituted and the terms "optionally substituted" and "unsubstituted or substituted" are used interchangeably herein. As used herein, when referring to more than one item or "each" item, "optionally substituted" and "unsubstituted or substituted" means that the items are independently unsubstituted or substituted with respect to one another, e.g., for item A and item B, both may be substituted, both may be unsubstituted, or one may be substituted and the other unsubstituted. Additionally, as used herein, the term "optionally substituted" when referring to more than one item means that if more than one of the items is substituted, the substitutions may be independent from one another, e.g., for item A and item B that are both substituted, item A may have a first substitution and item B may have a second substitution that is the same or different from the first substitution of item A.

[0097] As used herein, the term "one or more" item includes a single item selected from the list as well as two or more items (e.g., mixtures) selected from the list.

[0098] The term "substituted," as used herein, means, unless otherwise indicated, that the referenced group is substituted with one or more substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, C_1-C_4haloalkyl, OC_1-C_4haloalkyl, CN, OH, NH_2, $NH(C_1$-C_4alkyl), $N(C_1$-C_4alkyl)(C-C_4alkyl), SC_1-C_4alkyl, S(O)C-C_4alkyl, SO_2C_1-C_4alkyl, CO_2H, CO_2C_1-C_4alkyl, $C(O)NH_2$, $C(O)NHC_1$-C_4alkyl, $C(O)N(C_1$-C_4alkyl)(C_1-C_4alkyl), C_3-C_6cycloalkyl, and a 3- to 6-membered heterocyclic ring including 1 to 2 ring, or 1 to 3 ring, heteromoieties selected from O, S, S(O), SO_2, N, NH, and NC_1-C_4alkyl.

[0099] When a group is substituted with more than one substituent selected from a list of substituents, each of the substituents is independently selected from the listed group of substituents.

[0100] The term "available," as in "available hydrogen atoms" or "available atoms" refers to atoms that would be known to a person skilled in the art to be capable of replacement by a substituent.

[0101] The term "alternate isotope thereof," as used herein, refers to an isotope of an element that is other than the isotope that is most abundant in nature.

[0102] The term "all available atoms are optionally replaced with alternate isotope thereof" or "available atoms are optionally replaced with alternative isotope thereof," as used herein, means that available atoms, optionally each and every available atom, are optionally and independently replaced with an isotope of that atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. When a compound comprises an atom that has been replaced with an alternate isotope thereof, the compound comprises that alternate isotope in greater amounts than would otherwise be present in the compound if said replacement had not taken place.

[0103] The term "all available hydrogen atoms are optionally replaced with a halogen atom" or "available hydrogen atoms are optionally replaced with a halogen atom," as used herein, means that available hydrogen atoms, optionally each and every available hydrogen atom, are optionally and independently replaced with a halogen atom.

[0104] The term "all available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom" or "available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom," as used herein, means that available hydrogen atoms, optionally each and every available hydrogen atom, are optionally and independently replaced with a fluorine atom or a chlorine atom.

[0105] The term "pharmaceutically acceptable" means compatible with the treatment of subjects.

[0106] The term "pharmaceutically acceptable carrier" means a non-toxic solvent, dispersant, excipient, adjuvant, or other material which is mixed with the active ingredient in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to a subject.

[0107] The term "pharmaceutically acceptable salt" means either an acid addition salt or a base addition salt which is suitable for, or compatible with, the treatment of subjects.

[0108] An acid addition salt suitable for, or compatible with, the treatment of subjects is any non-toxic organic or inorganic acid addition salt of any basic compound.

[0109] A base addition salt suitable for, or compatible with, the treatment of subjects is any non-toxic organic or inorganic base addition salt of any acidic compound.

[0110] The term "solvate," as used herein, means a compound, or a salt or prodrug of a compound, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered.

[0111] The term "prodrug," as used herein, means a compound, or salt of a compound, that, after administration, is converted into an active drug.

[0112] The term "protecting group" or "PG" and the like, as used herein, refers to a chemical moiety which protects or masks a reactive portion of a molecule to prevent side reactions in those reactive portions of the molecule, while manipulating or reacting a different portion of the molecule. After the manipulation or reaction is complete, the protecting group is removed under conditions that do not degrade or decompose the remaining portions of the molecule. The selection of a suitable protecting group can be made by a person skilled in the art. Many conventional protecting groups are known in the art, for example as described in "Protective Groups in Organic Chemistry," McOmie, J. F. W. Ed., Plenum Press, 1973, in Greene, T. W. and Wuts, P. G. M., "Protective Groups in Organic Synthesis," John Wiley & Sons, 3rd Edition, 1999 and in Kocienski, P. Protecting Groups, 3rd Edition, 2003, Georg Thieme Verlag (The Americas).

[0113] The term "subject," as used herein, includes all members of the animal kingdom including mammals, and

suitably refers to humans. Thus, the methods of the present disclosure are applicable to both human therapy and veterinary applications.

[0114] The term "treating" or "treatment," as used herein, and as is well understood in the art, means an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, diminishment of the reoccurrence of disease and remission (whether partial or total), whether detectable or undetectable. "Treating" and "treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. "Treating" and "treatment," as used herein, also include prophylactic treatment. Treatment methods comprise administering to a subject a therapeutically effective amount of one or more of the compounds of the disclosure and optionally consist of a single administration, or alternatively comprise a series of administrations.

[0115] As used herein, the term "effective amount" or "therapeutically effective amount" means an amount of one or more compounds of the disclosure that is effective, at dosages and for periods of time necessary to achieve the desired result. For example, in the context of treating a disease, disorder, or condition mediated or treated by agonism or activation of serotonergic receptors and downstream second messengers, an effective amount is an amount that, for example, increases said activation compared to the activation without administration of the one or more compounds.

[0116] "Palliating" a disease, disorder, or condition means that the extent and/or undesirable clinical manifestations of a disease, disorder, or condition are lessened and/or time course of the progression is slowed or lengthened, as compared to not treating the disorder.

[0117] The term "administered," as used herein, means administration of a therapeutically effective amount of one or more compounds or compositions of the disclosure to a cell, tissue, organ, or subject.

[0118] The term "prevention" or "prophylaxis," or synonym thereto, as used herein, refers to a reduction in the risk or probability of a patient becoming afflicted with a disease, disorder, or condition or manifesting a symptom associated with a disease, disorder, or condition.

[0119] The term "disease, disorder, or condition," as used herein, refers to a disease, disorder, or condition treated or treatable by activation and/or binding of any serotonin receptor ($5HT_1$ to $5HT_7$) and their sub-receptors and subtypes(e.g., $5\text{-}HT_{1A}$, $5\text{-}HT_{2A}$, $5\text{-}HT_{2B}$, $5\text{-}HT_2c$) and particularly using one or more compounds of the disclosure herein described.

[0120] The term "treating a disease, disorder, or condition by activation of a serotonin receptor," as used herein, means that the disease, disorder, or condition to be treated is affected by, modulated by, and/or has some biological basis, either direct or indirect, that includes serotonergic activity, in particular increases in serotonergic activity. These diseases respond favorably when serotonergic activity associated with the disease, disorder, or condition is agonized by one or more of the compounds or compositions of the disclosure.

[0121] The term "activation," as used herein, includes agonism, partial agonist, and positive allosteric modulation of a serotonin receptor.

[0122] The term "$5\text{-}HT_{2A}$," as used herein, means the $5\text{-}HT_{2A}$ receptor subtype of the 5-HT2 serotonin receptor.

[0123] The terms "$5\text{-}HT_{1A}$," as used herein, means the $5\text{-}HT_{1A}$ receptor subtypes of the 5-HT1 serotonin receptor.

[0124] The term "$5\text{-}HT_{2B}$," as used herein, means the $5\text{-}HT_{2B}$ receptor subtype of the 5-HT2 serotonin receptor.

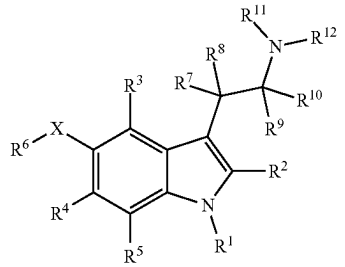
[0125] The term "$5\text{-}HT_{2C}$," as used herein, means the $5\text{-}HT_{2C}$ receptor subtype of the 5-HT2 serotonin receptor.

[0126] The term "therapeutic agent," as used herein, refers to any drug or active agent that has a pharmacological effect when administered to a subject.

II. Compounds

[0127] The present disclosure includes a compound of Formula (I):

Formula (I)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0128] wherein:

[0129] X is absent or selected from O, S, S(O), and SO_2;

[0130] R^1 is selected from H, C_1-C_6alkyl, C_1-C_6alkyleneP(O)$(OR^{13})_2$, C_1-C_6alkyleneOP(O)$(OR^{13})_2$C(O)R^{13}, CO_2R^{13}, C(O)N$(R^{13})_2$, S(O)R^{13}, and SO_2R^{13};

[0131] R^2 is selected from H, halo, and C_1-C_6alkyl;

[0132] R^3, R^4, and R^5 are independently selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

[0133] R^6 is selected from H, C_1-C_{10}alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15};

[0134] R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_6alkyl;

[0135] R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups

being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$; or

[0136] R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl;

[0137] Z is selected from O, C(O), $NR^{19}C(O)$, $NR^{18}C(O)O$, $C(O)NR^{19}$, $OC(O)NR^{19}$, and NR^{19};

[0138] Z' is selected from O, C(O), $NR^{20}C(O)$, $NR^{20}C(O)O$, $C(O)NR^{20}$, $OC(O)NR^{20}$, and NR^{20};

[0139] R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H and C_1-C_6alkyl;

[0140] R^{14} and R^{16} are independently selected from H, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl; and available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof, provided when X is O, R^1 is H, CH_3, or CD_3, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl, then R^{11} and R^{12} are not H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl;

[0141] provided when X is O, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is CH_3 or CHF_2, then R^{11} and $R^{12}$are not CH_3 or CD_3; and provided when X is absent and R^6 is H, then at least one of R^{11} and R^{12} is not H or C_1-C_6alkyl.

[0142] According to one or more embodiments, the present disclosure includes a compound of Formula (I) as defined above or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, wherein:

[0143] X is selected from S, S(O), and SO_2;

[0144] R^1 is selected from H, C_1-C_6alkyl, C_1-C_6alkyleneP(O)$(OR^{13})_2$, C_1-C_6alkyleneOP(O)$(OR^{13})_2$C(O)R^{13}, CO_2R^{13}, C(O)N$(R^{13})_2$, S(O)R^{13}, and SO_2R^{13};

[0145] R^2 is selected from H, halo, and C_1-C_6alkyl;

[0146] R^3, R^4, and R^5 are independently selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

[0147] R^6 is selected from H, C_1-C_{10}alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC$_3$-C_7cycloalkyl, C_1-C_6alkyleneC$_3$-C_{10}heterocycloalkyl, C_1-C_6alkyleneC$_6$-C_{10}aryl, and C_1-C_6alkyleneC$_5$-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and $C(O)R^{15}$;

[0148] R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_6alkyl;

[0149] R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC$_3$-C_7cycloalkyl, C_1-C_6alkyleneC$_3$-C_{10}heterocycloalkyl, C_1-C_6alkyleneC$_6$-C_{10}aryl, and C_1-C_6alkyleneC$_5$-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$; or

[0150] R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl;

[0151] Z is selected from O, C(O), $NR^{19}C(O)$, $NR^{18}C(O)O$, $C(O)NR^{19}$, $OC(O)NR^{19}$, and NR^{19};

[0152] Z' is selected from O, C(O), $NR^{20}C(O)$, $NR^{20}C(O)O$, $C(O)NR^{20}$, $OC(O)NR^{20}$, and NR^{20};

[0153] R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H and C_1-C_6alkyl;

[0154] R^{14} and R^{16} are independently selected from H, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl; and available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0155] According to one or more embodiments, the present disclosure includes a compound of Formula (I) as defined above or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof, wherein:

[0156] X is absent or O;

[0157] R^1 is selected from H, C_1-C_6alkyl, C_1-C_6alkyleneP(O)$(OR^{13})_2$, C_1-C_6alkyleneOP(O)$(OR^{13})_2$, C(O)R^{13}, CO_2R^{13}, C(O)N$(R^{13})_2$, S(O)R^{13}, and SO_2R^{13};

[0158] R^2 is selected from H, halo, and C_1-C_6alkyl;

[0159] R^3, R^4, and R^5 are independently selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

[0160] R^6 is selected from H, C_1-C_{10}alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC$_3$-C_7cycloalkyl, C_1-C_6alkyleneC$_3$-C_{10}heterocycloalkyl, C_1-C_6alkyleneC$_6$-C_{10}aryl, and C_1-C_6alkyleneC$_5$-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and $C(O)R^{15}$;

[0161] R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_6alkyl;

[0162] R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl,

C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$; or

[0163] R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl;

[0164] Z is selected from O, C(O), $NR^{19}C(O)$, $NR^{18}C(O)O$, $C(O)NR^{19}$, $OC(O)NR^{19}$, and NR^{19} Z' is selected from O, C(O), $NR^{20}C(O)$, $NR^{20}C(O)O$, $C(O)NR^{20}$, $OC(O)NR^{20}$, and NR^{20};

[0165] R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H and C_1-C_6alkyl;

[0166] R^{14} and R^{16} are independently selected from H, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl; and

[0167] available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof,

[0168] provided when X is O, R^1 is H, CH_3, or CD_3, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl, then R^{11} and R^{12} are not H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl;

[0169] provided when X is O, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is CH_3 or CHF_2, then R^{11} and R^{12} are not CH_3 or CD_3; and provided when X is absent and R^6 is H, then at least one of R^{11} and R^{12} is neither H nor C_1-C_6alkyl.

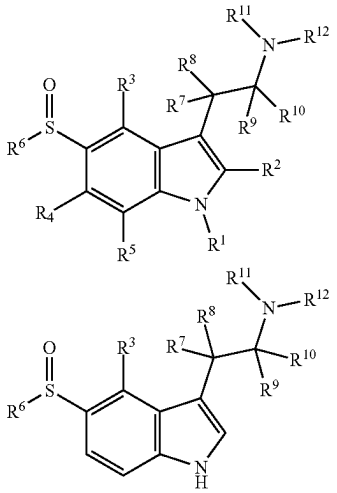
[0170] In some embodiments, when available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is independently selected from I, F, Cl, and Br. In some embodiments, when available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is independently selected from F, Cl, and Br. In some embodiments, when available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is independently selected from F, Cl, and I. In some embodiments, when available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is independently selected from F and I. In some embodiments, when available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is independently selected from F and Br. In some embodiments, when available hydrogen atoms are replaced with a halogen atom, the halogen atom is independently selected from F and Cl. In some embodiments, when available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is F.

[0171] In some embodiments, available hydrogen atoms are optionally independently replaced with an alternate isotope thereof. In some embodiments, the alternate isotope of hydrogen is deuterium.

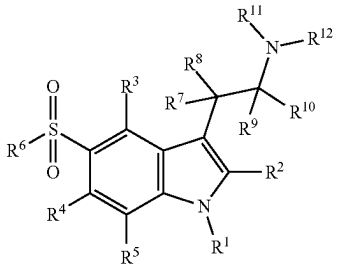
[0172] Therefore, in some embodiments, available hydrogen atoms are optionally replaced with a halogen atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, available hydrogen atoms are optionally replaced with a fluorine atom and/or available hydrogen atoms are replaced with deuterium. In some embodiments, available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

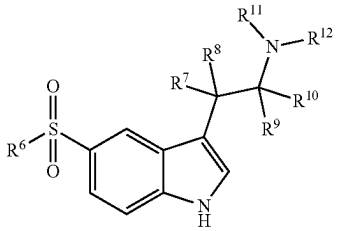
[0173] In some embodiments, the compounds of the disclosure are isotopically enriched with deuterium. In some embodiments, especially those in which X is S, S(O), or SO_2, as well as other embodiments in which X is 0 or absent, one or more of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} independently comprises one or more deuterium or one or more of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, and R^{14} independently is deuterium. In some embodiments, especially those in which X is absent or oxygen, as well as other embodiments of X, one or more of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17} R^{18}, R^{19}, and R^{20} independently comprises one or more deuterium or one or more of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} R^{14}, R^{15}, R^{16}, R^{17} R^{18}, R^{19}, and R^{20} independently is deuterium.

[0174] In some embodiments, X is S(O), as shown in the structures below, wherein in the bottom structure R^1, R^2, R^3, R^4, and R^5 are hydrogen but may be, for example, deuterium and/or a halogen:

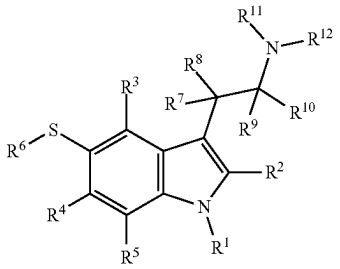


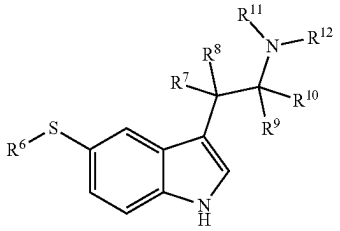
[0175] In some embodiments, X is SO_2, as shown in the structures below, wherein in the bottom structure R^1, R^2, R^3, R^4, and R^5 are hydrogen but may be, for example, deuterium and/or a halogen:



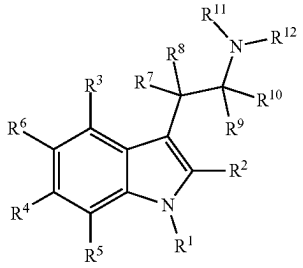


[0176] In some embodiments, X is S, as shown in the structures below, wherein in the bottom structure R^1, R^2, R^3, R^4, and R^5 are hydrogen but may be, for example, deuterium and/or a halogen:

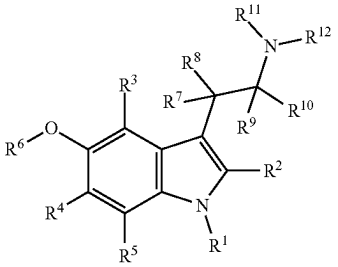


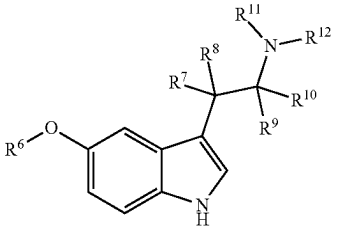


[0177] In some embodiments, X is absent (e.g., a direct bond), as shown below:



[0178] In some embodiments, X is O, as shown in the structures below, wherein in the bottom structure R^1, R^2, R^3, R^4, and R^5 are hydrogen but may be, for example, deuterium and/or a halogen:





[0179] In some embodiments, R^1 is selected from S(O) R13 and SO_2R^{13}.

[0180] In some embodiments, R^1 is selected from H, C_1-C_4alkyl, C_1-C_3alkylene$P(O)(OR^{13})_2$, C_1-C_4alkyleneOP$(O)(OR^{13})_2$, $C(O)R^{13}$, CO_2R^{13}, and $C(O)N(R^{13})_2$, wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^1 is selected from H, C_1-C_4alkyl, C_1-C_3alkylene$P(O)(OR^{13})_2$, C_1-C_4alkyleneOP$(O)(OR^{13})_2$, $C(O)R^{13}$, CO_2R^{13}, and $C(O)N(R^{13})_2$, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^1 is selected from H, C_1-C_3alkyl, $CH_2P(O)(OR^{13})_2$, $CH_2CH_2P(O)(OR^{13})_2$, $CH_2CH(CH_3)P(O)(OR^{13})_2$, $CH(CH_3)CH_2P(O)(OR^{13})_2$, $CH(CH_3)P(O)(OR^{13})_2$, $CH(CH_2CH_3)P(O)(OR^{13})_2$, $(CH_2)OP(O)(OR^{13})_2$, $C(O)R^{13}$, and CO_2R^{13}, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^1 is selected from H, CH_3, CH_2CH_3, $CH_2P(O)(OR^{13})_2$, $CH(CH_3)P(O)(OR^{13})$

$_2$, and $(CH_2)OP(O)(OR^{13})_2$, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^1 is selected from H, CH_3, CH_2CH_3, $CH_2P(O)(OR^{13})_2$, $CH(CH_3)P(O)(OR^{13})_2$, and $(CH_2)OP(O)(OR^{13})_2$ wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, especially those in which X is absent or oxygen, as well as other embodiments of X, R^1 is selected from H, CH_3, CH_2CH_3, $CH_2P(O)(OR^{13})_2$, $CH(CH_3)P(O)(OR^{13})_2$, and $(CH_2)OP(O)(OR^{13})_2$, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^1 is selected from H, CH_3, CH_2CH_3, $CH_2P(O)(OR^{13})_2$, and $(CH_2)OP(O)(OR^{13})_2$, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^1 is selected from H, CH_3, CH_2CH_3, $CH_2P(O)(OR^{13})_2$, $(CH_2)OP(O)(OR^{13})_2$, $C(O)R^{13}$, and CO_2R^{13}, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^1 is selected from H, CH_3, and CH_2CH_3, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^1 is selected from H and D. In some embodiments, R^1 is H.

[0181] In some embodiments, R^2 is selected from H, halo, and C_1-C_4alkyl wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^2 is selected from H, D, halo, and C_1-C_4alkyl wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^2 is selected from H, D, halo, and C_1-C_4alkyl wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^2 is selected from H, D, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl. In some embodiments, R^2 is selected from H, D, F, Br, Cl, CH_3, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, CH_2CH_3, CH_2CH_2F, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, and CD_2CD_3. In some embodiments, R^2 is selected from H, D, F, CH_3, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, and CD_2CD_3. In some embodiments, R^2 is selected from H, D, CH_3, CF_3, CHF_2, CH_2F, CD_2H, CDH_2, and CD_3. In some embodiments, R^2 is selected from H, D, CH_3, CF_3, and CD_3. In some embodiments, R^2 is H.

[0182] In some embodiments, R^3 is selected from H, halo, CN, C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^3 is selected from H, D, halo, CN, C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl, wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^3 is selected from H, D, halo, CN, C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^3 is selected from H, D, CN, halo, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4deuteroalkenyl, C_2-C_4deuterofluoroalkenyl C_2-C_4alkynyl, C_2-C_4deuteroalkynyl, C_2-C_4fluoroalkynyl, and C_2-C_4deuterofluoroalkynyl. In some embodiments, R^3 is selected from H, D, CN, halo, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C-C_4deuterofluoroalkyl, C_2-C_4alkenyl, and C_2-C_4fluoroalkenyl. In some embodiments, R^3 is selected from H, D, CN, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C-C_4deuterofluoroalkyl. In some embodiments, R^3 is selected from H, D, CN, F, Br, CI, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3, and CD_2CD_3. In some embodiments, R^3 is selected from H, D, CN, F, Cl, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, and CF_3. In some embodiments, R^3 is selected from H, F, and Cl. In some embodiments, R^3 is selected from H, F, and D. In some embodiments, R^3 is selected from H, F, and Cl. In some embodiments, R^3 is selected from H and D. In some embodiments, R^3 is H.

[0183] In some embodiments, R^3 is selected from H, CN, C_1-C_4alkyl, C_1-C_4haloalkyl, C_2-C_4alkenyl, C_2-C_4haloalkenyl, C_2-C_4alkynyl, and C_2-C_4haloalkynyl, wherein available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^3 is selected from H, CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4alkynyl, and C_2-C_4fluoroalkynyl, wherein available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^3 is selected from H, D, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4deuteroalkenyl, C_2-C_4deuterofluoroalkenyl, C_2-C_4alkynyl, C_2-C_4deuteroalkynyl, C_2-C_4fluoroalkynyl, and C_2-C_4deuterofluoroalkynyl. In some embodiments, R^3 is selected from H, D, CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4deuteroalkenyl, and C_2-C_4deuterofluoroalkenyl. In some embodiments, R^3 is selected from H, D, CN, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl. In some embodiments, R^3 is selected from H, D, CN, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3, and CD_2CD_3. In some embodiments, R^3 is H.

[0184] In some embodiments, R^4 and R^5 are independently selected from H, halo, CN, C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^4 and R^5 are independently selected from H, halo, CN, C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl, wherein available hydrogen atoms are option-

ally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^4 and R^5 are independently selected from H, halo, CN, C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^4 and R^5 are independently selected from H, D, CN, halo, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4deuteroalkenyl, C_2-C_4deuterofluoroalkenyl, C_2-C_4alkynyl, C_2-C_4deuteroalkynyl, C_2-C_4fluoroalkynyl, and C_1-C_4deuterofluoroalkynyl. In some embodiments, R^4 and R^5 are independently selected from H, D, CN, halo, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4alkynyl, and C_2-C_4fluoroalkynyl. In some embodiments, R^4 and R^5 are independently selected from H, D, CN, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl. In some embodiments, R^4 and R^5 are independently selected from H, D, CN, F, Cl, Br, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3, and CD_2CD_3. In some embodiments, R^4 and R^5 are independently selected from H, D, CN, F, Cl, Br, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, and CF_3. In some embodiments, R^4 and R^5 are selected from H, F, and D. In some embodiments, R^4 and R^5 are selected from H and D. In some embodiments, R^4 and R^5 are both H.

[0185] In some embodiments, each of R^3, R^4, and R^5 is H. In some embodiments, especially those in which X is absent or oxygen, as well as other embodiments, each of R^2, R^3, R^4, and R^5 is H. In some embodiments, at least one of R^3, R^4, and R^5 is D. In some embodiments, each of R^2, R^3, R^4, and R^5 is D.

[0186] In some embodiments, R^6 is selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15}, and wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^6 is selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15}, and wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^6 is selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15}, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0187] In some embodiments, R^6 is selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^6 is C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^6 is selected from C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, and C_1-C_4deuterofluoroalkyl. In some embodiments, R^6 is selected from CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CHD_3, $CH_2CDCH_2CD_3$, CH_2CD_3, CD_2CD_3, $CH_2CH_2CH_3$, $CH_2CH_2CHF_2$, $CH_2CH_2CFH_2$, $CH_2CH_2CF_3$, $CH_2CH_2CHD_2$, $CH_2CH_2CDH_2$, $CH_2CH_2CD_3$ $CH(CH_3)_2$, $CH(CF_3)_2$, $CH(CHF_2)_2$, $CH(CFH_2)_2$, $CH(CD_3)_2$, $CH(CHD_2)_2$, $CH(CDH_2)_2$, $C(CH_3)_3$, $C(CF_3)_3$, $C(CHF_2)_3$, $C(CFH_2)_3$, $C(CD_3)_3$, $C(CHD_2)_3$, $C(CDH_2)_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CF_3$, $CH_2CH_2CH_2CD_3$, $CH_2CH(CH_3)_2$, $CH_2CH(CD_3)_2$, $CH_2CH(CF_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)CH_2CF_3$, $CH(CH_3)CH_2CD_3$, $CH_2CH(CH_3)CH_3$, $CH_2CH(CH_3)CF_3$, $CH_2CH(CH_3)CD_3$, $CH_2C(CH_3)_3$, $CH_2C(CF_3)_3$, $CH_2C(CD_3)_3$, $CH_2CH_2C(CH_3)_3$, $CH_2CH_2C(CF_3)_3$, and $CH_2CH_2C(CD_3)_3$. In some embodiments, R^6 is selected from CH_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, $CH_2CH_2CH_3$, $CH_2CH_2CHF_2$, $CH_2CH_2CFH_2$, $CH_2CH_2CF_3$, $CH(CH_3)_2$, $CH(CF_3)_2$, $C(CH_3)_3$, $C(CF_3)_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CF_3$, $CH_2CH_2CH_2CHF_2$, $CH_2CH(CH_3)_2$, $CH_2CH(CF_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)CH_2CF_3$, $CH_2C(CH_3)_3$, $CH_2C(CF_3)_3$, $CH_2CH_2C(CH_3)_3$, and $CH_2CH_2C(CF_3)_3$. In some embodiments R^6 is selected from CH_3, CH_2CH_3, CH_2CF_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$, CD_3, CF_3, CHF_2, CH_2F, CH_2CF_2H, CH_2CH_2F, $CH_2CH_2CHF_2$, $CH_2CH_2CF_3$, and $CH_2CH_2CH_2CF_3$. In some embodiments, especially those in which X is S, S(O), or SO_2, as well as other embodiments, R^6 is selected from H, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, and $CH_2C(CH_3)_3$. In some embodiments, especially those in which X is absent or oxygen, as well as other embodiments, R^6 is selected from CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CF_2H, $CH_2CH_2CF_3$, $CH_2CH_2CH_2CF_3$, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, and $CH_2C(CH_3)_3$. In some embodiments, R^6 is selected from CH_3, CD_3, CD_2H, CDH_2, CF_2H, CFH_2, and CF_3. In some embodiments, R^6 is selected from CH_3 and CD_3. In some embodiments, R^6 is CH_3. In some embodiments, R^6 is CD_3. In some embodiments, R^6 is CF_3.

[0188] In some embodiments, R^6 is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0189] In some embodiments, R^6 is selected from C_4-C_6alkenyl and C_2-C_6alkynyl wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^6 is selected from C_2-C_6alkenyl, C_2-C_6fluoroalkenyl, C_2-C_6deuteroalkenyl, C_2-C_6deuterofluoroalkenyl, C_2-C_6alkynyl, C_2-C_6fluoroalkynyl, C_2-C_6deuteroalkynyl, and C_2-C_6deuterofluoroalkynyl. In some embodiments, R^6 is selected from C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4deuteroalkenyl, C_2-C_4deuterofluoroalkenyl, C_2-C_4alkynyl, C_2-C_4fluoroalkynyl, C_2-C_4deuteroalkynyl, and C_2-C_4deuterofluoroalkynyl. In some embodiments, R^6 is selected from $CH{=}CH_2$, $CH_2CH{=}CH_2$, $CF_2CH{=}CH_2$, $CD_2CH{=}CH_2$, $CH{=}CH_2CH_3$, $CH{=}CH_2CF_3$, $CH{=}CH_2CHF_2$, $CH{=}CH_2CH_2F$, $CH{=}CH_2CD_3$, $CH{=}CH_2CHD_2$, $CH{=}CH_2CH_2D$, $C{\equiv}CH$, $C{\equiv}CCH_3$, $C{\equiv}CCF_3$, $C{\equiv}CCHF_2$, $C{\equiv}CCFH_2$, $C{\equiv}CCD_3$, $C{\equiv}CCHD_2$, $C{\equiv}CCDH_2$, $CH_2C{\equiv}CH$, $CF_2C{\equiv}CH$, $CD_2C{\equiv}CH$, $CH_2C{\equiv}CCH_3$, $CF_2C{\equiv}CCH_3$, $CD_2C{\equiv}CCH_3$, $CH_2C{\equiv}CCD_3$, $CF_2C{\equiv}CCD_3$, $CD_2C{\equiv}CCD_3$, $CH_2C{\equiv}CCF_3$, $CF_2C{\equiv}CCF_3$, $CD_2C{\equiv}CCF_3$, $CH_2C{\equiv}CCHD_2$, $CF_2C{\equiv}CHD_2$, $CD_2C{\equiv}CHD_2$, $CH_2C{\equiv}CHF_2$, $CF_2C{\equiv}CHF_2$, and $CD_2C{\equiv}CHF_2$. In some embodiments, R^6 is selected from $CH{=}CH_2$, $CH_2CH{=}CH_2$, $C{\equiv}CH$, $C{\equiv}CCH_3$, $CH_2C{\equiv}CH$, and $CH_2C{\equiv}CCH_3$.

[0190] In some embodiments, R^6 is selected from C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, and C_2-C_6alkynyleneZR^{14}, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0191] In some embodiments, R^6 is selected from C_1-C_6alkyleneZR^{14}, C_1-C_6fluoroalkyleneZR^{14}, C_1-C_6deuteroalkyleneZR^{14}, C_1-C_6deuterofluoroalkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6fluoroalkenyleneZR^{14}, C_2-C_6deuteroalkenyleneZR^{14}, C_2-C_6deuterofluoroalkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_2-C_6fluoroalkynyleneZR^{14}, C_2-C_6deuteroalkynyleneZR^{14}, and C_2-C_6deuterofluoroalkynyleneZR^{14}. In some embodiments, R^6 is selected from C_1-C_6alkyleneZR^{14}, C_1-C_6fluoroalkyleneZR^{14}, C_1-C_6deuteroalkyleneZR^{14}, C_1-C_6deuterofluoroalkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, and C_2-C_6alkynyleneZR^{14}. In some embodiments, R^6 is selected from C_1-C_4alkyleneZR^{14}, C_1-C_4fluoroalkyleneZR^{14}, C_1-C_4deuteroalkyleneZR^{14}, C_1-C_4deuterofluoroalkyleneZR^{14}, C_2-C_4alkenyleneZR^{14}, C_2-C_4fluoroalkenyleneZR^{14}, C_2-C_4deuteroalkenyleneZR^{14}, C_2-C_4deuterofluoroalkenyleneZR^{14}, C_2-C_4alkynyleneZR^{14}, C_2-C_4fluoroalkynyleneZR^{14}, C_2-C_4deuteroalkynyleneZR^{14}, and C_2-C_4deuterofluoroalkynyleneZR^{14}. In some embodiments, R^6 is selected from C_1-C_4alkyleneZR^{14}, C_1-C_4fluoroalkyleneZR^{14}, C_1-C_4deuteroalkyleneZR^{14}, C_1-C_4deuterofluoroalkyleneZR^{14}, C_2-C_4alkenyleneZR^{14}, and C_2-C_4alkynyleneZR^{14}.

[0192] In some embodiments, R^6 is selected from CH_2ZR^{14}, $CH_2CH_2ZR^{14}$, $CH_2CH_2CH_2ZR^{14}$, $CH_2CH_2CH_2CH_2ZR^{14}$, $CH(CH_3)CH_2ZR^{14}$, $CH(CH_3)CH_2CH_2ZR^{14}$, $CH_2CH(CH_3)ZR^{14}$, CF_2ZR^{14}, $CFHZR^{14}$, CH_2CHFZR^{14}, $CH_2CF_2ZR^{14}$, $CF_2CF_2ZR^{14}$, $CH_2CH_2CF_2ZR^{14}$, $CH_2CH_2CFHZR^{14}$, $CH_2CH_2CF_2ZR^{14}$, $CH(CH_3)CF_2ZR^{14}$, $CH(CH_3)CHFZR^{14}$—$CH_2CH_2CH_2CF_2ZR^{14}$, $CH_2CH_2CH_2CHFZR^{14}$, $CH(CH_3)CH_2CF_2ZR^{14}$, $CH(CH_3)CH_2CHFZR^{14}$, CD_2ZR^{14}, $CDHZR^{14}$, CH_2CHDZR^{14}, $CH_2CD_2ZR^{14}$, $CD_2CD_2ZR^{14}$, $CH_2CH_2CD_2ZR^{14}$, $CH_2CH_2CDHZR^{14}$, $CH_2CH_2CD_2ZR^{14}$, $CH(CH_3)CD_2ZR^{12}$, $CH(CH_3)CHDZR^{14}$—$CH_2CH_2CH_2CD_2ZR^{14}$, $CH_2CH_2CH_2CHDZR^{14}$, $CH(CH_3)CH_2CD_2ZR^{14}$, $CH(CH_3)CH_2CHDZR^{14}$, $CH{=}CHZR^{14}$, $CH_2CH{=}CHZR^{14}$, $C{\equiv}CZR^{14}$, $C{\equiv}CCH_2ZR^{14}$, $CH_2C{\equiv}CZR^{14}$, and $CH_2C{\equiv}CH_2ZR^{14}$. In some embodiments, R^6 is selected from CH_2ZR^{14}, $CH_2CH_2ZR^{14}$, $CH_2CH_2CH_2ZR^{14}$, $CH_2CH_2CH_2CH_2ZR^{14}$, $CH(CH_3)CH_2ZR^{14}$, $CH(CH_3)CH_2CH_2ZR^{14}$, $CH_2CH(CH_3)ZR^{14}$, $CH{=}CHZR^{14}$, $CH_2CH{=}CHZR^{14}$, $CH{=}CH_2CHZR^{14}$, $C{\equiv}CCH_2ZR^{14}$, $CH_2C{\equiv}CZR^{14}$, and $CH_2C{\equiv}CH_2ZR^{14}$.

[0193] In some embodiments, R^6 is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^6 is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, C_1-C_4alkyleneC_5-C_{10}heteroaryl, C_1-C_4fluoroalkyleneC_3-C_7cycloalkyl, C_1-C_4fluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4fluoroalkyleneC_6-C_{10}aryl, C_1-C_4fluoroalkyleneC_5-C_{10}heteroaryl, C_1-C_4deuteroalkyleneC_3-C_7cycloalkyl, C_1-C_4deuteroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4deuteroalkyleneC_6-C_{10}aryl, C_1-C_4deuteroalkylene$C5$-C_{10}heteroaryl, C_1-C_4deuterofluoroalkyleneC_3-C_7cycloalkyl, C_1-C_4deuterofluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4deuterofluoroalkyleneC_6-C_{10}aryl, and C_1-C_4deuterofluoroalkyleneC_5-C_{10}heteroaryl, in which each of the cyclic groups is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^6 is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_2alkyleneC_3-C_7cycloalkyl, C_1-C_2alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2alkyleneC_6-C_{10}aryl, C_1-C_2alkyleneC_5-C_{10}heteroaryl, C_1-C_2fluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2fluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2fluoroalkyleneC_6-C_{10}aryl, C_1-C_2fluoroalkyleneC_5-

C_{10}heteroaryl, C_1-C_2deuteroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuteroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuteroalkyleneC_6-C_{10}aryl, C_1-C_2deuteroalkyleneC5-C_{10}heteroaryl, C_1-C_2deuterofluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuterofluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuterofluoroalkyleneC_6-C_{10}aryl, and C_1-C_2deuterofluoroalkyleneC_5-C_{10}heteroaryl, in which each of the cyclic groups is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0194] In some embodiments, the C_3-C_7cycloalkyl in R^6 is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each of which is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the C_3-C_7cycloalkyl in R^6 is selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, each of which is optionally substituted with one to three substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the C_3-C_7cycloalkyl in R^6 is selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, each of which is optionally substituted with one or two substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0195] In some embodiments, the C_3-C_{10}heterocycloalkyl in R^6 is a monocyclic C_3-C_7heterocycloalkyl or a bicyclic C_7-C_{10}heterocycloalkyl, each of which is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$.

[0196] In some embodiments, the monocyclic C_3-C_7heterocycloalkyl in R^6 is selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, 1,3-dioxolanyl, azetidinyl, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxothiolidinyl, thiazolidinyl, isothiazolidinyl, imidazolidinyl, imidazolinyl, dioxolanyl, dithiolanyl, triazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, dihydropyranyl, isothiazolidinyl, morpholinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl dioxide, dioxanyl, thiazolinyl, thianyl, thianyl oxide, thianyl dioxide, dithianyl, azepanyl, pyrazolidinyl, oxepanyl, thiepanyl, diazepanyl, and 2,5-pyrrolidinedionyl (e.g., succinimidyl), each of which is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$ and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the monocyclic C_3-C_7heterocycloalkyl in R^6 is selected from oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, tetrahydropyranyl, dihydropyranyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, thianyl, thianyl oxide, thianyl dioxide, dithianyl, and 2,5-pyrrolidinedionyl, each of which is optionally substituted with one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0197] In some embodiments, the bicyclic C_7-C_{10}heterocycloalkyl in R^6 is selected from benzoisoxazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzopyranyl, benzothiopyranyl, chromanyl, isochromanyl, dihydroindenyl, isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl (e.g., phthalimido), octahydroisoindolinyl, octahydro-isoindolin-1-onyl (e.g., tetrahydroisoquinolinyl), and hexahydroisoindoline-1, 3-dionyl (e.g., cis-hexahydrophthalimidyl), each of which are optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the bicyclic C_7-C_{10}heterocycloalkyl in R^6 is selected from isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl, octahydro-1H-isoindolinyl, octahydro-1H-isoindolin-1-onyl, and hexahydro-1H-isoindoline-1,3-dionyl, each of which is optionally substituted with one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0198] In some embodiments, the C_6-C_{10}aryl in R^6 is phenyl, optionally substituted with one to four, one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0199] In some embodiments, the C_5-C_{10}heteroaryl in R^6 is selected from azepinyl, benzofuranyl, benzofurazanyl, benzothiazolyl, benzothienyl, benzoxazolyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, thiazolyl, thienofura-

nyl, triazolyl, and thienyl (e.g., thiophenyl), each of which is optionally substituted with one to four, one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0200] In some embodiments, the substituents on R^6 are selected from one to four of F, Cl, Br, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, CH_2CH_2F, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CD_2CD_3, OR^{15}, and $C(O)R^{15}$. In some embodiments, the substituents on R^6 are selected from one to three of F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)_2$, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, OR^{14}, and $C(O)R^{14}$.

[0201] In some embodiments, one, more or all the substituents on R^6 are selected from one or two of F, Cl, CH_3, $CH(CH_3)_2$, $CH(CH_3)_2$, CF_3, CHF_2, CH_2F, OR^{15}, and $C(O)R^{15}$.

[0202] In some embodiments, Z is selected from $NR^{19}C(O)$, $NR^{19}C(O)O$, $C(O)NR^{19}$, $OC(O)NR^{19}$, and NR^{19}. In some embodiments, Z is selected from O, C(O), $NR^{19}C(O)$, and $NR^{19}C(O)O$. In some embodiments, Z is O. In some embodiments, Z is C(O). In some embodiments, Z is $NR^{19}C(O)$. In some embodiments, Z is $NR^{19}C(O)O$.

[0203] In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_4alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_4alkyl, wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_4alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, D, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl.

[0204] In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, D, F, Br, Cl, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3 CF_2CF_3, CH_2CH_2D, CH_2CD_2H, and CD_2CD_3. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, D, F, Br, Cl, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2D, CH_2CD_2H, and CD_2CD_3. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, D, F, Br, CH_3, CF_2H, CFH_2, CF_3, CD_2H, CDH_2, and CD_3. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, D, F, CH_3, CF_3, and CD_3. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, D, CH_3, and CD_3. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H, F, and D. In some embodiments, R^7, R^8, R^9, and R^{10} are independently selected from H and D.

[0205] In some embodiments, at least one of R^7, R^8, R^9, and R^{10} is D or at least one of R^7, R^8, R^9, and R^{10} comprises D. In some embodiments, R^7 and R^8 are D and R^9 and R^{10} are H. In some embodiments, R^7 and R^8 are H and R^9 and R^{10} are D. In some embodiments, R^7, R^8, R^9, and R^{10} are all H. In some embodiments, R^7, R^8, R^9, and R^{10} are all D.

[0206] In some embodiments, R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16} C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0207] In some embodiments, one of R^6, R^{11}, and R^{12} is neither H nor C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^6 is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and $C(O)R^{15}$; and R^{11} and R^{12} are independently selected from H and C_1-C_6alkyl, and wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^6 is selected from H and C_1-C_6alkyl and one or both of R^{11} and R^{12} are independently selected from C_2-C_6alkenyl,

C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0208] In some embodiments, one of R^{11} and R^{12} is selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium, and the other of R^{11} and R^{12} is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, one of R^{11} and R^{12} is selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium, and the other of R^{11} and R^{12} is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, and C_2-C_6alkynyleneZ'R^{16}, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, one of R^{11} and R^{12} is selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium, and the other of R^{11} and R^{12} is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0209] In some embodiments, R^{11} and R^{12} are both selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0210] In some embodiments, R^{11} and R^{12} are both selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0211] In some embodiments, at least one of R^{11} and R^{12} is selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom. In some embodiments, at least one of R^{10} is selected from H, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6fluoroalkyl, and C_1-C_4deuterofluoroalkyl. In some embodiments, at least one of R^{11} and R^{12} is selected from H, D, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3 CD_2CD_3, $CH_2CH_2CH_3$, $CH_2CH_2CHF_2$, $CH_2CH_2CFH_2$, $CH_2CH_2CF_3$, $CH_2CH_2CHD_2$, $CH_2CH_2CDH_2$, $CH_2CH_2CD_3$ $CH(CH_3)_2$, $CH(CF_3)_2$, $CH(CHF_2)_2$, $CH(CFH_2)_2$, $CH(CD_3)_2$, $CH(CHD_2)_2$, $CH(CDH_2)_2$, $C(CH_3)_3$, $C(CF_3)_3$, $C(CHF_2)_3$, $C(CFH_2)_3$, $C(CD_3)_3$, $C(CHD_2)_3$, $C(CDH_2)_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CF_3$, $CH_2CH_2CH_2CD_3$, $CH_2CH(CH_3)_2$, $CH_2CH(CD_3)_2$, $CH_2CH(CF_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)CH_2CF_3$, $CH(CH_3)CH_2CD_3$, $CH_2CH(CH_3)CH_3$, $CH_2CH(CH_3)CF_3$, $CH_2CH(CH_3)CD_3$, $CH_2C(CH_3)_3$, $CH_2C(CF_3)_3$, $CH_2C(CD_3)_3$, $CH_2CH_2C(CH_3)_3$, $CH_2CH_2C(CF_3)_3$, and $CH_2CH_2C(CD_3)_3$. In some embodiments, at least one of R^{11} and R^{12} is selected from H, H, CH_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, $CH_2CH_2CH_3$, $CH_2CH_2CHF_2$, $CH_2CH_2CFH_2$, $CH_2CH_2CF_3$, $CH(CH_3)_2$, $CH(CF_3)_2$, $C(CH_3)_3$, $C(CF_3)_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CF_3$, $CH_2CH_2CH_2CHF_2$, $CH_2CH(CH_3)_2$, $CH_2CH(CF_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)CH_2CF_3$, $CH_2C(CH_3)_3$, $CH_2C(CF_3)_3$, $CH_2CH_2C(CH_3)_3$, and $CH_2CH_2C(CF_3)_3$. In some embodiments at least one of R^{11} and R^{12} is selected from H, CH_3, CH_2CH_3, CH_2CF_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$, CD_3, CF_3, CHF_2, CH_2F, CH_2CF_2H, CH_2CH_2F, $CH_2CH_2CHF_2$, and $CH_2CH_2CF_3$.

[0212] In some embodiments, one of R^{11} and R^{12} is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, and $CH(CH_3)_2$ and the other of R^{11} and R^{12} is selected from CD_3, CF_3, CHF_2, CH_2F, CH_2CF_2H, CH_2CH_2F, and $CH_2CH_2CHF_2$.

[0213] In some embodiments, at least one of R^{11} and R^{12} is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0214] In some embodiments, at least one of R^{11} and R^{12} is selected from C_4-C_6alkenyl and C_2-C_6alkynyl wherein available hydrogen atoms are optionally replaced with a

fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, at least one of R^{11} and R^{12} is selected from C_2-C_6alkenyl, C_2-C_6fluoroalkenyl, C_2-C_6deuteroalkenyl, C_2-C_6deuterofluoroalkenyl, C_2-C_6alkynyl, C_2-C_6fluoroalkynyl, C_2-C_6deuteroalkynyl, and C_2-C_6deuterofluoroalkynyl. In some embodiments, at least one of R^{11} and R^{12} is selected from C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_6deuteroalkenyl, C_2-C_6deuterofluoroalkenyl, C_2-C_4alkynyl, C_2-C_4fluoroalkynyl, C_2-C_4deuteroalkynyl, and C_2-C_6deuterofluoroalkynyl. In some embodiments, at least one of R^{11} and R^{12} is selected from $CH{=}CH_2$, $CH_2CH{=}CH_2$, $CF_2CH{=}CH_2$, $CD_2CH{=}CH_2$, $CH{=}CH_2CH_3$, $CH{=}CH_2CF_3$, $CH{=}CH_2CHF_2$, $CH{=}CH_2CH_2F$, $CH{=}CH_2CD_3$, $CH{=}CH_2CHD_2$, $CH{=}CH_2CH_2D$, $C{\equiv}CH$, $C{\equiv}CCH_3$, $C{\equiv}CCF_3$, $C{\equiv}CCHF_2$, $C{\equiv}CCFH_2$, $C{\equiv}CCD_3$, $C{\equiv}CCHD_2$, $C{\equiv}CCDH_2$, $CH_2C{\equiv}CH$, $CF_2C{\equiv}CH$, $CD_2C{\equiv}CH$, $CH_2C{\equiv}CCH_3$, $CF_2C{\equiv}CCH_3$, $CD_2C{\equiv}CCH_3$, $CH_2C{\equiv}CCD_3$, $CF_2C{\equiv}CCD_3$, $CD_2C{\equiv}CCD_3$, $CH_2C{\equiv}CCF_3$, $CF_2C{\equiv}CCF_3$, $CD_2C{\equiv}CCF_3$, $CH_2C{\equiv}CCHD_2$, $CF_2C{\equiv}CHD_2$, $CD_2C{\equiv}CHD_2$, $CH_2C{\equiv}CHF_2$, $CF_2C{\equiv}CHF_2$, and $CD_2C{\equiv}CHF_2$.

[0215] In some embodiments, at least one of R^{11} and R^{12} is selected from $CH{=}CH_2$, $CH_2CH{=}C\ H_2$, $C{\equiv}CH$ $C{\equiv}CCH_3$, $CH_2C{\equiv}CH$, and $CH_2C{\equiv}CCH_3$.

[0216] In some embodiments, one of R^{11} and R^{12} is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, and $CH(CH_3)_2$ and the other of R^{11} and R^{12} is selected from $CH{=}CH_2$, $CH_2CH{=}CH_2$, $C{\equiv}CH$ $C{\equiv}CCH_3$, $CH_2C{\equiv}CH$, and $CH_2C{\equiv}CCH_3$.

[0217] In some embodiments, at least one of R^{11} and R^{12} is selected from C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, and C_2-C_6alkynyleneZ'R^{16}, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^{11} is selected from C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, and C_2-C_6alkynyleneZ'R^{16}, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0218] In some embodiments, at least one of R^{11} and R^{12} is selected from C_1-C_6alkyleneZ'R^{16}, C_1-C_6fluoroalkyleneZ'R^{16}, C_1-C_6deuteroalkyleneZ'R^{16}, C_1-C_6deuterofluoroalkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6fluoroalkenyleneZ'R^{16}, C_2-C_6deuteroalkenyleneZ'R^{16}, C_2-C_6deuterofluoroalkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_2-C_6fluoroalkynyleneZ'R^{16}, C_2-C_6deuteroalkynyleneZ'R^{16}, and C_2-C_6deuterofluoroalkynyleneZ'R^{16}. In some embodiments, R^{10} is selected from C_1-C_6alkyleneZ'R^{16}, C_1-C_6fluoroalkyleneZ'R^{16}, C_1-C_6deuteroalkyleneZ'R^{16}, C_1-C_6deuterofluoroalkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, and C_2-C_6alkynyleneZ'R^{16}. In some embodiments, R^{11} is selected from C_1-C_4alkyleneZ'R^{16}, C_1-C_4fluoroalkyleneZ'R^{16}, C_1-C_4deuteroalkyleneZ'R^{16}, C_1-C_4deuterofluoroalkyleneZ'R^{16}, C_2-C_4alkenyleneZ'R^{16}, C_2-C_4fluoroalkenyleneZ'R^{16}, C_2-C_4deuteroalkenyleneZ'R^{16}, C_2-C_4deuterofluoroalkenyleneZ'R^{16}, C_2-C_4alkynyleneZ'R^{16}, C_2-C_4fluoroalkynyleneZ'R^{16}, C_2-C_4deuteroalkynyleneZ'R^{16}, and C_2-C_4deuterofluoroalkynyleneZ'R^{16}. In some embodiments, R^{11} is selected from C_1-C_4alkyleneZ'R^{16}, C_1-C_4fluoroalkyleneZ'R^{16}, C_1-C_4deuteroalkyleneZ'R^{16}, C_1-C_4deuterofluoroalkyleneZ'R^{16}, C_2-C_4alkenyleneZ'R^{16}, and C_2-C_4alkynyleneZ'R^{16}.

[0219] In some embodiments, at least one of R^{11} and R^{12} is selected from $CH_2Z'R^{16}$, $CH_2CH_2Z'R^{16}$, $CH_2CH_2CH_2Z'R^{16}$, $CH_2CH_2CH_2CH_2Z'R^{16}$, $CH(CH_3)CH_2Z'R^{16}$, $CH(CH_3)CH_2CH_2Z'R^{16}$, $CH_2CH(CH_3)Z'R^{16}$, $CF_2Z'R^{16}$, CF HZ'R^{16}, $CH_2CHFZ'R^{16}$, $CH_2CF_2Z'R^{16}$, $CF_2CF_2Z'R^{16}$, $CH_2CH_2CF_2Z'R^{16}$, $CH_2CH_2CFHZ'R^{16}$, $CH_2CH_2CF_2Z'R^{16}$, $CH(CH_3)CF_2Z'R^{16}$, $CH(CH_3)CHFZ'R^{16}$—, $CH_2CH_2CH_2CF_2Z'R^{16}$, $CH_2CH_2CH_2CHFZ'R^{16}$, $CH(CH_3)CH_2CF_2Z'R^{16}$, $CH(CH_3)CH_2CHFZ'R^{16}$, $CD_2Z'R^{16}$, $CDHZ'R^{16}$, $CH_2CHDZ'R^{16}$, $CH_2CD_2Z'R^{16}$, $CD_2CD_2Z'R^{16}$, $CH_2CH_2CD_2Z'R^{16}$, $CH_2CH_2CDHZ'R^{16}$, $CH_2CH_2CD_2Z'R^{16}$, $CH(CH_3)CD_2Z'R^{16}$, $CH(CH_3)CHDZ'R^{16}$—, $CH_2CH_2CH_2CD_2Z'R^{16}$, $CH_2CH_2CH_2CHDZ'R^{16}$, $CH(CH_3)CH_2D_2Z'R^{16}$, $CH(CH_3)CH_2CHDZ'R^{16}$, $CH{=}CHZ'R^{16}$, $CH_2CH{=}CHZ'R^{16}$, $C{\equiv}CZ'R^{16}$, $C{\equiv}CCH_2Z'R^{16}$, $CH_2C{\equiv}CZ'R^{16}$, and $CH_2C{\equiv}CH_2Z'R^{16}$. In some embodiments, R″ is selected from $CH_2Z'R^{16}$, $CH_2CH_2Z'R^{16}$, $CH_2CH_2CH_2Z'R^{16}$, $CH_2CH_2CH_2CH_2Z'R^{16}$, $CH(CH_3)CH_2Z'R^{16}$, $CH(CH_3)CH_2CH_2Z'R^{16}$, $CH_2CH(CH_3)Z'R^{16}$, $CH{=}CHZ'R^{16}$, $CH_2CH{=}CHZ'R^{16}$, $CH{=}CH_2CHZ'R^{16}$, $C{\equiv}CCH_2Z'R^{16}$, $CH_2C{\equiv}CZ'R^{16}$, and $CH_2C{\equiv}CH_2Z'R^{16}$.

[0220] In some embodiments, one of R^{11} and R^{12} is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, and $CH(CH_3)_2$ and the other of R^{11} and R^{12} is selected from $CH_2Z'R^{16}$, $CH_2CH_2Z'R^{16}$, $CH_2CH_2CH_2Z'R^{16}$, $CH_2CH_2CH_2CH_2Z'R^{16}$, $CH(CH_3)CH_2Z'R^{16}$, $CH(CH_3)CH_2CH_2Z'R^{16}$, $CH_2CH(CH_3)Z'R^{16}$, $CH{=}CHZ'R^{16}$, $CH_2CH{=}CHZ'R^{16}$, $CH{=}CH_2CHZ'R^{16}$, $C{\equiv}CCH_2Z'R^{16}$, $CH_2C{\equiv}CZ'R^{16}$, and $CH_2C{\equiv}CH_2Z'R^{16}$.

[0221] In some embodiments, at least one of R^{11} and R^{12} is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, at least one of R^{11} and R^{12} is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, C_1-C_4alkyleneC_5-C_{10}heteroaryl, C_1-C_4fluoroalkyleneC_3-C_7cycloalkyl, C_1-C_4fluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4fluoroalkyleneC_6-C_{10}aryl, C_1-C_4fluoroalkyleneC_5-C_{10}heteroaryl, C_1-C_4deuteroalkyleneC3-C_7cycloalkyl, C_1-C_4deuteroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4deuteroalkyleneC_6-C_{10}aryl, C_1-C_4deuteroalkyleneC_5-C_{10}heteroaryl, C_1-C_4deuterofluoroalkyleneC_3-C_7cycloalkyl, C_1-C_4deuterofluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4deuterofluoroalkyleneC_6-C_{10}aryl, and C_1-C_4deuterofluoroalkyleneC_5-C_{10}heteroaryl, in which each of the cyclic groups is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein

available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, at least one of R^{11} and R^{12} is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_2alkyleneC_3-C_7cycloalkyl, C_1-C_2alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2alkyleneC_6-C_{10}aryl, C_1-C_2alkyleneC_5-C_{10}heteroaryl, C_1-C_2fluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2fluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2fluoroalkyleneC_6-C_{10}aryl, C_1-C_2fluoroaalkyleneC_5-C_{10}heteroaryl, C_1-C_2deuteroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuteroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuteroalkyleneC_6-C_{10}aryl, C_1-C_2deuteroalkyleneC_5-C_{10}heteroaryl, C_1-C_2deuterofluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuterofluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuterofluoroalkyleneC_6-C_{10}aryl, and C_1-C_2deuterofluoroalkyleneC_5-C_{10}heteroaryl, in which each of the cyclic groups is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0222] In some embodiments, one of R^{11} and R^{12} is selected from H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, and $CH(CH_3)_2$ and the other of R^{11} and R^{12} is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_2alkyleneC_3-C_7cycloalkyl, C_1-C_2alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2alkyleneC_6-C_{10}aryl, C_1-C_2alkyleneC_5-C_{10}heteroaryl, C_1-C_2fluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2fluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2fluoroalkyleneC_6-C_{10}aryl, C_1-C_2fluoroalkyleneC_5-C_{10}heteroaryl, C_1-C_2deuteroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuteroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuteroalkyleneC_6-C_{10}aryl, C_1-C_2deuteroalkylene$C5$-C_{10}heteroaryl, C_1-C_2deuterofluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuterofluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuterofluoroalkyleneC_6-C_{10}aryl, and C_1-C_2deuterofluoroalkyleneC_5-C_{10}heteroaryl, in which each of the cyclic groups is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$ and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0223] In some embodiments, the C_3-C_7cycloalkyl in R^{11} and/or R^{12} is independently selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each or which is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the C_3-C_7cycloalkyl in R^{11} and/or R^{12} is independently selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, each of which is optionally substituted with one to three substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the C_3-C_7cycloalkyl in R^{11} and/or R^{12} is independently selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, each of which is optionally substituted with one or two substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0224] In some embodiments, the C_3-C_{10}heterocycloalkyl in R^{11} and/or R^{12} is a monocyclic C_3-C_7heterocycloalkyl or a bicyclic C_7-C_{10}heterocycloalkyl, each of which is optionally substituted with one to four, one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0225] In some embodiments, the monocyclic C_3-C_7heterocycloalkyl in R^{11} and/or R^{12} is independently selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, 1,3-dioxolanyl, azetidinyl, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxothiolidinyl, thiazolidinyl, isothiazolidinyl, imidazolidinyl, imidazolinyl, dioxolanyl, dithiolanyl, triazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, dihydropyranyl, isothiazolidinyl, morpholinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl dioxide, dioxanyl, thiazolinyl, thianyl, thianyl oxide, thianyl dioxide, dithianyl, azepanyl, pyrazolidinyl, oxepanyl, thiepanyl, diazepanyl, and 2,5-pyrrolidinedionyl (e.g., succinimidyl), each of which is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the monocyclic C_3-C_7heterocycloalkyl in R^{11} and/or R^{12} is independently selected from oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, tetrahydropyranyl, dihydropyranyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, thianyl, thianyl oxide, thianyl dioxide, dithianyl, and 2,5-pyrrolidinedionyl, each of which is optionally substituted with one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0226] In some embodiments, the bicyclic C_7-C_{10}heterocycloalkyl in R^{11} and/or R^{12} is independently selected from benzoisoxazolyl, dihydrobenzofuranyl, dihy-

drobenzothienyl, benzopyranyl, benzothiopyranyl, chromanyl, isochromanyl, dihydroindenyl, isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl (e.g., phthalimido), octahydroisoindolinyl, octahydro-isoindolin-1-onyl (e.g., tetrahydroisoquinoline), and hexahydroisoindoline-1,3-dionyl (e.g., cis-hexahydrophthalimidyl), each of which is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the bicyclic C_7-C_{10}heterocycloalkyl in R^{11} and/or R^{12} is independently selected from isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl, octahydro-1H-isoindolinyl, octahydro-1H-isoindolin-1-onyl, and hexahydro-1H-isoindoline-1,3-dionyl, each of which is optionally substituted with one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{11}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0227] In some embodiments, the C_5-C_{10}aryl in R^{11} and/or R^{12} is phenyl, optionally substituted with one to four, one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{11}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0228] In some embodiments, the C_5-C_{10}heteroaryl in R^1 and/or R^{12} is independently selected from azepinyl, benzofuranyl, benzofurazanyl, benzothiazolyl, benzothienyl, benzoxazolyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, thiazolyl, thienofuranyl, triazolyl, and thienyl (e.g., thiophenyl), each of which optionally substituted with one to four, one to three, or one or two, substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^7, and $C(O)R^{11}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0229] In some embodiments, the substituents on R^{11} and/or R^{12} are independently selected from one to four of F, Cl, Br, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, CH_2CH_2F, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CD_2CD_3, OR^{17}, and $C(O)R^{11}$. In some embodiments, the substituents on R^{11} and/or R^{12} are independently selected from one to three of F, Cl, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH(CH_3)_2$, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, OR^{11}, and $C(O)R^{17}$. In some embodiments, the substituents on R^{11} and/or R^{12} are independently selected from one or two of F, Cl, CH_3, $CH(CH_3)_2$, $CH(CH_3)_2$, CF_3, CHF_2, CH_2F, OR^{17}, and $C(O)R^{17}$.

[0230] In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a monocyclic 3- to 7-membered heterocyclic ring or a bicyclic 7- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein each said 3- to 10-member heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0231] In some embodiments, especially when X is absent or oxygen, as well as other embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0232] In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a monocyclic 3- to 7-membered heterocyclic ring selected from aziridinyl, azetidinyl, diazetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, morpholinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl dioxide, azepanyl, diazepanyl, and 2,5-pyrrolidinedionyl (e.g., succinimidyl), each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and Cl.

[0233] C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a monocyclic 3- to 7-membered heterocyclic ring selected pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and thiomorpholinyl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form pyrrolidinyl or piperidinyl optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form pyr-

rolidinyl optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form piperidinyl optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0234] In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a bicyclic 7- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a bicyclic 7- to 10-membered heterocyclic ring selected from benzoisoxazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzopyranyl, benzothiopyranyl, chromanyl, isochromanyl, dihydroindenyl, isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl (e.g., phthalimido), octahydroisoindolinyl, octahydro-isoindolin-1-onyl (e.g., tetrahydroisoquinoline), and hexahydroisoindoline-1,3-dionyl (e.g., cis-hexahydrophthalimidyl), and further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and Cl.

[0235] C_6alkyleneOC_1-C_6alkyl, and wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a bicyclic 7- to 10-membered heterocyclic ring selected from benzoisoxazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzopyranyl, benzothiopyranyl, chromanyl, isochromanyl, dihydroindenyl, isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl (e.g., phthalimido), octahydroisoindolinyl, octahydro-isoindolin-1-onyl (e.g., tetrahydroisoquinoline), and hexahydroisoindoline-1,3-dionyl (e.g., cis-hexahydrophthalimidyl), and further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0236] In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a bicyclic 7- to 10-membered heterocyclic ring selected from isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl, octahydro-1H-isoindolinyl, octahydro-1H-isoindolin-1-onyl, and hexahydro-1H-isoindoline-1,3-dionyl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a bicyclic 7- to 10-membered heterocyclic ring selected from isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl, octahydro-1H-isoindolinyl, octahydro-1H-isoindolin-1-onyl, and hexahydro-1H-isoindoline-1,3-dionyl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0237] In some embodiments, the one to four substituents on the 3- to 10-membered heterocyclic ring (including the monocyclic 3- to 7-membered heterocyclic ring or a bicyclic 7- to 10-membered heterocyclic ring) formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween are independently selected from halo, C_1-C_4alkyl, OH, OC_1-C_4alkyl, C_1-C_4alkyleneOH, and C_1-C_4alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0238] In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from halo and C_1-C_4alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl. In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from F, Cl, Br, OH, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3 CD_2CD_3, $CH_2CH_2CH_3$, $CH_2CH_2CHF_2$, $CH_2CH_2CFH_2$, $CH_2CH_2CF_3$, $CH_2CH_2CHD_2$, $CH_2CH_2CDH_2$, $CH_2CH_2CD_3$ $CH(CH_3)_2$, $CH(CF_3)_2$, $CH(CHF_2)_2$, $CH(CFH_2)_2$, $CH(CD_3)_2$, $CH(CHD_2)_2$, $CH(CDH_2)_2$, $C(CH_3)_3$, $C(CF_3)_3$, $C(CHF_2)_3$, $C(CFH_2)_3$, $C(CD_3)_3$, $C(CHD_2)_3$, $C(CDH_2)_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CF_3$, $CH_2CH_2CH_2CD_3$, $CH_2CH(CH_3)_2$, $CH_2CH(CD_3)_2$, $CH_2CH(CF_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)CH_2CF_3$, $CH(CH_3)CH_2CD_3$, $CH_2C(CH_3)_3$, $CH_2C(CF_3)_3$, $CH_2C(CD_3)_3$, $CH_2CH_2C(CH_3)_3$, $CH_2CH_2C(CF_3)_3$, and $CH_2CH_2C(CD_3)_3$. In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from F, Cl, CH_3, CF_2H, CFH_2, CF_3, and CD_3. In some embodiments, at least one of the substituents on the 3- to

10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is F.

[0239] In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OC_1-C_4alkyl, C_1-C_4alkyleneOH, and C_1-C_4alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OC_1-C_4alkyl, OC_1-C_4deuteroalkyl, OC_1-C_4fluoroalkyl, OC_1-C_4deuterofluoroalkyl, C_1-C_4alkyleneOH, C_1-C_4fluoroalkyleneOH, C_1-C_4deuteroalkyleneOH, C_1-C_4deuterofluoroalkyleneOH, C_1-C_4alkyleneOC_1-C_4alkyl, C_1-C_4alkyleneOC_1-C_4fluoroalkyl, C_1-C_4alkyleneOC_1-C_4deuteroalkyl, C_1-C_4alkyleneOC_1-C_4deuterofluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4alkyl, C_1-C_4deuteroalkyleneOC_1-C_4alkyl, C_1-C_4deuterofluoroalkyleneOC_1-C_4alkyl, C_1-C_4fluoroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4deuteroalkyl, C_1-C_4deuteroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4deuteroalkyleneOC_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4deuterofluoroalkyl, and C_1-C_4deuterofluoroalkyleneOC_1-C_4deuterofluoroalkyl. In some embodiments, R^9 is selected from OH, OC_1-C_4alkyl, OC_1-C_4deuteroalkyl, OC_1-C_4fluoroalkyl, OC_1-C_4deuterofluoroalkyl, C_1-C_4alkyleneOH, C_1-C_4fluoroalkyleneOH, C_1-C_4alkyleneOC_1-C_4alkyl, C_1-C_4alkyleneOC_1-C_4fluoroalkyl, C_1-C_4alkyleneOC_1-C_4deuteroalkyl, and C_1-C_4alkyleneOC_1-C_4deuterofluoroalkyl. In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OC_1-C_4alkyl, OC_1-C_4deuteroalkyl, OC_1-C_4fluoroalkyl, OC_1-C_4deuterofluoroalkyl, C_1-C_4alkyleneOH, C_1-C_4fluoroalkyleneOH, C_1-C_4deuteroalkyleneOH, C_1-C_4deuterofluoroalkyleneOH, C_1-C_4alkyleneOC_1-C_3alkyl, and C_1-C_4alkyleneOC_1-C_3fluoroalkyl.

[0240] In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OCH_3, OCD_2H, $OCDH_2$, OCD_3, OCF_2H, $OCFH_2$, OCF_3, OCH_2CH_3, OCH_2CH_2F, OCH_2CF_2H, OCH_2CF_3, OCF_2CF_3, OCH_2CH_2D, OCH_2CD_2H, OCH_2CD_3 OCD_2CD_3, $OCH_2CH_2CH_3$, $OCH_2CH_2CHF_2$, $OCH_2CH_2CFH_2$, $OCH_2CH_2CF_3$, $OCH_2CH_2CHD_2$, $OCH_2CH_2CDH_2$, $OCH_2CH_2CD_3$, $OCH(CH_3)_2$, $OCH(CF_3)_2$, $OCH(CHF_2)_2$, $OCH(CFH_2)_2$, $OCH(CD_3)_2$, $OCH(CHD_2)_2$, $OCH(CDH_2)_2$, $OC(CH_3)_3$, $OC(CF_3)_3$, $OC(CHF_2)_3$, $OC(CFH_2)_3$, $OC(CD_3)_3$, $OC(CHD_2)_3$, $OC(CDH_2)_3$, $OCH_2CH_2CH_2CH_3$, $OCH_2CH_2CH_2CF_3$, $OCH_2CH_2CH_2CD_3$, $OCH_2CH(CH_3)_2$, $OCH_2CH(CD_3)_2$, $OCH_2CH(CF_3)_2$, $OCH(CH_3)CH_2CH_3$, $OCH(CH_3)CH_2CF_3$, $OCH(CH_3)CH_2CD_3$, $OCH_2C(CH_3)_3$, $OCH_2C(CF_3)_3$, $OCH_2C(CD_3)_3$, $OCH_2CH_2C(CH_3)_3$, $OCH_2CH_2C(CF_3)_3$, $OCH_2CH_2C(CD_3)_3$, CH_2OH, CF_2OH, CD_2OH, CH_2CH_2OH, CF_2CF_2OH, CH_2CF_2OH, CH_2CD_2OH, CD_2CD_2OH, CH_2OCH_3, CH_2OCD_2H, CH_2OCDH_2, CH_2OCD_3, CH_2OCF_3, CH_2OCHF_2, CH_2OCH_2F, $CH_2CH_2OCH_3$, $CH_2CH_2OCD_2H$, $CH_2CH_2OCDH_2$, $CH_2CH_2OCD_3$, $CH_2CH_2OCF_3$, $CH_2CH_2OCHF_2$, and $CH_2CH_2OCH_2F$. In some embodiments, at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OCH_3, OCF_2H, $OCFH_2$, OCF_3, and OCD_3. In some embodiments, at least one of the substituents on the 3- to 7-membered heterocyclic ring formed by R^{11} or R^{12} is selected from OCF_2H, $OCFH_2$, and $OCHF_2$.

[0241] In some embodiments, Z' is selected from $NR^{20}C(O)$, $NR^{20}C(O)O$, $C(O)NR^{20}$, $OC(O)NR^{20}$, and NR^{20}. In some embodiments, Z' is selected from O, C(O), $NR^{20}C(O)$, and $NR^{20}C(O)O$. In some embodiments, Z' is O. In some embodiments, Z' is C(O). In some embodiments, Z' is $NR^{20}C(O)$. In some embodiments, Z' is $NR^{20}C(O)O$.

[0242] In some embodiments, R^{14} and R^{16} are independently selected from H, C_1-C_4alkyl, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{14} and R^{16} are independently selected from H, C_1-C_4alkyl, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to three substituents independently selected from F, Cl, C_1-C_4alkyl, and OC_1-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^{14} and R^{16} are independently selected from H, C_1-C_4alkyl, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to three substituents independently selected from F, Cl, C_1-C_4alkyl, and OC_1-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0243] In some embodiments, R^{14} and R^{16} are independently selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, R^{14} and R^{16} are independently selected from H, D, C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, and C_1-C_6deuterofluoroalkyl.

[0244] In some embodiments, R^{14} and R^{16} are independently selected from H, D, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, CF_2H, CFH_2, CF_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, $CH_2CH_2CHF_2$, $CH_2CH_2CFH_2$, $CH_2CH_2CF_3$, $CH(CF_3)_2$, $CH(CHF_2)_2$, $CH(CFH_2)_2$, $C(CF_3)_3$, $C(CHF_2)_3$, $C(CFH_2)_3$, $CH_2CH_2CH_2CF_3$, $CH_2CH(CF_3)_2$, $CH(CH_3)CH_2CF_3$, CD_2H, CDH_2, CD_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3, CD_2CD_3, $CH_2CH_2CHD_2$, $CH_2CH_2CDH_2$, $CH_2CH_2CD_3$, $CH(CD_3)_2$, $CH(CHD_2)_2$, $CH(CDH_2)_2$, $C(CD_3)_3$, $C(CHD_2)_3$, $C(CDH_2)_3$, $CH_2CH_2CH_2CD_3$, $CH_2CH(CD_3)_2$, and

$CH(CH_3)CH_2CD_3$. In some embodiments, R^{14} and R^{16} are independently selected from H, D, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CF_2H, CFH_2, CF_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, $CH(CF_3)_2$, $CH(CHF_2)_2$, $CH(CFH_2)_2$, $C(CF_3)_3$, $C(CHF_2)_3$, $C(CFH_2)_3$, CD_2H, CDH_2, CD_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3, $CH(CD_3)_2$, $CH(CHD_2)_2$, $CH(CDH_2)_2$, $C(CD_3)_3$, $C(CHD_2)_3$, and $C(CDH_2)_3$. In some embodiments, R^{14} and R^{16} are independently selected from H, D, CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, CF_2H, CDF_2, CF_3, CD_2H, CDH_2, and CD_3

[0245] In some embodiments, R^{14} and R^{16} are independently selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, each of which is optionally substituted with one to four substituents independently selected from halo, C-C_4alkyl, OC_1-C_4alkyl and $C(O)C_1$-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0246] In some embodiments, the C_3-C_7cycloalkyl in R^{14} and R^{16} is independently selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0247] In some embodiments, the C_3-C_{10}heterocycloalkyl in R^{14} and R^{16} is independently a monocyclic C_3-C_7heterocycloalkyl or a bicyclic C_7-C_{10}heterocycloalkyl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and C(O)C-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0248] In some embodiments, the monocyclic C_3-C_7heterocycloalkyl in R^{14} and R^{16} is independently selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, 1,3-dioxolanyl, azetidinyl, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxothiolidinyl, thiazolidinyl, isothiazolidinyl, imidazolidinyl, imidazolinyl, dioxolanyl, dithiolanyl, triazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, dihydropyranyl, isothiazolidinyl, morpholinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, tetrahydropyridinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl dioxide, dioxanyl, thiazolinyl, thianyl, thianyl oxide, thianyl dioxide, dithianyl, azepanyl, pyrazolidinyl, oxepanyl, thiepanyl, diazepanyl, and 2,5-pyrrolidinedionyl (e.g., succinimidyl), each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the monocyclic C_3-C_7heterocycloalkyl in R^{14} and R^{11} is independently selected from oxetanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, tetrahydropyranyl, dihydropyranyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, piperidinyl, piperazinyl, thianyl, thianyl oxide, thianyl dioxide, dithianyl, and 2,5-pyrrolidinedionyl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0249] In some embodiments, the bicyclic C_7-C_{10}heterocycloalkyl in R^{14} and R^{16} is independently selected from benzoisoxazolyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzopyranyl, benzothiopyranyl, chromanyl, isochromanyl, dihydroindenyl, isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl (e.g., phthalimido), octahydroisoindolinyl, octahydro-isoindolin-1-onyl (e.g., tetrahydroisoquinoline), and hexahydroisoindoline-1,3-dionyl (e.g., cis-hexahydrophthalimidyl), each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and C(O)C-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium. In some embodiments, the bicyclic C_7C_{10}heterocycloalkyl in R^{14} and R^{16} is independently selected from isoindolinyl, 1-oxoisoindolinyl, 3-oxoisoindolinyl, 1,3-dioxoisoindolinyl, octahydro-1H-isoindolinyl, octahydro-1H-isoindolin-1-onyl, and hexahydro-1H-isoindoline-1,3-dionyl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0250] In some embodiments, the C_6-C_{10}aryl in R^{14} and R^{16} is independently phenyl, which is optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

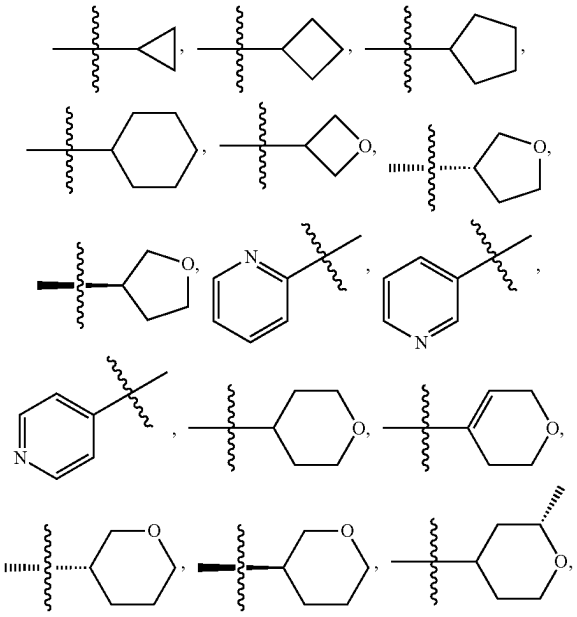
[0251] In some embodiments, the C_5-C_{10}heteroaryl in R^{14} and R^{16} are independently selected from azepinyl, benzofuranyl, benzofurazanyl, benzothiazolyl, benzothienyl, benzoxazolyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, thiazolyl, thienofuranyl, triazolyl, and thienyl (e.g., thiophenyl), each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and C(O)C-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0252] In some embodiments, the substituents on R^{14} and R^{16} are independently selected from one to four, one to three, or one or two, of F, Cl, Br, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, CH_2CH_2F, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CD_2CD_3, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH(CH_3)_2$, $OC(CH_3)_3$, OCD_2H, $OCDH_2$, OCD_3, OCF_3, $OCHF_2$, OCH_2F, OCH_2CH_2F, OCF_2CF_3, OCH_2CH_2D,

OCH_2CD_2H, OCD_2CD_3, $C(O)CH_3$, $C(O)CH_2CH_3$, $C(O)CH_2CH_2CH_3$, $C(O)CH(CH_3)_2$, $C(O)C(CH_3)_3$, $C(O)CD_2H$, $C(O)CDH_2$, $C(O)CD_3$, $C(O)CF_3$, $C(O)CHF_2$, $C(O)CH_2F$, $C(O)CH_2CH_2F$, $C(O)CF_2CF_3$, $C(O)CH_2CH_2D$, $C(O)CH_2CD_2H$, and $C(O)CD_2CD_3$.

[0253] In some embodiments, R^{13}, R i, R^{11}, R^{18}, R^{19}, and R^{20} are independently selected from H, D, and C_1-C_4alkyl wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H, D, and C_1-C_4alkyl, wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H, D, and C_1-C_4alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available atoms are optionally replaced with an alternate isotope thereof. In some embodiments, R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl. In some embodiments, R^{13}, R^{15}, R^{17}, R^{18}, R^{19} and R^{20} are independently selected from H, D, F, Br, Cl, CH_3, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, CH_2CH_3, CH_2CH_2F, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, and CD_2CD_3. In some embodiments, R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H, CH_3, CF_3, CHF_2, CD_2H, CDH_2, and CD_3. In some embodiments, R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H, D, CH_3, CF_3, CHF_2, CH_2F, CD_2H, CDH_2, and CD_3. In some embodiments, R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H, D, CH_3, CF_3, and CD_3.

[0254] In some embodiments, especially those in which X is S, S(O), or SO_2, as well as embodiments in which X is 0 or absent, R^6 is selected from CH_3, CD_3, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$, CH_2F, CHF_2, CH_2CHF_2, CH_2CF_3, $CH_2CH_2CF_3$,



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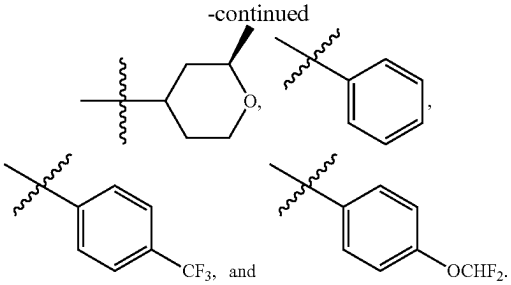


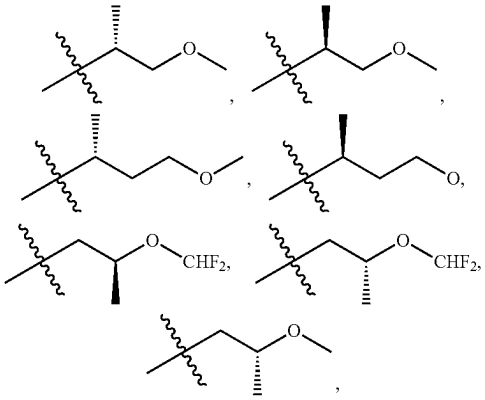
[0255] In some embodiments, R^{11} and R^{12} are independently selected from or R^6, R^{11}, and R^{12} are independently selected from:

[0256] H, CH_3, CD_3, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$,

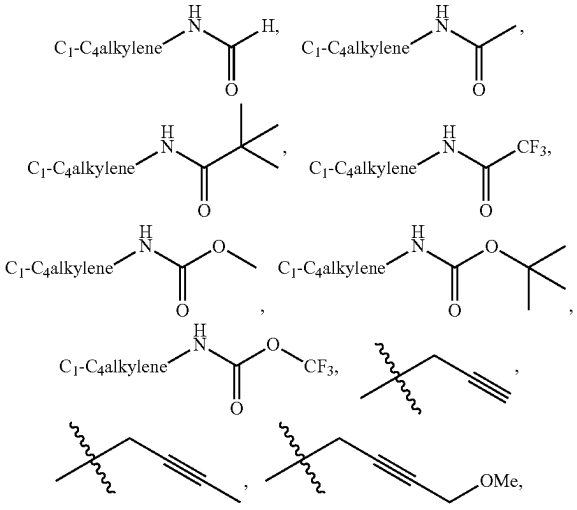
[0257] $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$,

[0258] CH_2F, CHF_2, CH_2CHF_2, CH_2CF_3, $CH_2CH_2CF_3$,

[0259] C_1-C_4alkyleneOCH$_3$, C_1-C_4alkyleneOCHF$_2$, C_1-C_4alkyleneOCH$_2$F,



[0260] C_1-C_4alkyleneC(O)CHF$_2$, C_1-C_4alkyleneC(O)CF$_3$,



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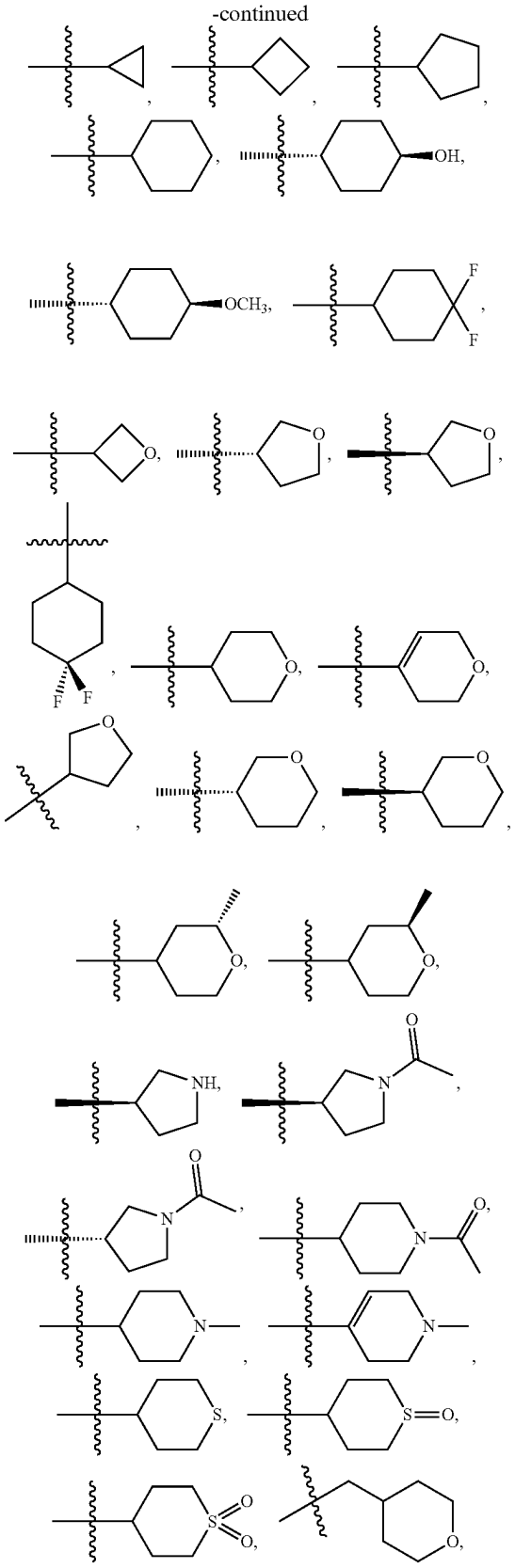

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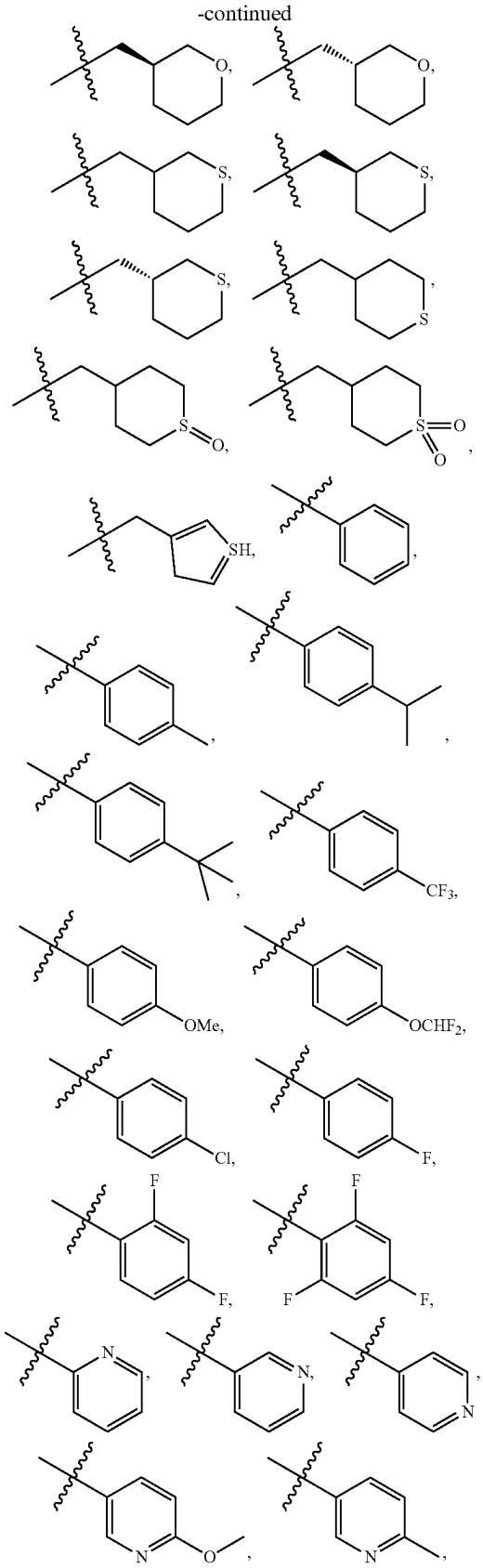

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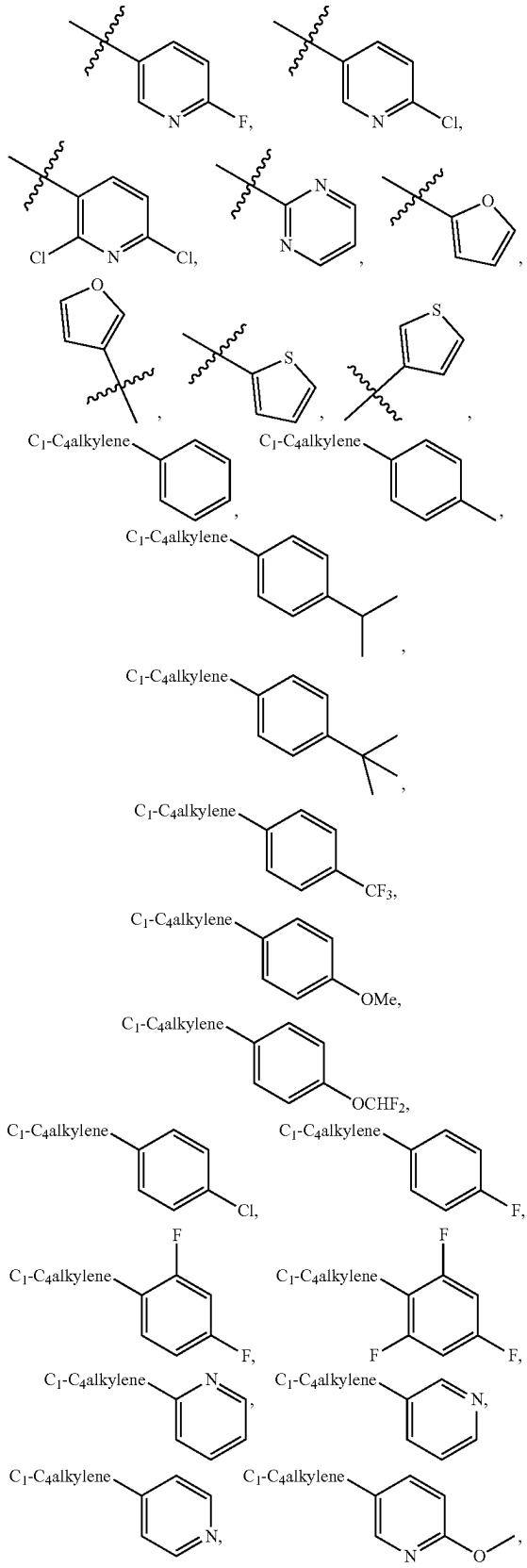

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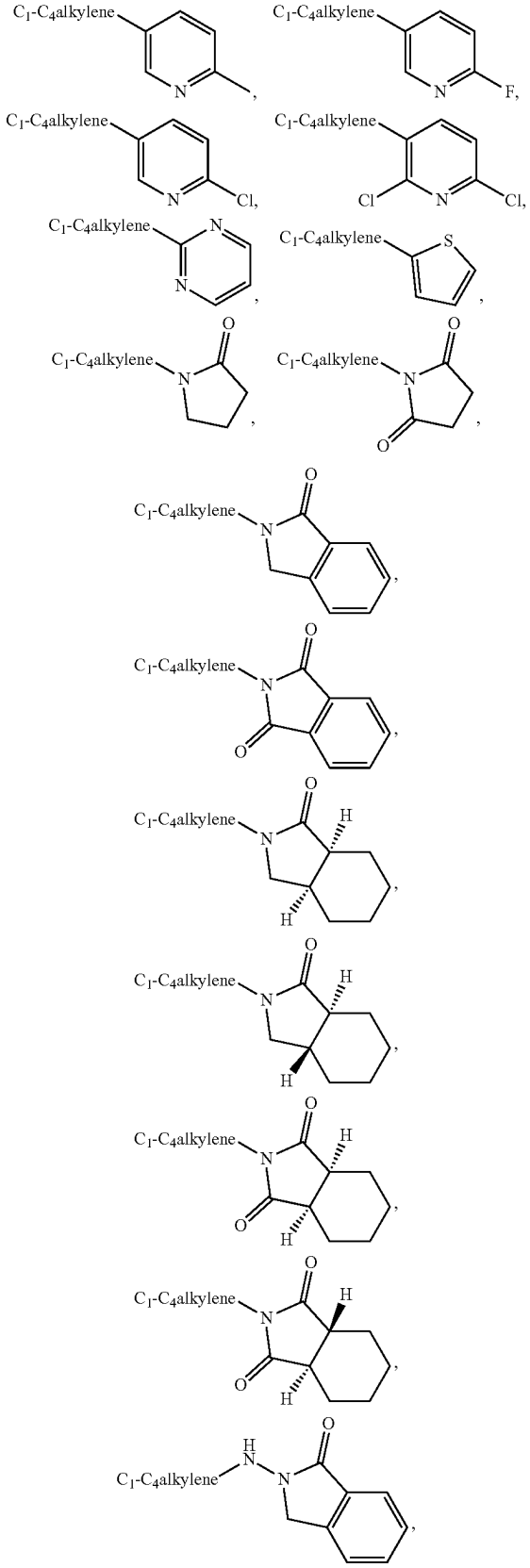

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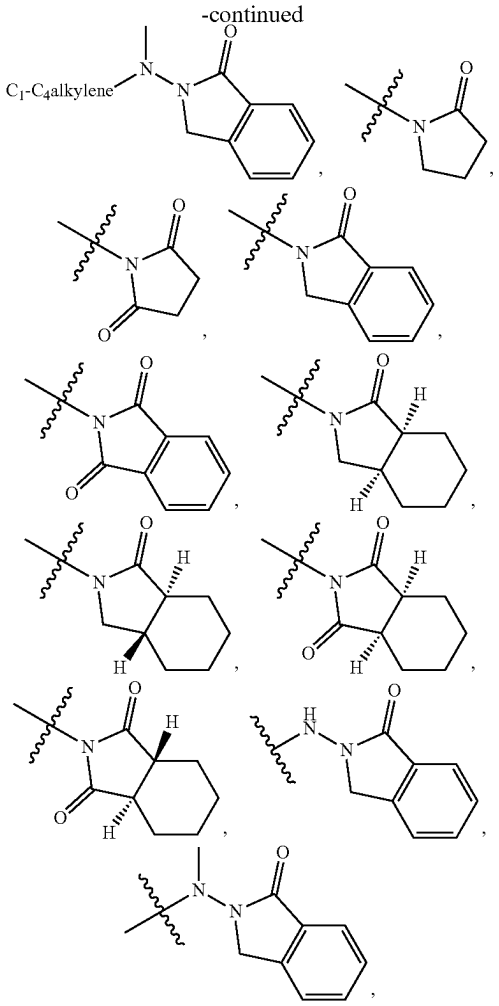
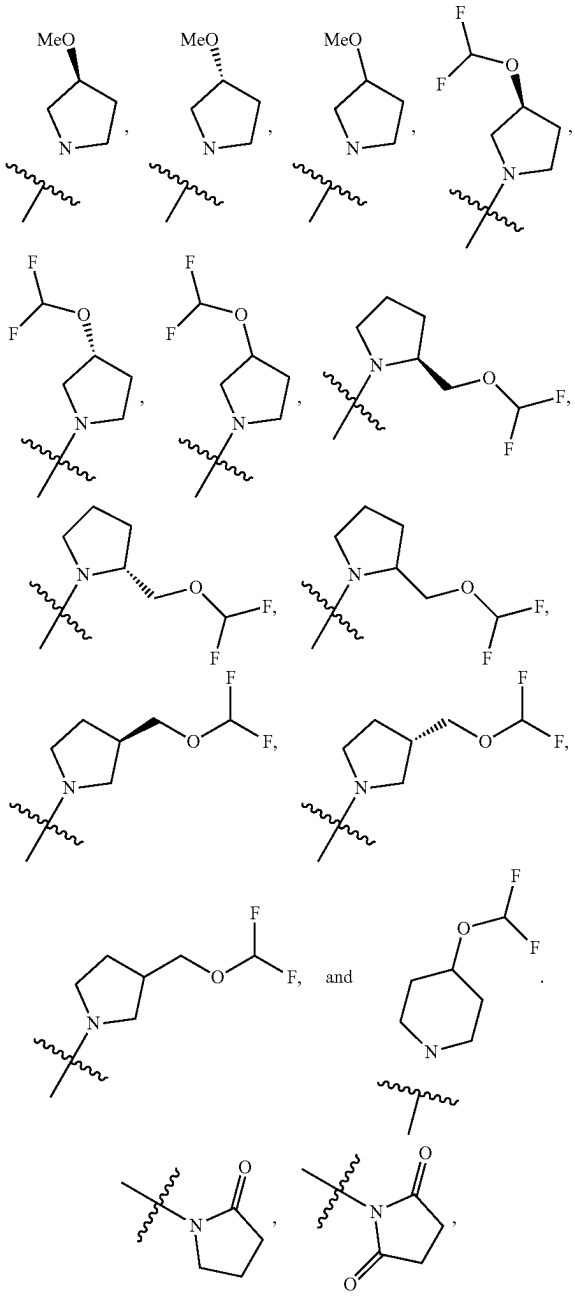


[0261] In the above embodiments and in other embodiments using the term herein, C_1-C_4alkylene includes, for example, —CH—, —CH_2CH_2—, —$CH_2CH_2CH_2$—, —$CH_2CH_2CH_2CH_2$—, —$CH(CH_3)CH_2$—, —$CH_2CH(CH_3)$—, —$C(CH_3)_2$—, —$CH(CH_3)CH_2CH_2$—, —$CH_2CH(CH_3)CH_2$—, —$CH_2CH_2CH(CH_3)$—, —$C(CH_3)_2CH_2$—, —$CH_2C(CH_3)_2$—, and —$CH(CH_3)CH(CH_3)$—. Available hydrogen(s) on the C_1-C_4alkylene is/are optionally substituted with deuterium and/or one or more halogen atoms, for example but not limited to, —CF_2—, —CBr_2—, —CCl_2—, —CHD-, —CD_2-, —CDF-, —CF_2CF_2—, —CH_2CD_2-, —CD_2CH_2—, —CH_2CHD-, —$CHDCH_2$—, —CH_2CHY—, —$CHYCH_2$—, —CH_2CY_2—, —CY_2CH_2—, —CHYCHY—, —CHDCHY—, —CHYCHD-, —CD_2CHY—, $CHYCD_2$, —$CHDCY_2$—, —CY_2CHD-, —CY_2CD_2-, —CD_2CY_2—, —CD_2CHD-, —$CHDCD_2$-, —CD_2CD_2-, —$CD_2CD_2CD_2$-, —$CH_2CD_2CD_2$-, —$CD_2CH_2CH_2$—, —$CH_2CH_2CD_2$-, —$CD_2CD_2CH_2$—, —$CH_2CD_2CH_2$—, —CH_2CH_2CHD-, —$CHDCHDCH_2$—, —$CH_2CHDCHD$-, —$CD_2CD(CH_3)$—, —CD_2CHDCH_2—, —$CH_2CD(CH_3)$—, —CH_2CHDCH_2—, —$CD_2CH(CH_3)$—, —$CHDCH_2CH_2$—, —$CHDCH(CH_3)$—, etc. (wherein each Y is independently selected from F, Cl, Br, and I).

[0262] In some embodiments, R^{11} and R^{12}, in addition to the list above, are further independently H.

[0263] In some embodiments, R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, C_1-C_6alkyleneOC_1-C_6alkyl, selected from



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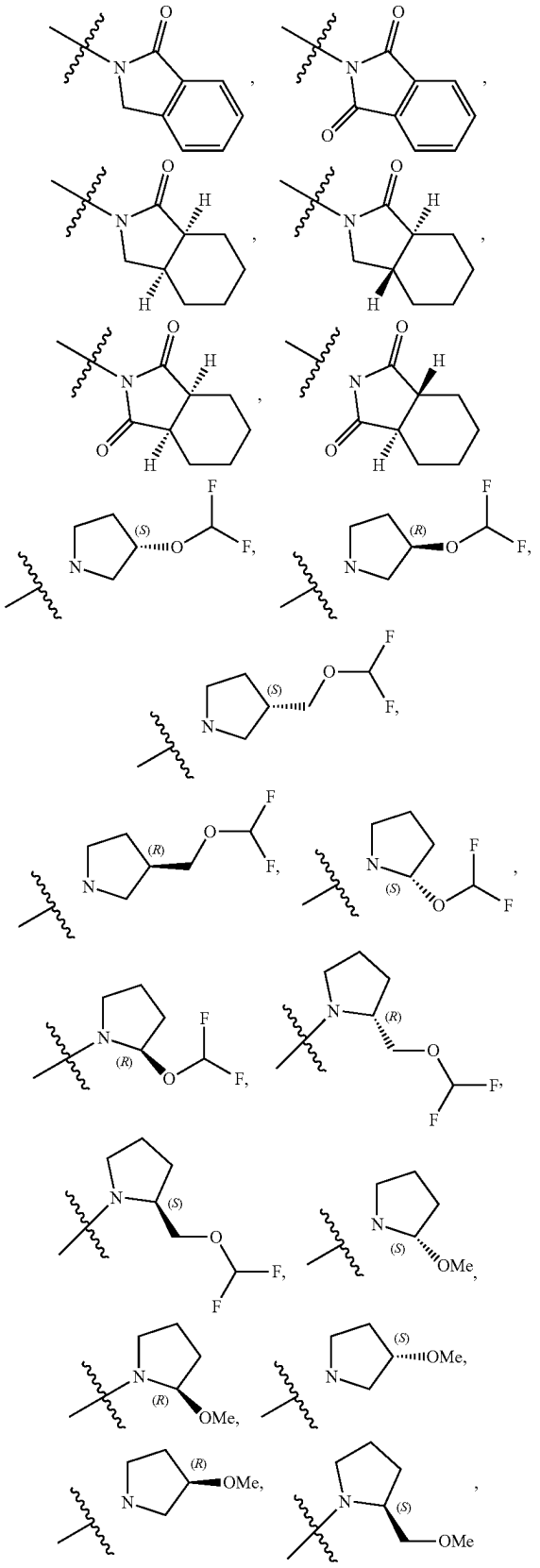

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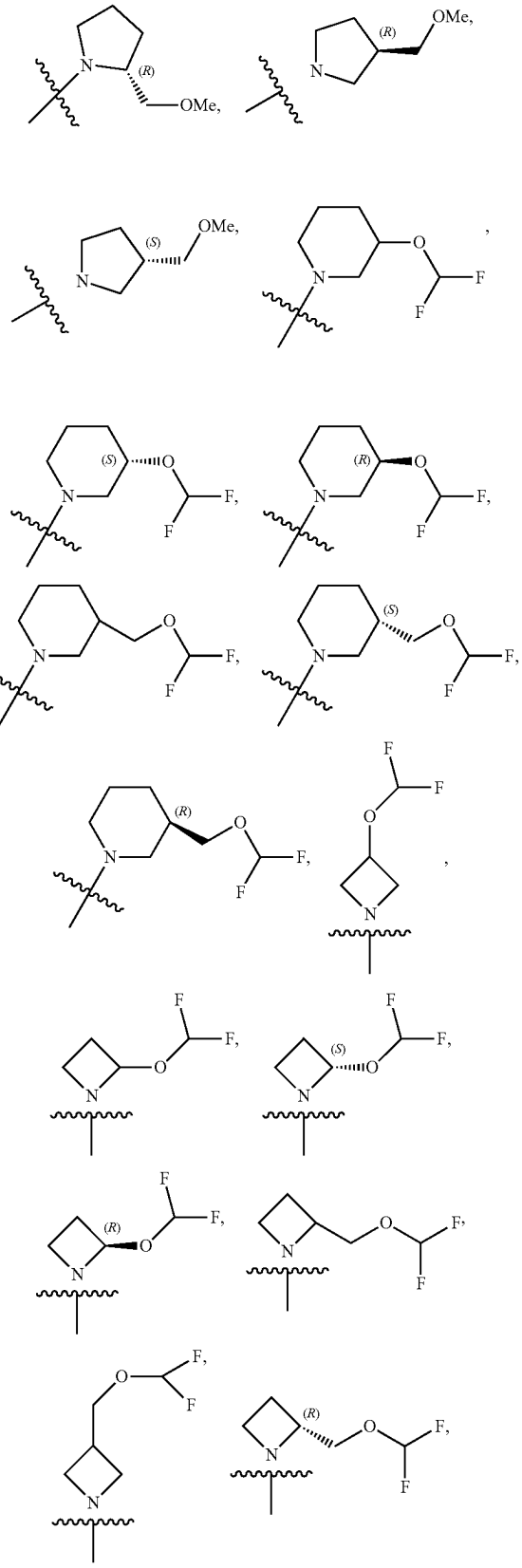

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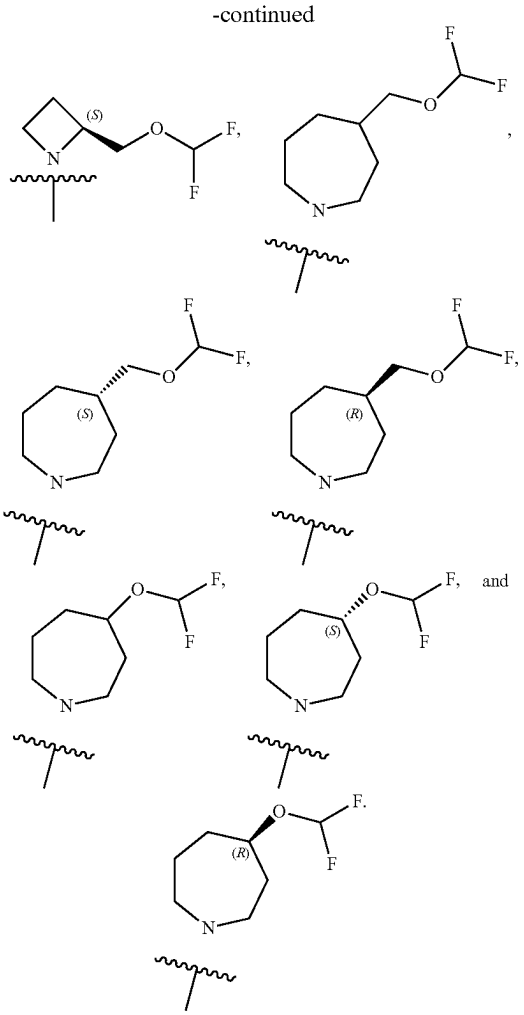
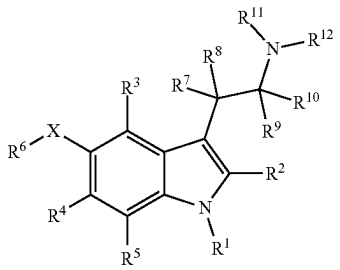


[0264] In some embodiments, the compound of Formula (I) is a compound of Formula (I-A):

Formula (I-A)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0265] wherein:

[0266] X is selected from S, S(O), and SO_2;

[0267] R^1 is selected from H, C_1-C_6alkyl, C_1-C_6alkylene$P(O)(OR^{13})_2$, C_1-C_6alkyleneOP(O)$(OR^{13})_2$, $C(O)R^{13}$, CO_2R^{13}, $C(O)N(R^{13})_2$, $S(O)R^{13}$, and SO_2R^{13};

[0268] R^2 is selected from H, halo, and C_1-C_6alkyl;

[0269] R^3, R^4, and R^5 are independently selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

[0270] R^6 is selected from H, C_1-C_{10}alkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl;

[0271] R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_6alkyl;

[0272] R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl; or

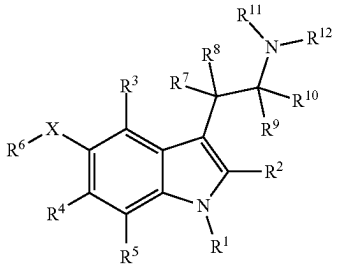
[0273] R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 7-membered heterocyclic ring optionally including 1 to 2 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{14}, wherein said 3- to 7-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from OH, halo, C_1-C_6alkyl, and OC_1-C_6alkyl;

[0274] R^{13} is selected from H and C_1-C_6alkyl;

[0275] R^{14} is selected from H, C_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl; and available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0276] In some embodiments, the compound of Formula (I) is a compound of Formula (I-B):

Formula (I-B)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

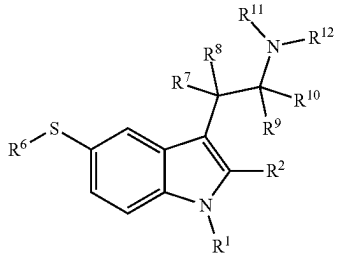
[0277] wherein:

[0278] X, R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in Formula (I) including embodiments thereof, wherein X is selected from S, S(O), and SO_2;

[0279] R^3 is selected from H, D, CN, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and available atoms are optionally replaced with an alternate isotope thereof.

[0280] In some embodiments, X is S and R^3, R^4, and R^5 are all H, and the compound of Formula (I) is a compound of Formula (I-C). Accordingly, in some embodiments, the present disclosure includes a compound of Formula (I-C):

Formula (I-C)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

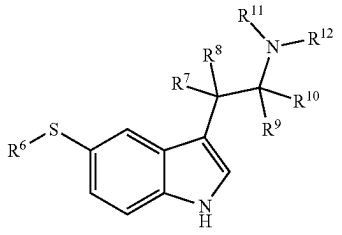
[0281] wherein:

[0282] R^1, R^2, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in Formula (I) including embodiments thereof;

[0283] wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0284] In some embodiments, X is S and R^1, R^2, R^3, R^4, and $R^5$are all H, and the compound of Formula (I) is a compound of Formula (I-D). Accordingly, in some embodiments, the present disclosure includes a compound of Formula (I-D):

Formula (I-D)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

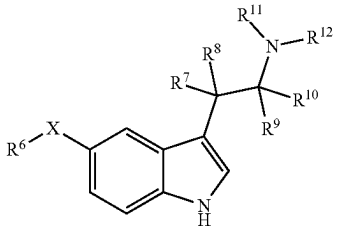
[0285] wherein:

[0286] R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in Formula (I) including embodiments thereof;

[0287] wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0288] In some embodiments, R^1, R^2, R^3, R^4, and R^5 are all H, and the compound of Formula (I) is a compound of Formula (I-E). Accordingly, in some embodiments, the present disclosure includes a compound of Formula (I-E):

Formula (I-E)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0289] wherein:

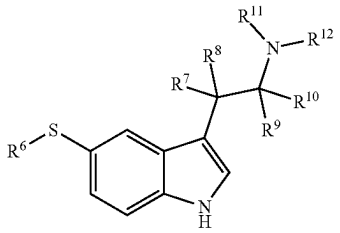
[0290] X, R^6, R^7, R^8, R^9, and R^{10} are as defined in Formula (I) including embodiments thereof, wherein X is selected from S, S(O), and SO_2;

[0291] R^{11} and R^{12} are independently selected from H, D, and C_1-C_6alkyl; and

[0292] available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0293] In some embodiments, X is S and R^1, R^2, R^3, R^4, and $R^5$are all H, and the compound of Formula (I) is a compound of Formula (I-F). Accordingly, in some embodiments, the present disclosure includes a compound of Formula (I-F):

Formula (I-F)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0294] wherein:

[0295] R^{11} and R^{12} are independently selected from C_1-C_6alkyleneOH and C_1-C_6alkyleneOC_1-C_6alkyl; or

[0296] R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 7-membered heterocyclic ring optionally including 1 to 2 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{14}, wherein said 3- to 7-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from OH, halo, C_1 C_6alkyl, and OC_1-C_6alkyl;

[0297] R^6, R^7, R^8, R^9, R^{10}, and R^{14} are as defined in Formula (I) including embodiments thereof; and

[0298] available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0299] In some embodiments, the compound of Formula (I) is selected from one or more of the compounds listed in Table 1 below:

TABLE 1

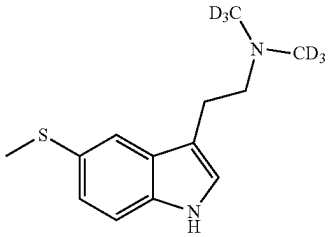
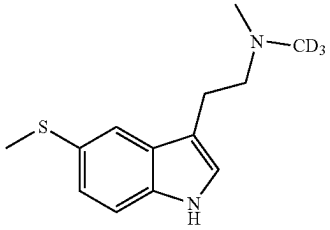
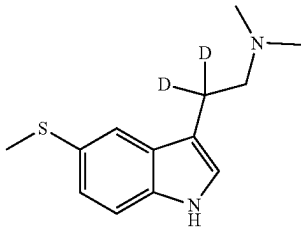
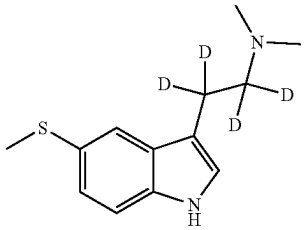
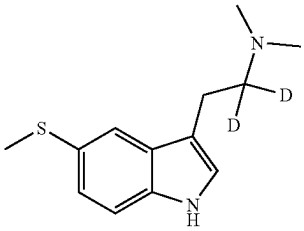
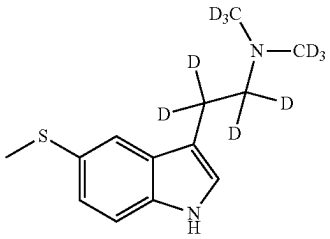
Compound	Structure
I-1	
I-2	
I-3	
I-4	
I-5	
I-6	

TABLE 1-continued

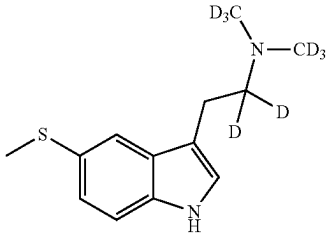
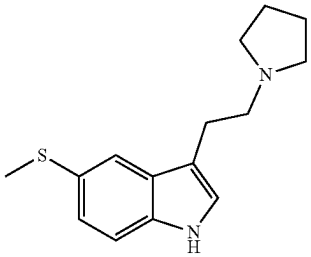
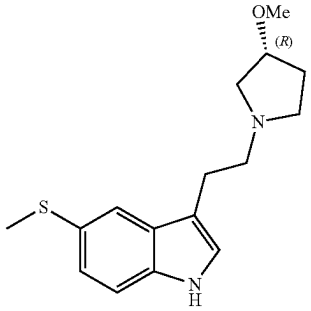
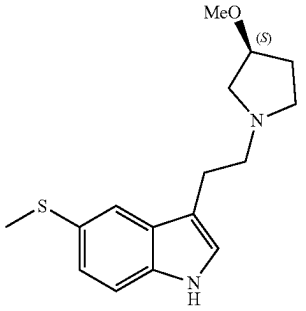
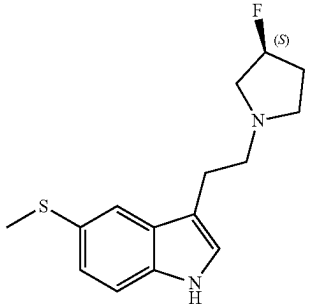
Compound	Structure
I-7	
I-8	
(R) I-9	
(S) I-9	
(R) I-10	

TABLE 1-continued

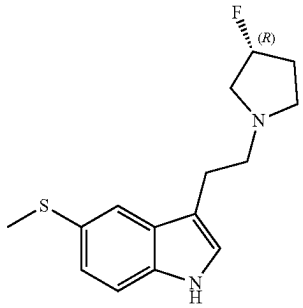
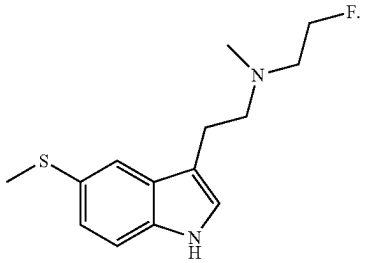
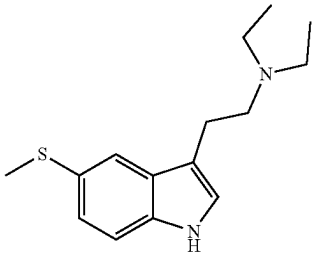
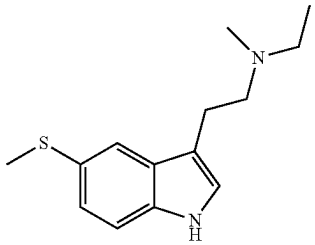
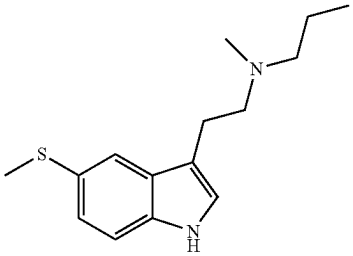
Compound	Structure
(S) I-10	
I-11	
I-12	
I-13	
I-14	

TABLE 1-continued

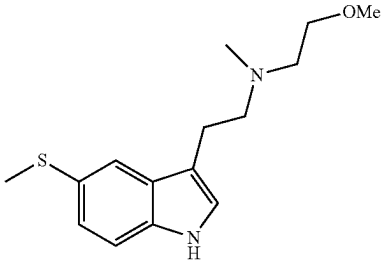
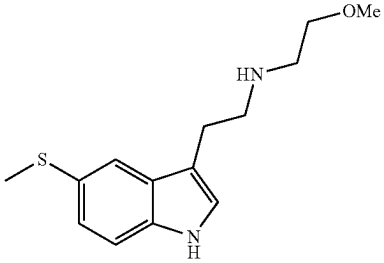
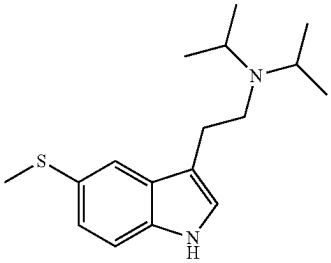
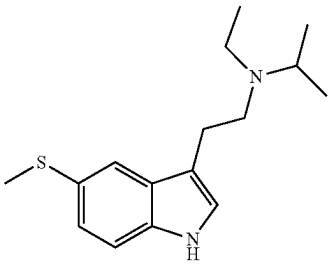
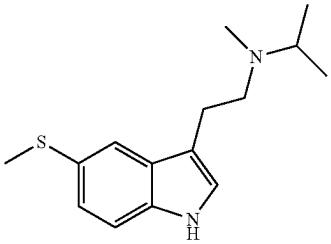
Compound	Structure
I-15	
I-16	
I-17	
I-18	
I-19	

TABLE 1-continued

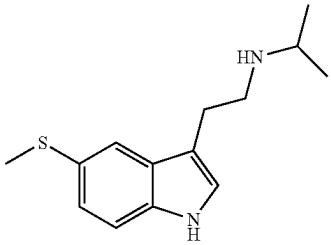
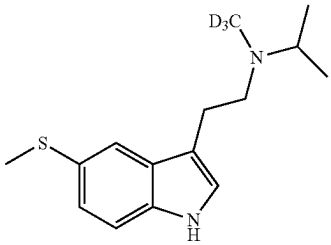
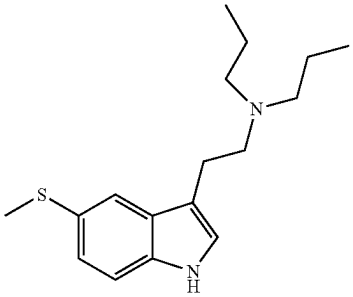
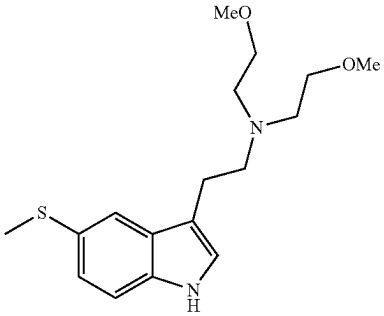
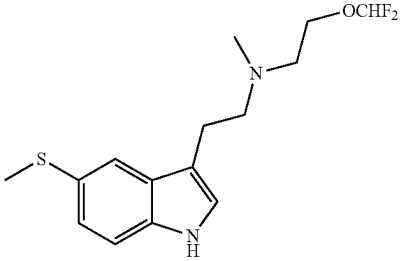
Compound	Structure
I-20	
I-21	
I-22	
I-23	
I-24	

TABLE 1-continued

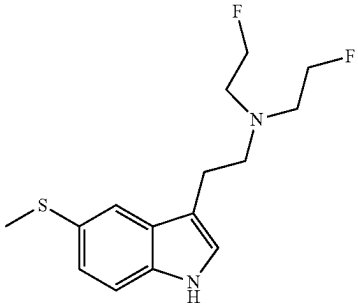
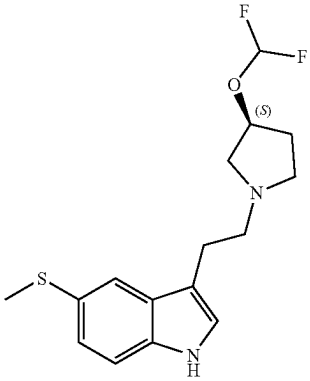
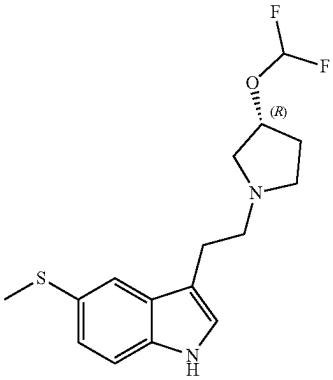
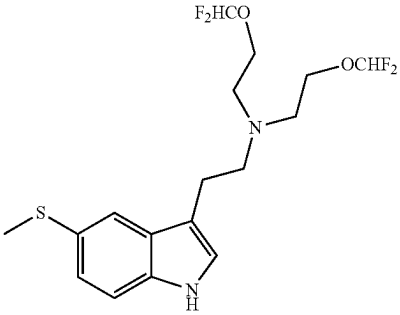
Compound	Structure
I-25	
(S) I-26	
(R) I-26	
I-27	

TABLE 1-continued

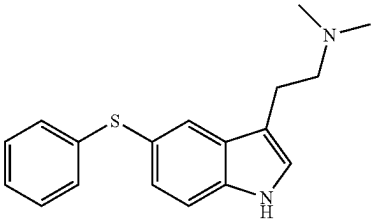
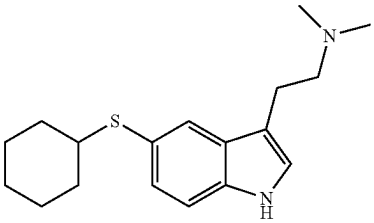
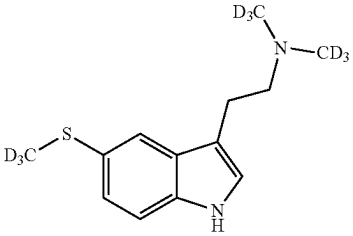
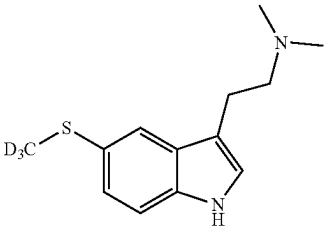
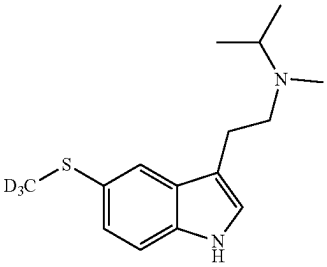
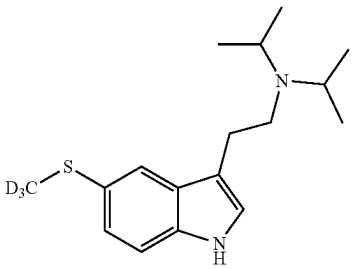
Compound	Structure
I-28	
I-29	
I-30	
I-31	
I-32	
I-33	

TABLE 1-continued

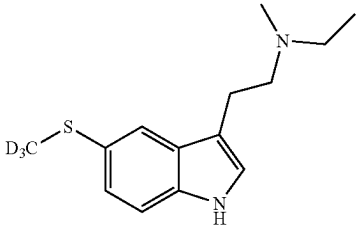
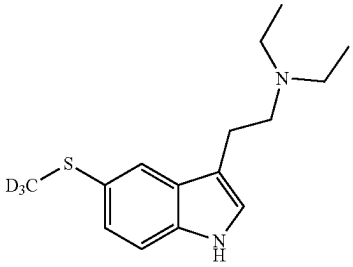
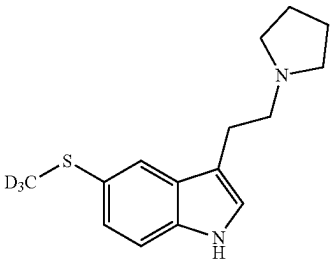
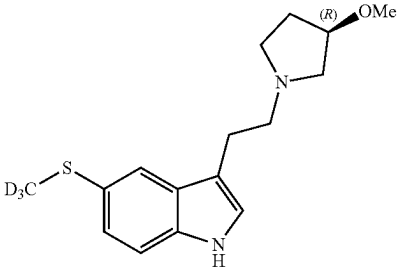
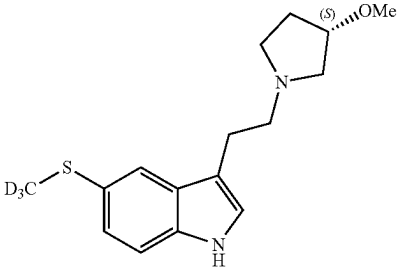
Compound	Structure
I-34	
I-35	
I-36	
(R) I-37	
(S) I-37	

TABLE 1-continued

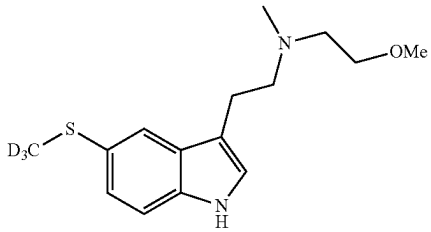
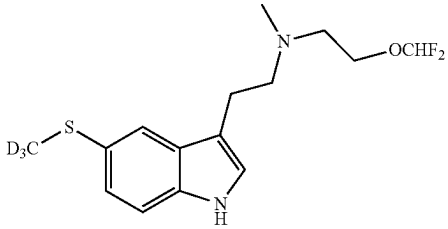
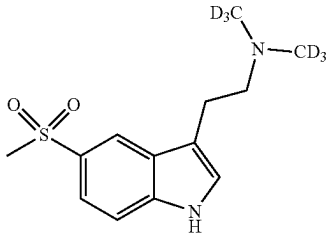
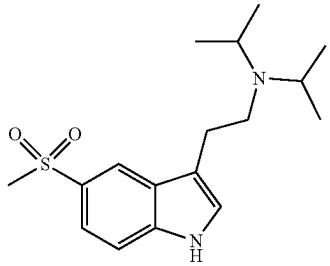
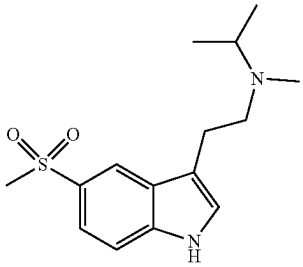
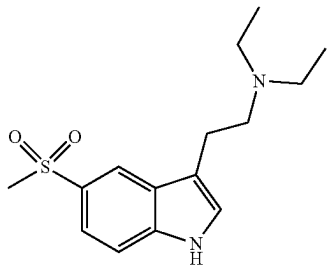
Compound	Structure
I-38	
I-39	
I-40	
I-41	
I-42	
I-43	

TABLE 1-continued

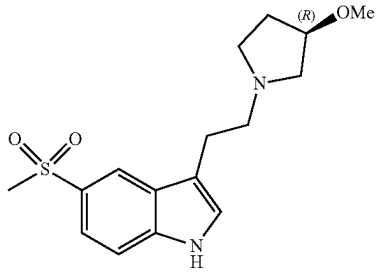
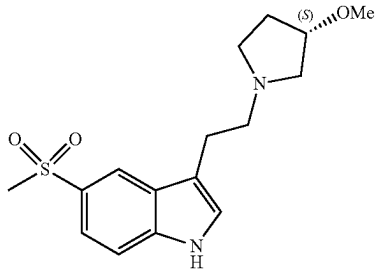
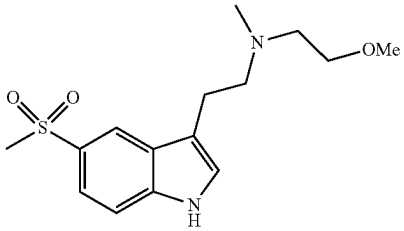
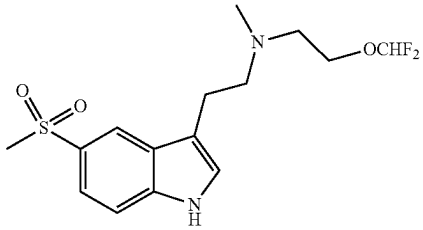
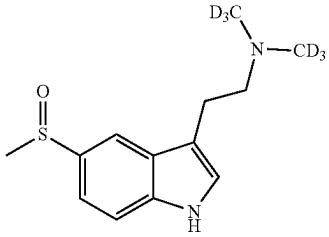
Compound	Structure
(R) I-44	
(S) I-44	
I-45	
I-46	
I-47	

TABLE 1-continued

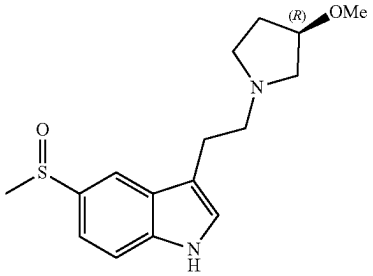
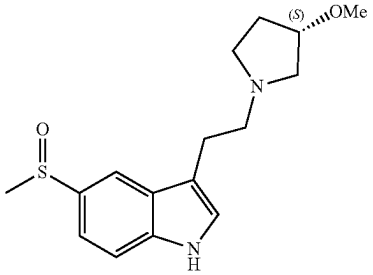
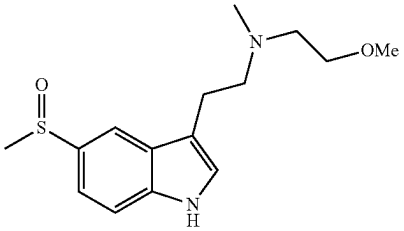
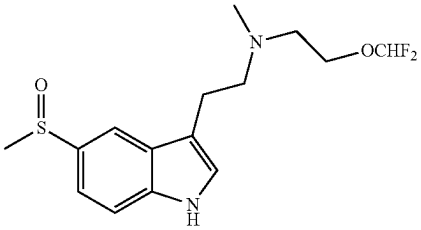
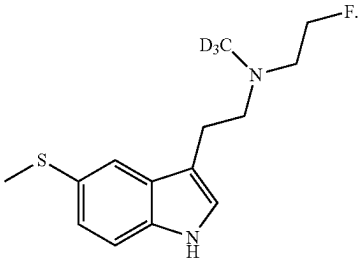
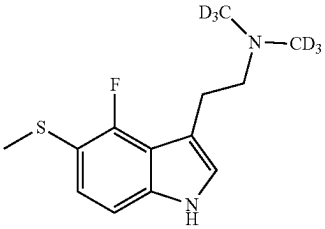
Compound	Structure
(R) I-48	
(S) I-48	
I-49	
I-50	
I-52	
I-53	

TABLE 1-continued

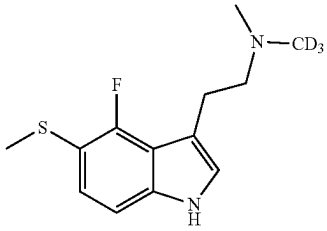
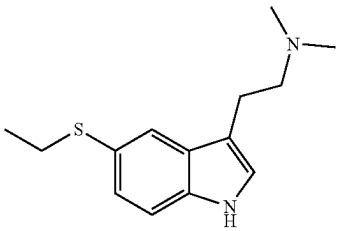
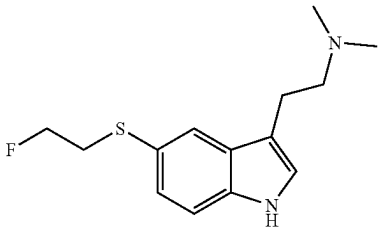
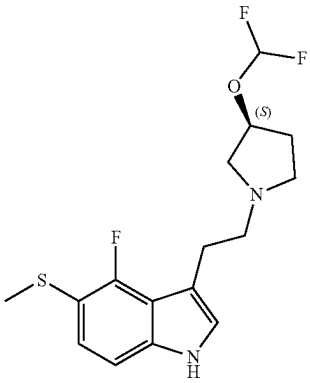
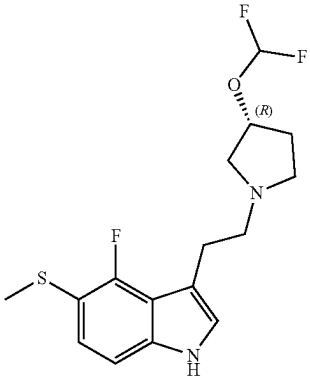
Compound	Structure
I-54	
I-55	
I-56	
(R) I-57	
(S) I-57	

TABLE 1-continued

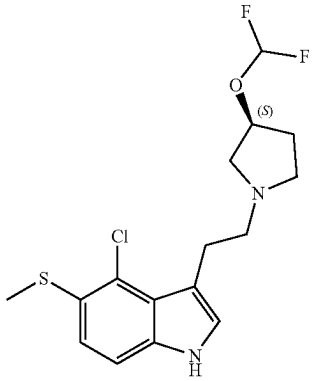
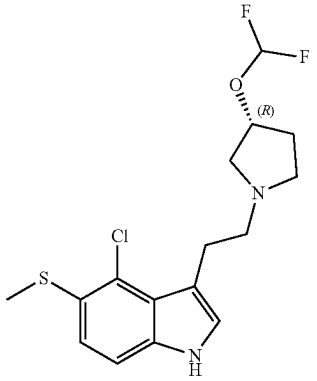
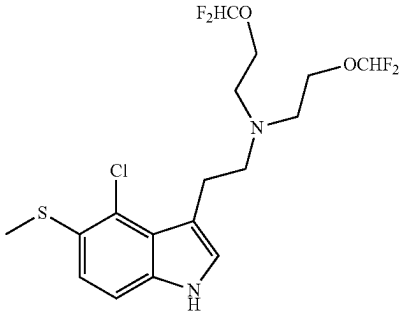
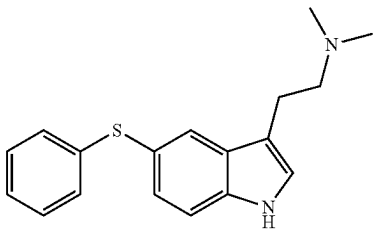
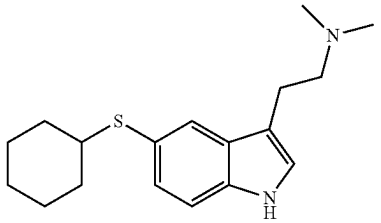
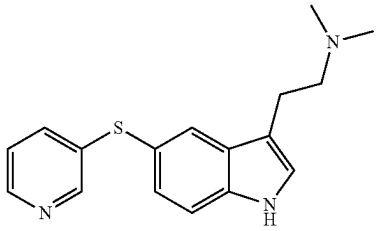
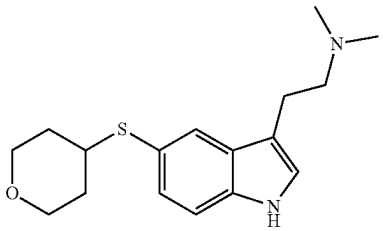
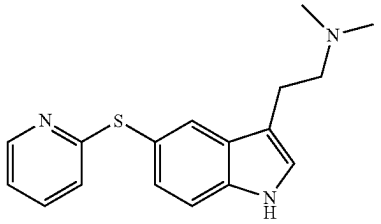
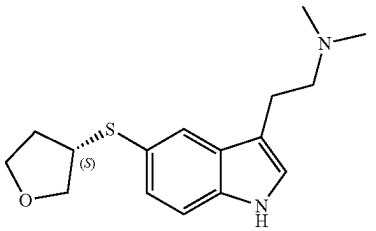
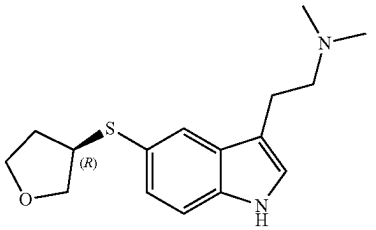
Compound	Structure
(R) I-58	
(S) I-58	
I-59	
I-60	

TABLE 1-continued

Compound	Structure
I-61	
I-62	
I-63	
I-64	
(S) I-65	
(R) I-65	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0300] In some embodiments, the compound of Formula (I) is selected from one or more of the compounds listed in Table 2 below:

TABLE 2

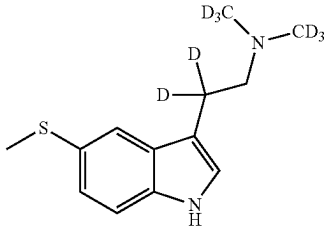
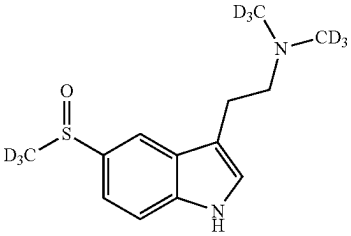
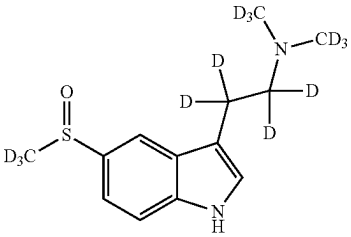
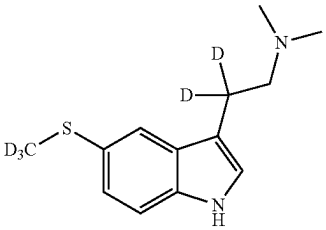
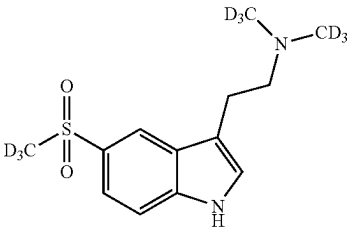
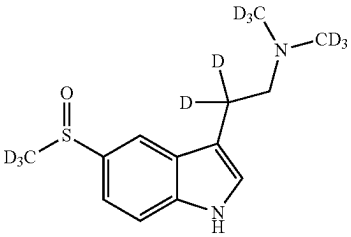
Compound	Structure
II-01	
II-02	
II-03	
II-04	
II-05	
II-06	

TABLE 2-continued

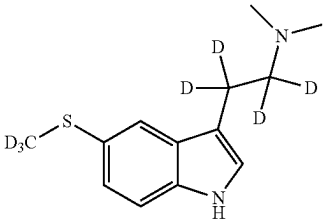
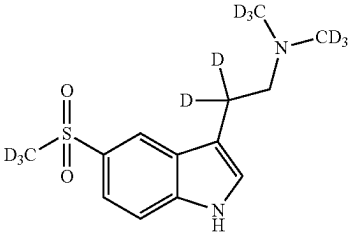
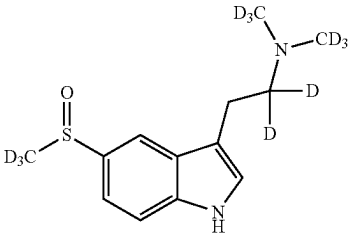
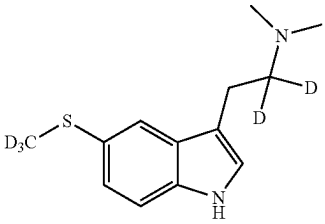
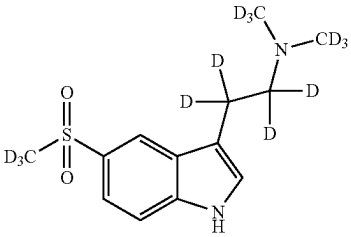
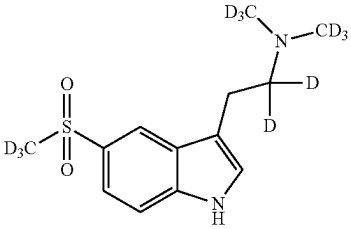
Compound	Structure
II-07	
II-08	
II-09	
II-10	
II-11	
II-12	

TABLE 2-continued

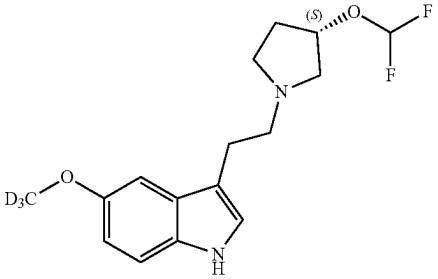
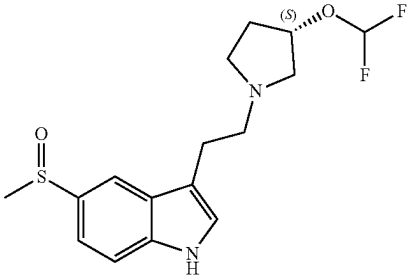
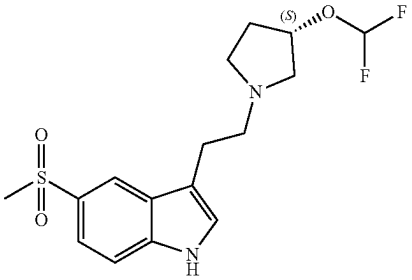
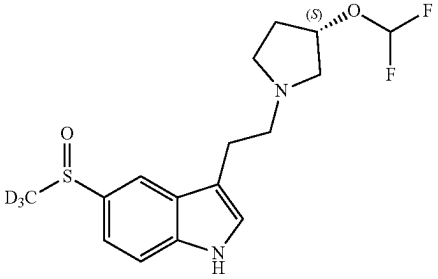
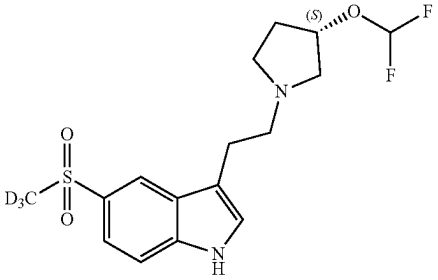
Compound	Structure
(S) II-13	
(S) II-14	
(S) II-15	
(S) II-16	
(S) II-17	

TABLE 2-continued

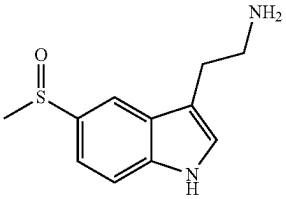
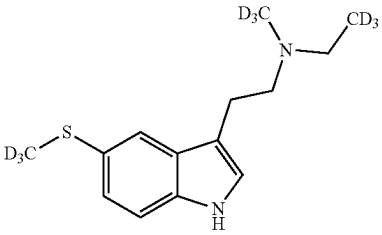
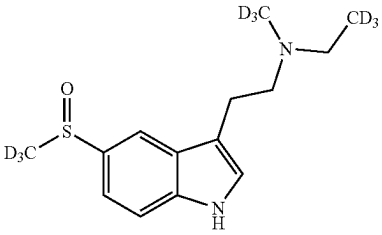
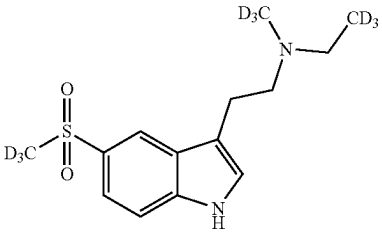
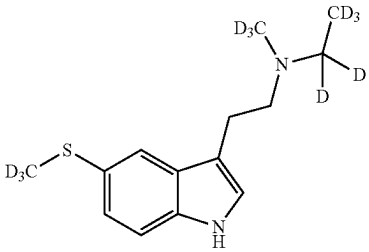
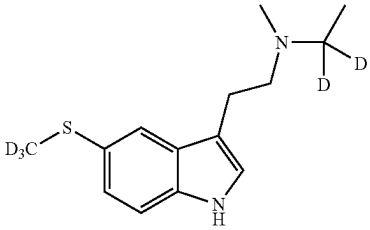
Compound	Structure
II-18	
II-19	
II-20	
II-21	
II-22	
II-23	

TABLE 2-continued

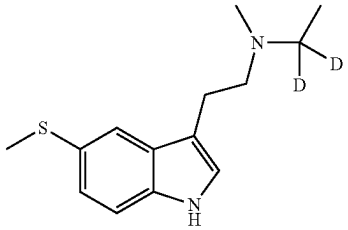
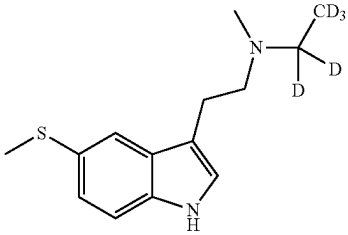
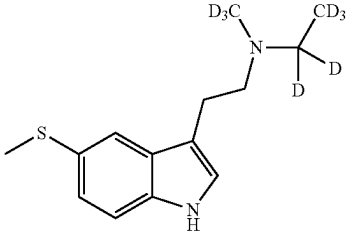
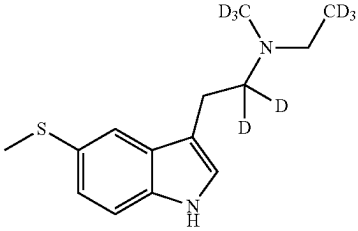
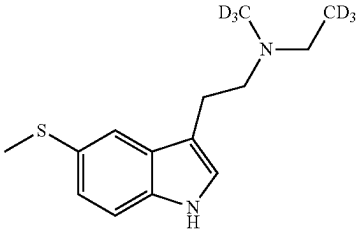
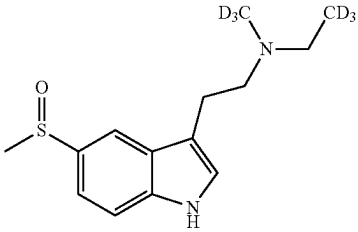
Compound	Structure
II-24	
II-25	
II-26	
II-27	
II-28	
II-29	

TABLE 2-continued

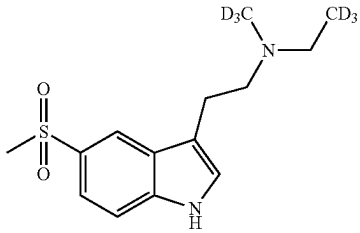
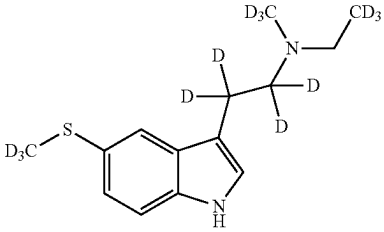
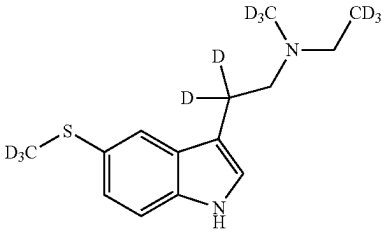
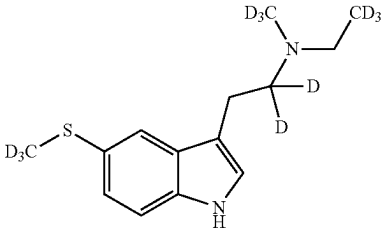
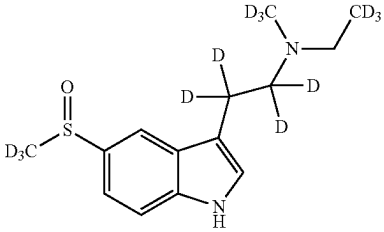
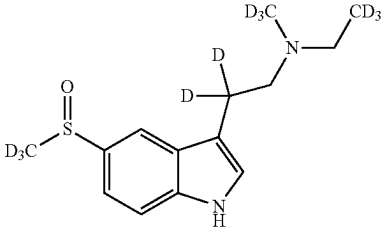
Compound	Structure
II-30	
II-31	
II-32	
II-33	
II-34	
II-35	

TABLE 2-continued

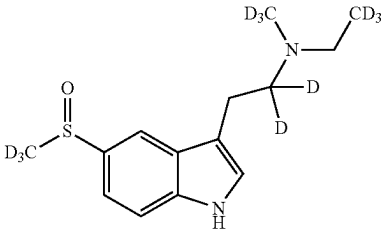
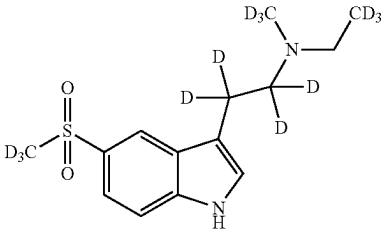
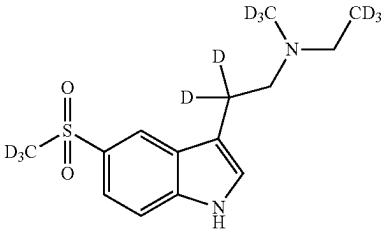
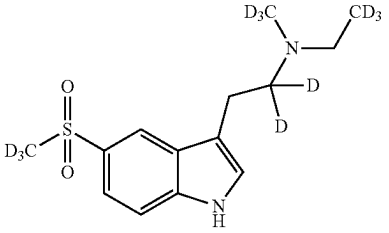
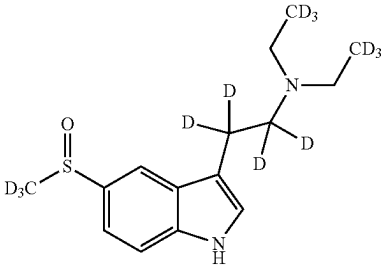
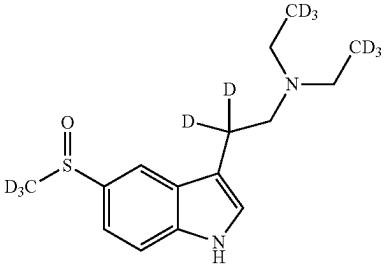
Compound	Structure
II-36	
II-37	
II-38	
II-39	
II-40	
II-41	

TABLE 2-continued

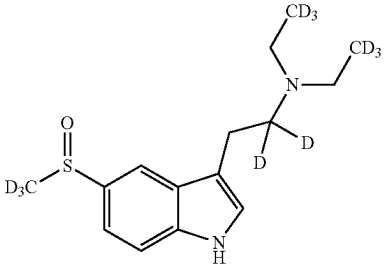
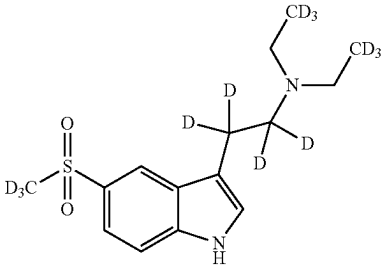
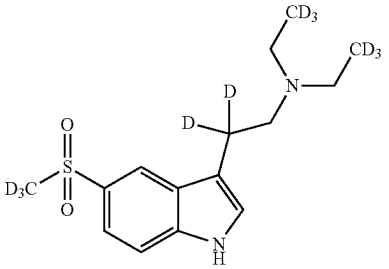
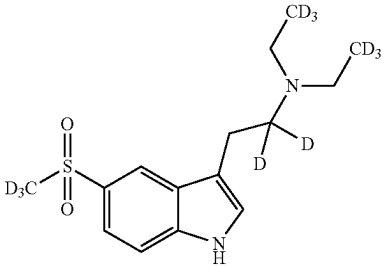
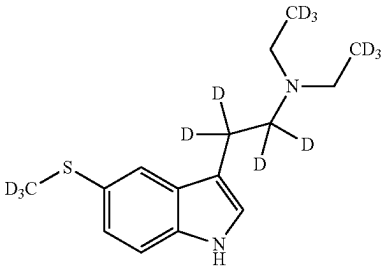
Compound	Structure
II-42	
II-43	
II-44	
II-45	
II-46	

TABLE 2-continued

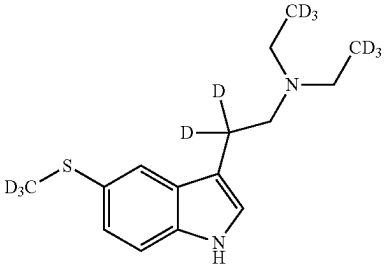
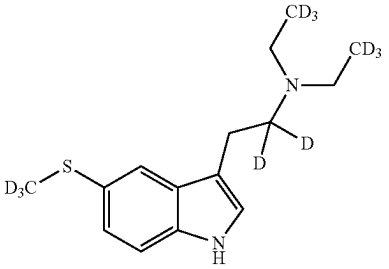
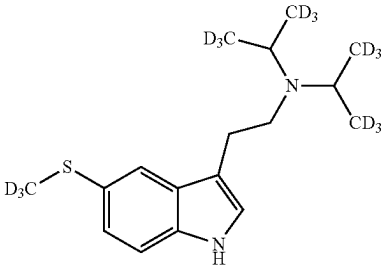
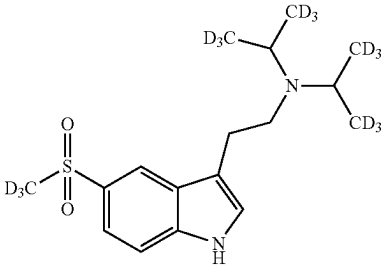
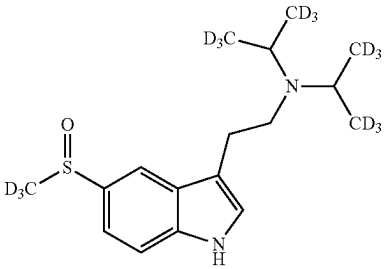
Compound	Structure
II-47	
II-48	
II-49	
II-50	
II-51	

TABLE 2-continued

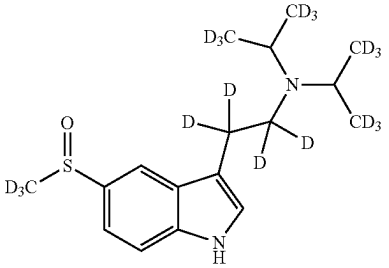
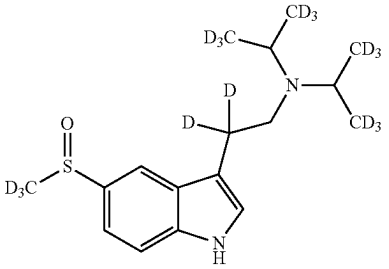
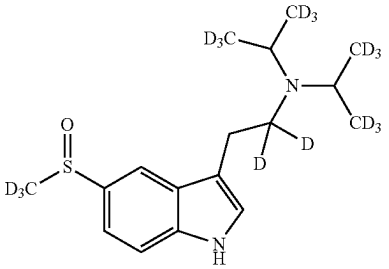
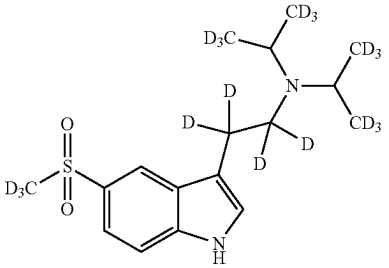
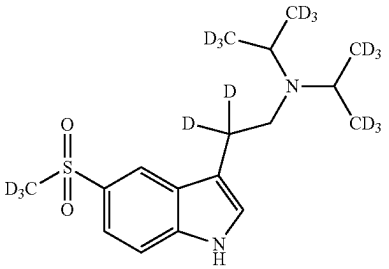
Compound	Structure
II-52	
II-53	
II-54	
II-55	
II-56	

TABLE 2-continued

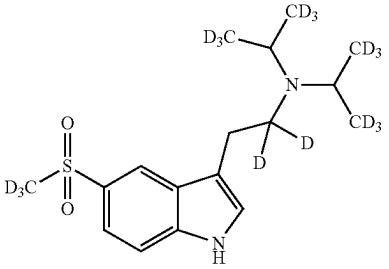
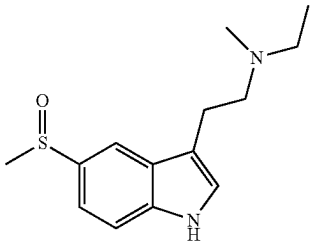
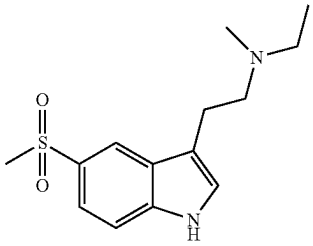
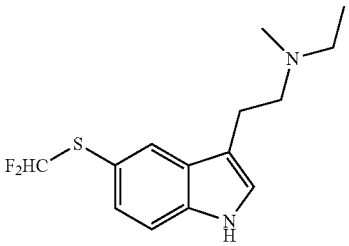
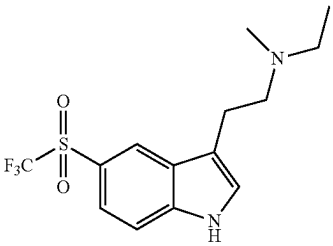
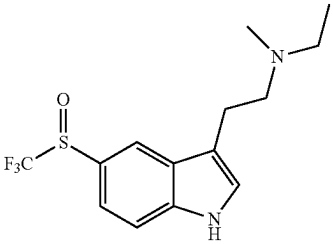
Compound	Structure
II-57	
II-58	
II-59	
II-60	
II-61	
II-62	

TABLE 2-continued

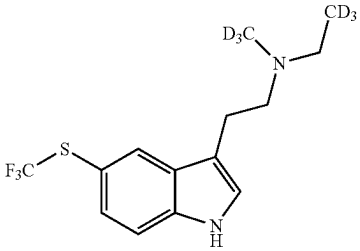
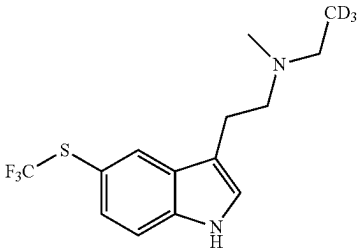
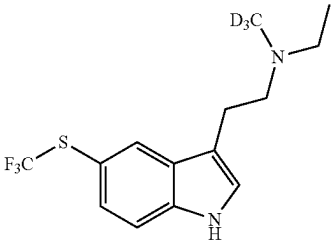
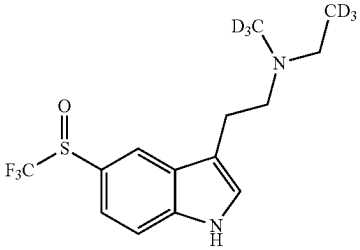
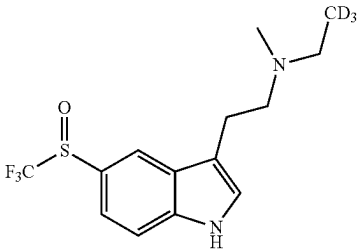
Compound	Structure
II-63	
II-64	
II-65	
II-66	
II-67	

TABLE 2-continued

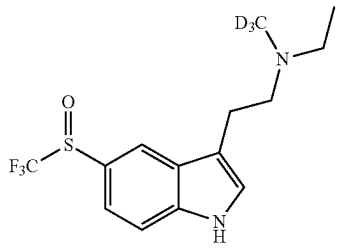
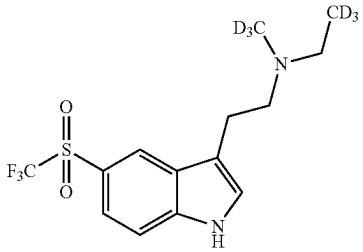
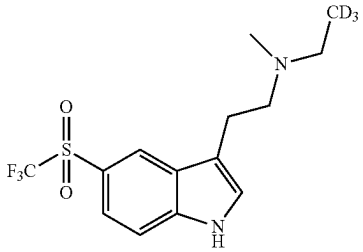
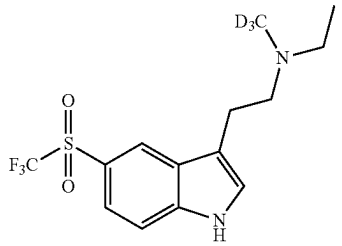
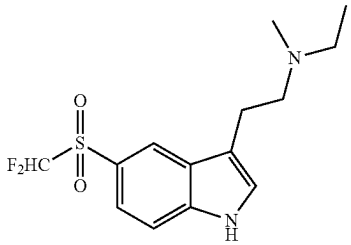
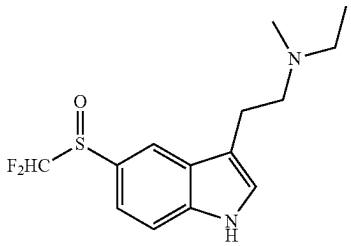
Compound	Structure
II-68	
II-69	
II-70	
II-71	
II-72	
II-73	

TABLE 2-continued

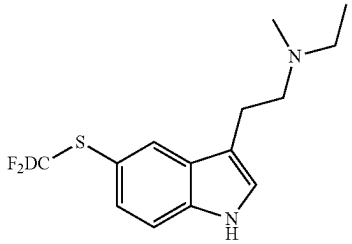
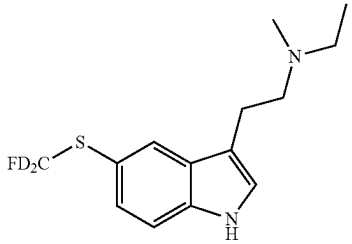
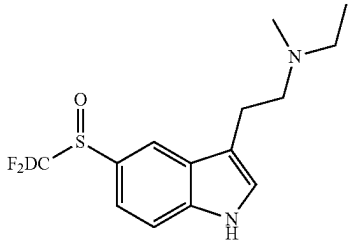
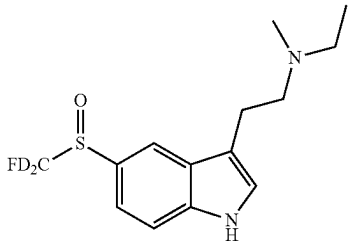
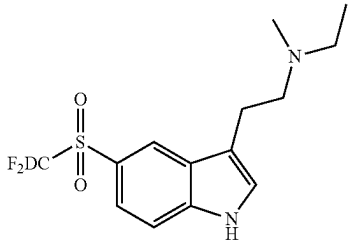
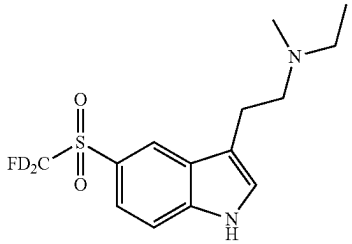
Compound	Structure
II-74	
II-75	
II-76	
II-77	
II-78	
II-79	

TABLE 2-continued

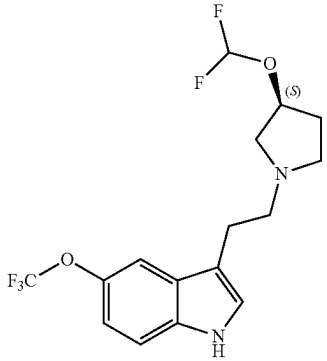
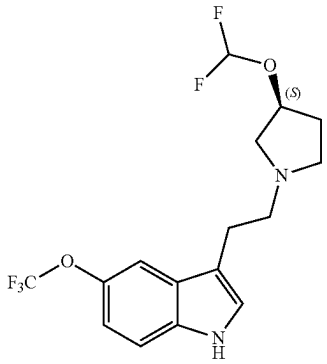
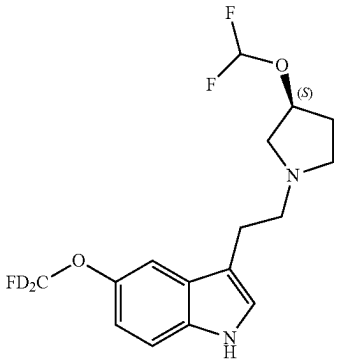
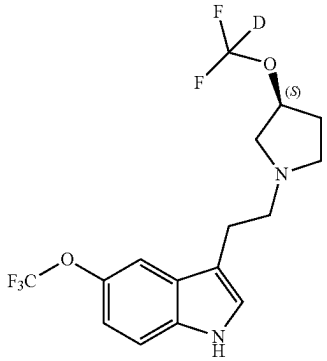
Compound	Structure
II-80	
II-81	
II-82	
II-83	

TABLE 2-continued

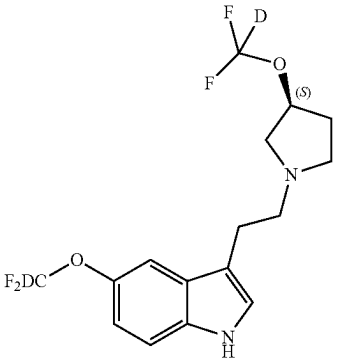
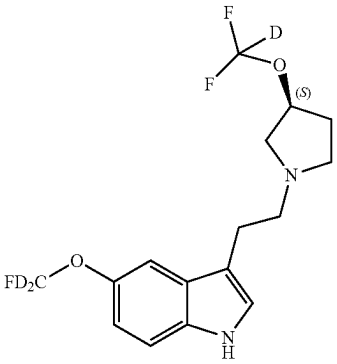
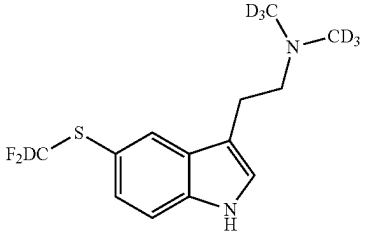
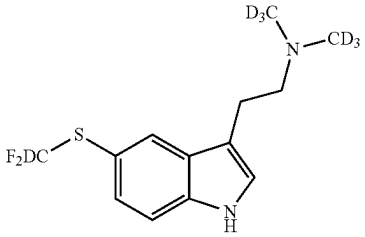
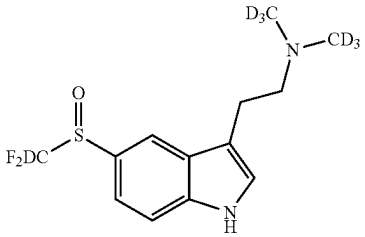
Compound	Structure
II-84	
II-85	
II-86	
II-87	
II-88	

TABLE 2-continued

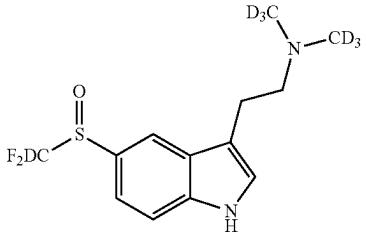
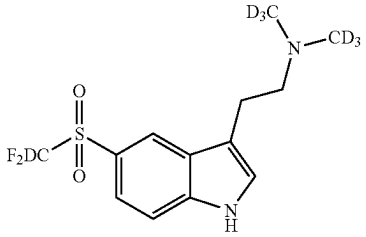
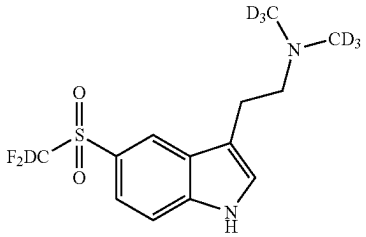
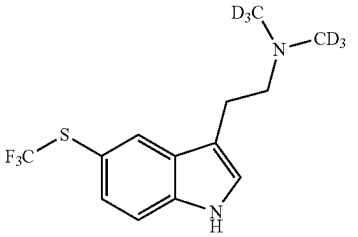
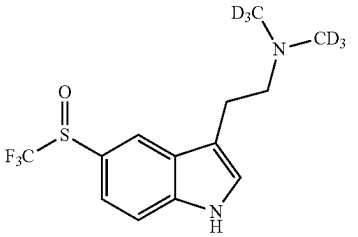
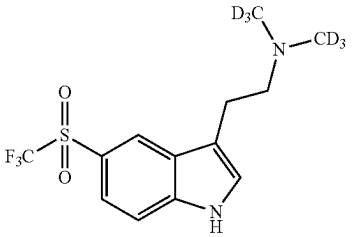
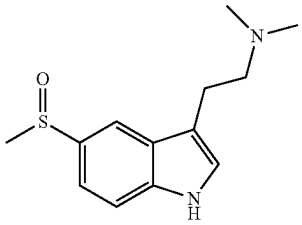
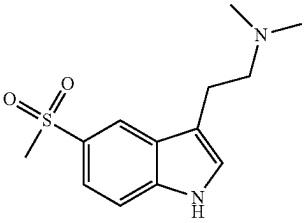
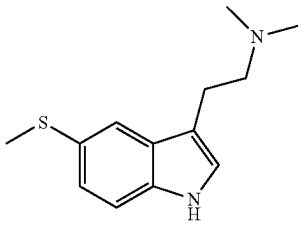
Compound	Structure
II-89	
II-90	
II-91	
II-92	
II-93	
II-94	

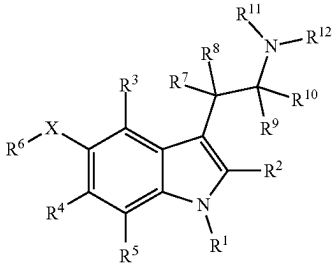
TABLE 2-continued

Compound	Structure
II-95	
II-96	
	and
II-97	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0301] In some embodiments, the compound of Formula (I) is a compound of Formula (I-G):

Formula (I-G)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0302] wherein:

[0303] X is absent or oxygen, and R^1, R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in Formula (I) including embodiments thereof;

[0304] R^3 is selected from H, D, CN, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl; and

[0305] available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof,

[0306] provided when X is O, R^1 is H, CH_3, or CD_3, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl, then R^{11} and R^{12} are not H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl;

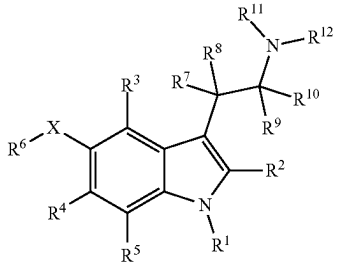
[0307] when X is O, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is CH_3 or CHF_2, then R^{11} and $R^{12}$are not CH_3 or CD_3; and

[0308] when X is absent and R^6 is H, then at least one of R^{11} and R^{12} is not H or C_1-C_6alkyl,

[0309] wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0310] In some embodiments, the compound of Formula (I) is a compound of Formula (I-H):

Formula (I-H)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0311] wherein:

[0312] X is absent or oxygen, R^1, R^2, R^3, R^4, R^5, R^6, R^1, R^8, R^9, and R^{10} are as defined in Formula (I) including embodiments thereof;

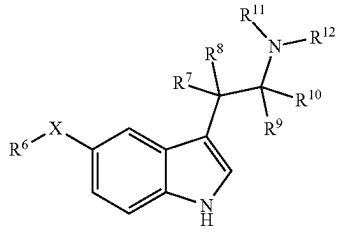
[0313] one of R^{11} and R^{12} is selected from H and C_1-C_6alkyl and the other of R^{11} and R^{12} is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl; or

[0314] R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl;

[0315] Z', R^{16}, and R^{18} are as defined in Formula (I) including embodiments thereof; and available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0316] In some embodiments, R^2, R^3, R^4, and R^5 are all H and the compound of Formula (I) is a compound of Formula (I-I). Accordingly, in some embodiments, the present disclosure includes a compound of Formula (I-I):

Formula (I-I)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof:

[0317] wherein:

[0318] X is absent or oxygen, and R^1, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in Formula (I) including embodiments thereof;

[0319] wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof,

[0320] provided when X is O, R^1 is H, CH_3, or CD_3; R^7, R^8, R^9, and R^{10} are H or D, and R^6 is H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl, then R^{11} and R^{12} are not H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl;

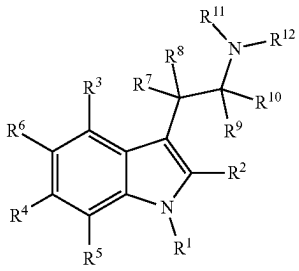
[0321] when X is O, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is CH_3 or CHF_2, then R^{11} and $R^{12}$are not CH_3 or CD_3; and

[0322] when X is absent and R^6 is H, then at least one of R^{11} and R^{12} is not H or C_1-C_6alkyl,

[0323] wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0324] In some embodiments, X is absent and the compound of Formula (I) is a compound of Formula (I-J):

Formula (I-J)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0325] wherein:

[0326] R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are as defined in Formula (I) including embodiments thereof,

[0327] provided when R^6 is H, then at least one of R^{11} and R^{12} is not H or C_1-C_6alkyl, and

[0328] available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0329] In some embodiments, the compound of Formula (I) is selected from one or more of the compounds listed in Table 3 below:

TABLE 3

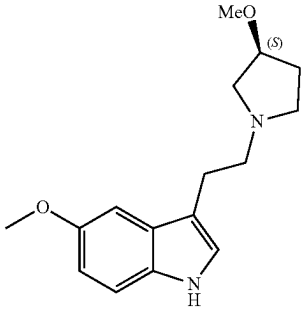
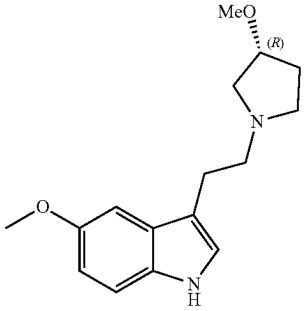
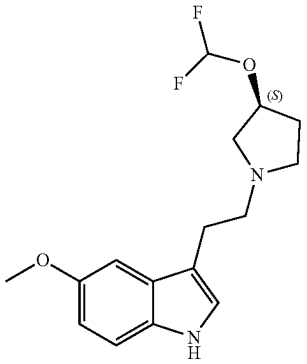
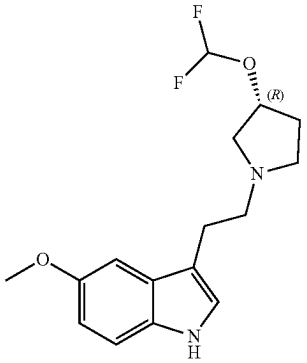
Compound	Structure
(S) I-66	
(R) I-66	
(S) I-67	
(R) I-67	

TABLE 3-continued

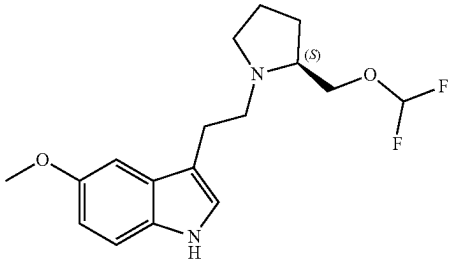
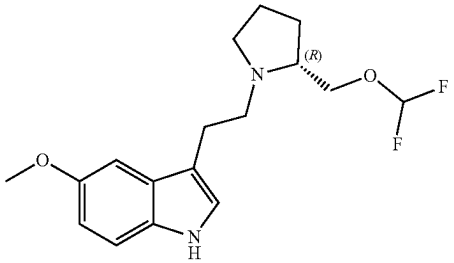
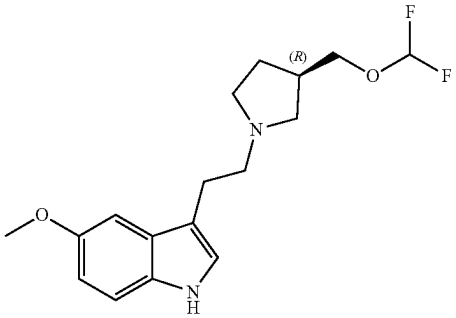
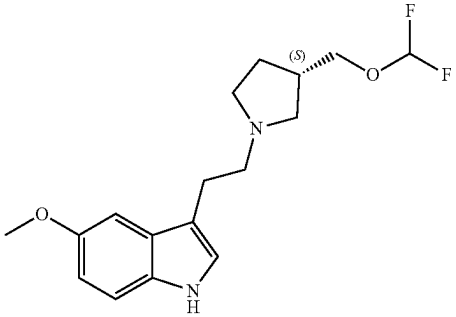
Compound	Structure
(S) I-68	
(R) I-68	
(R) I-69	
(S) I-69	

TABLE 3-continued

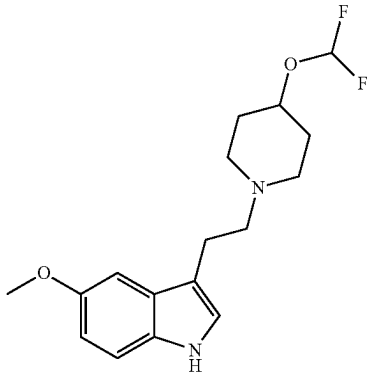
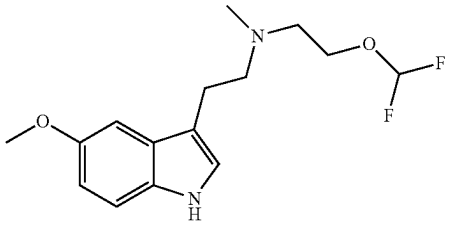
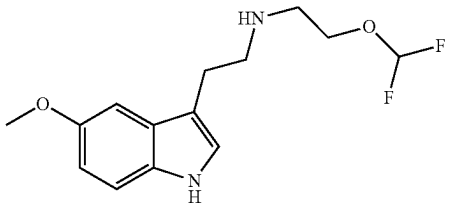
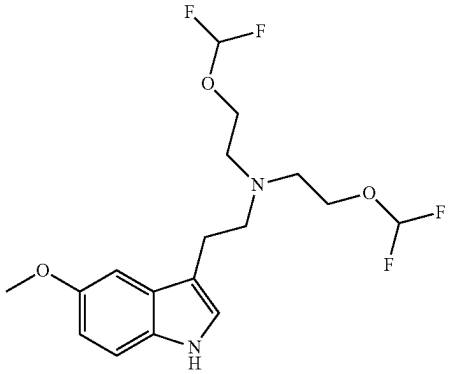
Compound	Structure
I-70	
I-71	
I-72	
I-73	

TABLE 3-continued

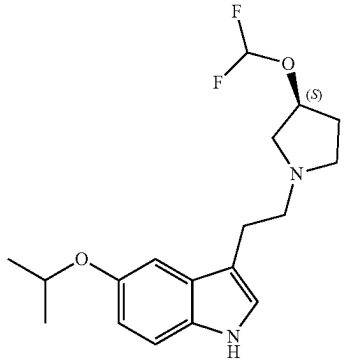
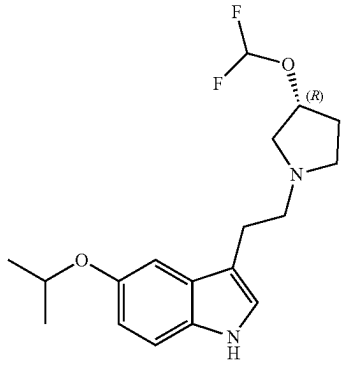
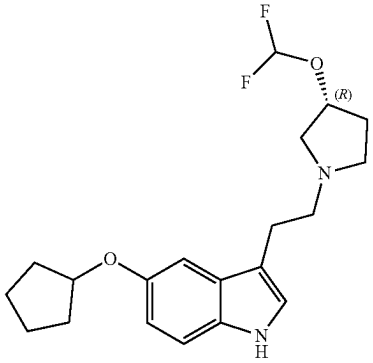
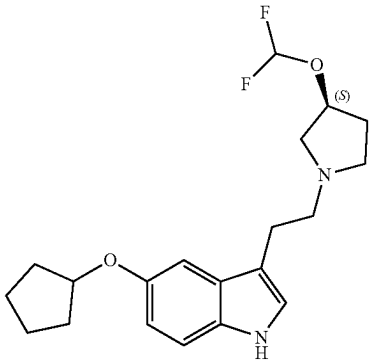
Compound	Structure
(S) I-74	
(R) I-74	
(R) I-75	
(S) I-75	

TABLE 3-continued

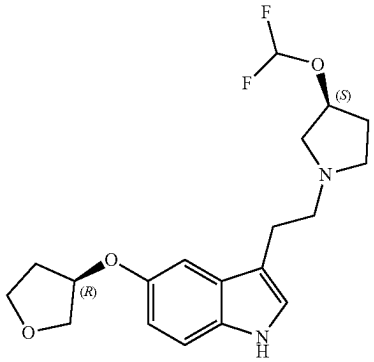
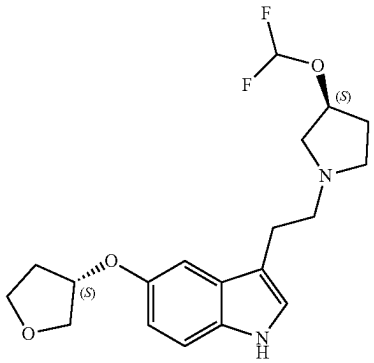
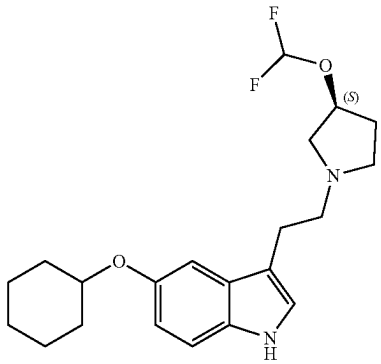
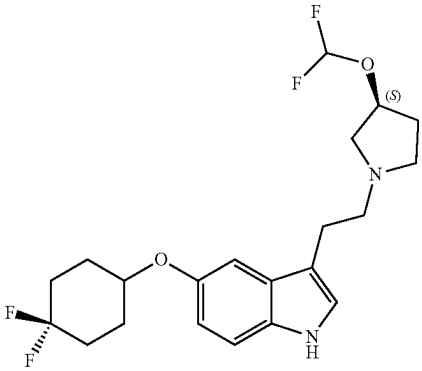
Compound	Structure
(R, S) I-76	
(S, S) I-76	
(S) I-77	
(S) I-78	

TABLE 3-continued

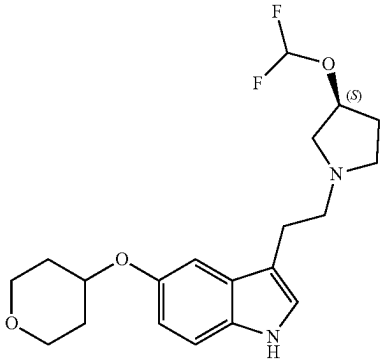
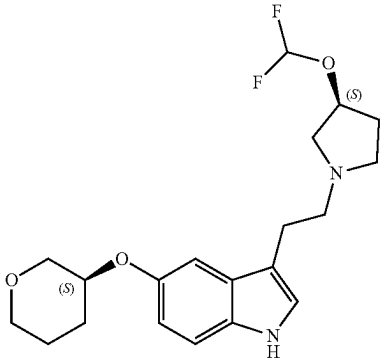
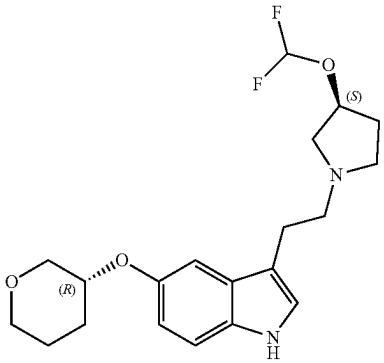
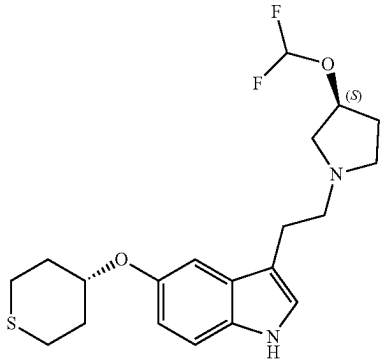
Compound	Structure
(S) I-79	
(S, S) I-80	
(R, S) I-80	
(S) I-81	

TABLE 3-continued

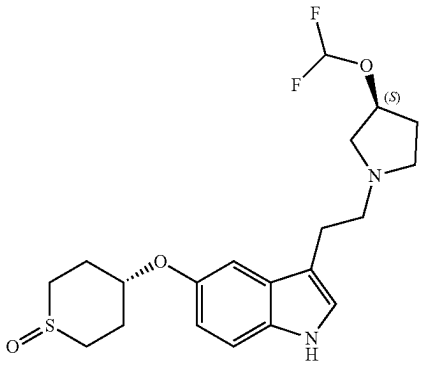
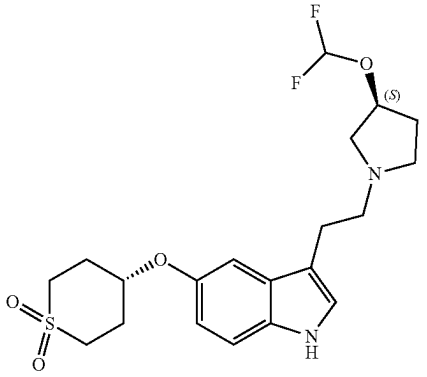
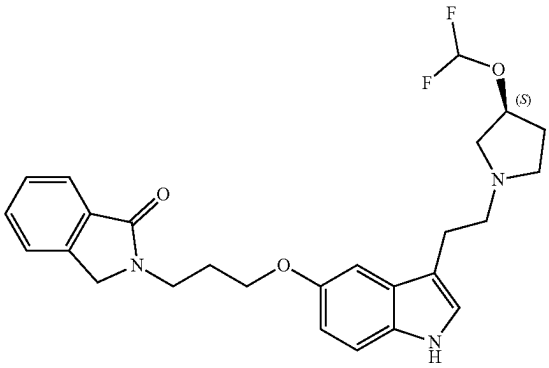
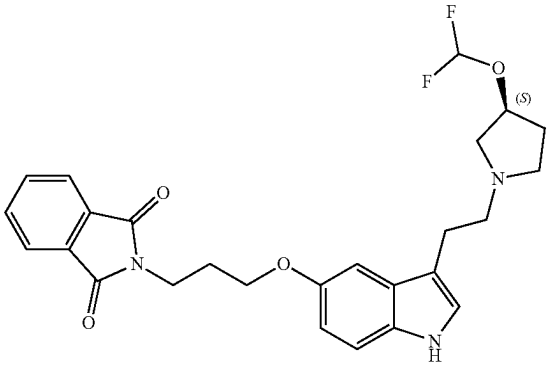
Compound	Structure
(S) I-82	
(S) I-83	
(S) I-84	
(S) I-85	

TABLE 3-continued

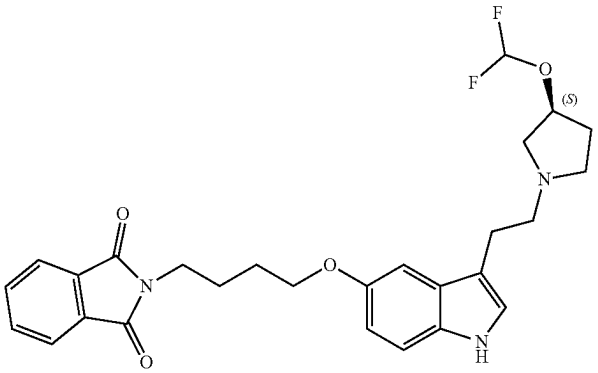
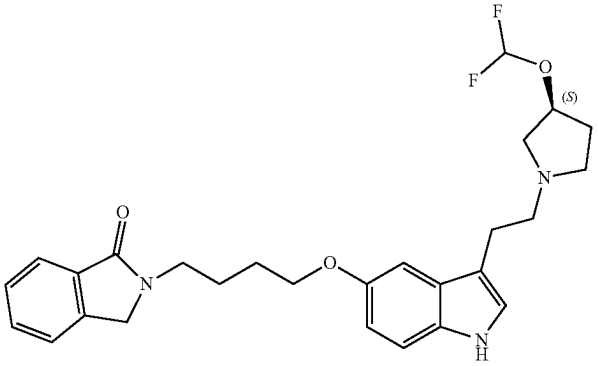
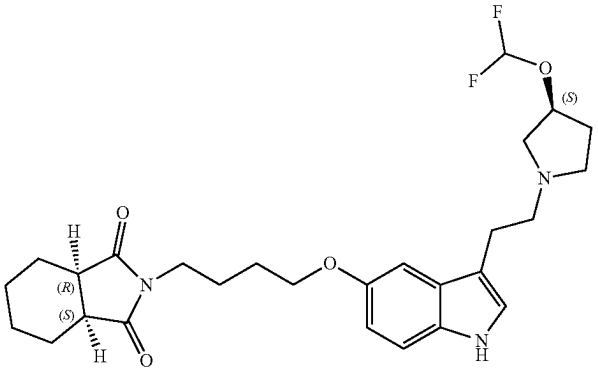
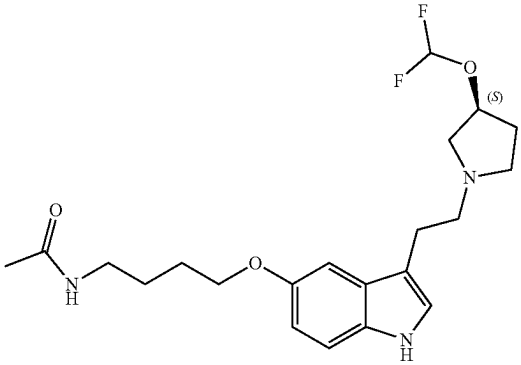
Compound	Structure
(S) I-86	
(S) I-87	
Cis (S) I-88	
(S) I-89	

TABLE 3-continued

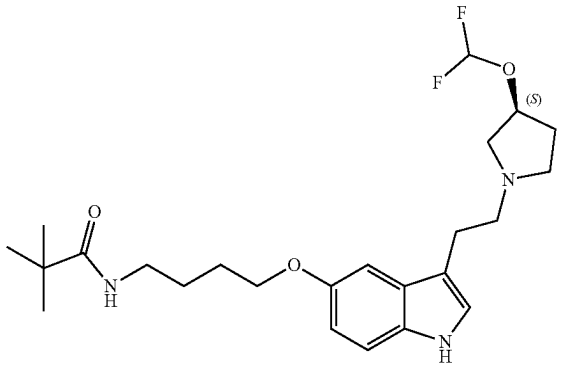
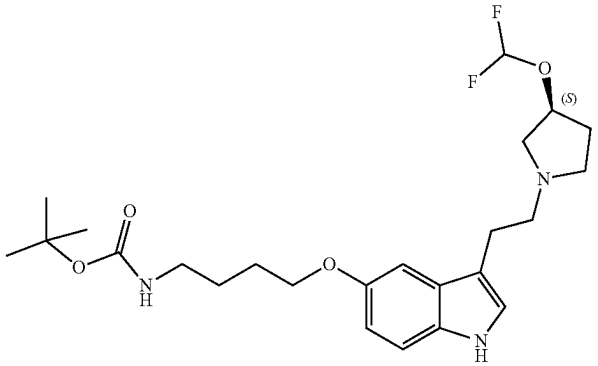
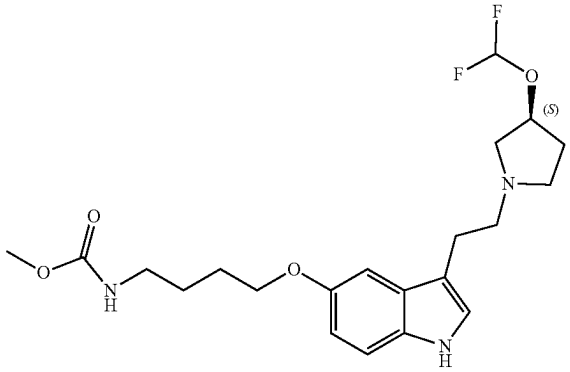
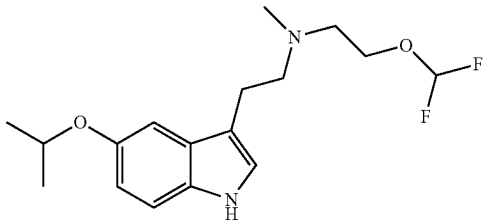
Compound	Structure
(S) I-90	
(S) I-91	
(S) I-92	
I-93	

TABLE 3-continued

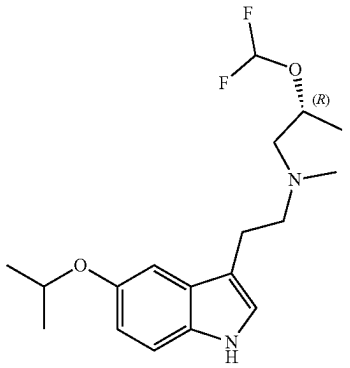
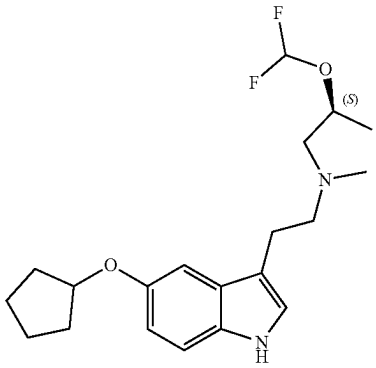
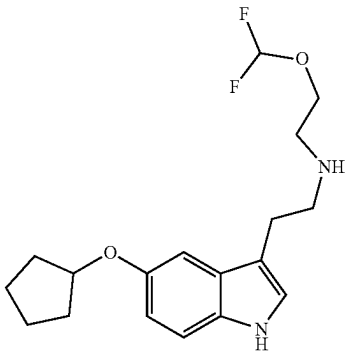
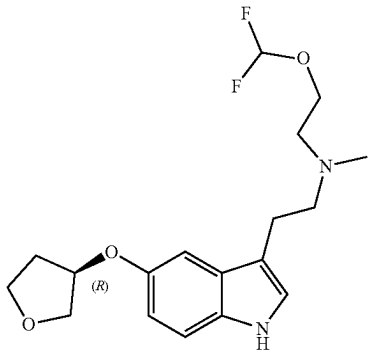
Compound	Structure
(R) I-94	
(S) I-95	
I-96	
(R) I-97	

TABLE 3-continued

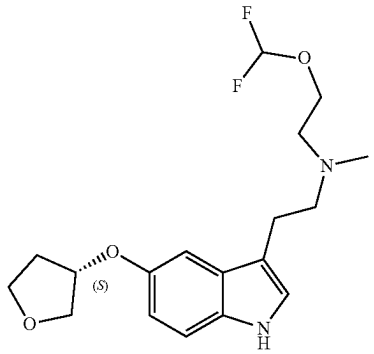
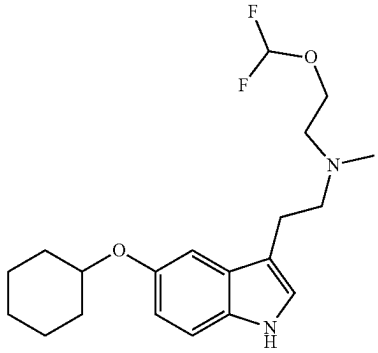
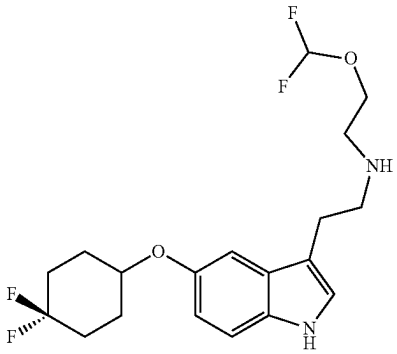
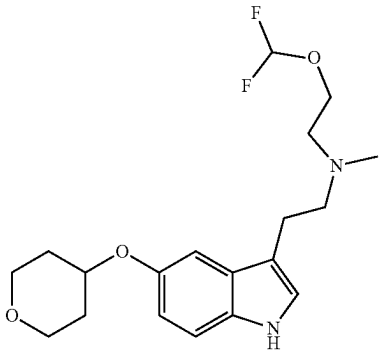
Compound	Structure
(S) I-97	
I-98	
I-99	
I-100	

TABLE 3-continued

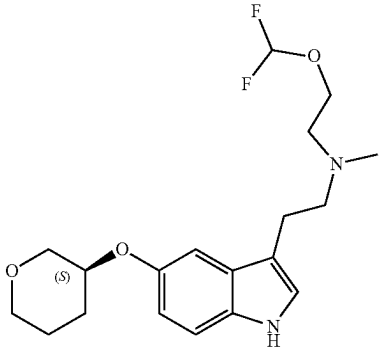
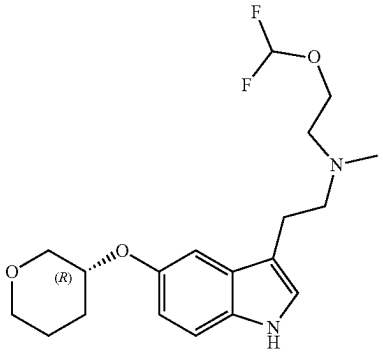
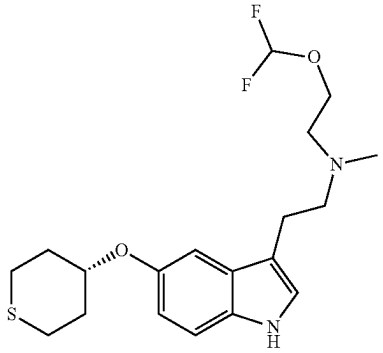
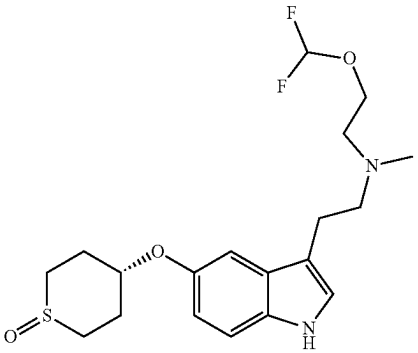
Compound	Structure
(S) I-101	
(R) I-101	
I-102	
I-103	

TABLE 3-continued

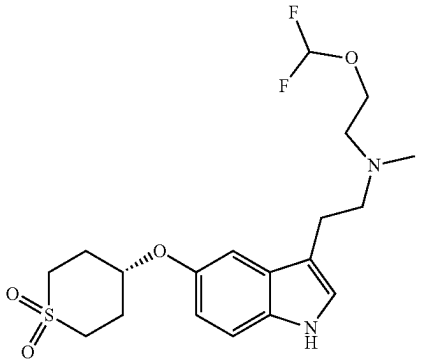
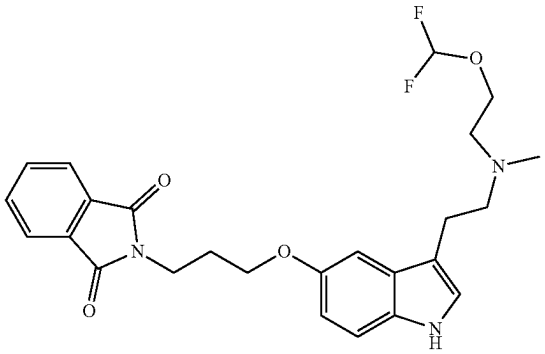
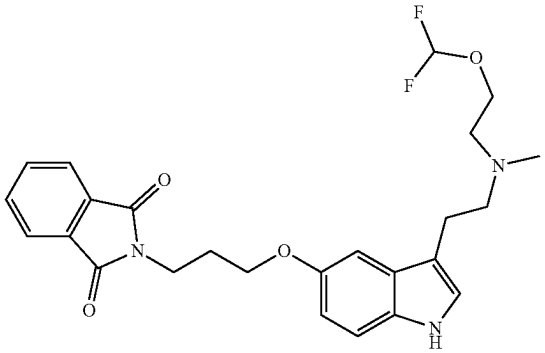
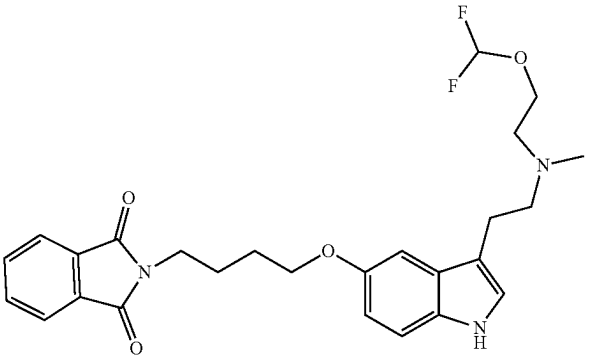
Compound	Structure
I-104	
I-105	
I-106	
I-107	

TABLE 3-continued

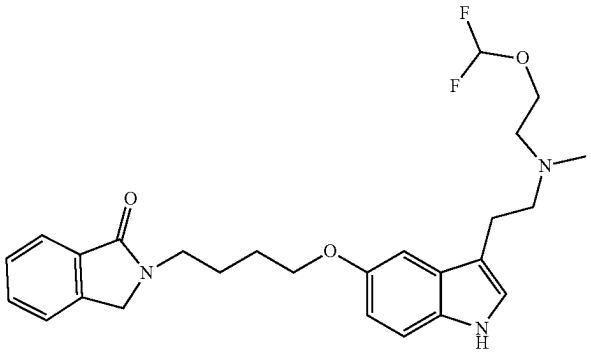
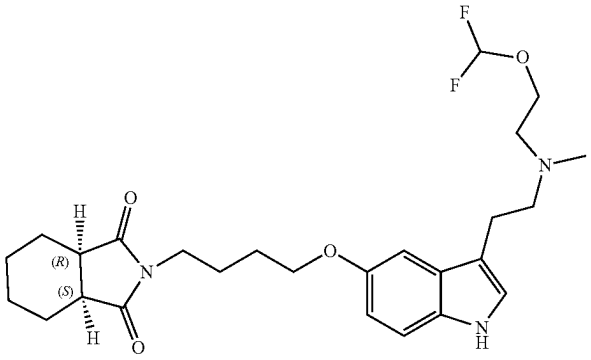
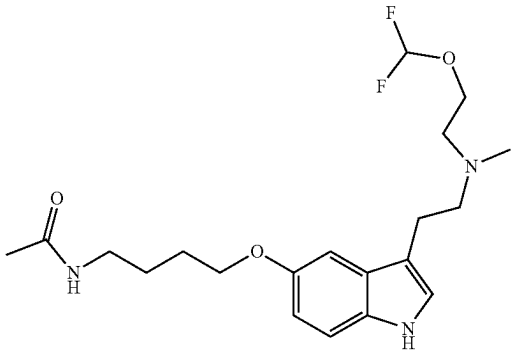
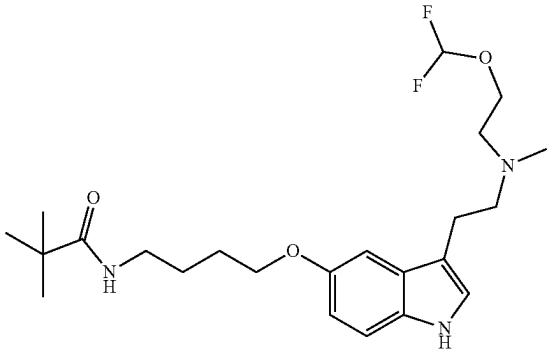
Compound	Structure
I-108	
Cis I-109	
I-110	
I-111	

TABLE 3-continued

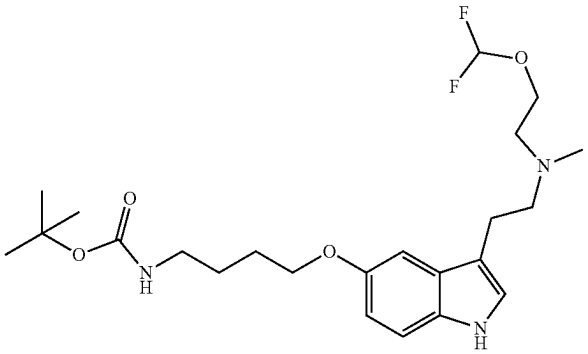
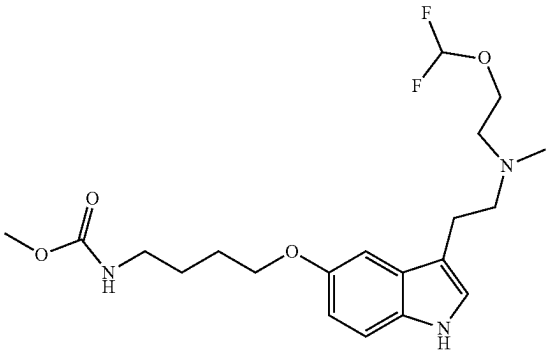
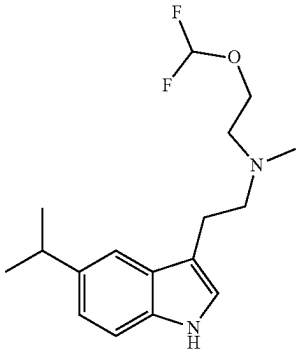
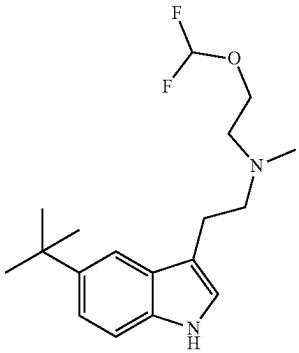
Compound	Structure
I-112	
I-113	
I-114	
I-115	

TABLE 3-continued

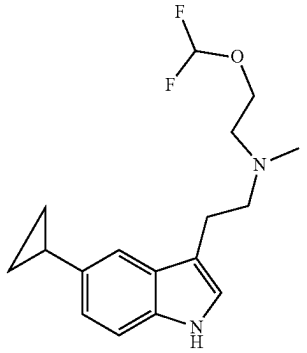
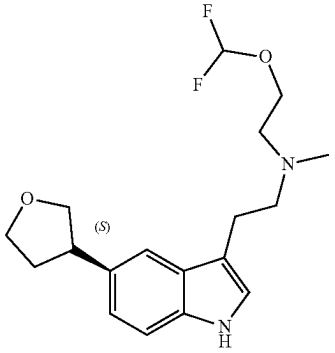
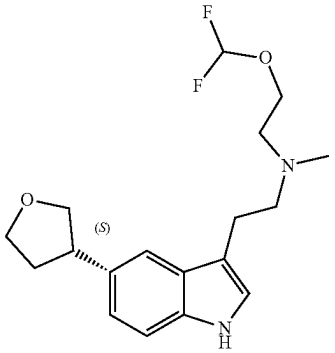
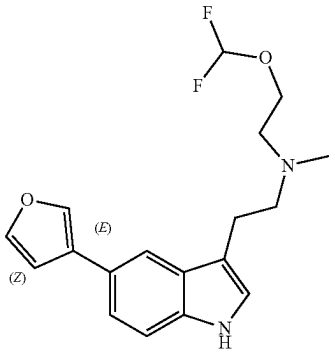
Compound	Structure
I-116	
(S) I-117	
(R) I-117	
I-118	

TABLE 3-continued

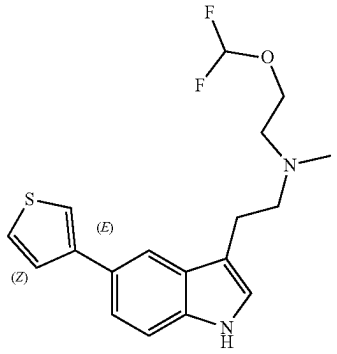
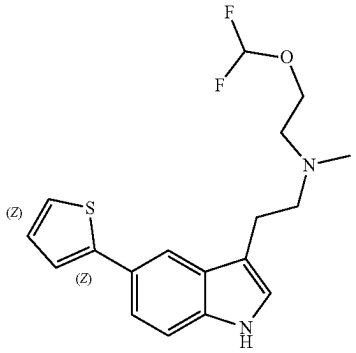
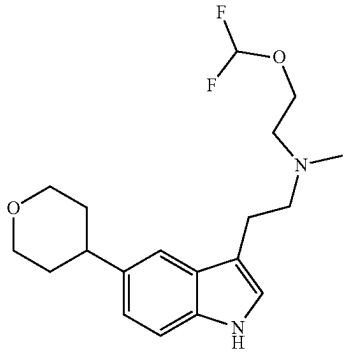
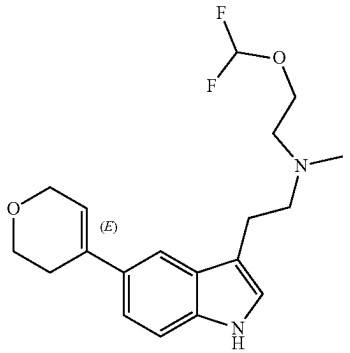
Compound	Structure
I-119	
I-120	
I-121	
I-122	

TABLE 3-continued

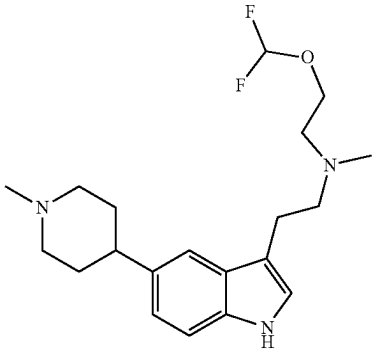
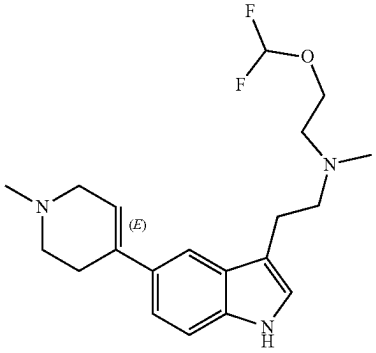
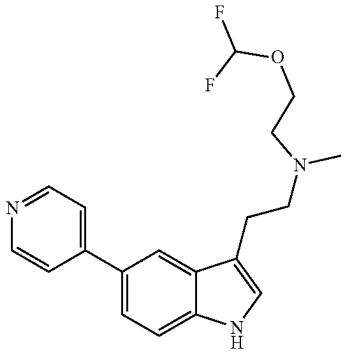
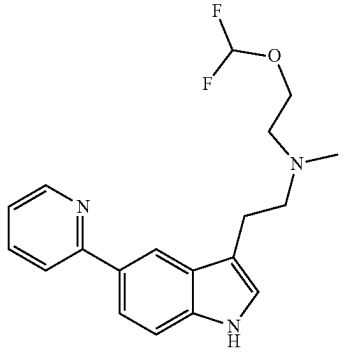
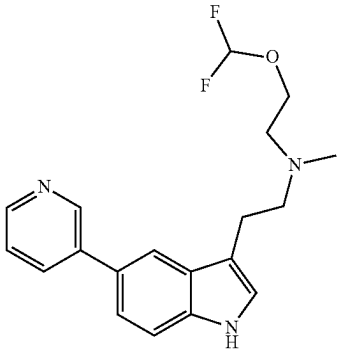
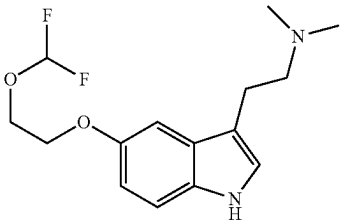
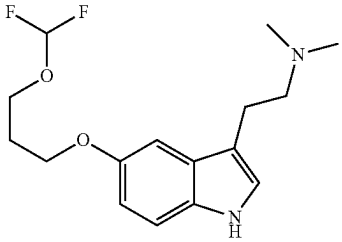
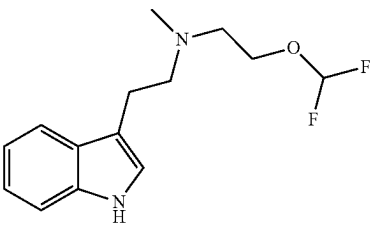
Compound	Structure
I-123	
I-124	
I-125	
I-126	

TABLE 3-continued

Compound	Structure
I-127	
I-128	
I-129	
	and
I-130	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0330] In some embodiments, the compound of Formula (I) is selected from one or more of the compounds listed in Table 4 below:

TABLE 4

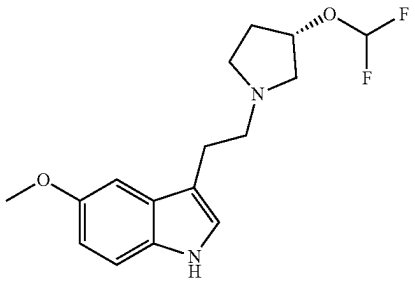
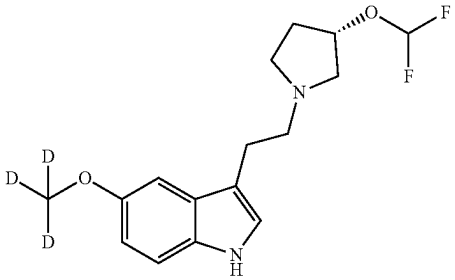
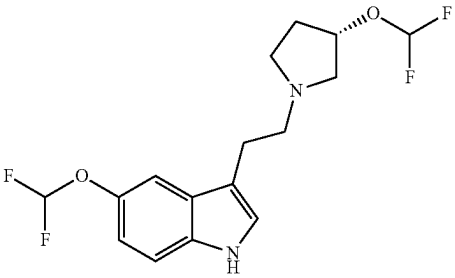
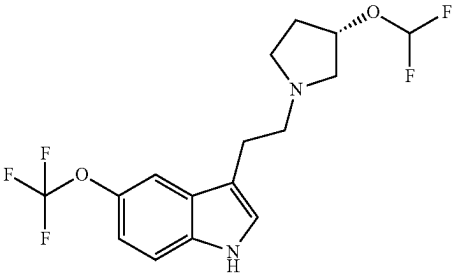
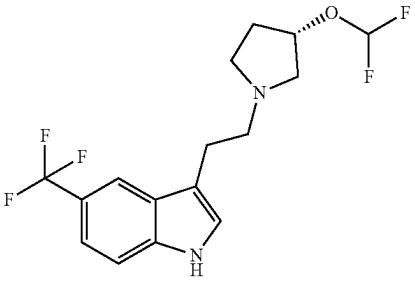
Compound	Structure	IUPAC Name
I-131		(S)-3-(2-(3-(difluoromethoxy)pyrrolidin-1-yl)ethyl)-5-methoxy-1H-indole
I-132		(S)-3-(2-(3-(difluoromethoxy)pyrrolidin-1-yl)ethyl)-5-(methoxy-d3)-1H-indole
I-133		(S)-5-(difluoromethoxy)-3-(2-(3-(difluoromethoxy)pyrrolidin-1-yl)ethyl)-1H-indole
I-134		(S)-3-(2-(3-(difluoromethoxy)pyrrolidin-1-yl)ethyl)-5-(trifluoromethoxy)-1H-indole
I-135		(S)-3-(2-(3-(difluoromethoxy)pyrrolidin-1-yl)ethyl)-5-(trifluoromethyl)-1H-indole

TABLE 4-continued

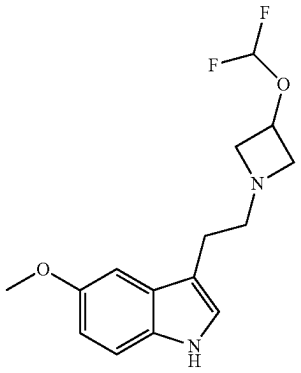
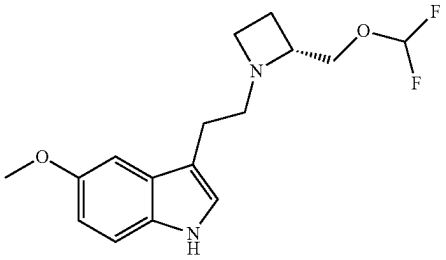
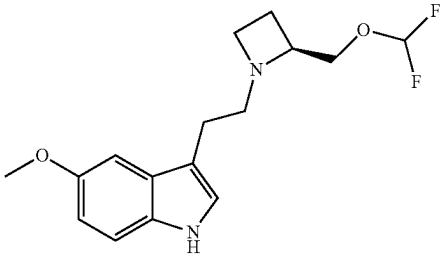
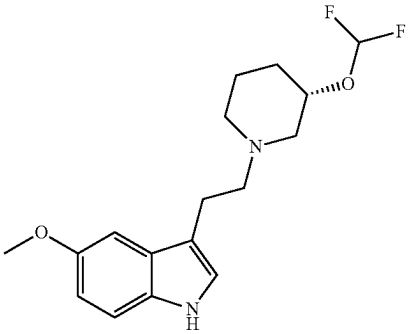
Compound	Structure	IUPAC Name
I-136		3-(2-(3-(difluoromethoxy)azetidin-1-yl)ethyl)-5-methoxy-1H-indole
I-137		(R)-3-(2-(2-((difluoromethoxy)methyl)azetidin-1-yl)ethyl)-5-methoxy-1H-indole
I-138		(S)-3-(2-(2-((difluoromethoxy)methyl)azetidin-1-yl)ethyl)-5-methoxy-1H-indole
I-139		(S)-3-(2-(3-(difluoromethoxy)piperidin-1-yl)ethyl)-5-methoxy-1H-indole

TABLE 4-continued

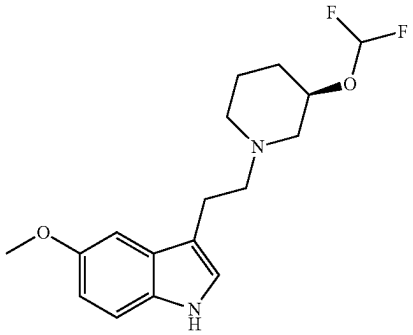
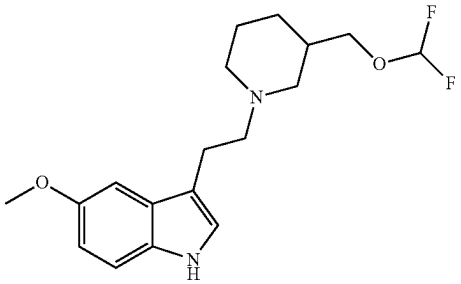
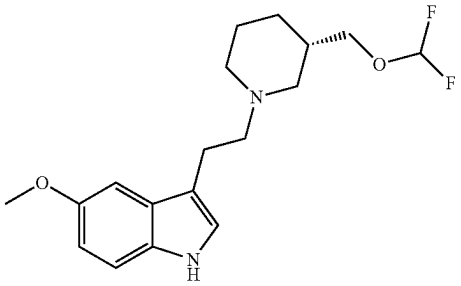
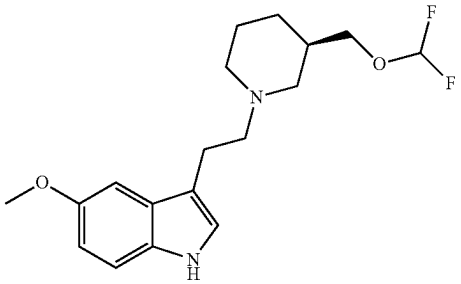
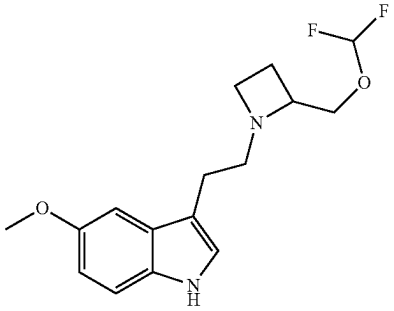
Compound	Structure	IUPAC Name
I-140		(R)-3-(2-(3-(difluoromethoxy)piperidin-1-yl)ethyl)-5-methoxy-1H-indole
I-141		3-(2-(3-((difluoromethoxy)methyl)piperidin-1-yl)ethyl)-5-methoxy-1H-indole
I-142		(S)-3-(2-(3-((difluoromethoxy)methyl)piperidin-1-yl)ethyl)-5-methoxy-1H-indole
I-143		(R)-3-(2-(3-((difluoromethoxy)methyl)piperidin-1-yl)ethyl)-5-methoxy-1H-indole
I-144		3-(2-(2-((difluoromethoxy)methyl)azetidin-1-yl)ethyl)-5-methoxy-1H-indole

TABLE 4-continued

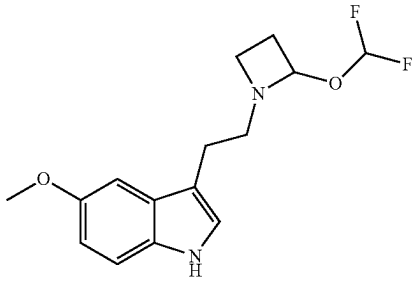
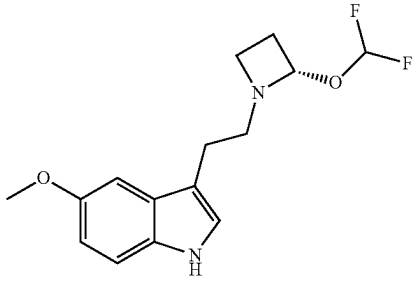
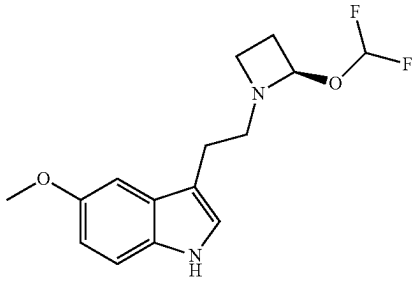
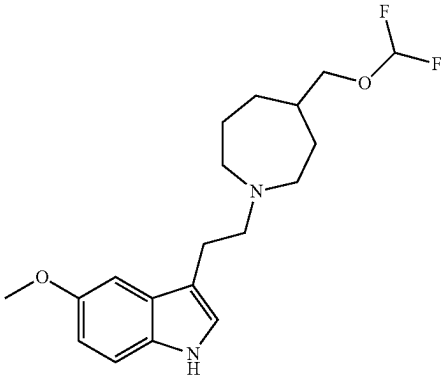
Compound	Structure	IUPAC Name
I-145		3-(2-(2-(difluoromethoxy)azetidin-1-yl)ethyl)-5-methoxy-1H-indole
I-146		(S)-3-(2-(2-(difluoromethoxy)azetidin-1-yl)ethyl)-5-methoxy-1H-indole
I-147		(R)-3-(2-(2-(difluoromethoxy)azetidin-1-yl)ethyl)-5-methoxy-1H-indole
I-148		3-(2-(4-((difluoromethoxy)methyl)azepan-1-yl)ethyl)-5-methoxy-1H-indole

TABLE 4-continued

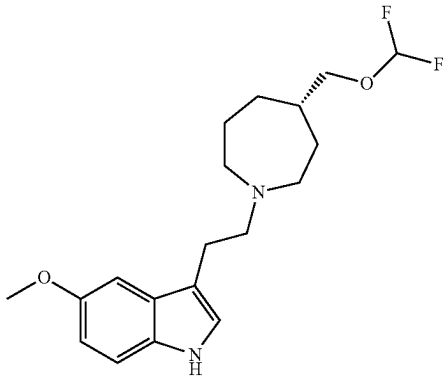
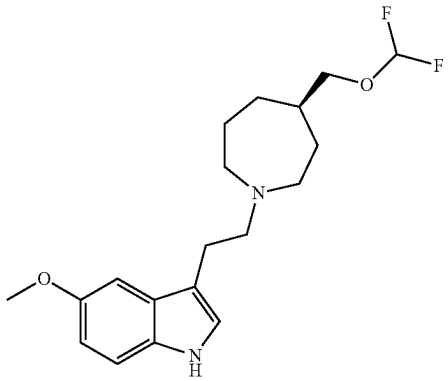
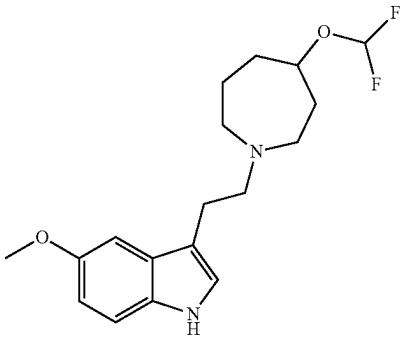
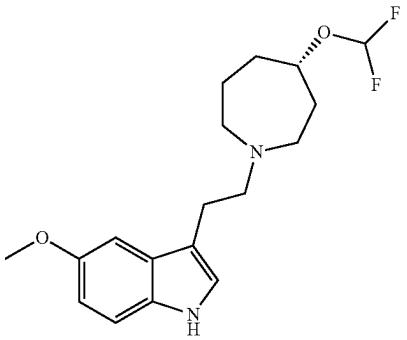
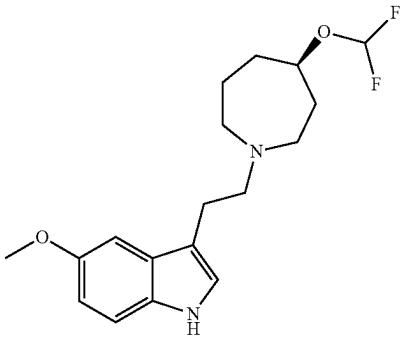
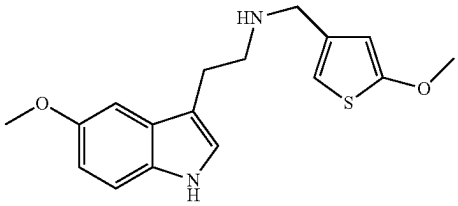
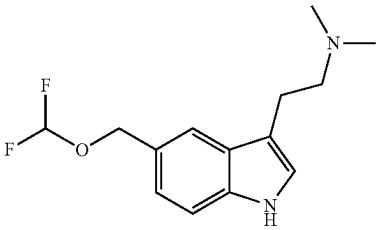
Compound	Structure	IUPAC Name
I-149		(S)-3-(2-(4-((difluoromethoxy)methyl)azepan-1-yl)ethyl)-5-methoxy-1H-indole
I-150		(R)-3-(2-(4-((difluoromethoxy)methyl)azepan-1-yl)ethyl)-5-methoxy-1H-indole
I-151		3-(2-(4-(difluoromethoxy)azepan-1-yl)ethyl)-5-methoxy-1H-indole
I-152		(S)-3-(2-(4-(difluoromethoxy)azepan-1-yl)ethyl)-5-methoxy-1H-indole

TABLE 4-continued

Compound	Structure	IUPAC Name
I-153		(R)-3-(2-(4-(difluoromethoxy)azepan-1-yl)ethyl)-5-methoxy-1H-indole
I-154		2-(5-methoxy-1H-indol-3-yl)-N-((5-methoxythiophen-3-yl)methyl)ethan-1-amine and
I-155		2-(5-((difluoromethoxy)methyl)-1H-indol-3-yl)-N,N-dimethylethan-1-amine

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0331] In some embodiments, the compound of Formula (I) is selected from one or more of the compounds listed in Table 5 below:

TABLE 5

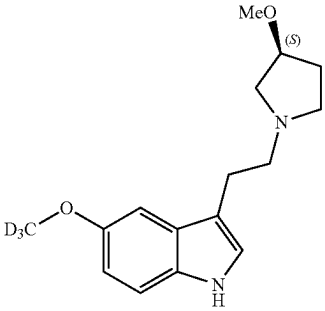
Compound	Structure
(S) I-157	

TABLE 5-continued

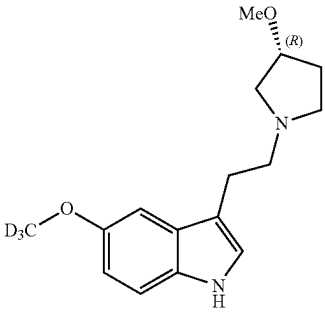
Compound	Structure
(R) I-157	

TABLE 5-continued

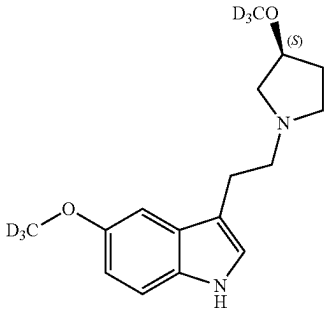
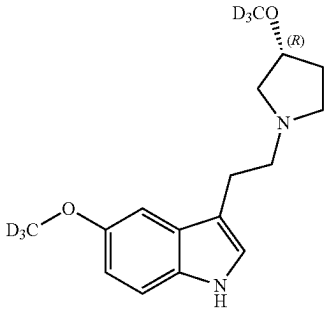
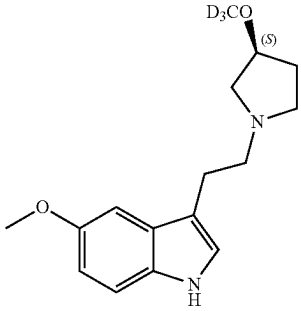
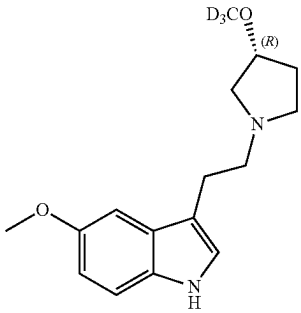
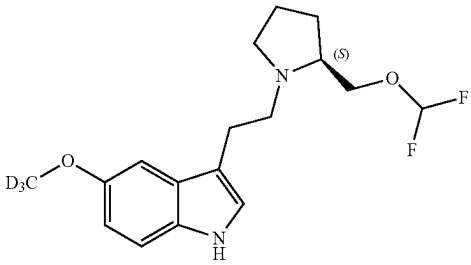
Compound	Structure
(S) I-158	
(R) I-158	
(S) I-159	
(R) I-159	
I-160	

TABLE 5-continued

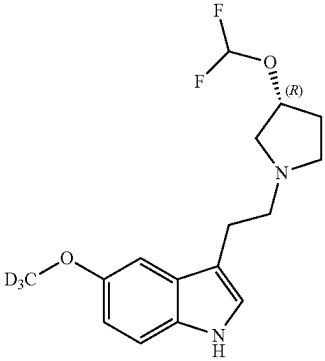
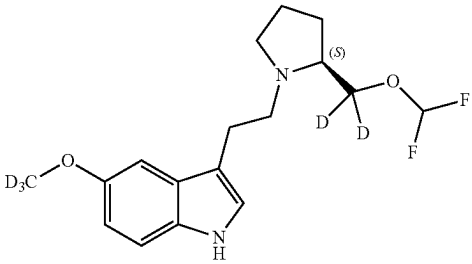
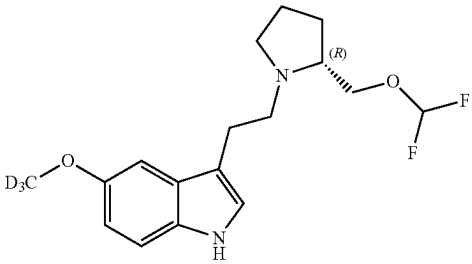
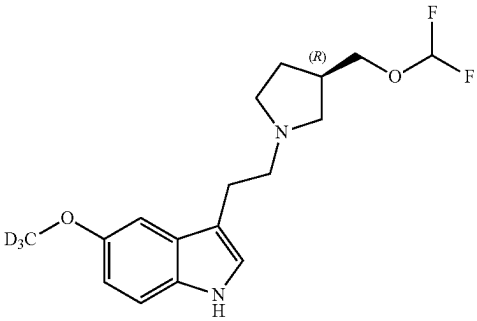
Compound	Structure
(R) I-161	
(S) I-162	
(R) I-163	
(R) I-164	

TABLE 5-continued

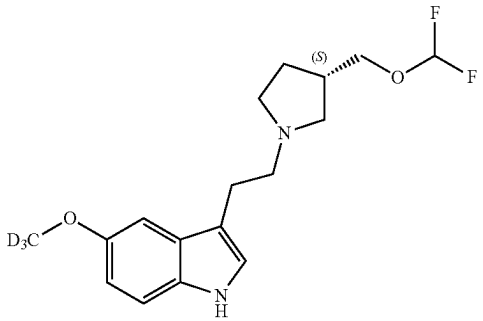
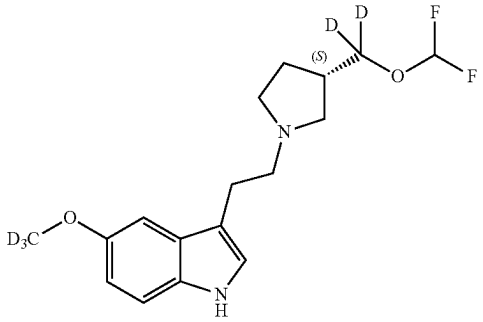
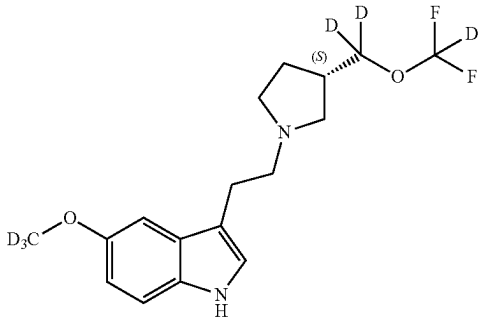
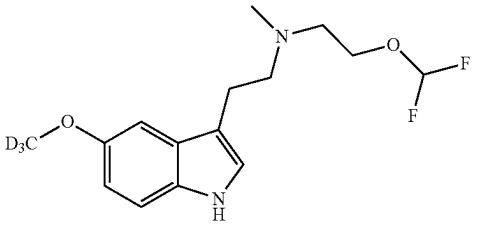
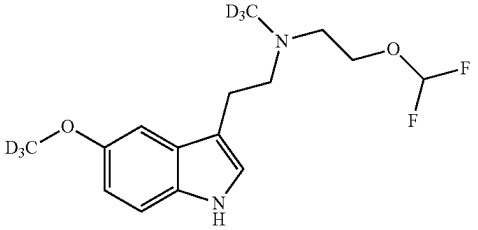
Compound	Structure
(S) I-164	
(S) I-165	
((S) I-166	
I-167	
I-168	

TABLE 5-continued

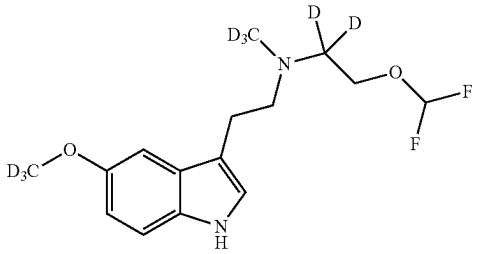
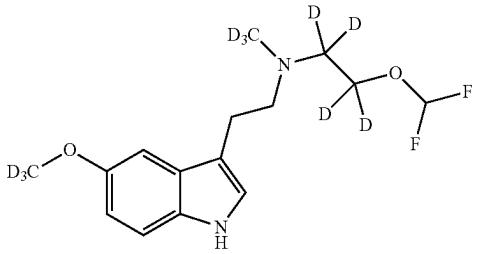
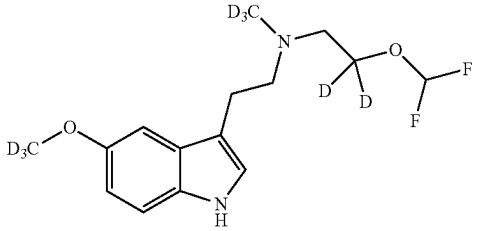
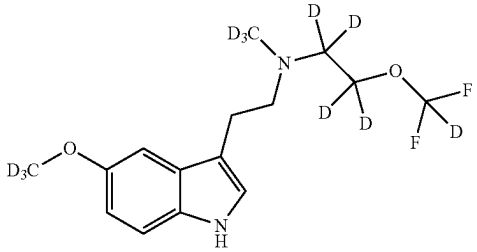
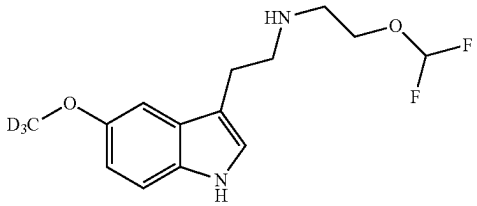
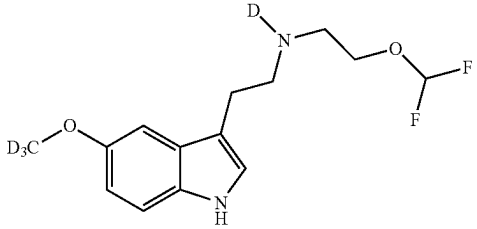
Compound	Structure
I-169	
I-170	
I-171	
I-172	
I-173	
I-174	

TABLE 5-continued

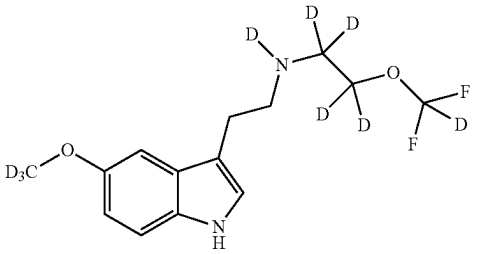
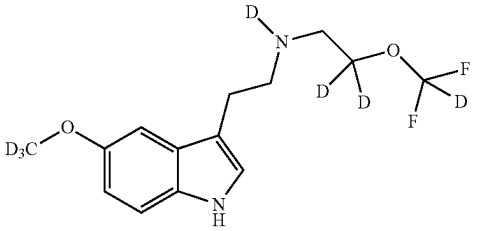
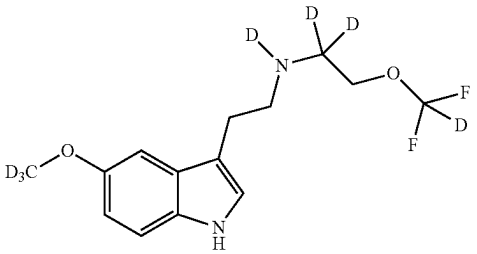
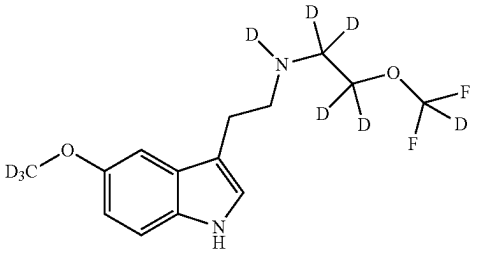
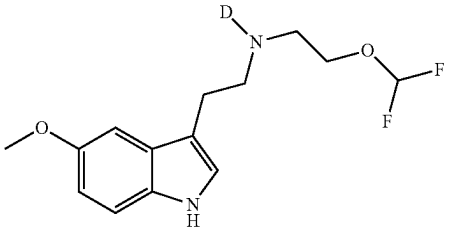
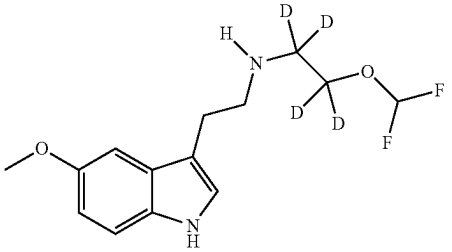
Compound	Structure
I-175	
I-176	
I-177	
I-178	
I-179	
I-180	

TABLE 5-continued

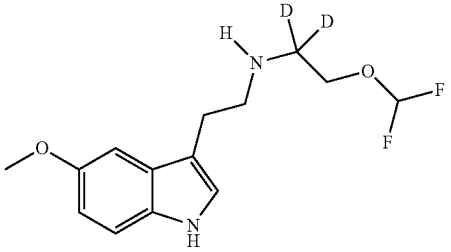
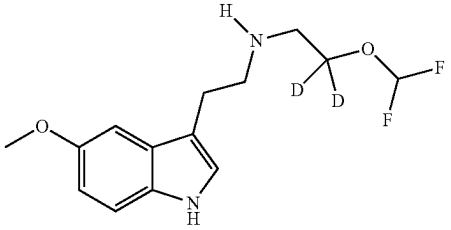
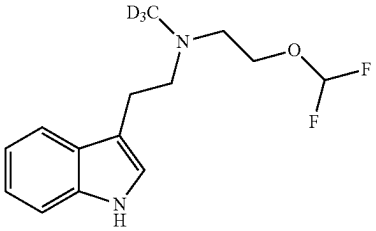
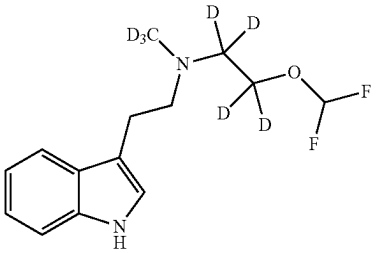
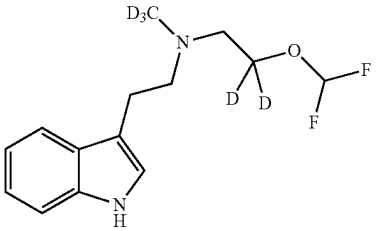
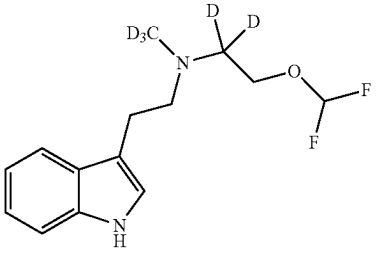
Compound	Structure
I-181	
I-182	
I-183	
I-184	
I-185	
I-186	

TABLE 5-continued

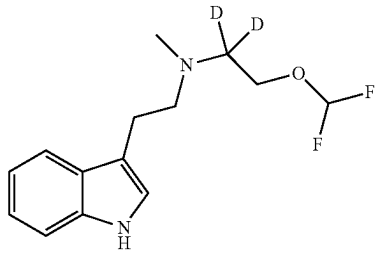
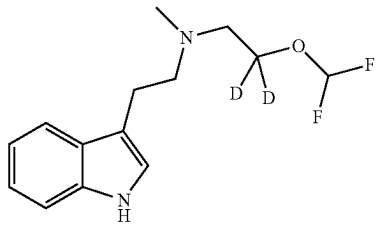
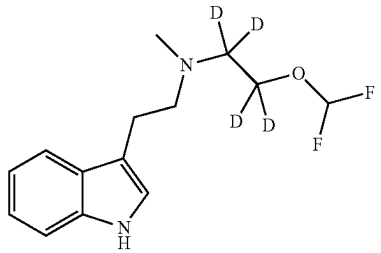
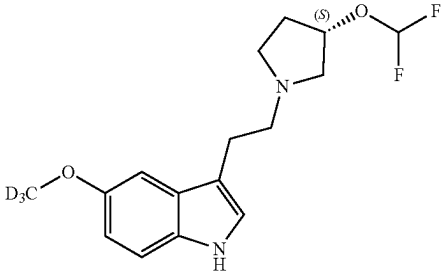
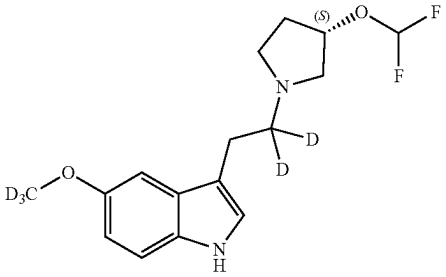
Compound	Structure
I-187	
I-188	
I-189	
(S) I-190	
(R) I-190	

TABLE 5-continued

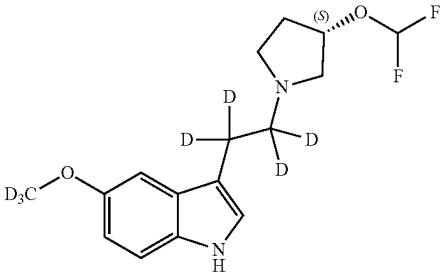
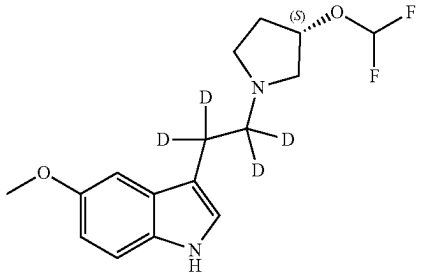
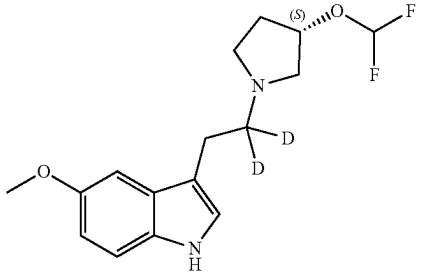
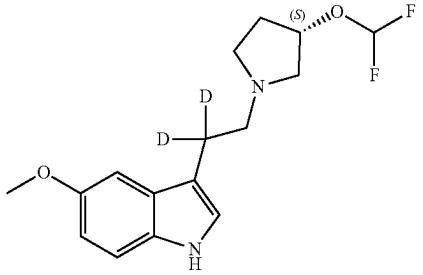
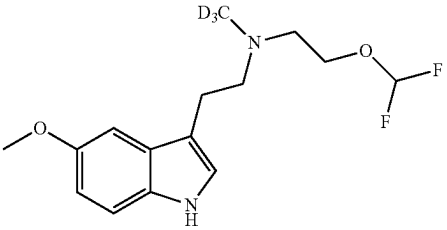
Compound	Structure
I-191	
(S) I-192	
(S) I-193	
(S) I-194	
I-195	

TABLE 5-continued

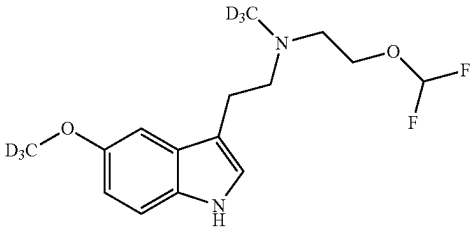
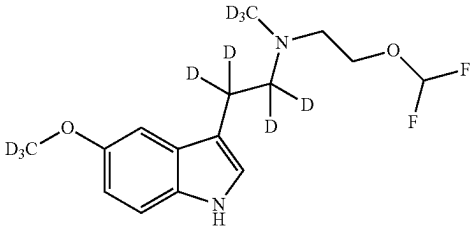
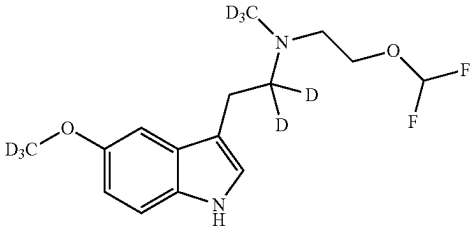
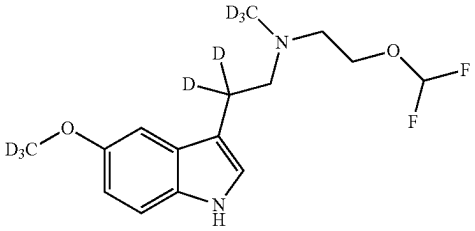
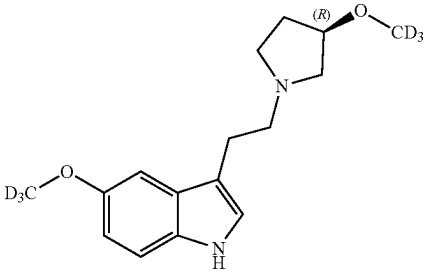
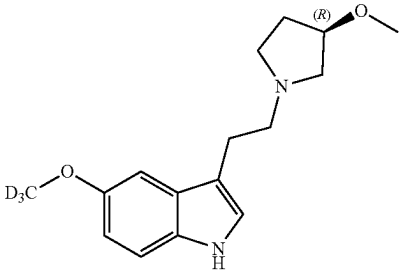
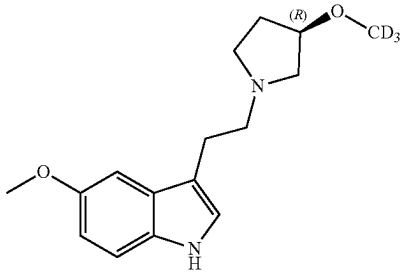
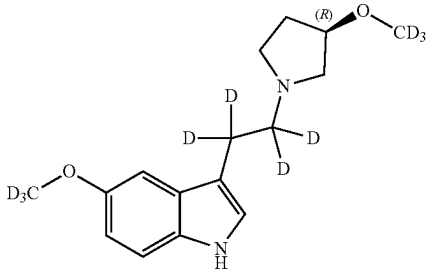
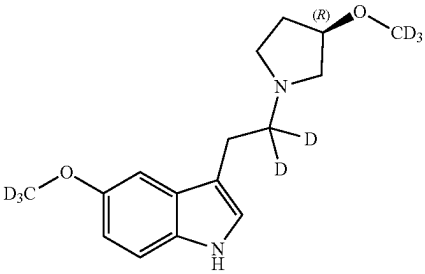
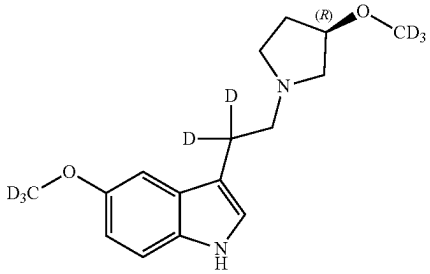
Compound	Structure
I-196	
I-197	
I-198	
I-199	
(R) I-200	
(R) I-201	

TABLE 5-continued

Compound	Structure
(R) I-202	
(R) I-203	
(R) I-204	 and
(R) I-205	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0332] In some embodiments, the pharmaceutically acceptable salt is an acid addition salt or a base addition salt. The selection of a suitable salt may be made by a person skilled in the art. Suitable salts include acid addition salts that may, for example, be formed by mixing a solution of a compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifiuoroacetic acid, or benzoic acid. Additionally, acids that are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) and Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley VCH; S. Berge et al, Journal of Pharmaceutical Sciences 1977 66(1) 1-19; P.

Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book (Food & Drug Administration, Washington, D.C. on their website).

[0333] An acid addition salt suitable for, or compatible with, the treatment of subjects is any non-toxic organic or inorganic acid addition salt of any basic compound. Basic compounds that form an acid addition salt include, for example, compounds comprising an amine group. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric, nitric and phosphoric acids, as well as acidic metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include mono-, di-, and tricarboxylic acids. Illustrative of such organic acids are, for example, acetic, trifluoroacetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, mandelic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid, and other sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, and 2-hydroxyethanesulfonic acid. In some embodiments, exemplary acid addition salts also include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates ("mesylates"), naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates), and the like. In some embodiments, the mono- or di-acid salts are formed and such salts exist in either a hydrated, solvated, or substantially anhydrous form. In general, acid addition salts are more soluble in water and various hydrophilic organic solvents and generally demonstrate higher melting points in comparison to their free base forms. The selection criteria for the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts such as but not limited to oxalates may be used, for example in the isolation of compounds of the disclosure for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

[0334] A base addition salt suitable for, or compatible with, the treatment of subjects is any non-toxic organic or inorganic base addition salt of any acidic compound. Acidic compounds that form a basic addition salt include, for example, compounds comprising a carboxylic acid group. Illustrative inorganic bases which form suitable salts include lithium, sodium, potassium, calcium, magnesium, or barium hydroxide as well as ammonia. Illustrative organic bases which form suitable salts include aliphatic, alicyclic, or aromatic organic amines such as isopropylamine, methylamine, trimethylamine, picoline, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine. The selection of the appropriate salt may be useful, for example, so that an ester functionality, if any, elsewhere in a compound is not hydrolyzed. The selection criteria for the appropriate salt will be known to one skilled in the art. In some embodiments, exemplary basic salts also include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamine, butyl amine, choline, and salts with amino acids such as arginine, lysine, and the like. Basic nitrogen containing groups may be quarternized with agents such as lower alkyl halides (e.g., methyl, ethyl and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides, and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others. Compounds carrying an acidic moiety can be mixed with suitable pharmaceutically acceptable salts to provide, for example, alkali metal salts (e.g., sodium or potassium salts), alkaline earth metal salts (e.g., calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (—COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

[0335] All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the disclosure and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the disclosure. In addition, when a compound of the disclosure contains both a basic moiety, such as, but not limited to an aliphatic primary, secondary, tertiary, or cyclic amine, an aromatic or heteroaryl amine, pyridine or imidazole, and an acidic moiety, such as, but not limited to tetrazole or carboxylic acid, zwitterions ("inner salts") may be formed and are included within the terms "salt(s)" as used herein. It is understood that certain compounds of the disclosure may exist in zwitterionic form, having both anionic and cationic centers within the same compound and a net neutral charge. Such zwitterions are included within the disclosure.

[0336] Solvates of compounds of the disclosure include, for example, those made with solvents that are pharmaceutically acceptable. Examples of such solvents include water (resulting solvate is called a hydrate) and ethanol and the like. Suitable solvents are physiologically tolerable at the dosage administered.

[0337] Prodrugs of the compounds of the present disclosure include, for example, conventional esters formed with available hydroxy, thiol, amino, or carboxyl groups. Some common esters which have been utilized as prodrugs are phenyl esters, aliphatic (C_1-C_{24}) esters, acyloxymethyl esters, carbamates, and amino acid esters.

[0338] It is understood and appreciated that in some embodiments, compounds of the present disclosure may have at least one chiral center and therefore can exist as enantiomers and/or diastereomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present disclosure. It is to be further understood that while the stereochemistry of the compounds may be as shown in any given compound listed herein, such compounds may also contain certain amounts (for example, less than 20%, suitably less than 10%, more suitably less than 5%) of compounds of the present disclosure having an alternate stereochemistry. It is intended that any optical isomers, as separated, pure, or

partially purified optical isomers or racemic mixtures thereof are included within the scope of the present disclosure.

[0339] In some embodiments, the compounds of the present disclosure can also include tautomeric forms, such as keto-enol tautomers and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is intended that any tautomeric forms which the compounds form, as well as mixtures thereof, are included within the scope of the present disclosure.

[0340] The compounds of the present disclosure may further exist in varying amorphous and polymorphic forms, and it is contemplated that any amorphous forms, polymorphs, or mixtures thereof, which form are included within the scope of the present disclosure.

[0341] In the compounds of general Formula (I) and pharmaceutically acceptable salts, solvates, and/or prodrug thereof, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure is meant to include all suitable isotopic variations of the compounds of the disclosure and pharmaceutically acceptable salts, solvates, and/or prodrug thereof. For example, different isotopic forms of hydrogen (H) include protium (1H), deuterium (2H), and tritium (3H). Protium is the predominant hydrogen isotope found in nature.

[0342] The compounds of the present disclosure may further be radiolabeled and accordingly all radiolabeled versions of the compounds of the disclosure are included within the scope of the present disclosure. The compounds of the disclosure also include those in which one or more radioactive atoms are incorporated within their structure.

III. Compositions

[0343] The compounds of the present disclosure are suitably formulated in a conventional manner into compositions using one or more carriers. Accordingly, the present disclosure also includes a composition comprising one or more compounds of the disclosure and a carrier. The compounds of the disclosure are suitably formulated into pharmaceutical compositions for administration to subjects in a biologically compatible form suitable for administration in vivo. Accordingly, the present disclosure further includes a pharmaceutical composition comprising one or more compounds of the disclosure and a pharmaceutically acceptable carrier. In embodiments of the disclosure, pharmaceutical compositions are used in the treatment of any of the diseases, disorders, or conditions described herein.

[0344] The compounds of the disclosure are administered to a subject in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. For example, a compound of the disclosure is administered by oral, inhalation, parenteral, buccal, sublingual, insufflation, epidurally, nasal, rectal, vaginal, patch, pump, minipump, topical, or transdermal administration and the pharmaceutical compositions formulated accordingly. In some embodiments, administration is by means of a pump for periodic or continuous delivery. Conventional procedures and ingredients for the selection and preparation of suitable compositions are described, for example, in Remington's Pharmaceutical Sciences (2000-20th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999.

[0345] Parenteral administration includes systemic delivery routes other than the gastrointestinal (GI) tract and includes, for example intravenous, intra-arterial, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary (for example, by use of an aerosol), intrathecal, rectal, and topical (including the use of a patch or other transdermal delivery device) modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

[0346] In some embodiments, a compound of the disclosure is orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it is enclosed in hard- or soft-shell gelatin capsules, or it is compressed into tablets, or it is incorporated directly with the food of the diet. In some embodiments, the compound is incorporated with excipient(s) and used in the form of ingestible tablets, buccal tablets, troches, capsules, caplets, pellets, granules, lozenges, chewing gum, powders, syrups, elixirs, wafers, aqueous solutions, suspensions, and the like. In the case of tablets, carriers that are used include lactose, corn starch, sodium citrate, and salts of phosphoric acid. Pharmaceutically acceptable excipients include binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone, or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose, or calcium phosphate); lubricants (e.g., magnesium stearate, talc, or silica); disintegrants (e.g., potato starch or sodium starch glycolate); wetting agents (e.g., sodium lauryl sulphate); and/or solvents (e.g., medium chain triglycerides, ethanol, or water). In embodiments, the tablets are coated by methods well known in the art. In the case of tablets, capsules, caplets, pellets, or granules for oral administration, pH sensitive enteric coatings, such as Eudragits™, designed to control the release of active ingredients are optionally used. Oral dosage forms also include modified release, for example immediate release and timed-release, formulations. Examples of modified-release formulations include, for example, sustained-release (SR), extended-release (ER, XR, or XL), time-release or timed-release, controlled-release (CR), or continuous-release (CR or Contin), employed, for example, in the form of a coated tablet, an osmotic delivery device, a coated capsule, a microencapsulated microsphere, an agglomerated particle, e.g., as of molecular sieving type particles, or, a fine hollow permeable fiber bundle, or chopped hollow permeable fibers, agglomerated or held in a fibrous packet. Timed-release compositions are formulated, for example, as liposomes or those wherein the active compound is protected with differentially degradable coatings, such as by microencapsulation, multiple coatings, etc. Liposome delivery systems include, for example, small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. In some embodiments, liposomes are formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. For oral administration in a capsule form, useful carriers, solvents, or diluents include lactose, medium chain triglycerides, ethanol, and dried corn starch.

[0347] In some embodiments, liquid preparations for oral administration take the form of, for example, solutions, syrups, or suspensions, or they are suitably presented as a dry product for constitution with water or other suitable vehicle before use. When aqueous suspensions and/or emulsions are administered orally, the compound of the disclo-

sure is suitably suspended or dissolved in an oily phase that is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents are added. Such liquid preparations for oral administration are prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose, or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., medium chain triglycerides, almond oil, oily esters, or ethyl alcohol); and/or preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid). Useful diluents include lactose and high molecular weight polyethylene glycols.

[0348] It is also possible to freeze-dry the compounds of the disclosure and use the lyophilizates obtained, for example, for the preparation of products for injection.

[0349] In some embodiments, a compound of the disclosure is administered parenterally. For example, solutions of a compound of the disclosure are prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. In some embodiments, dispersions are prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. A person skilled in the art would know how to prepare suitable formulations. For parenteral administration, sterile solutions of the compounds of the disclosure are usually prepared and the pH's of the solutions are suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic. For ocular administration, ointments, or droppable liquids are delivered, for example, by ocular delivery systems known to the art such as applicators or eye droppers. In some embodiments, such compositions include mucomimetics such as hyaluronic acid, chondroitin sulfate, hydroxypropyl methylcellulose, or polyvinyl alcohol, preservatives such as sorbic acid, EDTA, or benzyl chromium chloride and the usual quantities of diluents or carriers. For pulmonary administration, diluents or carriers will be selected to be appropriate to allow the formation of an aerosol.

[0350] In some embodiments, a compound of the disclosure is formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection are, for example, presented in unit dosage form, e.g., in ampoules or in multidose containers, with an added preservative. In some embodiments, the compositions take such forms as sterile suspensions, solutions, or emulsions in oily or aqueous vehicles and contain formulating agents such as suspending, stabilizing, and/or dispersing agents. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. Alternatively, the compounds of the disclosure are suitably in a sterile powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0351] In some embodiments, compositions for nasal administration are conveniently formulated as aerosols, drops, gels, and powders. For intranasal administration or administration by inhalation, the compounds of the disclosure are conveniently delivered in the form of a solution, dry powder formulation, or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which, for example, take the form of a cartridge or refill for use with an atomising device. Alternatively, the sealed container is a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which is, for example, a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. Suitable propellants include but are not limited to dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, heptafluoroalkanes, carbon dioxide, or another suitable gas. In the case of a pressurized aerosol, the dosage unit is suitably determined by providing a valve to deliver a metered amount. In some embodiments, the pressurized container or nebulizer contains a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator are, for example, formulated containing a powder mix of a compound of the disclosure and a suitable powder base such as lactose or starch. The aerosol dosage forms can also take the form of a pump-atomizer.

[0352] Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, wherein a compound of the disclosure is formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

[0353] Suppository forms of the compounds of the disclosure are useful for vaginal, urethral, and rectal administrations. Such suppositories will generally be constructed of a mixture of substances that is solid at room temperature but melts at body temperature. The substances commonly used to create such vehicles include but are not limited to theobroma oil (also known as cocoa butter), glycerinated gelatin, other glycerides, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol. See, for example: Remington's Pharmaceutical Sciences, 16th Ed., Mack Publishing, Easton, PA, 1980, pp. 1530-1533 for further discussion of suppository dosage forms.

[0354] In some embodiments a compound of the disclosure is coupled with soluble polymers as targetable drug carriers. Such polymers include, for example, polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxy-ethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, in some embodiments, a compound of the disclosure is coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacet als, polydihydropyrans, polycyanoacrylates, and crosslinked or amphipathic block copolymers of hydrogels.

[0355] A compound of the disclosure including pharmaceutically acceptable salts, solvates, and/or prodrugs thereof is suitably used on their own but will generally be administered in the form of a pharmaceutical composition in which

the one or more compounds of the disclosure (the active ingredient) is in association with a pharmaceutically acceptable carrier. Depending on the mode of administration, the pharmaceutical composition will comprise from about 0.05 wt % to about 99 wt %, or about 0.10 wt % to about 70 wt %, of the active ingredient and from about 1 wt % to about 99.95 wt %, or about 30 wt % to about 99.90 wt % of a pharmaceutically acceptable carrier, all percentages by weight being based on the total composition.

[0356] In some embodiments, the compounds of the disclosure including pharmaceutically acceptable salts, solvates, and/or prodrugs thereof are used are administered in a composition comprising an additional therapeutic agent. Therefore, the present disclosure also includes a pharmaceutical composition comprising one of more compounds of the disclosure, or pharmaceutically acceptable salts, solvates, and/or prodrugs thereof and an additional therapeutic agent, and optionally one or more pharmaceutically acceptable excipients. In some embodiments, the additional therapeutic agent is another known agent useful for treatment of a disease, disorder, or condition by activation of a serotonin receptor, for example those listed in the Methods and Uses section below. In some embodiments, the additional therapeutic agent is a psychoactive drug.

[0357] In the above, the term "a compound" also includes embodiments wherein one or more compounds are referenced.

IV. Methods and Uses of the Disclosure

[0358] The compounds of the disclosure are serotonergic binding agents that act as agonists or partial agonists at a serotonin receptor.

[0359] Accordingly, the present disclosure includes a method for activating a serotonin receptor in a cell, either in a biological sample or in a patient (in vivo), comprising administering an effective amount of one or more compounds of the disclosure to the cell. The disclosure also includes use of one or more compounds of the disclosure for activating a serotonin receptor in a cell as well as use of one or more compounds of the disclosure for the preparation of a medicament for activating a serotonin receptor in a cell. The disclosure further includes one or more compounds of the disclosure for use in activating a serotonin receptor in a cell. In some embodiments, the method for activating a serotonin receptor is in or on a cell.

[0360] As the compounds of the disclosure are capable of activating a serotonin receptor, the compounds of the disclosure are useful for treating diseases, disorders, or conditions by activating a serotonin receptor. Therefore, the compounds of the present disclosure are useful as medicaments. Accordingly, the disclosure also includes a compound of the disclosure for use as a medicament.

[0361] The present disclosure also includes a method of treating a disease, disorder, or condition by activation of a serotonin receptor comprising administering a therapeutically effective amount of one or more compounds of the disclosure to a subject in need thereof.

[0362] The present disclosure also includes use of one or more compounds of the disclosure for treatment of a disease, disorder, or condition by activation of a serotonin receptor as well as use of one or more compounds of the disclosure for the preparation of a medicament for treatment of a disease, disorder, or condition by activation of a serotonin receptor. The disclosure further includes one or more compounds of the disclosure for use in treating a disease, disorder, or condition by activation of a serotonin receptor.

[0363] In some embodiments, the serotonin receptor is 5-HT_{2A}. Accordingly, the present disclosure includes a method for activating 5-HT_{2A} in a cell, either in a biological sample or in a patient (in vivo), comprising administering an effective amount of one or more compounds of the disclosure to the cell. The disclosure also includes use of one or more compounds of the disclosure for activating 5-HT_{2A} in a cell as well as use of one or more compounds of the disclosure for the preparation of a medicament for activating 5-HT_{2A} in a cell. The disclosure further includes one or more compounds of the disclosure for use in activating 5-HT_{2A} in a cell. In some embodiments, the method for activating 5-HT_{2A} is in or on a cell.

[0364] The present disclosure also includes a method of treating a disease, disorder, or condition by activation of 5-HT_{2A} comprising administering a therapeutically effective amount of one or more compounds of the disclosure to a subject in need thereof. The present disclosure also includes use of one or more compounds of the disclosure for treatment of a disease, disorder, or condition by activation of 5-HT_{2A} as well as use of one or more compounds of the disclosure for the preparation of a medicament for treatment of a disease, disorder, or condition by activation of 5-HT_{2A}. The disclosure further includes one or more compounds of the disclosure for use in treating a disease, disorder, or condition by activation of 5-HT_{2A}.

[0365] In some embodiments, the compounds of the disclosure are useful for preventing, treating, and/or reducing the severity of a mental illness disorder and/or condition in a subject. Therefore, in some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is a mental illness. Accordingly, the present disclosure also includes a method of treating a mental illness comprising administering a therapeutically effective amount of one or more compounds of the disclosure to a subject in need thereof. The present disclosure also includes use of one or more compounds of the disclosure for treatment a mental illness, as well as use of one or more compounds of the disclosure for the preparation of a medicament for treatment of a mental illness. The disclosure further includes one or more compounds of the disclosure for use in treating a mental illness.

[0366] In some embodiments, the mental illness is selected from anxiety disorders such as generalized anxiety disorder, panic disorder, social anxiety disorder, and specific phobias; depression such as, hopelessness, loss of pleasure, fatigue, and suicidal thoughts; mood disorders, such as depression, bipolar disorder, cancer-related depression, major depressive disorder (MDD), treatment-resistant depression (TRD), postpartum depression (PPD), anxiety, and cyclothymic disorder; psychotic disorders, such as hallucinations, delusions, and schizophrenia; impulse control and addiction disorders, such as pyromania (starting fires), kleptomania (stealing), and compulsive gambling; alcohol addiction (e.g., reduction in alcohol consumption); drug addiction, such as opioid addiction; personality disorders, such as antisocial personality disorder, obsessive-compulsive personality disorder, and paranoid personality disorder; obsessive-compulsive disorder (OCD), such as thoughts or fears that cause a subject to perform certain rituals or routines; post-traumatic stress disorder (PTSD); stress response syndromes (formerly called adjustment disorders);

dissociative disorders, formerly called multiple personality disorder, or "split personality," and depersonalization disorder; factitious disorders; sexual and gender disorders, such as sexual dysfunction, gender identity disorder, and the paraphilia's; somatic symptom disorders, formerly known as a psychosomatic disorder or somatoform disorder; body dysmorphic disorder; influencing goal-directed behavior; emotional state disorders (e.g., diminishment of negative emotions and promoting positive emotions); enhancements in creativity; and combinations thereof.

[0367] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor comprises cognitive impairment (e.g., amplifies cognitive capabilities, enhance and/or improve cognitive flexibility); ischemia including stroke; neurodegeneration; refractory substance use disorders; sleep disorders; pain, such as social pain, acute pain, cancer pain, chronic pain, breakthrough pain, bone pain, soft tissue pain, nerve pain, referred pain, phantom pain, neuropathic pain, cluster headaches, and migraine; obesity and eating disorders; epilepsies and seizure disorders; neuronal cell death; excitotoxic cell death; inflammation (e.g., autoimmune neuroinflammation); or a combination thereof.

[0368] In some embodiments, the mental illness is selected from hallucinations and delusions and a combination thereof.

[0369] In some embodiments, the hallucinations are selected from visual hallucinations, visual disorders (e.g., Prosopometamorphopsia (PMO), influencing facial recognition, and improving the processing of emotional faces in treatment-resistant depression (TRD)), auditory hallucinations, olfactory hallucinations, gustatory hallucinations, tactile hallucinations, proprioceptive hallucinations, equilibrioceptive hallucinations, nociceptive hallucinations, thermoceptive hallucinations, and chronoceptive hallucinations, and a combination thereof.

[0370] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is psychosis or psychotic symptoms. Accordingly, the present disclosure also includes a method of treating psychosis or psychotic symptoms comprising administering a therapeutically effective amount of one or more compounds of the disclosure to a subject in need thereof.

[0371] The present disclosure also includes use of one or more compounds of the disclosure for treatment of psychosis or psychotic symptoms, as well as use of one or more compounds of the disclosure for the preparation of a medicament for treatment of psychosis or psychotic symptoms. The disclosure further includes one or more compounds of the disclosure for use in treating psychosis or psychotic symptoms.

[0372] In some embodiments, administering to said subject in need thereof a therapeutically effective amount of the compounds of the disclosure does not result in a worsening of psychosis or psychotic symptoms such as, but not limited to, hallucinations and delusions. In some embodiments, administering to said subject in need thereof a therapeutically effective amount of the compounds of the disclosure results in an improvement of psychosis or psychotic symptoms such as, but not limited to, hallucinations and delusions. In some embodiments, administering to said subject in need thereof a therapeutically effective amount of the compounds of the disclosure results in an improvement of psychosis or psychotic symptoms.

[0373] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is a central nervous system (CNS) disease, disorder, or condition and/or a neurological disease, disorder, or condition. Accordingly, the present disclosure also includes a method of treating a CNS disease, disorder, or condition and/or a neurological disease, disorder, or condition that is treated by activation of a serotonin receptor comprising administering a therapeutically effective amount of one or more compounds of the disclosure to a subject in need thereof, that is a subject having the central nervous system (CNS) disease, disorder, or condition and/or a neurological disease, disorder, or condition. The present disclosure also includes use of one or more compounds of the disclosure for treatment a CNS disease, disorder, or condition and/or a neurological disease, disorder, or condition that is treated by activation of a serotonin receptor, as well as use of one or more compounds of the disclosure for the preparation of a medicament for treatment of a CNS disease, disorder, or condition and/or a neurological disease, disorder, or condition that is treated by activation of a serotonin receptor. The disclosure further includes one or more compounds of the disclosure for use in treating a CNS disease, disorder, or condition and/or a neurological disease, disorder, or condition that is treated by activation of a serotonin receptor.

[0374] In some embodiments the CNS disease, disorder, or condition and/or neurological disease, disorder, or condition is selected from neurological diseases including neurodevelopmental diseases and neurodegenerative diseases such as Alzheimer's disease (e.g., restoring mGluR2 expression); presenile dementia; senile dementia; vascular dementia; Lewy body dementia; cognitive impairment; Parkinson's disease and Parkinsonian related disorders such as Parkinson's dementia, corticobasal degeneration, and supranuclear palsy; epilepsy; CNS trauma; CNS infections; CNS inflammation; stroke; multiple sclerosis; Huntington's disease; mitochondrial disorders; Fragile X syndrome; Angelman syndrome; hereditary ataxias; neuro-otological and eye movement disorders; neurodegenerative diseases of the retina amyotrophic lateral sclerosis; tardive dyskinesias; hyperkinetic disorders; attention deficit hyperactivity disorder and attention deficit disorders; restless leg syndrome; Tourette's syndrome; schizophrenia; autism spectrum disorders; tuberous sclerosis; Rett syndrome; cerebral palsy; disorders of the reward system including eating disorders such as anorexia nervosa ("AN") and bulimia nervosa ("BN"); binge eating disorder ("BED"); pica; rumination disorder; avoidant/restrictive food intake disorder; trichotillomania; dermotillomania; nail biting; migraine; fibromyalgia; and peripheral neuropathy of any etiology; reduction in convergent thinking; increase in spontaneous divergent thinking and goal-oriented divergent thinking; and combinations thereof.

[0375] The present disclosure also includes a method of treating nonpsychiatric conditions, such as: fibromyalgia, irritable bowel syndrome (IBS), Fragile X, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUHNA), chronic cluster, persistent postconcussive syndrome (PPCS), Alzheimer's disease, Lyme disease, neuropathic pain, migraines, Parkinson's disease, cluster headache, stroke, traumatic brain injury (TBI), pain, obesity, and smoking cessation.

[0376] In some embodiments, the subject is a mammal. In another embodiment, the subject is human. In some embodi-

ments, the subject is a non-human animal. In some embodiments, the subject is canine. In some embodiments, the subject is feline. Accordingly, the compounds, methods and uses of the present disclosure are directed to both human and veterinary diseases, disorders, and conditions.

[0377] In some embodiments, the "subject in need thereof" is a subject having the disease, disorder, or condition to be treated.

[0378] In some embodiments, the compounds of the disclosure are useful for treating behavioral problems in subjects that are felines or canines.

[0379] Therefore, in some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is behavioral problems in subjects that are felines or canines. Accordingly, the present disclosure also includes a method of treating a behavioral problem comprising administering a therapeutically effective amount of one or more compounds of the disclosure to a non-human subject in need thereof. The present disclosure also includes use of one or more compounds of the disclosure for treatment of a behavioral problem in a non-human subject, as well as use of one or more compounds of the disclosure for the preparation of a medicament for treatment of a behavioral problem in a non-human subject. The disclosure further includes one or more compounds of the disclosure for use in treating a behavioral problem in a non-human subject.

[0380] In some embodiments, the behavioral problems are selected from, but are not limited to, anxiety, fear, stress, sleep disturbances, cognitive dysfunction, aggression, excessive noise making, scratching, biting, and a combination thereof.

[0381] In some embodiments, the non-human subject is canine. In some embodiments, the non-human subject is feline.

[0382] The present disclosure also includes a method of treating a disease, disorder, or condition by activation of a serotonin receptor comprising administering a therapeutically effective amount of one or more compounds of the disclosure in combination with another known agent useful for treatment of a disease, disorder, or condition by activation of a serotonin receptor to a subject in need thereof. The present disclosure also includes use of one or more compounds of the disclosure in combination with another known agent useful for treatment of a disease, disorder, or condition by activation of a serotonin receptor for treatment of a disease, disorder, or condition by activation of a serotonin receptor, as well as use of one or more compounds of the disclosure in combination with another known agent useful for treatment of a disease, disorder, or condition by activation of a serotonin receptor for the preparation of a medicament for treatment of a disease, disorder, or condition by activation of a serotonin receptor. The disclosure further includes one or more compounds of the disclosure in combination with another known agent useful for treatment of a disease, disorder, or condition by activation of a serotonin receptor for use in treating a disease, disorder, or condition by activation of a serotonin receptor.

[0383] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is a mental illness. In some embodiments, the mental illness is selected from hallucinations and delusions and a combination thereof. In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is a central nervous system (CNS) disorder. In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is psychosis or psychotic symptoms. In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is behavioral problems in a non-human subject.

[0384] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is a mental illness and the one or more compounds of the disclosure are administered in combination with one or more additional treatments for a mental illness. In some embodiments, the additional treatments for a mental illness is selected from antipsychotics, including typical antipsychotics and atypical antipsychotics; antidepressants including selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and monoamine oxidase inhibitors (MAOIs) (e.g., bupropion); anti-anxiety medication including benzodiazepines such as alprazolam; mood stabilizers such as lithium; and anticonvulsants such as carbamazepine, divalproex (valproic acid), lamotrigine, gabapentin, and topiramate.

[0385] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is selected from attention deficit hyperactivity disorder and attention deficit disorder and a combination thereof. In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is attention deficit hyperactivity disorder and/or attention deficit disorder and a combination thereof and the one or more compounds of the disclosure are administered in combination with one or more additional treatments for attention deficit hyperactivity disorder and/or attention deficit disorder and a combination thereof. In some embodiments, the additional treatments for attention deficit hyperactivity disorder and/or attention deficit disorder are selected from methylphenidate, atomoxetine, amphetamine, and a combination thereof.

[0386] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is dementia or Alzheimer's disease and the one or more compounds of the disclosure are administered in combination with one or more additional treatments for dementia or Alzheimer's disease. In some embodiments, the additional treatments for dementia and Alzheimer's disease are selected from acetylcholinesterase inhibitors, NMDA antagonists, and muscarinic agonists and antagonists, and nicotinic agonists.

[0387] In some embodiments, the acetylcholinesterase inhibitors are selected from donepezil, galantamine, rivastigmine, phenserine, and combinations thereof.

[0388] In some embodiments, the NMDA antagonists are selected from MK-801, ketamine, phencyclidine, memantine, and combinations thereof.

[0389] In some embodiments, the nicotinic agonist is nicotine, nicotinic acid, nicotinic alpha7 agonist, alpha2 beta4 agonist, or combinations thereof.

[0390] In some embodiments, the muscarinic agonist is a muscarinic M1 agonist, a muscarinic M4 agonist, or combinations thereof.

[0391] In some embodiments, the muscarinic antagonist is a muscarinic M2 antagonist.

[0392] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is psychosis or psychotic symptoms and the one or more

compounds of the disclosure are administered in combination with one or more additional treatments for psychosis or psychotic symptoms. In some embodiments, the additional treatments for psychosis or psychotic symptoms are selected from typical antipsychotics and atypical antipsychotics.

[0393] In some embodiments, the typical antipsychotics are selected from acepromazine, acetophenazine, benperidol, bromperidol, butaperazine, carfenazine, chlorproethazine, chlorpromazine, chlorprothixene, clopenthixol, cyamemazine, dixyrazine, droperidol, fluanisone, flupentixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, lenperone, loxapine, mesoridazine, metitepine, molindone, moperone, oxypertine, oxyprotepine, penfluridol, perazine, periciazine, perphenazine, pimozide, pipamperone, piperacetazine, pipotiazine, prochlorperazine, promazine, prothipendyl, spiperone, sulforidazine, thiopropazate, thioproperazine, thioridazine, thiothixene, timiperone, trifluoperazine, trifluperidol, triflupromazine, zuclopenthixol, and combinations thereof.

[0394] In some embodiments, the atypical antipsychotics are selected from amoxapine, amisulpride, aripiprazole, asenapine, blonanserin, brexpiprazole, cariprazine, carpipramine, clocapramine, clorotepine, clotiapine, clozapine, iloperidone, levosulpiride, lurasidone, melperone, mosapramine, nemonapride, olanzapine, paliperidone, perospirone, quetiapine, remoxipride, reserpine, risperidone, sertindole, sulpiride, sultopride, tiapride, veralipride, ziprasidone, zotepine, and combinations thereof.

[0395] In some embodiments, the disease, disorder, or condition that is treated by activation of a serotonin receptor is a mental illness and the one or more compounds of the disclosure are administered in combination with one or more additional treatments for a mental illness. In some embodiments, the additional treatment for a mental illness is selected from typical antipsychotics and atypical antipsychotics.

[0396] In some embodiments, effective amounts vary according to factors such as the disease state, age, sex, and/or weight of the subject or species. In some embodiments, the amount of a given compound or compounds that will correspond to an effective amount will vary depending upon factors, such as the given drug(s) or compound(s), the pharmaceutical formulation, the route of administration, the type of condition, disease, or disorder, the identity of the subject being treated, and the like, but can nevertheless be routinely determined by one skilled in the art.

[0397] In some embodiments, the compounds of the disclosure are administered one, two, three, or four times a year. In some embodiments, the compounds of the disclosure are administered at least once a week. However, in another embodiment, the compounds are administered to the subject from about one time per one week, two weeks, three weeks, or one month. In another embodiment, the compounds are administered about one time per week to about once daily. In another embodiment, the compounds are administered 1, 2, 3, 4, 5, or 6 times daily. The length of the treatment period depends on a variety of factors, such as the severity of the disease, disorder, or condition, the age of the subject, the concentration and/or the activity of the compounds of the disclosure, and/or a combination thereof. It will also be appreciated that the effective dosage of the compound used for the treatment may increase or decrease over the course of a particular treatment regime. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances, chronic administration is required. For example, the compounds are administered to the subject in an amount and for duration sufficient to treat the subject.

[0398] In some embodiments, the compounds of the disclosure are administered at doses that are hallucinogenic or psychotomimetic and taken in conjunction with psychotherapy or therapy and may occur once, twice, three, or four times a year. However, in some embodiments, the compounds are administered to the subject once daily, once every two days, once every 3 days, once a week, once every two weeks, once a month, once every two months, or once every three months at doses that are not hallucinogenic or psychotomimetic.

[0399] A compound of the disclosure is either used alone or in combination with other known agent(s) useful for treating diseases, disorders, or conditions by activation of a serotonin receptor, such as the compounds of the disclosure. When used in combination with other known agent(s) useful in treating diseases, disorders, or conditions by activation of a serotonin receptor, it is an embodiment that a compound of the disclosure is administered contemporaneously with those agents. As used herein, "contemporaneous administration" of two substances to a subject means providing each of the two substances so that they are both active in the individual at the same time. The exact details of the administration will depend on the pharmacokinetics of the two substances in the presence of each other and can include administering the two substances within a few hours of each other, or even administering one substance within 24 hours of administration of the other, if the pharmacokinetics are suitable. Design of suitable dosing regimens is routine for one skilled in the art. In particular embodiments, two substances will be administered substantially simultaneously, i.e., within minutes of each other, or in a single composition that contains both substances. It is a further embodiment of the present disclosure that a combination of agents is administered to a subject in a non-contemporaneous fashion. In some embodiments, a compound of the present disclosure is administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present disclosure provides a single unit dosage form comprising one or more compounds of the disclosure, an additional therapeutic agent and/or a pharmaceutically acceptable carrier.

[0400] The dosage of a compound of the disclosure varies depending on many factors such as the pharmacodynamic properties of the compound, the mode of administration, the age, health, and weight of the recipient, the nature and extent of the symptoms, the frequency of the treatment, and the type of concurrent treatment, if any, and the clearance rate of the compound in the subject to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. In some embodiments, one or more compounds of the disclosure are administered initially in a suitable dosage that is adjusted as required, depending on the clinical response. Dosages will generally be selected to maintain a serum level of the one or more compounds of the disclosure from about 0.01 μg/cc to about 1000 μg/cc, or about 0.1 μg/cc to about 100 μg/cc. As a representative example, oral dosages of one or more compounds of the disclosure will range between about 10 μg per day to about 1000 mg per day for an adult, suitably about 10 μg per day

to about 500 mg per day, more suitably about 10 μg per day to about 200 mg per day. F or parenteral administration, a representative amount is from about 0.0001 mg/kg to about 10 mg/kg, about 0.0001 mg/kg to about 1 mg/kg, about 0.01 mg/kg to about 0.1 mg/kg, or about 0.0001 mg/kg to about 0.01 mg/kg will be administered. For oral administration, a representative amount is from about 0.001 μg/kg to about 10 mg/kg, about 0.1 μg/kg to about 10 mg/kg, about 0.01 μg/kg to about 1 mg/kg, or about 0.1 μg/kg to about 1 mg/kg. For administration in suppository form, a representative amount is from about 0.1 mg/kg to about 10 mg/kg or about 0.1 mg/kg to about 1 mg/kg. In some embodiments of the disclosure, compositions are formulated for oral administration and the one or more compounds are suitably in the form of tablets containing 0.1, 0.25, 0.5, 0.75, 1.0, 5.0, 10.0, 20.0, 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 75.0, 80.0, 90.0, 100.0, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, or 1000 mg of active ingredient (one or more compounds of the disclosure) per tablet. In some embodiments of the disclosure the one or more compounds of the disclosure are administered in a single daily, weekly, or monthly dose or the total daily dose is divided into two, three, or four daily doses.

[0401] In some embodiments, the compounds of the disclosure are used or administered in an effective amount which comprises administration of doses or dosage regimens that are devoid of clinically meaningful psychedelic/psychotomimetic actions. In some embodiments, the compounds of the disclosure are used or administered in an effective amount which comprises administration of doses or dosage regimens that provide clinical effects similar to those exhibited by a human plasma psilocin C_{max} of 4 ng/mL or less and/or human 5-HT_{2A} human CNS receptor occupancy of 40% or less or those exhibited by a human plasma psilocin C_{max} of 1 ng/mL or less and/or human 5-HT_{2A} human CNS receptor occupancy of 30% or less. In some embodiments, the compounds of the disclosure are used or administered in an effective amount which comprises administration of doses or dosage regimens that provide clinical effects similar to those exhibited by a human plasma psilocin T_{max} in excess of 60 minutes, in excess of 120 minutes or in excess of 180 minutes.

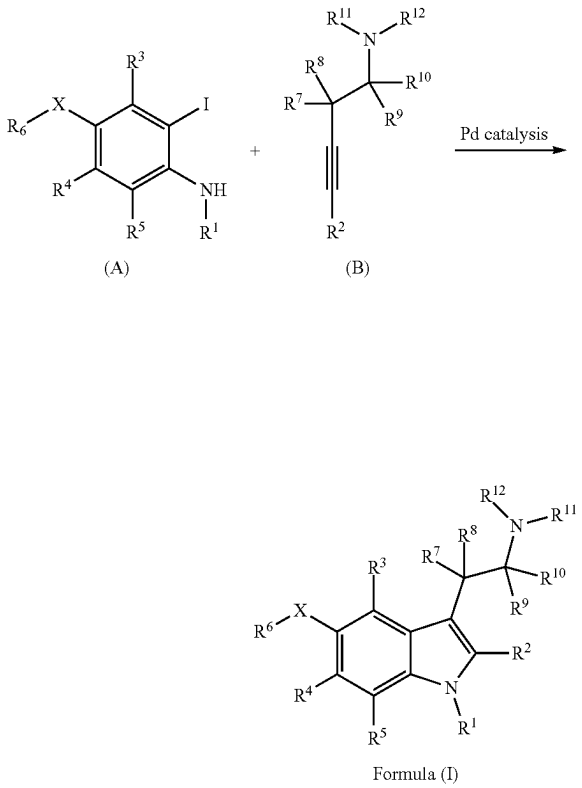
[0402] To be clear, in the above, the term "a compound" also includes embodiments wherein one or more compounds are referenced. Likewise, the term "compounds of the disclosure" also includes embodiments wherein only one compound is referenced.

V. Preparation of Compounds

[0403] Compounds of the present disclosure can be prepared by various synthetic processes. The choice of particular structural features and/or substituents may influence the selection of one process over another. The selection of a particular process to prepare a given compound of the disclosure is within the purview of the person of skill in the art. Some starting materials for preparing compounds of the present disclosure are available from commercial chemical sources or may be extracted from cells, plants, animals, or fungi. Other starting materials, for example as described below, are readily prepared from available precursors using straightforward transformations that are well known in the art. In the Schemes below showing some embodiments of methods of preparation of compounds of the disclosure, all variables are as defined in Formula (I), unless otherwise stated.

[0404] In some embodiments, the compounds of Formula (I) are prepared as shown in Scheme I.

Scheme I

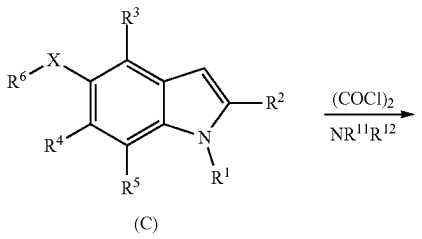


[0405] Therefore, in some embodiments, compounds of Formula (I) can be synthesized by treating ortho-iodoaniline (A) derivatives with suitable unsaturated precursors (B).

[0406] Through this route, the compounds of Formula (I) were formed directly by utilizing Pd catalysis [Fricke et al., Chem. Eur. J., 2019, 25(4):897-903].

[0407] In some embodiments, compounds of Formula (I) are prepared according to Scheme II:

Scheme II



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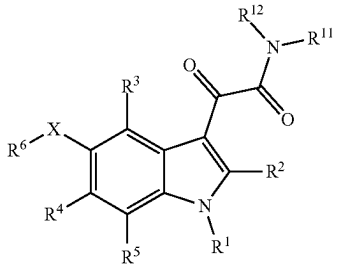
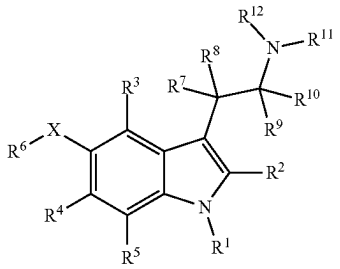


(D)

Al-reduction

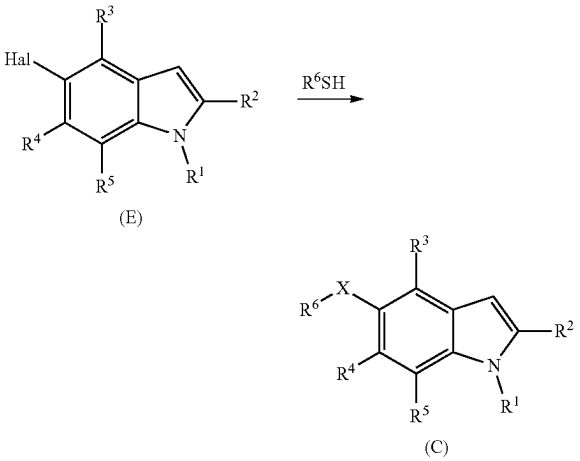


Formula (I)

[0408] Therefore, in some embodiments, as shown in Scheme II, compounds of Formula (I) are synthesized by first treating appropriately substituted indole (C) with oxalyl chloride followed by suitable amines N H $R^{11}R^{12}$, leading to the intermediate indole (D). Subsequent AI-based reduction, for example, in the presence of lithium aluminum hydride or lithium aluminum deuteride, yields compounds of Formula (I).

[0409] In some embodiments, compounds of Formula (C) wherein X is S are prepared as shown in Scheme Ill.

Scheme III



(E)

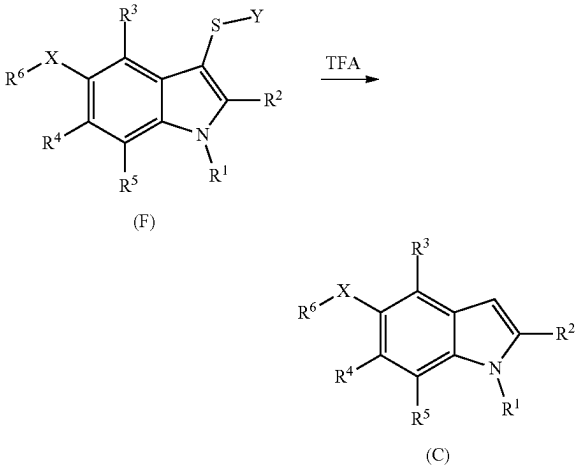
(C)

[0410] Therefore, in some embodiments, as shown in Scheme Ill, compounds of Formula (C) wherein X is S are synthesized by coupling the indole of compound (E) wherein Hal is halide, such as I or Br, with a thiol compound of Formula R^6SH under suitable coupling conditions such as in the presence of a suitable catalyst such as a palladium catalyst (e.g., bis(dibenzylideneacetone)palladium(0) (Pd $(dba)_2$)), ligand (e.g., 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthen (Xantphos)), and base such as ethyldiisopropylamine in a suitable inert solvent such as dioxane.

[0411] In some embodiments, compounds of Formula (C) wherein X is S are synthesized using methods known in the art as shown in Scheme III, for example, the methods described in Shmatova, O. I., Eur. J. Org. Chem. 2015, 6479-6488.

[0412] In some embodiments, compounds of Formula (C) wherein X is S are prepared as shown in Scheme IV.

Scheme IV



(F)

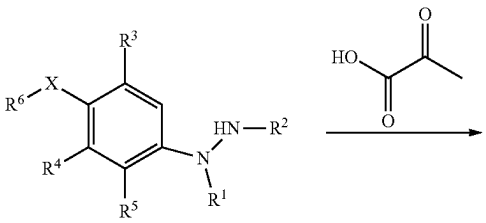
(C)

[0413] Therefore, in some embodiments, as shown in Scheme IV, compounds of Formula (C) wherein X is S are synthesized by the desulfenylation of a compound of Formula (F) wherein Y is an alkyl or aryl group in the presence of trifluoroacetic acid and a thiol as trapping agent, such as methyl thiosalicylate.

[0414] In some embodiments, compounds of Formula (C) wherein X is S are prepared as shown in Scheme IV using methods known in the art, for example, the methods described in Hamel, P., J. Org. Chem. 1994, 59, 6372-6377.

[0415] In some embodiments, compounds of Formula (C) wherein X is S are prepared as shown in Scheme V.

Scheme V



(G)

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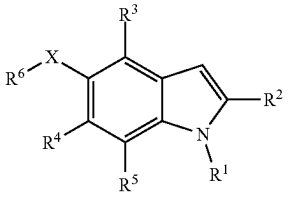


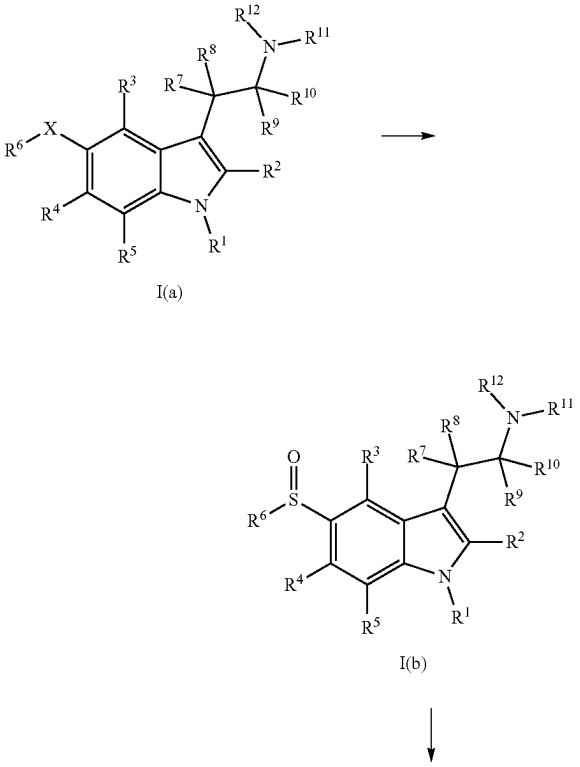
(C)

[0416] Therefore, in some embodiments, as shown in Scheme V, compounds of Formula (C) wherein X is S are synthesized using the Fischer indole synthesis method. For example, in some embodiments, hydrazine compounds of compound G are reacted with pyruvic acid under suitable conditions such as in the presence of zinc chloride and phosphorus pentachloride to provide the compounds of Formula (C).

[0417] In some embodiments, compounds of Formula (C) wherein X is S are prepared as shown in Scheme V using methods known in the art, for example, the methods described in Bratulescu, G., Letters 49 (2008) 984-986.

[0418] In some embodiments, compounds of Formula (I) wherein X is S(O) (compounds of Formula I(b)) and X is SO_2 (compounds of Formula I(c)) are prepared from compounds of Formula (I) wherein X is S (compounds of Formula I(a)) according to Scheme VI.

Scheme VI



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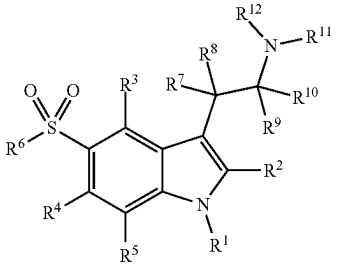


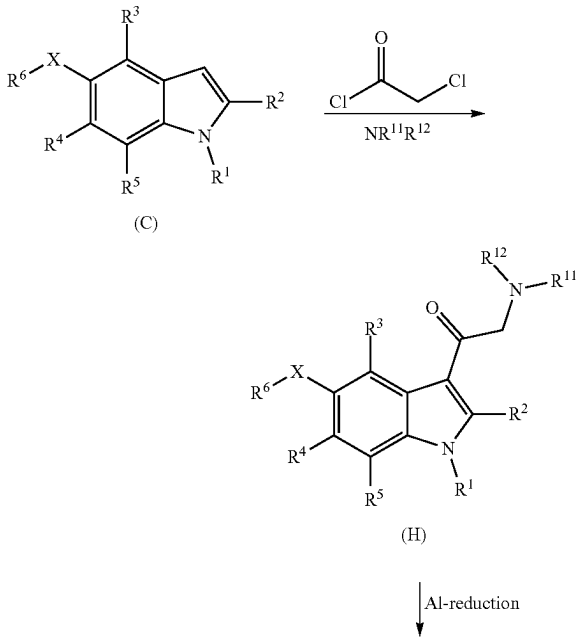
I(c)

[0419] In some embodiments, as shown in Scheme VI, compounds of Formula (I) wherein X is S (compounds of Formula I(a)) are oxidized to compounds of Formula (I) wherein X is S(O) (compounds of Formula I(b)) under suitable oxidizing conditions such as 1 equivalent of meta-chloroperoxybenzoic acid (m-CPBA). Compounds of Formula (I) wherein X is S(O) (compounds of Formula I(b)) are then oxidized under suitable oxidizing conditions such as meta-chloroperoxybenzoic acid (m-CPBA) to compounds of Formula (I) wherein X is SO_2 (compounds of Formula I(c)).

[0420] In some embodiments, compounds of Formula (I) wherein X is S(O) (compounds of Formula I(b)) and X is SO_2 (compounds of Formula I(c)) are prepared from compounds of Formula (I) wherein X is S (compounds of Formula I(a)) as shown in Scheme VI using methods known in the art, for example, the methods described in United States patent application 2004/0043965.

[0421] In some embodiments, compounds of Formula (I) are prepared according to Scheme VII.

Scheme VII



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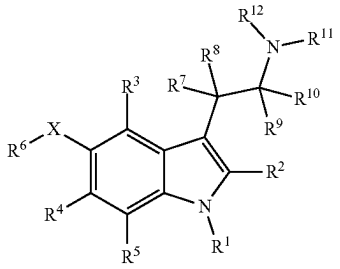


Formula (I)

[0422] Therefore, in some embodiments, as shown in Scheme VII, compounds of Formula (C) are first treated with 2-chloroacetyl chloride then followed by suitable amine $NHR^{11}R^{12}$, leading to the intermediate indole of Formula (H). Subsequent AI-based reduction, for example, in the presence of lithium aluminum hydride or lithium aluminum deuteride, yields compounds of Formula (I).

[0423] In some embodiments, compounds of Formula (I) are prepared as shown in Scheme VII using methods known in the art, for example, the methods described in Gitto R., et al., Bioorg. Med. Chem. 17 (2009) 1640-1647.

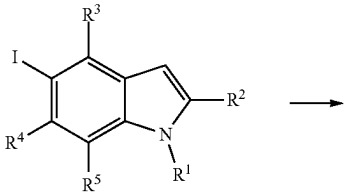
[0424] In some embodiments, compounds of Formula (I) are prepared according to Scheme VIII.

[0425] Therefore, in some embodiments, as shown in Scheme VIII, compounds of Formula (C) are first treated with oxalyl chloride followed by suitable amines $NHR^{11}R^{12}$, leading to the intermediate indole (D). Subsequent reduction in the presence of a suitable reducing agents such as triethylsilane with trifluoroacetic acid provides compounds of Formula (J). Further, AI-based reduction, for example, in the presence of lithium aluminum hydride or lithium aluminum deuteride, yields compounds of Formula (I).

[0426] In some embodiments, compounds of Formula (I) are prepared as shown in Scheme VIII using methods known in the art, for example, the methods described in International Patent Application Publication No. WO9801428A1.

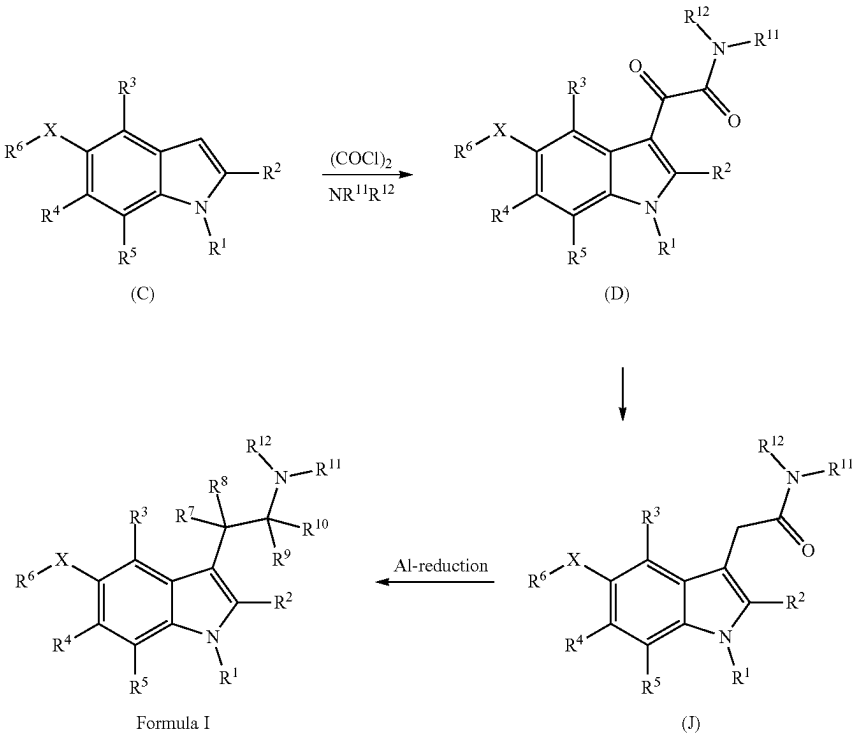
[0427] In some embodiments, compounds of Formula (C) wherein X is S and R^6 is CD_3 (compounds of Formula (C')) are prepared as shown in Scheme IX.

Scheme IX



(E')

Scheme VIII



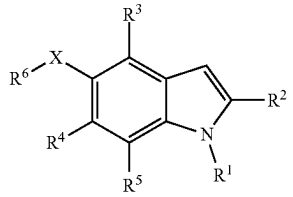
(C)

(D)

Formula I

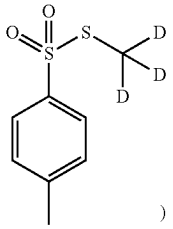
(J)

-continued



(C')

[0428] Therefore, in some embodiments, as shown in Scheme IX, compounds of Formula (C) wherein X is S and R^6 is CD_3 (compounds of Formula (C')) are synthesized by coupling the indole of Formula (E) wherein Hal is I (compound of Formula (E')) in the presence of a suitable catalyst such as a nickel based catalyst (e.g., nickel acetate) with a suitable electrophilic SCD_3 reagent such as S-(methyl-D3) 4-methylbenzenesulfonothioate



in the presence of a suitable reductant such as zinc powder and a base such as 2,2-bipyridyl to provide compounds of Formula (C) wherein X is S and R^6 is CD_3 (compounds of Formula (C')).

[0429] In some embodiments, compounds of Formula (C) wherein X is S and R^6 is CD_3 (compounds of Formula (C') as shown in Scheme IX) are synthesized using methods known in the art, for example, the methods described in Zhang, Y., Org. Lett. 2022, 24, 6794-6799.

[0430] Compounds of Formula (I), wherein one or more of R^1-R^5 and A are deuterium are available, for example, using a hydrogen-deuterium exchange reaction on a suitable starting substrate, wherein this exchange reaction is catalyzed by Pd/C in D_2O as described in Esaki, H. et al., Tetrahedron, 2006, 62:10954-10961, and modifications thereof known to a person skilled in the art.

[0431] Compounds of Formula (I), wherein one or more of R^1-R^5 are deuterium are available, for example, using a hydrogen-deuterium exchange reaction on a suitable starting substrate, wherein this exchange reaction is catalyzed by Pd/C in D_2O as described in Esaki, H. et al., Tetrahedron, 2006, 62:10954-10961, and modifications thereof known to a person skilled in the art.

[0432] Compounds of Formula (I), wherein X—R^6 is OCD_3 are available, for example, using methods as described in Xu, Y—Z and Chen, C. J. Label Compd. Radiopharm. (2006) 49:897-902, and modifications thereof known to a person skilled in the art.

[0433] A person skilled in the art would appreciate that further manipulation of the substituent groups using known chemistry can be performed on the intermediates and final compounds in the Schemes above to provide alternative compounds of the disclosure.

[0434] For example, a person skilled in the art would appreciate that R^1 is H in compounds of Formulae (C) and (D) above resulting in a compound of Formula (I) wherein R^1 is H, then the compound of Formula (I) wherein R^1 is H can be further reacted to prepare further compounds of Formula (I). For example, the compound of Formula (I) wherein R^1 is H can be alkylated with an alkyl halide in the presence of suitable based such as NaH, NaOtBu, or LiHMDS.

[0435] Salts of compounds of the disclosure may be formed by methods known to those of ordinary skill in the art, for example, by reacting a compound of the disclosure with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in aqueous medium followed by lyophilization.

[0436] The formation of solvates will vary depending on the compound and the solvate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions. The selection of suitable conditions to form a particular solvate can be made by a person skilled in the art. Examples of suitable solvents are ethanol, water, and the like. When water is the solvent, the molecule is referred to as a "hydrate." The formation of solvates of the compounds of the disclosure will vary depending on the compound and the solvate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent The solvate is typically dried or azeotroped under ambient conditions. The selection of suitable conditions to form a particular solvate can be made by a person skilled in the art.

[0437] Isotopically-enriched compounds of the disclosure and pharmaceutically acceptable salts, solvates, and/or prodrug thereof, can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using suitable isotopically-enriched reagents and/or intermediates.

[0438] Throughout the processes described herein it is to be understood that, where appropriate, suitable protecting groups will be added to and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis," T. W. Green, P. G. M. Wuts, Wiley-Interscience, New York, (1999). It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to one skilled in the art Examples of transformations are given herein and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions of other suitable transformations are given in "Com-

prehensive Organic Transformations—A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry," March, 4th ed. McGraw Hill (1992) or, "Organic Synthesis," Smith, McGraw Hill, (1994). Techniques for purification of intermediates and final products include, for example, straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid or solid-liquid extraction, which will be readily understood by one skilled in the art.

[0439] It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities, and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to one skilled in the art. Examples of transformations are given herein, and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions of other suitable transformations are given in "Comprehensive Organic Transformations—A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry," March, 4th ed. McGraw Hill (1992) or, "*Organic Synthesis*," Smith, McGraw Hill, (1994).

[0440] Techniques for purification of intermediates and final products include, for example, straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation, and liquid-liquid or solid-liquid extraction, which will be readily understood by one skilled in the art.

[0441] The products of processes disclosed in the disclosure may be isolated according to known methods, for example, the compounds may be isolated by evaporation of the solvent, by filtration, centrifugation, chromatography, or other suitable method.

[0442] Prodrugs of the compounds of the present disclosure may be, for example, conventional esters formed with available hydroxy, thiol, amino, or carboxyl groups. For example, available hydroxy or amino groups may be acylated using an activated acid in the presence of a base, and optionally, in inert solvent (e.g., an acid chloride in pyridine).

[0443] One skilled in the art will recognize that where a reaction step of the present disclosure is carried out in a variety of solvents or solvent systems, said reaction step may also be carried out in a mixture of the suitable solvents or solvent systems.

EXAMPLES

[0444] The following non-limiting examples are illustrative of the present disclosure.

General Methods

[0445] All starting materials used herein were commercially available or earlier described in the literature. The ^{1}H and ^{13}C NMR spectra were measured using a Bruker 300, Bruker DPX400, or Varian+400 spectrometer operating at 300, 400, and 400 MHz for ^{1}H NMR, respectively. TMS or the residual solvent signal was used as an internal reference; deuterated chloroform was used as the solvent unless otherwise indicated. All reported chemical shifts are in ppm on the delta-scale, and the fine splitting of the signals as appearing in the recordings is generally indicated, for example as s: singlet, br s: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet. Unless otherwise indicated, in the tables below, ^{1}H NMR data was obtained at 400 MH z, using $CDCl_3$ as the solvent.

[0446] Purification of products was carried out using Chem Elut Extraction Columns (Varian, cat #1219-8002), Mega BE-SI (Bond Elut Silica) SPE Columns (Varian, cat #12256018; 12256026; 12256034), or by flash chromatography in silica-filled glass columns.

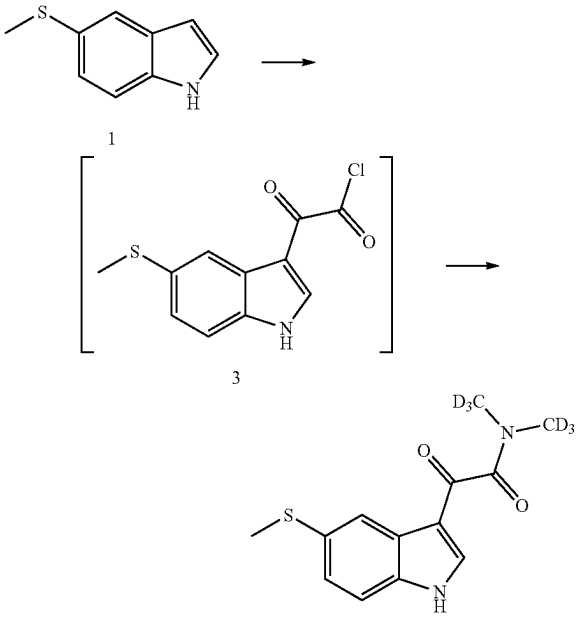
[0447] IUPAC names were generated with CHEMDRAW Professional 22.2.0 64-bit.

Part I

[0448] The following compounds were prepared using one or more of the synthetic methods outlined in Schemes I and II.

A. Synthesis of Exemplary Compounds of the Disclosure

Example 1: Synthesis of N,N-Bis(methyl-d_3)-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (I-1)



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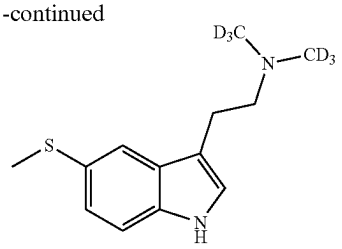


I-1

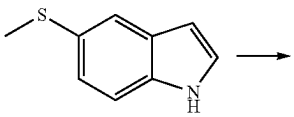
Synthesis of N,N-bis(methyl-d_3)-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (4)

[0449] A solution of 5-(methylthio)-1H-indole (2.0 g, 12.25 mmol) in dry THF (tetrahydrofuran) (50 mL) was treated with oxalyl chloride (1.03 mL, 12.25 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to 0° C., treated with bis(methyl-d_3)amine hydrochloride (2.68 g, 30.63 mmol, free based with Et_3N in THF) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was quenched with water (100 mL) and product was extracted into ethyl acetate (2×100 mL). Combined ethyl acetate layer was washed with water (50 mL), brine (50 mL), and dried (Na_2SO_4). Solvent was evaporated and crude was purified by column chromatography (2 M NH_3 in MeOH:CH_2Cl_2, 5:95) on silica gel followed by recrystallization from 30% CH_2Cl_2 in hexanes to obtain the title compound 4 (1.37 g, 41.8%) as a yellow solid. ^{1}H NMR (DMSO-d_6): δ 12.31 (s, 1H), 8.10 (s, 1H), 8.02 (s, 1H), 7.49 (d, 1H, J=6.0 Hz), 7.23 (dd, 1H, J=6.0 Hz), 2.52 (s, 3H); ESI-MS (m/z, %): 290 (M+Na, 100), 269 (MH^+).

Synthesis of N,N-bis(methyl-d_3)-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (I-1)

[0450] A solution of N,N-bis(methyl-d_3)-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (1.37 g, 5.10 mmol) in dry THF (30 mL) was treated with $LiAlH_4$ (1.54 g, 40.84 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound I-1 (0.93 g, 75.6%) as an off-white solid. ^{1}H NMR (DMSO-de): 6 10.83 (s, 1H), 7.48 (s, 1H), 7.30 (d, 1H, J=6.0 Hz), 7.16 (s, 1H), 7.07 (d, 1H, J=6.0 Hz), 2.79 (t, 2H, J=6.0 Hz), 2.52-2.48 (m, 5H); ESI-MS (m/z, %): 241 (MH^+, 100).

Example 2: N-Isopropyl-N-(2-(5-(methylthio)-1H-indol-3-yl)ethyl)propan-2-amine (I-17)



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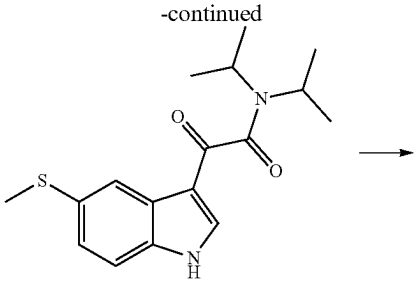

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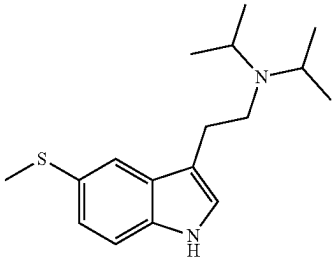


I-17

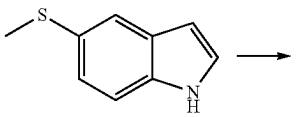
Synthesis of N,N-diisopropyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (6)

[0451] A solution of 5-(methylthio)-1H-indole (2.1 g, 12.86 mmol) in dry THF (50 mL) was treated with oxalyl chloride (1.08 mL, 12.86 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to 0° C., treated with diisopropylamine (4.54 mL, 32.16 mmol) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound 6 (3.0 g, 73.2%) as a yellow solid.

Synthesis of N-Isopropyl-N-(2-(5-(methylthio)-1H-indol-3-yl)ethyl)propan-2-amine (I-17)

[0452] A solution of N,N-diisopropyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (3.0 g, 9.61 mmol) in dry TH F (50 mL) was treated with $LiAlH_4$ (2.9 g, 76.87 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16 h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound I-17 (1.4 g, 51%) as a pale-yellow glue. ^{1}H NMR (DMSO-de): 5 10.81 (s, 1H), 7.43 (s, 1H), 7.29 (d, 1H, J=6.0 Hz), 7.16 (s, 1H), 7.06 (d, 1H, J=6.0 Hz), 3.07-3.04 (m, 2H), 2.71-2.69 (m, 2H), 2.65-2.60 (m, 2H), 2.46 (s, 3H), 1.10-0.92 (m, 12H); ESI-MS (m/z, %): 291 (MH^+, 100).

Example 3: N,N-Diethyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (I-12)



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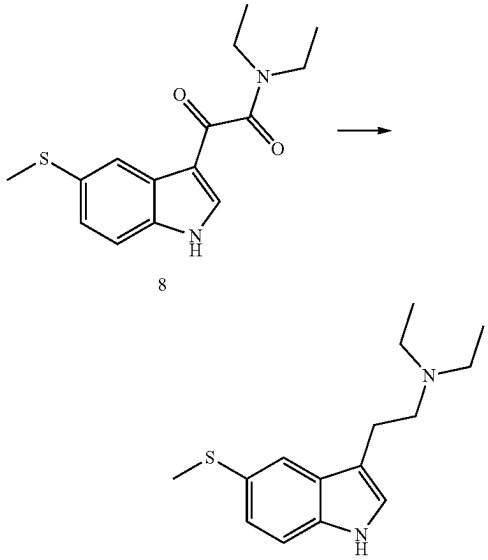

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I-12

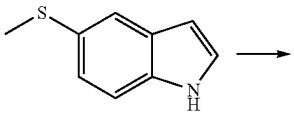
Synthesis of N,N-diethyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (8)

[0453] A solution of 5-(methylthio)-1H-indole (1.5 g, 9.19 mmol) in dry THF (30 mL) was treated with oxalyl chloride (0.78 mL, 9.19 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to 0° C., treated with diethyl amine (2.39 mL, 22.98 mmol) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound 8 (2.66 g, quantitative) as a beige solid. ^{1}H NM R (DMSO-de): δ 12.28 (s, 1H), 8.04-8.00 (m, 2H), 7.50 (d, 1H, J=6.0 Hz), 7.24 (dd, 1H, J=3.0, 6.0 Hz), 3.30-3.16 (m, 4H), 2.52 (s, 3H), 1.12-1.03 (m, 6H); ESI-MS (m/z, %): 291 (MH^+, 100).

Synthesis of N,N-diethyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (I-12)

[0454] A solution of N,N-diethyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (2.0 g, 6.88 mmol) in dry TH F (50 mL) was treated with $LiAlH_4$ (2.08 g, 55.10 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound I-12. (1.5 g, 83%) as a light brown oil. ^{1}H NMR (DMSO-de): δ 10.83 (s, 1H), 7.46 (d, 1H, J=3.0 Hz), 7.30 (d, 1H, J=6.0 Hz), 7.16 (d, 1H, J=3.0 Hz), 7.06 (dd, 1H, J=3.0, 6.0 Hz), 2.80-2.59 (m, 8H), 2.55 (s, 3H), 1.00 (t, 3H, J=6.0 Hz); ESI-MS (m/z, %): 263 (MH^+, 100).

Example 4: N-Ethyl-N-methyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (I-13)



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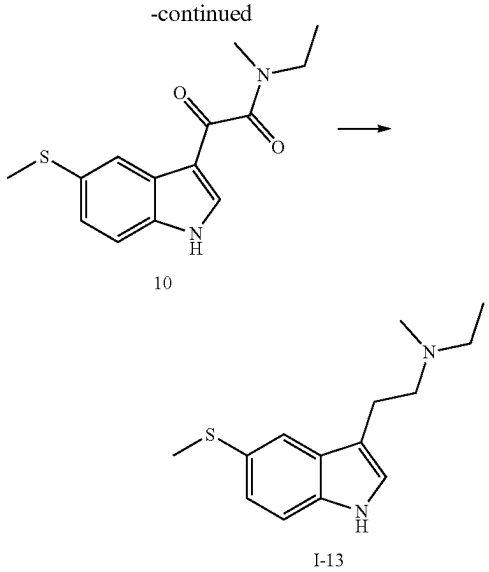


10

I-13

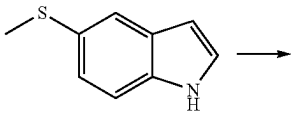
Synthesis of N-ethyl-N-methyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (10)

[0455] A solution of 5-(methylthio)-1H-indole (1.5 g, 9.19 mmol) in dry TH F (30 mL) was treated with oxalyl chloride (0.78 mL, 9.19 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to 0° C., treated with N-ethyl methylamine (1.97 mL, 22.98 mmol) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound 10 (2.0 g, 78.7%) as a beige solid. ^{1}H NMR (DMSO-de): δ 12.30 (s, 1H), 8.10-8.01 (m, 2H), 7.49 (dd, 1H, J=3.0, 6.0 Hz), 7.27-7.23 (m, 1H), 3.26 (q, 2H), 2.97 (s, 3H), 2.53 (s, 3H), 1.15-1.04 (m, 3H); ESI-MS (m/z, %): 299 (M+Na, 100), 277 (MH^+).

Synthesis of N-ethyl-N-methyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (I-13)

[0456] A solution of N-ethyl-N-methyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (2.0 g, 7.24 mmol) in dry TH F (50 mL) was treated with $LiAlH_4$ (2.19 g, 57.90 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16 h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound I-13 (1.26 g, 70%) as a beige solid. ^{1}H NMR (DMSO-de): δ 10.83 (s, 1H), 7.47 (d, 1H, J=3.0 Hz), 7.30 (d, 1H, J=3.0 Hz), 7.16 (s, 1H), 7.07 (dd, 1H, J=1.5, 6.0 Hz), 2.80 (t, 2H, J=6.0 Hz), 2.61-2.42 (m, 7H), 2.24 (s, 3H), 1.01 (t, 3H, J=6.0 Hz); ESI-MS (m/z, %): 249 (MH^+, 100).

Example 5: N-Methyl-N-(2-(5-(methylthio)-1H-indol-3-yl)ethyl)propan-2-amine (I-19)



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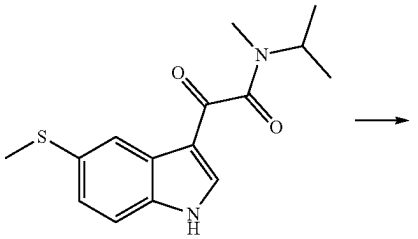

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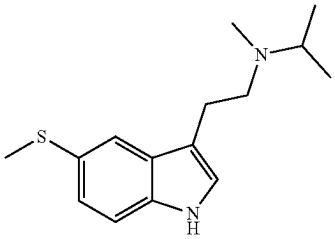


I-19

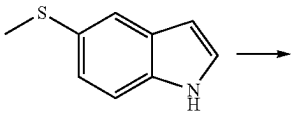
Synthesis of N-isopropyl-N-methyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (12)

[0457] A solution of 5-(methylthio)-1H-indole (1.5 g, 9.19 mmol) in dry THF (30 mL) was treated with oxalyl chloride (0.78 mL, 9.19 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to 0° C., treated with N-isopropyl methylamine (2.4 mL, 22.98 mmol) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound 12 (2.5 g, 93.6%) as a beige solid. ^{1}H NMR (DMSO-d_6): δ 12.30 (s, 1H), 8.11-8.00 (m, 2H), 7.49 (dd, 1H, J=3.0, 6.0 Hz), 7.26-7.23 (m, 1H), 3.30 (s, 3H), 2.76-2.70 (m, 1H), 2.52 (s, 3H), 1.16-1.09 (m, 6H); ESI-MS (m/z, %): 291 (MH$^+$, 100).

Synthesis of N-methyl-N-(2-(5-(methylthio)-1H-indol-3-yl)ethyl)propan-2-amine (I-19)

[0458] A solution of N-isopropyl-N-methyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (2.5 g, 8.61 mmol) in dry TH F (50 mL) was treated with $LiAlH_4$ (2.60 g, 68.87 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16 h). The reaction was worked-up and purified as described for compound 4 to obtain the title compound I-19 (1.81 g, 80%) as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 10.82 (s, 1H), 7.47 (s, 1H), 7.30 (d, 1H, J=6.0 Hz), 7.16 (d, 1H, J=3.0 Hz), 7.07 (dd, 1H, J=3.0, 4.5 Hz), 2.89-2.76 (m, 3H), 2.63-2.59 (m, 2H), 2.52 (s, 3H), 2.45 (s, 3H), 0.96 (d, 6H, J=6.0 Hz); ESI-MS (m/z, %): 263 (MH$^+$, 100).

Example 5A: N,N-Dimethyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine-1,1,2,2-d_4 (I-4)



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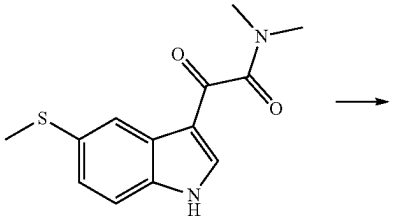
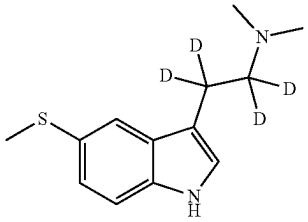


12A



I-4

Synthesis of N,N-dimethyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (12A)

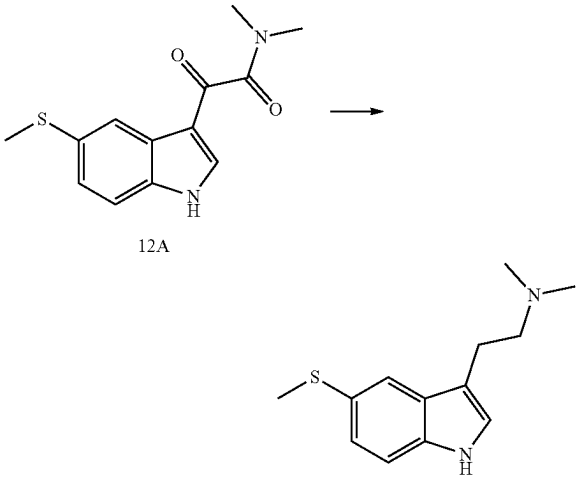
[0459] A solution of 5-(methylthio)-1H-indole (2.0 g, 12.25 mmol) in dry THF (30 mL) was treated with oxalyl chloride (1.0 mL, 12.25 mmol) at ° C. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was cooled to 0° C., treated with dimethylamine (15.3 mL, 30.63 mmol) over a period of 5 min. The reaction was brought to room temperature and stirred for over night (16 h). The reaction was quenched with water (100 mL) and product was extracted into ethyl acetate (2×75 mL). Combined ethyl acetate layer was washed with brine (25 mL) and dried (Na_2SO_4). Solvent was evaporated to obtain crude title compound 12A (2.4 g, 75.0%) as pale-yellow solid.

Synthesis of N,N-dimethyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine-1,1,2,2-d_4 (I-4)

[0460] A solution of N,N-dimethyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (1.0 g, 3.81 mmol) in dry TH F (25 mL) was treated with lithium aluminum deuteride (1.28 g, 30.49 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature, then refluxed for additional 16 hours. The reaction was brought to room temperature, then cooled to O ° C. and quenched with the sequential addition of water (1.0 mL), 4N NaOH solution (1.0 mL) and water (1.0 mL). The reaction was brought to room temperature and stirred for additional 30 min.

[0461] The reaction was filtered, and washed with THF (2×50 mL). Combined THF layer was evaporated and crude was purified by column chromatography (2 M NH_3 in MeOH: CH_2Cl_2, 5:95) on silica gel to obtain the title compound I-4 (0.67 g, 77.7%) as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 10.84 (s, 1H), 7.48 (s, 1H), 7.30 (d, 1H, J=6.0 Hz), 7.15 (d, 1H, J=3.0 Hz), 7.07 (dd, 1H, J=1.5, 6.0 Hz), 2.51 (s, 3H), 2.22 (s, 6H); ESI-MS (m/z, %): 239 (MH$^+$, 100).

Example 5B: N,N-Dimethyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (11-97)



12A

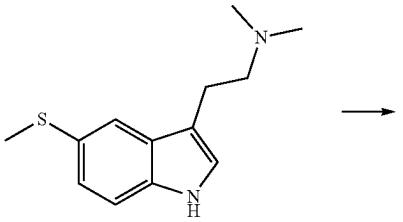
II-97

Synthesis of N,N-dimethyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (11-97)

[0462] A solution of N,N-dimethyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide (1.4 g, 5.33 mmol) in dry TH F (30 mL) was treated with lithium aluminum deuteride (1.61 g, 42.63 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature, then refluxed for additional 16 hours. The reaction was brought to room temperature, then refluxed for additional 16 hours. The reaction was brought to room temperature, then cooled to 0° C. and quenched with the sequential addition of water (1.0 mL), 4N NaOH solution (1.0 mL) and water (1.0 mL). The reaction was brought to room temperature and stirred for additional 30 min.

[0463] The reaction was filtered, and washed with THF (2×50 mL). Combined THF layer was evaporated and crude was purified by column chromatography (2 M NH_3 in MeOH: CH_2Cl_2, 5:95) on silica gel to obtain the title compound 11-97 (1.2 g, 96%) as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 10.84 (s, 1H), 7.48 (s, 1H), 7.30 (d, 1H, J=6.0 Hz), 7.16 (d, 1H, J=3.0 Hz), 7.07 (dd, 1H, J=1.5, 6.0 Hz), 2.80 (t, 2H, J=6.0 Hz), 2.52-2.47 (m, 5H, merged with DMSO peak), 2.22 (s, 6H); ESI-MS (m/z, %): 235 (MH^+, 100).

Example 5C: N,N-Dimethyl-2-(5-(methylsulfinyl)-1H-indol-3-yl)ethan-1-amine (11-95)



II-97

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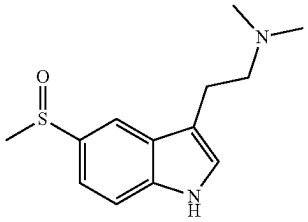
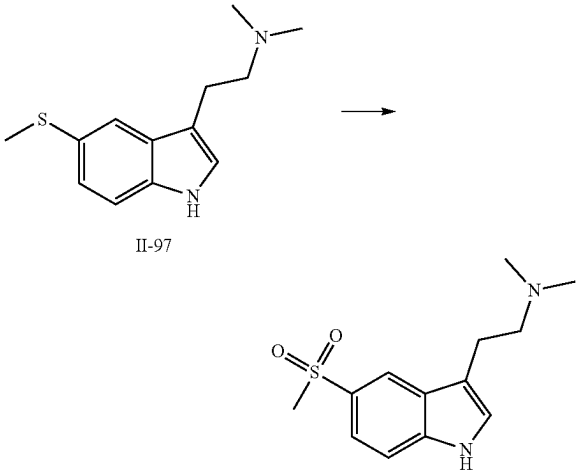


II-95

Synthesis of N,N-dimethyl-2-(5-(methylsulfinyl)-1H-indol-3-yl)ethan-1-amine (11-95)

[0464] A solution of N,N-dimethyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (0.5 g, 2.13 mmol) in acetic acid (15 mL) was treated with hydrogen peroxide (0.22 mL, 2.13 mmol, 30% in water) at 0-5° C. over a period of 5 min. The reaction was brought to room temperature and stirred for additional 1 h. The reaction was basified with 4 N NaOH solution and product was extracted into CH_2Cl_2 (3×50 mL). Combined CH_2Cl_2 layer was dried (Na_2SO_4) and crude was purified by column chromatography (2 M NH_3 in MeOH: CH_2Cl_2, 5:95) on silica gel to obtain the title compound 11-95 (0.45 g, 84.9%) as a colorless glue. ^{1}H NMR (DMSO-d_6): δ 11.18 (s, 1H), 7.87 (s, 1H), 7.52 (d, 1H, J=6.0 Hz), 7.36 (d, 1H, J=6.0 Hz), 7.31 (d, 1H, J=3.0 Hz), 2.86 (t, 2H, J=6.0 Hz), 2.72 (s, 3H), 2.56 (t, 2H, J=6.0 Hz), 2.23 (s, 6H); ESI-M S (m/z, %): 251 (MH^+, 100).

Example 5D: N,N-dimethyl-2-(5-(methylsulfonyl)-1H-indol-3-yl)ethan-1-amine (11-96)



II-97

II-96

[0465] Synthesis of N,N-dimethyl-2-(5-(methylsulfonyl)-1H-indol-3-yl)ethan-1-amine (11-96): A solution of N,N-dimethyl-2-(5-(methylthio)-1H-indol-3-yl)ethan-1-amine (0.5 g, 2.13 mmol) in acetic acid (15 mL) was treated with mCPBA (1.03 g, 4.69 mmol, 77%) at 0-5° C. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was basified with 4 N NaOH solution and product was extracted into CH_2Cl_2 (3×50 mL). Combined

CH_2Cl_2 layer was dried (Na_2SO_4) and crude was purified by column chromatography (2 M NH_3 in MeOH:CH_2Cl_2, 5:95) on silica gel to obtain the title compound 11-96 (0.35 g, 61.6%) as a pale-yellow foam. ^{1}H NMR (DMSO-de): δ 11.40 (s, 1H), 8.11 (s, 1H), 7.63-7.53 (m, 2H), 7.40 (s, 1H), 3.17 (s, 3H), 2.88 (t, 2H, J=6.0 Hz), 2.54 (t, 2H, J=6.0 Hz), 2.23 (s, 6H); ESI-MS (m/z, %): 267 (MH^+, 100).

B. Biological Testing

Example 6: Human 5-HT_{2A}: Functional FLIPR Assay

Objective:

[0466] The potential excitatory effects of compounds targeting on human 5-hydroxytryptamine receptor 2A (5-HT_{2A}) under agonist mode was assessed.

TABLE 7-continued

1.2 Materials

Regents	Vendor	Cat#
Hygromycin B	Invivogen	Ant-hg-5
Tetracycline hydrochloride	Abcam	ab141223
TrypLE ™ Express	Gibco	12604-013
DPBS	Gibco	14190250
DMSO	Millipore	1029312500
Probenecid	Sigma	P8761
FLIPR Calcium 6 Assay Kit	Molecular Device	R8191
HEPES	Invitrogen	15630
Hank's Buffered Saline Solution	Invitrogen	14025
Serotonin HCl	Selleck	S4244

TABLE 8

1.3 Instrumentation and consumables

Item	Supplier	Cat#
Fluorometric Imaging Plate Reader (FLIPR)	Molecular Device	Tetra
Countess Automated Cell Counter	Invitrogen	Countess
Cell Counting Chamber Slides	Invitrogen	C10312
STERI-CYCLE CO2 Incubator	Thermo	371
1300 Series Class II Biological Safety Cabinet	Thermo	1389
Table-type Large Capacity Low Speed Centrifuge	Cence	L550
Centrifuge	Eppendorf	5702
Echo	Labcyte	550
Echo	Labcyte	655
Electro-thermal incubator	Shanghai Yiheng	DHP-9031
plate shaker	IKA	MS3 digital
Water Purification System	ULUPURE	UPH-III-20T
Versatile and Universal pH and Conductivity Meters	Mettler Toledo	S220
384-Well plate	Corning	3764
384-Well LDV Clear microplate	LABCYTE	LP-0200
384-Well Polypropylene microplate	LABCYTE	PP-0200
384-well compound plate	Corning	3657
T25 cell culture flask	Corning	430639
50 mL Polypropylene Centrifuge Tube	JET	CFT011500
15 mL Polypropylene Centrifuge Tube	JET	CFT011150

1 Materials and Instrumentation

TABLE 6

1.1 Cell line

Cell line Name	Target	Host cell
HTR_{2A}&Gα15-HEK293	5-HT_{2A}	Flp-In-293

TABLE 7

1.2 Materials

Regents	Vendor	Cat#
DMEM	Gibco	10569-010
Dialyzed FBS	BIOSUN	BS-0005-500
Penicillin-Streptomycin	Invitrogen	15140

2 Experimental Methods

2.1 Cell Culture

[0467] HTR_{2A}&Gα15-HEK293 cells were cultured in DMEM medium containing 10% dialyzed FBS and 1×penicillin-streptomycin, 100 μg/mL Hygromycin B and 300 μg/mL G418. The cells were passaged about three times a week, maintained between ~30% to ~90% confluence.

2.2 Cell plating

[0468] 1. The cell culture medium (DMEM medium containing 10% dialyzed FBS and 1×penicillin-streptomycin, 100 μg/mL Hygromycin B and 300 μg/mL G418), TrypLE™ Express and DPBS to R.T. was warmed in advance.

[0469] 2. For induction, 1 μg/ml tetracycline (final concentration) was added to cell culture medium and incubated for 48 hours prior to seeding cells into plate at 37° C., 5% (v/v) C_{O2}. The cell culture medium was removed from flask. Cells were washed with DPBS.

[0470] 3. 2 mL TrypLE™ Express was added to the flask, mixed well by gentle shaking and cells were incubated at 37° C. for a few minutes.

[0471] 4. The cells were checked for morphological change under microscope, the digestion was stopped by adding 4 mL cell culture medium to the flask when most of cells turned to round.

[0472] 5. The cell suspension was transferred into a 15 mL centrifuge tube, and then centrifuged at 1,200 rpm for 5 minutes.

[0473] 6. The supernatant was removed. The cell pellet was resuspended with 2 mL cell culture medium.

[0474] 7. The cell density was counted using cell counter. Only cells with >85% viability were used for the assay.

[0475] 8. Cells were diluted to 6.67×10^5/mL with cell culture medium.

[0476] 9. 30 μL/well cell suspensions added into a 384-well cell plate (The cell density was 20,000 cells/well).

[0477] 10. The cell plate was incubated overnight at 37° C., 5% (v/v) CO_2.

2.3 Cell Handling

[0478] On the day of experiments, culture medium was removed from the cell plate.

[0479] 10 μL of assay buffer (20 mM HEPES, in 1x HBSS, pH 7.4) was added to each well of the cell plate.

[0480] 2×dye solution was prepared following the manual of the F LIP R® Calcium 6 Assay Kit:

[0481] i. The dye was diluted with assay buffer.

[0482] ii. Probenecid was added to the final concentration of 5 mM.

[0483] iii. Vortexed vigorously for I-2 minutes.

[0484] 4. 10 μL of 2x dye solution was added to each well of the cell plate.

[0485] 5. The cell plate was placed on plate shaker, followed by shaking at 600 rpm for 2 minutes.

[0486] 6. The plate was incubated at 37° C. for 2 hours followed by an additional 15-minute incubation at 25° C.

2.4 Prepare 3×Compound.

[0487] 1. Serotonin HCl was prepared to the concentration of 10 mM with DMSO.

[0488] 2. The test compounds were prepared to the concentration of 10 mM with DMSO.

[0489] 3. The compounds were added to a 384-well compound source plate.

[0490] 4. 3-folds serial dilutions were performed with DMSO.

[0491] 5. 90 nL/well of serial diluted compounds was transferred from source plate to a 384-well compound plate by using an Echo.

[0492] 6. 30 μL/well of assay buffer (20 mM HEPES in 1x HBSS, pH 7.4) was added to the compound plate.

[0493] 7. The plate was mixed on-plate shaker for 2 minutes.

2.5 FLIP R Assay

[0494] 1. After the cells were incubated with dye solution, the cell plate, compound plate containing 3×compounds and F LIP R tips were placed into F LIP R.

[0495] 2. 10 μL of 3×compounds transferred from the compound plate to the cell plate by FLIP R.

[0496] 3. The plate was read for 160 sec with 1 sec interval and the data of agonist mode was obtained.

3 Data Analysis

[0497] 1. The normalized fluorescence reading (RFU) was calculated as shown below, wherein F max and F min stand for maximum and minimum of calcium signal during defined time window:

$$RFU = F_{max} - F_{min}$$

[0498] 2. EC_{50} by fitting R F U against log of compound concentrations with Hill equation was calculated using XLfit.

Results and Discussion

[0499] The results of potential competition binding properties of the exemplary compounds of the disclosure targeting the human 5-hydroxytryptamine receptor 2A (5-HT_{2A}) are summarized in Table 9. The results of exemplary compounds of the disclosure are presented as EC_{50} is provided in Table 9.

TABLE 9

Effect of exemplary compounds of Formula (I) using FLIPR functional assay on human 5-HT_{2A} receptor

Compound ID	h5-HT_{2A}, EC_{50} [nM]	RFU@10 μM [(1)]
5-MeO-DMT	63	5,667
DMT	163	3,493
I-1	45	7,177
I-17	37	8,546
I-12	77	1,041
I-13	18	726
I-19	33	819

[(1)] Curve fitting with activation (%) @ 10 mM with RFU

II. Results and Discussion

[0500] Exemplary compounds of Formula (I) were evaluated using FLIPR functional assay on human 5-HT_{2A} receptor. EC_{50} (nM) concentrations are illustrated in Table 9. This assay confirms that compounds of the disclosure are effective agonists of the target human 5-HT_{2A} receptors.

Example 6A: h-5HT_{2A}-β-Arrestin Assay

Protocol:

[0501] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT_{2A} receptor in stably transfected U2OS cells was determined in a G protein-coupled receptors (GPCR) cell based p-arrestin reporter assay. Cells were seeded in a total volume of 20 μL into white walled, 384-well microplates and incubated at 37° C. overnight before analysis. For agonist determination, cells were incubated with sample to induce response. Intermediate dilution of sample stocks was performed to generate 5×sample in assay buffer. 5 μL of 5×sample was added to cells and incubated at 37° C. for 120 minutes. Final assay vehicle concentration was 1%. The results are expressed as

a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 10.

TABLE 10

Effect of exemplary compounds of Formula (I) using a β-arrestin reporter assay on human 5-HT_{2A} receptor:

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	0.1136	38.86
5MeO-DMT	0.02945	72.41
I-1	0.058367	74
I-13	0.059535	75.27

Example 7: Human 5-HT_{2A}: Radioligand Binding Assay

Objective

[0502] The objective of this study was to evaluate the binding properties of exemplary compounds of Formula (I) on 5-hydroxytryptamine receptor 2A (5-HT_{2A}).

1 Materials and Instrumentation

TABLE 11

1.1 Regents

Items	Vendor	Cat#
Ketanserin Hydrochloride, [Ethylene-3H]-	PerkinElmer	NET791250UC
Ketanserin	MedChemExpress	HY-10562
Bovine Serum Albumin (BSA)	Sigma	A1933
Calcium chloride ($CaCl_2$)	Sigma	C5670
Tris(hydroxymethyl)aminomethane (Tris)	Alfa Aesar	A18494
Polyethylenimine, branched (PEI)	Sigma	408727

TABLE 12

1.2 Instrumentation and Consumables

Item	Supplier	Cat#
Microbeta^2 Microplate Counter	PerkinElmer	2450-0060
UniFilter-96 GF/B	PerkinElmer	6005177
TopSeal	Biotss	SF-800
MicroBeta Filtermate-96	PerkinElmer	D961962
Seven Compact pH meter	Mettler Toledo	S220
Ultrapure Water Meter	Sichuan Ulupure	UPH-III-20T
Benchtop Centrifuge	Hunan Xiangyi	L550
Microplate Shaker	Allsheng	MX100-4A
384-Well Polypropylene Microplate	Labcyte	PP-0200
96 Round Well Plate	Corning	3799
96 Round Deep Well Plate	Axygen	P-DW-11-C
Echo	LABCYTE	550

2 Experimental Methods

[0503] 1. The assay buffer was prepared following Table 13 below.

TABLE 13

Reagent	Concentration
Tris	50 mM
$CaCl_2$	4 mM
BSA	0.1% (w/v)

[0504] Adjust pH to 7.4 followed by 0.2 μM sterile filtration

[0505] 2. 8 doses of reference and test compounds starting from 10 mM stock solution as required was prepared by 5-fold serial dilutions with 100% (v/v) DMSO.

[0506] 3. UniFilter-96 GF/B plate was pretreated:

- **[0507]** i. 50 μl/well of 0.5% (v/v) PEI was added to UniFilter-96 GF/C plates. The plates were sealed and incubated at 4° C. for 3 hrs.
- **[0508]** ii. After incubation, the plates were washed 3 times with ice-cold wash buffer (50 mM Tris, pH7.4).

[0509] 4. The assay plate was prepared:

- **[0510]** i. Cell membrane was diluted with assay buffer and 330 μl/well was added to 96 round deep well plates to reach a concentration of 20 μg/well.
- **[0511]** ii. 8 concentrations of reference or test compounds were prepared and 110 μl/well was added to 96 round deep well plates.
- **[0512]** iii. [3H]-ketanserin was diluted with assay buffer to 5 nM (5×final concentration) and 110 μl/well was added to 96 round deep well plates.

[0513] 5. The plate was centrifuged at 1000 rpm for 30 secs and then agitated at 600 rpm, R.T. for 5 min.

[0514] 6. The plates were sealed, and the plate incubated at 27° C. for 90 min.

[0515] 7. The incubation was stopped by vacuum filtration onto GF/B filter plates followed by 4 times washing with ice-cold wash buffer (50 mM Tris, pH7.4).

[0516] 8. The plates were dried at 37° C. for 45 min.

[0517] 9. The filter plates were sealed and 40 μl/well of scintillation cocktail was added.

[0518] 10. The plate was read by using a Microbeta^2 microplate counter.

3 Data Analysis

[0519] 1. For reference and test compounds, the results were expressed as % Inhibition, using the normalization equation: N=100−100×(U-C2)/(C1-C2), where U is the unknown value, C_1 is the average of high controls, and C_2 is the average of low controls.

[0520] 2. The IC_{50} was determined by fitting percentage of inhibition as a function of compound concentrations with Hill equation using XLfit.

Results and Discussion

[0521] The results of potential competition binding properties of the exemplary compounds of the disclosure targeting the human 5-hydroxytryptamine receptor 2A (5-HT_{2A}) are summarized in Table 14. The results of exemplary compounds of the disclosure are presented as IC_{50} provided in Table 14.

TABLE 14

Effect of exemplary compounds of Formula (I) using Radioligand binding assay on human 5-HT_{2A} receptor	
Compound ID	h5-HT_{2A}, IC_{50} [nM]
5-MeO-DMT	603
DMT	954
I-1	392
I-17	1,983
I-12	780
I-13	253
I-19	936

II. Results and Discussion

[0522] Exemplary compounds of Formula (I) were evaluated using radioligand binding assay on human 5-HT_{2A} receptor. IC_{50} (nM) concentrations are illustrated in Table 14. This assay confirms that precursor parent compounds or their respective metabolites of the disclosure are effective ligands of the target human 5-HT_{2A} receptors.

Example 8: Human 5-HT_{1A}: Functional FLIPR Assay

1 Objective

[0523] The potential excitatory effects of compounds targeting on 5-hydroxytryptamine receptor 1A (5-HT_{1A}) under agonist mode was assessed.

2 Materials and Instrumentation

TABLE 15

2.1 Cell line		
Cell line Name	Target	Host cell
HTR1A&Gα15-CHO	5-HT_{1A}	Flp-in CHO

TABLE 16

2.2 Materials		
Regents	Vendor	Cat#
DMEM/F12	Gibco	11330057
Dialyzed FBS	BIOSUN	BS-0005-500
Penicillin-Streptomycin	Invitrogen	15140
Hygromycin B	Invivogen	Ant-hg-5
TrypLE ™Express	Gibco	12604-013
DPBS	Gibco	14190250
DMSO	Millipore	1029312500
Probenecid	Sigma	P8761
FLIPR Calcium 6 Assay Kit	Molecular Device	R8191
HEPES	Invitrogen	15630
Hank's Buffered Saline Solution	Invitrogen	14025
Serotonin HCl	Selleck	S4244

TABLE 17

2.3 Instrumentation and consumables		
Item	Supplier	Cat#
Fluorometric Imaging Plate Reader (FLIPR)	Molecular Device	Tetra

TABLE 17-continued

2.3 Instrumentation and consumables		
Item	Supplier	Cat#
Countess Automated Cell Counter	Invitrogen	Countess
Cell Counting Chamber Slides	Invitrogen	C10312
STERI-CYCLE CO2 Incubator	Thermo	371
1300 Series Class II Biological Safety Cabinet	Thermo	1389
Table-type Large Capacity Low Speed Centrifuge	Cence	L550
Centrifuge	Eppendorf	5702
Echo	Labcyte	550
Echo	Labcyte	655
Electro-thermal incubator	Shanghai Yiheng	DHP-9031
plate shaker	IKA	MS 3 digital
Water Purification System	ULUPURE	UPH-III-20T
Versatile and Universal pH and Conductivity Meters	Mettler Toledo	S220
384-Well plate	Corning	3764
384-Well LDV Clear microplate	LABCYTE	LP-0200
384-Well Polypropylene microplate	LABCYTE	PP-0200
384-well compound plate	Corning	3657
T25 cell culture flask	Corning	430639
50 mL Polypropylene Centrifuge Tube	JET	CFT011500
15 mL Polypropylene Centrifuge Tube	JET	CFT011150

3 Experimental Methods

3.1 Cell Culture

[0524] HTR_{1A}&Gα15-CH_0 cells were cultured in DMEM/F12 medium containing 10% dialyzed FBS, 1×penicillin-streptomycin and 600 μg/mL Hygromycin B. The cells were passaged about three times a week, maintained between ~30% to ~90% confluence.

3.2 Cell Plating

[0525] 1. The cell culture medium (DMEM/F12 medium containing 10% dialyzed FBS, 1×penicillin-streptomycin and 600 μg/mL Hygromycin B), TrypLE™ Express and DPBS was warmed to R.T. in advance.

[0526] 2. The cell culture medium was removed from flask. Washed cells with DPBS.

[0527] 3. 1 mL TrypLE™ Express was added to the flask, mixed well by gentle shaking and cells were incubated at 37° C. for a few minutes.

[0528] 4. The cells were checked for morphological change under microscope, the digestion was stopped by adding 2 mL cell culture medium to the flask when most of cells turned to round.

[0529] 5. The cell suspension was transferred into a 15 mL centrifuge tube, and then centrifuged at 1,200 rpm for 5 minutes.

[0530] 6. The supernatant was removed. The cell pellets were resuspended with 2 mL cell culture medium.

[0531] 7. The cell density was counted using a cell counter. Only cells with >85% viability were used for the assay.

[0532] 8. Cells were diluted to 4×10^5/mL with cell culture medium.

[0533] 9. 30 μL/well cell suspensions were added into a 384-well cell plate (the cell density was 12,000 cells/well).

[0534] 10. The cell plate was incubated overnight at 37° C., 5% (v/v) CO_2.

3.3 Cell Handling

[0535] 1. On the day of experiments, culture medium was removed from the cell plate.

[0536] 2. 10 μL of assay buffer (20 mM HEPES, in 1x HBSS, pH 7.4) was added to each well of the cell plate.

[0537] 3. 2×dye solution was prepared following the manufacturer's instruction of the FLIPR® Calcium 6 assay kit:

[0538] i. The dye was diluted with assay buffer.

[0539] ii. probenecid was added to the final concentration of 5 mM.

[0540] iii. Vortexed vigorously for I-2 minutes, adjust pH to 7.4.

[0541] 4. 10 μL of 2×dye solution was added to each well of the cell plate.

[0542] 5. The cell plate was placed on plate shaker, followed by shaking at 600 rpm for 2 minutes.

[0543] 6. The plate was incubated at 37° C. for 2 hours followed by an additional 15-minute incubation at 25° C.

3.4 Prepare 3×Compounds.

[0544] 1. Serotonin was prepared to the concentration of 10 mM with DMSO, 3-folds serial dilutions were performed with DMSO.

[0545] 2. Prepared the test compound to the concentration of 10 mM with DMSO, preform 3-folds serial dilutions with DMSO.

[0546] 3. The compounds were added to a 384-well compound source plate.

[0547] 4. 90 nL/well of serial diluted compounds were transferred from source plate to a 384-well compound plate by using an Echo.

[0548] 5. 30 μL/well of assay buffer was added to the compound plate.

[0549] 6. The plate was mixed on-plate shaker for 2 minutes.

3.5 FLIPR Assay

[0550] 1. After the cells incubated with dye solution, the cell plate, compound plate containing 3×compounds and F LIP R tips were placed into F LIP R.

[0551] 2. 10 μL of 3×compounds were transferred from the compound plate to the cell plate by F LIP R.

[0552] 3. The plate was read for 160 sec with 1 sec interval to obtain the data of agonist mode.

4 Data Analysis

[0553] 1. The normalized fluorescence reading (RFU) was calculated as shown below, wherein F_{max} and F_{min} stand for maximum and minimum of calcium signal during defined time window:

$$RFU=F_{max}-F_{min}$$

[0554] 2. EC_{50} was calculated by fitting RFU against log of compound concentrations with Hill equation using XLfit.

Results and Discussion

[0555] The results of potential competition binding properties of the exemplary compounds of the disclosure targeting the human 5-hydroxytryptamine receptor 1A (5-HT_{1A}) are summarized in Table 18. The results of exemplary compounds of the disclosure are presented as EC_{50} provided in Table 18.

TABLE 18

Effect of exemplary compounds of Formula (I) using FLIPR functional assay on human 5-HT_{1A} receptor

Compound ID	h5-HT_{1A}, EC_{50} [nM]	RFU@10 μM [(1)]
5-MeO-DMT	1,066	3,891
DMT	ND[(2)]	204
I-1	928	2,858
I-17	3,382	2,289
I-12	675	3,735
I-13	693	4,279
I-19	3,870	2,161

[(1)] Curve fitting with activation (%) @ 10 mM with RFU
[(2)] Not detected

[0556] Exemplary compounds of Formula (I) were evaluated using functional FLIP R assay on human 5-HT_{1A} receptor. EC_{50} (nM) concentrations are illustrated in Table 18. This assay confirms that compounds of the disclosure are functionally active at the target human 5-HT_{1A} receptors.

Example 9: Human 5-HT_{1A}: Radioligand Binding Assay

1 Objective

[0557] The objective of this study was to evaluate the binding properties of test compounds on 5-hydroxytryptamine receptor 1A (5-HT_{1A}).

2 Materials and Instrumentation

TABLE 19

2.1 Regents

Items	Vendor	Cat#
[3H]-8-Hydroxy-DPAT	PE	NET929250UC
Serotonin HCl	Selleck	S4244
Bovine Serum Albumin (BSA)	Sigma	A1933
Calcium chloride ($CaCl_2$)	Sigma	C5670
$MgCl_2$	Sigma	M1028
Tris(hydroxymethyl)aminomethane (Tris)	Alfa Aesar	A18494
Polyethylenimine, branched (PEI)	Sigma	408727

TABLE 20

2.2 Instrumentation and Consumables

Item	Supplier	Cat#
Microbeta[2] Microplate Counter	PerkinElmer	2450-0060
UniFilter-96 GF/B	PerkinElmer	6005177
TopSeal	Biotss	SF-800
MicroBeta Filtermate-96	PerkinElmer	D961962
Seven Compact pH meter	Mettler Toledo	S220
Ultrapure Water Meter	Sichuan Ulupure	UPH-III-20T
Benchtop Centrifuge	Hunan Xiangyi	L550

TABLE 20-continued

2.2 Instrumentation and Consumables		
Item	Supplier	Cat#
Microplate Shaker	Allsheng	MX100-4A
384-Well Polypropylene Microplate	Labcyte	PP-0200
96 Round Well Plate	Corning	3799
96 Round Deep Well Plate	Axygen	P-DW-11-C
Echo	LABCYTE	550

3 Experimental Methods

[0558] 1. The assay buffer was prepared following Table 21 below.

TABLE 21

Reagent	Concentration
Tris	25 mM
$MgCl_2$	10 mM
$CaCl_2$	1 mM
BSA	0.5% (w/v)

Adjust pH to 7.4 followed by 0.2 μM sterile filtration

[0559] 2. 8 doses of reference and test compounds were prepared starting from 10 mM stock solution as required by 5-fold serial dilutions with 100% (v/v) DMSO.

[0560] 3. UniFilter-96 GF/B plate was pretreated:

[0561] i. 50 μl/well of 0.5% (v/v) PEI was added to UniFilter-96 G F/B plates. The plates were sealed and incubated at 4° C. for 3 hrs.

[0562] ii. After incubation, the plates were washed 3 times with ice-cold wash buffer (50 mM Tris, pH7.4).

[0563] 4. Assay plate was prepared:

[0564] i. Cell membrane was diluted with assay buffer and 100 μl/well was added to 96 round well plates to reach a concentration of 20 μg/well.

[0565] ii. 8 concentrations of reference or test compounds were prepared and 50 μl/well was added to 96 round deep well plates.

[0566] iii. [3H]-8-Hydroxy-DPAT was diluted with assay buffer to 2 nM (4×final concentration) and 50 μl/well was added to 96 round well plates.

[0567] 5. The plate was centrifuged at 1000 rpm for 30 secs and then agitated at 600 rpm, R.T. for 5 min.

[0568] 6. The plates were sealed, and the plate was incubated at 27° C. for 90 min.

[0569] 7. The incubation was stopped by vacuum filtration onto GF/B filter plates followed by 4 times washing with ice-cold wash buffer (50 mM Tris, pH7.4).

[0570] 8. The plates were dried at 37° C. for 45 min.

[0571] 9. The filter plates were sealed and 40 μl/well of scintillation cocktail was added.

[0572] 10. The plate was read by using a Microbeta^2 microplate counter.

4 Data Analysis

[0573] 1. For reference and test compounds, the results were expressed as % Inhibition, using the normalization equation: $N=100-100x(U-C_2)/(C_1-C_2)$, where U is the unknown value, C_1 is the average of high controls, and C_2 is the average of low controls.

[0574] 2. The IC_{50} was determined by fitting percentage of inhibition as a binding of compound concentrations with Hill equation using XLfit.

Results and Discussion

[0575] The results of potential competition binding properties of the exemplary compounds of the disclosure targeting the human 5-hydroxytryptamine receptor (5-HT_{1A}) are summarized in Table 22. The results of exemplary compounds of the disclosure are presented as IC_{50} provided in Table 22.

TABLE 22

Effect of exemplary compounds of Formula (I) using Radioligand binding assay on human 5-HT_{1A} receptor	
Compound ID	h5-HT_{1A}, IC_{50} [nM]
5-MeO-DMT	6
DMT	689
I-1	3.9
I-17	46
I-12	2
I-13	2
I-19	17

Results and Discussion

[0576] Exemplary compounds of Formula (I) thereof were evaluated using radioligand binding assay on human 5-HT_{1A} receptor. C_{50} (nM) concentrations are illustrated in Table 22. This assay confirms that compounds of Formula (a) of the disclosure are effective ligands of the target human 5-HT_{1A} receptors.

Example 9A: Human 5-HT_2B: Radioligand Binding Assay

[0577] The objective of this study was to evaluate the binding properties of test compounds on 5-HT_{2B}.

TABLE 23

Materials		
Materials	Vendor	Cat#
[3H]-LSD	PerkinElmer	NET638250UC
Yohimbine	MedChemExpress	HY-N0127
Bovine Serum Albumin (BSA)	Sigma	A1933
Calcium chloride ($CaCl_2$)	Sigma	C5670
Tris(hydroxymethyl)aminomethane (Tris)	Alfa Aesar	A18494
Polyethylenimine, branched (PEI)	Sigma	408727

TABLE 24

Instrumentation and Consumables		
Item	Supplier	Cat#
Microbeta2 Microplate Counter	PerkinElmer	2450-0060
UniFilter-96 GF/B	PerkinElmer	6005177
TopSeal	Biotss	SF-800
MicroBeta Filtermate-96	PerkinElmer	D961962
Seven Compact pH meter	Mettler Toledo	S220
Ultrapure Water Meter	Sichuan Ulupure	UPH-III-20T
Benchtop Centrifuge	Hunan Xiangyi	L550

TABLE 24-continued

Instrumentation and Consumables		
Item	Supplier	Cat#
Microplate Shaker	Allsheng	MX100-4A
384-Well Polypropylene Microplate	Labcyte	PP-0200
96 Round Well Plate	Corning	3799
96 Round Deep Well Plate	Axygen	P-DW-11-C
Echo	LABCYTE	550

Experimental Methods

[0578] 1) The assay buffer was prepared following Table 25-below.

TABLE 25

Reagent	Concentration
Tris	50 mM
$CaCl_2$	4 mM
BSA	0.1% (w/v)

Adjust pH to 7.4 followed by 0.2 μM sterile filtration

[0579] 2) Eight doses of reference and test compounds starting from 10 mM stock solution as requested by 5-fold serial dilutions with 100% (v/v) DMSO.

[0580] 3) UniFilter-96 GF/B plate was pretreated:

[0581] a. 50 μl/well of 0.5% (v/v) PEI to UniFilter-96 G F/B plates. The plates were sealed and incubated at 4° C. for 3 hrs.

[0582] b. After incubation, the plates were washed 3 times with ice-cold wash buffer (50 mM Tris, pH7.4).

[0583] 4) Assay plate preparation:

[0584] a. Cell membrane was diluted with assay buffer and 330 μl/well added to 96 round deep well plates to reach a concentration of 1 unit/well.

[0585] b. Eight concentrations of reference or test compounds were prepared and 110 μl/well added to 96 round deep well plates.

[0586] c. [3H]-LSD was diluted with assay buffer to 5 nM (5×final concentration) and 110 μl/well was added to 96 round deep well plates.

[0587] 5) The plate was centrifuged at 1000 rpm for 30 secs and then agitate at 600 rpm, R.T. for 5 min.

[0588] 6) The plates were sealed and incubated at 37° C. for 90 min.

[0589] 7) The incubation was stopped by vacuum filtration onto GF/B filter plates followed by 4 times washing with ice-cold wash buffer (50 mM Tris, pH7.4).

[0590] 8) The plates were dried at 37° C. for 45 min.

[0591] 9) The filter plates were sealed and 40 μl/well of scintillation cocktail was added.

[0592] 10) The plate was read using a Microbeta2 microplate counter.

Data Analysis

[0593] For reference and test compounds, the results are expressed as % Inhibition, using the normalization equation: $N=100-100x(U-C_2)/(C_1-C_2)$, where U is the unknown value, Cl is the average of high controls, and C_2 is the average of low controls. The IC_{50} is determined by fitting percentage of inhibition as a function of compound concentrations with Hill equation using XLfit.

TABLE 26

Effect of exemplary compounds of Formula (I) using Radioligand binding assay on 5-HT_{2B} receptor		
Compound ID	5-HT_{2B}, IC_{50} [nM]	5-HT_{2B}, Ki [nM]
5-MeO-DMT	248.92	128.79
DMT	423.14	218.92
I-1	74.54	38.57
I-17	220.70	114.18
I-12	450.80	233.23
I-13	64.04	33.13
I-19	276.16	142.88

Example 9B: Human-5HT1A-cAMP Assay

Protocol:

[0594] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT1A receptor in stably transfected CHO-K1 cells was determined in a GPCR cell-based cAMP assay.

[0595] Cells were seeded in a total volume of 20 μL into white walled, 384-well microplates and incubated at 37° C. overnight before analysis. Prior to testing, cell plating media was exchanged with 10 μL of Assay buffer (HBSS+10 mM HE P E S). Briefly, intermediate dilution of sample stocks was performed to generate 4×sample in assay buffer. 5 μL of 4×sample+5 μL of 4×forskolin was added to cells and incubated at 37° C. for 30 minutes. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 27.

TABLE 27

Effect of exemplary compounds of Formula (I) using cAMP functional assay on human 5-HT1A receptor		
Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	0.97437	87.1
5MeO-DMT	0.012699	99.98
I-1	0.011111	96.18
I-13	0.0090569	100.52

Example 9C: h-5HT_{2B} FLIPR Assay

Protocol:

[0596] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT_2B receptor in stably transfected HEK293 cells was determined in a calcium mobilization-based assay.

[0597] Cells were seeded in a total volume of 20 μL into white walled, 384-well microplates and incubated at 37° C. overnight. Prior to testing, cell plating media was exchanged with 20 μL of Dye Loading buffer (HBSS+20 mM HEPES containing 1×Dye, 1×Additive A and 2.5 mM Probenecid). Plates were incubated at 37° C. for 45 mins followed by 15 mins at room temperature.

[0598] 10 μl of assay buffer (HBSS+20 mM HEPES) was added to cells. Intermediate dilution of sample stocks was performed to generate 4×sample in assay buffer. Assay plates, compound plates were loaded into F LIP R instrument. 10 μL of sample was added using F LIP R onboard

robotics after 5 seconds of starting calcium measurement. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 28.

TABLE 28

Effect of exemplary compounds of Formula (I) using FLIPR functional assay on human 5-HT_{2B} receptor

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	>10	13.4
5MeO-DMT	0.015452	28.88
I-1	>10	19.8
I-13	>10	21.04

Example 9D: h-5HT_{2B}—Positive Allosteric Modulator (PAM) Assay

Protocol:

[0599] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT_2B receptor in stably transfected HEK293 cells was determined in a GPC R cell-based assay.

[0600] For Positive Allosteric Modulator determination, cells were pre-incubated with sample followed by EC20 addition. Intermediate dilution of sample stocks was performed to generate 5×sample in assay buffer. 5 μL of 5×sample was added to cells and incubated at 37° C. for 10 minutes. 5 μL of agonist at 6×EC20 concentration was added and cells were incubated at 37° C. for 120 minutes. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 29.

TABLE 29

Effect of exemplary compounds of Formula (I) using PAM functional assay on human 5-HT_{2B} receptor

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	>10	0
5MeO-DMT	>10	0
I-1	>10	0
I-13	>10	0

Example 9E: h-5HT_{2C} FLIPR Assay

Protocol:

[0601] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT_{2C}receptor in stably transfected U2OS cells was determined in a calcium mobilization-based assay.

[0602] Cells were seeded in a total volume of 20 μL into white walled, 384-well microplates and incubated at 37° C. overnight. Prior to testing, cell plating media was exchanged with 20 μL of Dye Loading buffer (HBSS+20 mM HEPES containing 1×Dye, 1×Additive A and 2.5 mM Probenecid). Plates were incubated at 37° C. for 45 mins followed by 15 mins at room temperature.

[0603] 10 μl of assay buffer (HBSS+20 mM HEPES) was added to cells. Intermediate dilution of sample stocks was performed to generate 4×sample in assay buffer. Assay plates, compound plates were loaded into F LIP R instrument. 10 μL of sample was added using F LIP R onboard robotics after 5 seconds of starting calcium measurement. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 30.

TABLE 30

Effect of exemplary compounds of Formula (I) using FLIPR functional assay on human 5-HT_{2C} receptor

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	0.01112	94.56
5MeO-DMT	0.0027312	95.42
I-1	0.0023653	98.89
I-13	0.0028922	92.77

Example 10: Psychedelic-Like Effect of Exemplary Compounds of Formula

[0604] The effect of different doses of exemplary compounds of Formula (I) were evaluated on head-twitch response (HTR) as a behavior-based model of psychedelic activity.

Protocols

Head Twitch Response (HTR) Assay Protocol

[0605] Adult C57BL/6J mice (body weight range 20-30 g) were each placed into an open-top test cage made of transparent plastic for 20-30 min of habituation prior to testing. Habituation and testing were both conducted under low light conditions (~100 lux). Mice received a subcutaneous (SC) injection of either vehicle, positive control substance (e.g., 2,5-dimethoxy-4-iodoamphetamine (DOI)), or test compound at appropriate doses and volumes (10 mL/kg). Immediately post-treatment each mouse was placed back in its respective test cage. The cages were placed at approximately 50 cm from each other on a white, adjustable height table/flat surface so that the experimenter could easily monitor fine behaviors of both mice within the testing environment. An opaque divider was placed between the cages to prevent animals from observing each other. Immediately after placing the mice back into the test cages, the experimenter sat directly in front of the two containers, and recorded in real time the number of head twitch responses (HTR, defined as rapid side-to-side rotational shaking of the head) performed by each mouse for 20 min, subdivided in 5 min intervals with the use of a silent timer. To ensure scoring accuracy and consistency, one experienced experimenter performed HTR recording for all mice included in a study. While mice were subjected to HTR testing, another mouse pair underwent habituation in a separate set of test cages, so that at the end of the HTR scoring period new animals were ready to undergo substance administration and testing.

Between individual HTR tests, cages were cleaned with water, disinfected with a 70% ethanol aqueous solution, and dried using paper towels.

Results and Discussion

[0606] FIG. **1**, FIG. **2**, FIG. **3**, FIG. **4**, and FIG. **5** are graphs showing the effect of various doses (i.e., 3 mg/kg and 30 mg/kg) of exemplary compounds of Formula (I), specifically I-1, I-12, I-13, I-17, and I-19, respectively, on head-twitch response (HTR) in male C57BL6 mice. The mice were treated with compounds I-1, I-12, I-13, I-17, or I-19 by SC route, and the total number of head twitches were recorded over a 20 min period. Data are expressed as mean±SEM. The induction of head twitches elicited by 5-HT_{2A} receptor agonists is believed to represent a behavioral proxy of their psychedelic effects. Also, locomotor activity and other 5-HT receptor signs measured (FIGS. **1-5**).

Example 11: Pharmacokinetic Studies in Rat

Protocol

Study Details:

[0607] Animals: Male Sprague-Dawley rats (~225-350 g) from Charles River Labs were acclimatized for a minimum of 5 days prior to start of study procedures. Body weights were recorded on the day of dosing.

[0608] Food restriction: None.

[0609] Clinical observations: Animals were observed at the time of dosing and each sample collection. Any abnormalities were documented including presence/absence of wet dog shakes/back muscle contractions (WDS/BMC).

[0610] Dosing: Formulations were administered intravenously (i.v.) via the tail vein using a 25 G needle connected to a 1 cc syringe.

Formulation:

[0611] The Compounds of Formula (I) were freshly prepared at the appropriate concentrations in 5% Tween-80 in saline.

Sample Collection:

[0612] Blood collection time (h): 0.25, 1 and 4.

[0613] Volume/time-point: ~0.25 mL mL (saphenous vein).

Bioanalytical Method Development and Sample Analysis:

Analytes: Compounds of Formula (I).

[0614] Matrix: Rat plasma.

[0615] Instrumentation: AB Sciex QTRAP 4000 or 6500 MS/MS system equipped with an LC system with a binary pump, a solvent degasser, a thermostatted column compartment and a multiplate autosampler.

[0616] Bioanalytical method(s) development included:

[0617] 1. The selection of the ion transition for the test compounds and potential internal standards (i.e., identification of the parent and product ions).

[0618] 2. The optimization of mass spectrometric operating parameters.

[0619] 3. The establishment of the chromatographic condition for the analytes.

[0620] 4. The selection of an appropriate internal standard (IS).

[0621] 5. The development of sample clean-up method using protein precipitation.

Method(s) Qualification:

[0622] 1. The determination of the quantification dynamic range using non-zero calibration standards (STDs) in singlet. The STDs consisted of a blank matrix sample (without IS), a zero sample (with IS), and at least 6 non-zero STDs covering the expected range and including the lower level of quantitation (LLOQ).

[0623] 2. Triplicate injections of a system suitability sample (neat solution containing the analyte and IS) bracketing the batch.

Method(s) Acceptance Criteria:

[0624] 1. At least 75% of non-zero STDs must be included in the calibration curve with all back-calculated concentrations within ±20% deviation from nominal concentrations (±25% for the lower level of quantification, LLOQ).

[0625] 2. The correlation coefficient (r) of the calibration curve must be greater than or equal to 0.99 using quadratic regression analysis ($1/x^2$ weighting).

[0626] 3. The area ratio variation between the pre- and post-run injections of the system suitability samples is within ±25%.

Sample Analysis Batch:

[0627] 1. Triplicate injections of a system suitability sample bracketing the batch.

[0628] 2. The STDs in ascending order.

[0629] 3. The study samples and the dosing solutions diluted as 3 independent dilutions into blank matrix (plasma).

[0630] 4. For more than 40 study samples in a batch, two sets of STDs bracketing the samples were utilized.

[0631] Samples which were 25% greater than the highest calibration standard, were be diluted and re-assayed along with a corresponding dilution quality control standard. Dilution standards were acceptable if they are within 25% accuracy of the target concentration.

PK Analysis

[0632] Analysis software: Phoenix® WinNonlin® 8.3 (Pharsight, Certara, Mountainview, CA).

[0633] Analysis methods: non-compartmental analysis, linear up/log down trapezoidal rule.

[0634] PK parameters: $t_{1/2}$ and $AUC_{0\text{-}tlast}$ were be estimated.

Results

[0635] Table 31 shows the plasma concentration of exemplary compounds of Formula (I) following i.v. administration.

TABLE 31

Plasma concentrations of I-1 following 1.10 mg/kg i.v. administration (Group 2).

Example ID	Dose	Experimental time (h)/Rat#	Plasma concentration (ng/mL)			
I-1	1.10		R04	R05	R06	Mean ± SD
	mg/kg	0.25	16.6	15.7	16.9	16.4 ± 0.624
		1	0.835	0.354	0.298	0.496 ± 0.295
		4	BLQ	BLQ	BLQ	n/a
I-17	1.33		R07	R08	R09	Mean ± SD
	mg/kg	0.25	139	197	259	198 ± 60.0
		1	101	89.3	120	103 ± 15.5
		4	25.8	17.7	15.6	19.7 ± 5.39
I-12	1.2		R01	R02	R03	Mean ± SD
	mg/kg	0.25	53.6	72.4	30.1	52.0 ± 21.2
		1	27.6	36.4	29.7	31.2 ± 4.60
		4	3.88	2.55	6.48	4.30 ± 2.00
I-13	1.14		R04	R05	R06	Mean ± SD
	mg/kg	0.25	45.7	86.5	113	81.7 ± 33.9
		1	52.2	46.7	29.7	42.9 ± 11.7
		4	3.51	1.11	0.449	1.69 ± 1.61
I-19	1.2		R07	R08	R09	Mean ± SD
	mg/kg	0.25	13.4	70.3	84.4	56.0 ± 37.6
		1	30.4	34.4	41.4	35.4 ± 5.57
		4	6.76	4.95	4.34	5.35 ± 1.26

*Values in italics are below the lower limit of quantitation (BLQ, 0.5 ng/mL) but were included in calculations.
*BLQ denotes below the lower limit of quantitation (0.5 ng/mL).

[0636] Table 32 is a summary of the plasma apparent $t_{1/2}$ and $AUC_{0\text{-}tlast}$ for exemplary compound I-1 following 1.10 mg/kg i.v. administration (Group 2).

TABLE 32

Summary of plasma apparent $t_{1/2}$ and $AUC_{0\text{-}tlast}$ for I-1 following 1.10 mg/kg i.v. administration (Group 2).

Example ID	Dose (mg/kg)	Parameter	Parameter estimate for each animal			
I-1	1.10		R04	R05	R06	Mean ± SD
	mg/kg	Apparent $t_{1/2}$ (h)[a]	0.174	0.137	0.129	0.147 ± 0.0240
		$AUC_{0\text{-}tlast}$ (h*ng/mL)	11.1	10.9	12.0	11.3 ± 0.587
I-17	1.33		R07	R08	R09	Mean ± SD
	mg/kg	Apparent $t_{1/2}$ (h)[a]	1.54	1.13	0.950	1.21 ± 0.301
		$AUC_{0\text{-}tlast}$ (h*ng/mL)	291	291	363	315 ± 41.4
I-12	1.2		R01	R02	R03	Mean ± SD
	mg/kg	Apparent $t_{1/2}$ (h)[a]	1.01	0.778	nc	0.894 (n = 2)
		$AUC_{0\text{-}tlast}$ (h*ng/mL)	80.6	97.8	75.7	84.7 ± 11.6
I-13	1.14		R04	R05	R06	Mean ± SD
	mg/kg	Apparent $t_{1/2}$ (h)[a]	nc	0.585	0.477	0.531 (n = 2)
		$AUC_{0\text{-}tlast}$ (h*ng/mL)	102	109	103	105 ± 3.64
I-19	1.2		R07	R08	R09	Mean ± SD
	mg/kg	Apparent $t_{1/2}$ (h)[a]	nc	1.00	0.889	0.947 (n = 2)
		$AUC_{0\text{-}tlast}$ (h*ng/mL)	66.9	103	118	96.1 ± 26.4

[a]Apparent $t_{1/2}$ was estimated from 2 points only
nc denotes not calculable.

Example 12: Human, Rat, and Mouse Liver Microsomes Stability

Objective

[0637] The objective of this study was to estimate in vitro metabolic stability of exemplary compounds of Formula (I) or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof in pooled human, male rat, and male mouse liver microsomes. The concentrations of compounds in reaction systems were evaluated by LC-MS/MS for estimating the stability in pooled human, male rat, and male mouse liver microsomes. The in vitro intrinsic clearances of test compounds were determined as well.

Protocol

[0638] A master solution in the "Incubation Plate" containing phosphate buffer, ultra-pure H_2O, $MgCl_2$ solution and liver microsomes was made according to Table 33. The mixture was pre-warmed at 37° C. water bath for 5 minutes.

TABLE 33

Preparation of master solution

Reagent	Stock Concentration	Volume	Final Concentration
Phosphate buffer	200 mM	200 μL	100 mM
Ultra-pure H_2O	—	106 μL	—
$MgCl_2$ solution	50 mM	40 μL	5 mM
Microsomes	20 mg/mL	10 μL	0.5 mg/mL

[0639] 40 μL of 10 mM nicotinamide adenine dinucleotide phosphate (NADPH) solution was added to each well. The final concentration of NADPH was 1 mM. The negative control samples were prepared by replacing NADPH with 40 μL of ultra-pure H_2O. Samples were prepared in duplicate. Negative controls were prepared in singlet.

[0640] The reaction was started with the addition of 4 μL of 200 μM exemplary test compounds of the disclosure or control compounds to each master solution to get the final concentration of 2 μM. This study was performed in duplicate.

[0641] Aliquots of 50 μL were taken from the reaction solution at 0, 15, 30, 45, and 60 minutes. The reaction solutions were stopped by the addition of 4 volumes of cold methanol with IS (100 nM alprazolam, 200 nM imipramine, 200 nM labet alol and 2 μM ketoprofen). Samples were centrifuged at 3,220 g for 40 minutes. Aliquot of 90 μL of the supernatant was mixed with 90 μL of ultra-pure H2O and then was used for LC-MS/MS analysis.

[0642] LC/MS analysis was performed for all samples from this study using a Shimadzu liquid chromatograph separation system equipped with degasser DGU-20A5R; solvent delivery unit LC-30AD; system controller SIL-30AC; column oven CTO-30A; CTC Analytics HTC PAL System. Mass spectrometric analysis was performed using a Triple Quad™ 5500 instrument.

[0643] All calculations were carried out using Microsoft Excel. Peak area ratios of test compound to internal standard (listed in the below table) were determined from extracted ion chromatograms.

[0644] All calculations were carried out using Microsoft Excel. Peak areas were determined from extracted ion chromatograms. The slope value, k, was determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve.

[0645] The in vitro half-life (in vitro $t_{1/2}$) was determined from the slope value:

$$\text{in vitro } t_{1/2} = -(0.693/k)$$

[0646] Conversion of the in vitro $t_{1/2}$(min) into the in vitro intrinsic clearance (in vitro CL_{int}, in μL/min/mg proteins) was done using the following equation (mean of duplicate determinations):

$$\text{in vitro } CL_{int} = \left(\frac{0.693}{(t_{1/2})}\right) * \left(\frac{\text{volume of incubation } (\mu L)}{\text{amount of proteins (mg)}}\right)$$

[0647] For the exemplary compounds of the disclosure or control compound that showed an initial fast disappearance followed by a slow disappearance, only the time points that were within the initial rate were included in the calculation.

Results and Discussion

[0648] Human, rat, and mouse liver microsomes contain a wide variety of drug metabolizing enzymes and are commonly used to support in vitro ADME (absorption, distribution, metabolism, and excretion) studies. These microsomes are used to examine the potential first-pass metabolism by-products of orally administered drugs. Representative compounds of the disclosure were evaluated for their stability in human, rat, and mouse liver microsomes (Table 34).

TABLE 34

Metabolic Stability of Test Compounds in Liver Microsomes of Different Species (a)

Compound ID	Species	$t_{1/2}$ (min)	CL_{int} (μL/min/mg protein)	Scaled-up CL_{int} (mL/min/Kg)	Predicted hepatic CL (mL/min/kg)
Diclofenac	Human	10.73	129.12	161.94	18.35
	Rat	15.22	91.05	163.16	41.25
	Mouse	43.31	32.00	140.00	54.78
5-MeO-DMT	Human	12.14	114.19	143.22	18.09
	Rat	5.68	244.17	437.56	49.02
	Mouse	44.52	31.13	136.21	54.19

TABLE 34-continued

Metabolic Stability of Test Compounds in Liver Microsomes of Different Species (a)

Compound ID	Species	$t_{1/2}$ (min)	CL_{int} (μL/min/mg protein)	Scaled-up CL_{int} (mL/min/Kg)	Predicted hepatic CL (mL/min/kg)
Diclofenac	Human	10.59	130.91	164.18	18.38
	Rat	15.27	90.79	162.69	41.22
	Mouse	40.69	34.06	149.03	56.11
I-1	Human	6.04	229.66	288.02	19.31
	Rat	<4.51	>307.01	>550.16	>50.17
	Mouse	6.61	209.82	917.98	81.96
I-17	Human	6.99	198.26	248.65	19.11
	Rat	37.76	36.71	65.78	30.01
	Mouse	<4.51	>307.01	>1343.17	>84.35
I-12	Human	25.77	53.78	67.45	15.84
	Rat	37.41	37.04	66.38	30.14
	Mouse	6.13	226.27	989.92	82.50
I-13	Human	11.72	118.23	148.28	18.16
	Rat	13.65	101.51	181.91	42.35
	Mouse	<4.51	>307.01	>1343.17	>84.35
I-19	Human	18.71	74.09	92.92	16.93
	Rat	103.48	13.39	24.00	16.73
	Mouse	10.01	138.46	605.78	78.36

DISCUSSION

[0649] Exemplary compounds of the disclosure were evaluated for their stability in human, rat, and mouse liver microsomes. Table 34 shows the results of the stability studies. These results show that the compounds of the disclosure show a spectrum of stability across different species, including human, rat, and mouse.

Example 13: Human, Rat, Mouse, and Dog: Plasma Stability

1. Preparation of Stock Solutions

[0650] The stock solution of test compound was prepared in DMSO and diluted at the final concentration of 200 μM. 1 mM lovastatin and propantheline working solution was prepared in DMSO and acetonitrile, respectively. Lovastatin was used as positive control for rat and dog plasma stability assay. Propantheline was used as positive control in human, mouse, and monkey plasma stability assay.

2. Procedures for Plasma Stability

[0651] a. 2.5 μL of 200 μM or 1 mM test compound or control compound solution was spiked to 497.5 μL plasma to reach a final concentration of 1 μM or 5 μM. The final concentration of organic solvents was 0.5%. The assay was performed in duplicate.

[0652] b. The reaction samples were incubated at 37° C. at approximately 60 rpm in a water bath.

[0653] c. Aliquots of 50 μL were taken from the reaction samples at 0, 30, 60, 120, 180, and 240 minutes. The reaction was stopped by the addition of 7 volumes of cold acetonitrile containing internal standards (IS: 100 nM alprazolam, 200 nM imipramine, 200 nM labet alol and 2 μM ketoprofen).

[0654] d. All samples were vortexed for 2 minutes, followed by centrifugation at 3,220 g for 30 minutes to precipitate proteins. 100 μL of the supernatant is transferred to a new plate. The supernatant was diluted with ultrapure water according to the LC-MS signal response and peak shape.

3. Sample Analysis

[0655] Samples were analyzed by LC-MS/MS.

[0656] LC system: Shimadzu

[0657] MS analysis: Triple Quad™ 6500+ from AB Inc (Canada) with an ESI interface

[0658] Column temperature: 40° C.

[0659] Column: Xselect® Hss T3 2.5 p (2.1×30 mm) is coupled with preguard column

[0660] Mobile phase: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) (Table 35)

TABLE 35

Time (min)	0	0.1	0.5	0.8	0.81	1.0
% B	5	5	100	100	5	5

4. Data Analysis

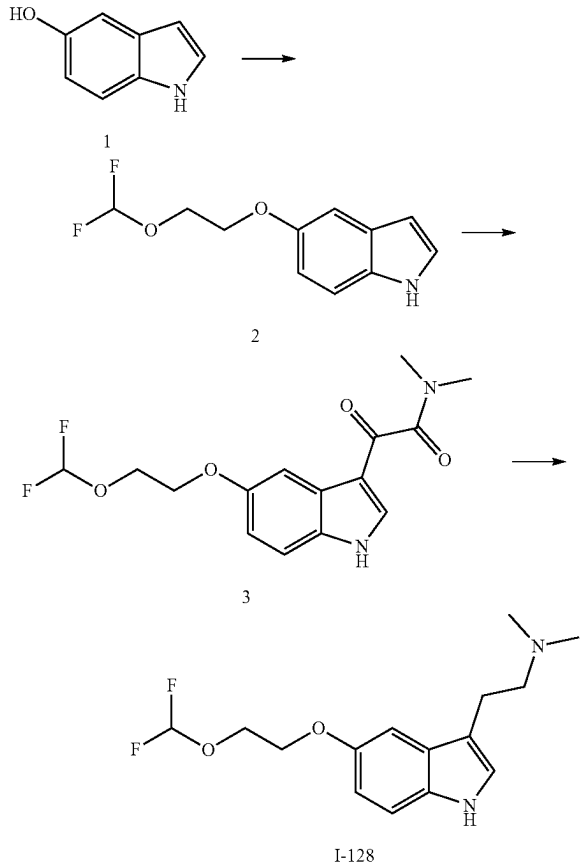
[0661] All calculations were carried out using Microsoft Excel. Remaining percentages of parent compounds at each time point were estimated by determining the peak area ratios from extracted ion chromatograms.

Part II

[0662] The following compounds were prepared using one or more of the synthetic methods outlined in Schemes I and II.

A. Synthesis of Exemplary Compounds of the Disclosure

Example 14: Synthesis of 2-(5-(2-(Difluoromethoxy)ethoxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine (I-128)



Synthesis of 5-(2-(difluoromethoxy)ethoxy)-1H-indole (2)

[0663] A solution of 1H-indol-5-ol (2.5 g, 18.77 mmol) in dry DMF (50 mL) was treated with Cs_2CO_3 (9.17 g, 28.16 mmol), followed by 2-(difluoromethoxy)ethyl 4-methylbenzenesulfonate (9.99 g, 37.55 mmol) at room temperature and the reaction was stirred for additional 48 h. The reaction was quenched with water (200 mL) and product was extracted into ethyl acetate (2×100 mL). Combined ethyl acetate layer was washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated and crude was purified by column chromatography (EtOAc: Hexanes, 1:4) on silica gel to obtain the title compound 2 (2.30 g, 54%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 8.11 (brs, 1H), 7.83 (d, 1H, J=6.0 Hz), 7.38 (d, 1H, J=6.0 Hz), 7.31 (t, 1H, J=6.0 Hz), 7.28 (s, 1H), 6.92 (dd, 1H, J=1.5, 6.0 Hz), 6.18 (t, 1H, J=54 Hz), 4.25-4.20 (m, 4H); ^{19}F NMR ($CDCl_3$): δ−85.07 (d, J=60 Hz), −84.31 (d, J=60 Hz).

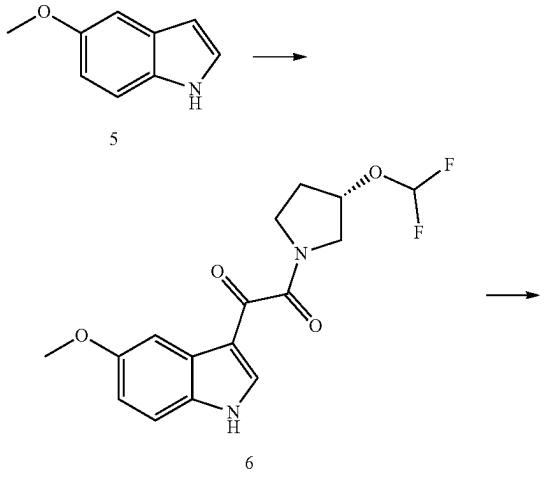
Synthesis of 2-(5-(2-(difluoromethoxy)ethoxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide (3)

[0664] A solution of 5-(2-(difluoromethoxy)ethoxy)-1H-indole (2.3 g, 10.14 mmol) in dry TH F (50 mL) was treated with oxalyl chloride (0.85 mL, 10.14 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to 0° C., treated with dimethylamine (25.36 mL, 50.72 mmol, 2 M solution in TH F) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was quenched with water (100 mL) and product was extracted into ethyl acetate (2×100 mL). Combined ethyl acetate layer was washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated and crude was purified by column chromatography (2 M N H_3 in MeOH: C H_2Cl_2, 5:95) on silica gel followed by recrystallization from 30% CH_2Cl_2 in hexanes to obtain the title compound 3 (1.86 g, 56%) as a white solid. ^{1}H NMR (DMSO-de): δ 12.21 (s, 1H), 8.04 (s, 1H), 7.62 (d, 1H, J=3.0 Hz), 7.45 (d, 1H, J=6.0 Hz), 6.97-6.93 (m, 1H), 6.78 (t, 1H, J=57 Hz), 4.21 (s, 4H), 3.00 (s, 3H), 2.92 (s, 3H); ^{19}F NMR (DMSO-d_6): δ−82.43 (d, J=63 Hz); ES I-MS (m/z, %): 349 (M+N a, 100).

Synthesis of 2-(5-(2-(difluoromethoxy)ethoxy)-1H-indol-3-yl)-N,N-dimethylethan-1-amine (I-128)

[0665] A solution of 2-(5-(2-(difluoromethoxy)ethoxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide (1.86 g, 5.70 mmol) in dry THF (50 mL) was treated with $LiAlH_4$ (1.72 g, 45.60 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16 h). The reaction was cooled to 0° C., quenched with water (1.72 mL), 4 N NaOH solution (1.72 mL) and water (1.72 mL). The reaction was brought to room temperature and stirred for additional 30 min. The reaction was filtered through a pad of sodium sulfate and washed with THF (3×25 mL). Combined THF layer was evaporated and crude was purified by column chromatography (2 M NH_3 in MeOH:CH_2Cl_2, 5:95) on silica gel to obtain the title compound I-128 (1.3 g, 76.5%) as a white solid. ^{1}H NMR (DMSO-d_5): δ 10.62 (s, 1H), 7.22 (d, 1H, J=6.0 Hz), 7.10 (s, 1H), 7.01 (s, 1H), 6.95-6.57 (m, 2H), 4.17 (s, 4H), 2.77 (t, 2H, J=6.0 Hz), 2.50-2.45 (m, 2H), 2.21 (s, 6H); ESI-MS (m/z, %): 299 (MH^+, 100).

Example 15: (S)-3-(2-(3-(Difluoromethoxy)pyrrolidin-1-yl)ethyl)-5-methoxy-1H-indole ((S) I-67)



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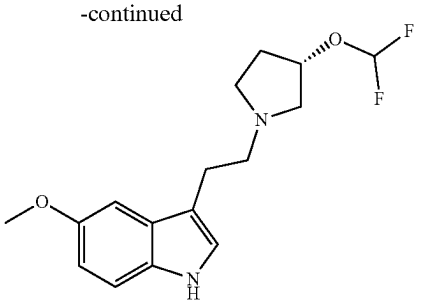


(S) I-67

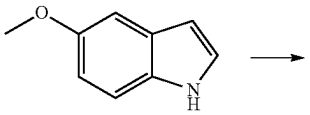
Synthesis of (S)-1-(3-(difluoromethoxy)pyrrolidin-1-yl)-2-(5-methoxy-1H-indol-3-yl)ethane-1,2-dione (6)

[0666] A solution of 5-methoxy-1H-indole (1.52 g, 10.37 mmol) in dry THF (30 mL) was treated with oxalyl chloride (0.87 mL, 10.37 mmol) at ° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to O ° C., treated with (S)-3-(difluoromethoxy) pyrrolidine hydrochloride (4.5 g, 25.92 mmol, free based with Et_3N in TH F) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was worked-up and purified as described for compound 3 to obtain the title compound 6 (2.78 g, 80%) as a gray solid. ^{1}H NMR (DMSO-de): δ 12.19 (s, 1H), 8.12 (dd, 1H, J=3.0, 9.0 Hz), 7.65 (s, 1H), 7.44 (d, 1H, J=6.0 Hz), 6.93-6.54 (m, 2H), 4.95-4.85 (m, 1H), 3.81 (s, 3H), 3.76-3. 50 (m, 4H), 2.18-2.10 (m, 2H); E SI-M S (m/z, %): 361 (M+Na, 100), 339 (MH^+).

Synthesis of (S)-3-(2-(3-(difluoromethoxy)pyrrolidin-1-yl)ethyl)-5-methoxy-1H-indole ((S) I-67)

[0667] A solution of (S)-1-(3-(difluoromethoxy)pyrrolidin-1-yl)-2-(5-methoxy-1H-indol-3-yl)ethane-1,2-dione (2.2 g, 6.50 mmol) in dry TH F (50 mL) was treated with $LiAlH_4$ (1.97 g, 52.02 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16 h). The reaction was worked-up and purified as described for compound I-128 to obtain the title compound (S) I-67 (0.8 g, 36%) as a pale-yellow glue. ^{1}H NMR (DMSO-d_6): δ 10.59 (s, 1H), 7.20 (d, 1H, J=3.0 Hz), 7.09 (d, 1H, J=3.0 Hz), 6.97 (d, 1H, J=1.5 Hz), 6.82-6.52 (m, 2H), 4.72-4.67 (m, 1H), 3.75 (s, 3H), 2.81-2. 65 (m, 7H), 2.50-2.42 (m, 1H), 2.18-2.14 (m, 1H), 1.79-1.75 (m, 1H); ^{19}F NMR (DMSO-d_6): δ−80.37 (dd, J=3.0, 48 Hz); ESI-MS (m/z, %): 311 (MH^+, 100).

Example 16: 2-(Difluoromethoxy)-N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-N-methylethan-1-amine (I-71)



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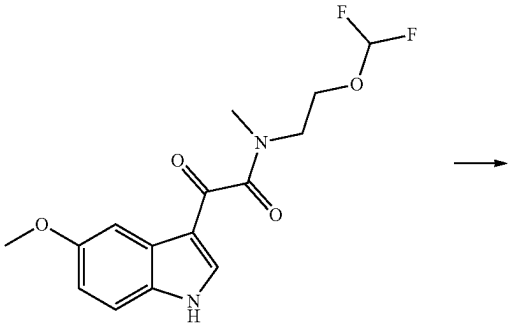

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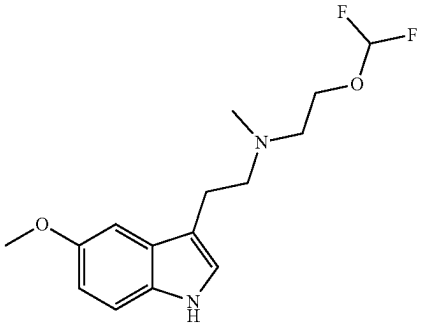


I-71

Synthesis of N-(2-(difluoromethoxy)ethyl)-2-(5-methoxy-1H-indol-3-yl)-N-methyl-2-oxoacetamide (8)

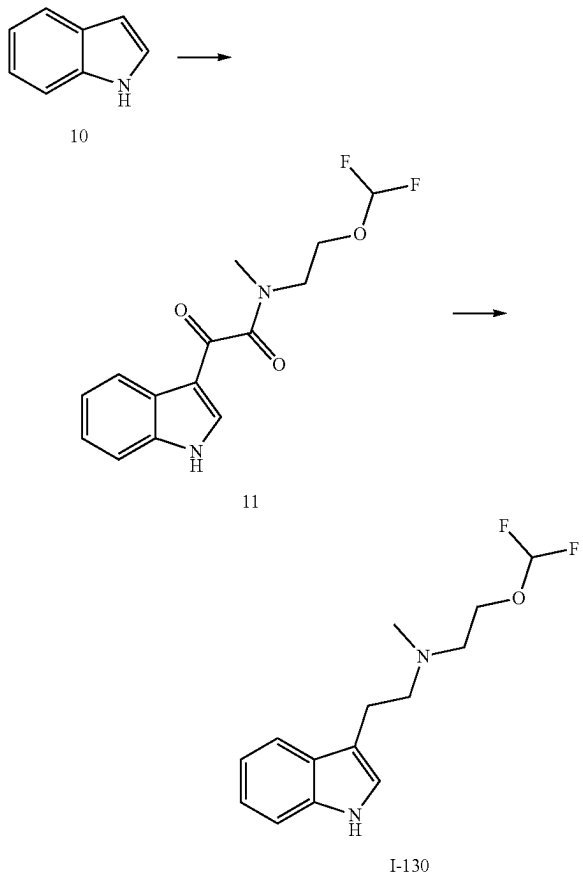
[0668] A solution of 5-methoxy-1H-indole (1.45 g, 9.90 mmol) in dry THF (30 mL) was treated with oxalyl chloride (0.83 mL, 9.90 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to 0° C., treated with 2-(difluoromethoxy)-N-methylethan-1-amine hydrochloride (4.0 g, 24.75 mmol, free based with Et_3N in THF) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was worked-up and purified as described for compound 3 to obtain the title compound 8 (2.2 g, 68.5%) as a pale-yellow solid. ^{1}H NMR (DMSO-de): δ 12.22, 12.17 (2s, 1H), 7.98, 7.94 (2s, 1H), 7.62-7.60 (m, 1H), 7.44-7.41 (m, 1H), 6.92-6.43 (m, 2H), 4.12-4.09 (m, 1H), 4.00-3.94 (m, 1H), 3.80 (s, 3H), 3.72-3.70 (m, 1H), 3.55-3.53 (m, 1H), 3.01, 2.96 2s, 3H); ^{19}F NMR (DMSO-de): 6-82.73 (d, J=48 Hz), −83.11 (d, J=48 Hz); ESI-MS (m/z, %): 452 (100), 349 (M+Na), 327 (MH^+).

Synthesis of 2-(difluoromethoxy)-N-(2-(5-methoxy-1H-indol-3-yl)ethyl)-N-methylethan-1-amine (I-71)

[0669] A solution of N-(2-(difluoromethoxy)ethyl)-2-(5-methoxy-1H-indol-3-yl)-N-methyl-2-oxoacetamide (2.2 g, 6.74 mmol) in dry THF (50 mL) was treated with $LiAlH_4$ (2.04 g, 53.93 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16 h). The reaction was worked-up and purified as described for compound I-128 to obtain the title compound I-71 (0.57 g, 28%) as a pale-yellow glue. ^{1}H NMR (DMSO-d_6): δ 10.59 (s, 1H), 7.21 (d, 1H, J=6.0 Hz), 7.09 (d, 1H, J=3.0 Hz), 6.96 (d, 1H, J=3.0 Hz), 6.80-6.50 (m,

2H), 3.91 (t, 2H, J=3.0 Hz), 3.75 (s, 3H), 2.80-2.78 (m, 2H), 2.68-2.64 (m, 4H), 2.31 (s, 3H); ^{19}F NM R (DMSO-de): 6-82.18 (d, J=48 Hz); ESI-MS (m/z, %): 299 (MH$^+$, 100).

Example 17: N-(2-(1H-Indol-3-yl)ethyl)-2-(difluoromethoxy)-N-methylethan-1-amine (I-130)



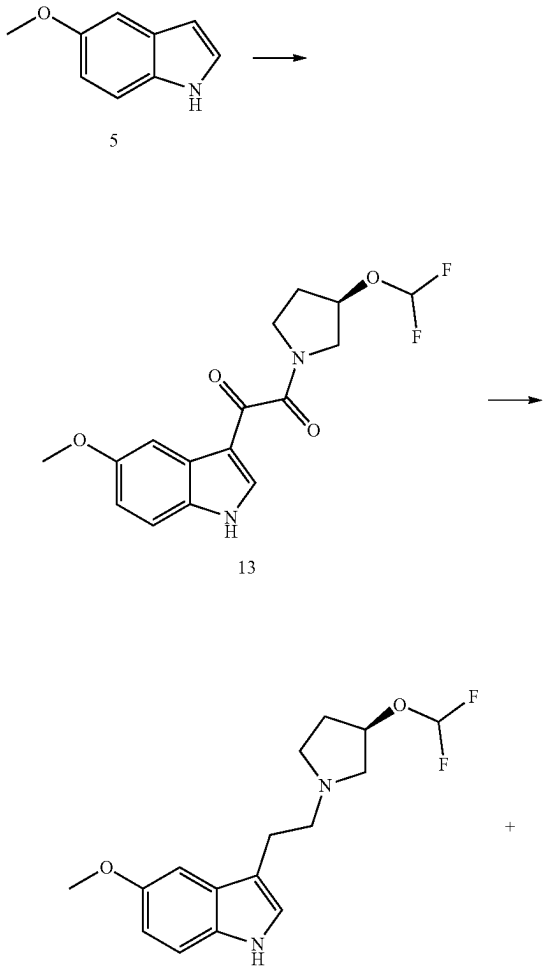
Synthesis of N-(2-(difluoromethoxy)ethyl)-2-(1H-indol-3-yl)-N-methyl-2-oxoacetamide (11)

[0670] A solution of indole (1.16 g, 9.90 mmol) in dry TH F (30 mL) was treated with oxalyl chloride (0.83 mL, 9.90 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to 0° C., treated with 2-(difluoromethoxy)-N-methylethan-1-amine hydrochloride (4.0 g, 24.75 mmol, free based with Et_3N in THF) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was worked-up and purified as described for compound 3 to obtain the title compound 11 (2.47 g, 83%) as a pale-yellow glue. ^{1}H NMR (DMSO-de): δ 12.32 (s, 1H), 8.13-8.03 (m, 2H), 7.54-7.52 (m, 1H), 7.30-7.23 (m, 2H), 6.92-6.43 (m, 1H), 4.12-4.10 (m, 1H), 4.02-3.94 (m, 1H), 3.73-3.71 (m, 1H), 3.62-3.55 (m, 1H), 2.96, 2.92 (2s, 3H); ^{19}F NMR (DMSO-d_6): δ−82.75 (d, J=48 Hz), −83.13 (d, J=48 Hz); ESI-MS (m/z, %): 422 (100), 319 (M+Na), 297 (MH$^+$).

Synthesis of N-(2-(1H-Indol-3-yl)ethyl)-2-(difluoromethoxy)-N-methylethan-1-amine (I-130)

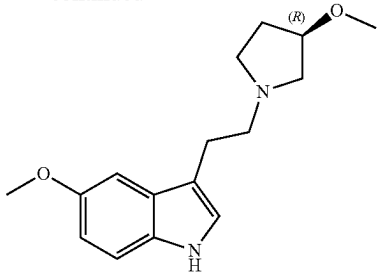
[0671] A solution of N-(2-(difluoromethoxy)ethyl)-2-(1H-indol-3-yl)-N-methyl-2-oxoacetamide (2.4 g, 8.10 mmol) in dry TH F (50 mL) was treated with $LiAlH_4$ (2.45 g, 64.80 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16 h). The reaction was worked-up and purified as described for compound I-128 to obtain the title compound I-130 (0.24 g, 11%) as a pale-yellow glue. ^{1}H NMR (DMSO-d_6): δ 10.76 (s, 1H), 7.50 (d, 1H, J=6.0 Hz), 7.32 (d, 1H, J=6.0 Hz), 7.14 (s, 1H), 7.06-7.03 (m, 1H), 6.98-6.95 (m, 1H), 6.65 (t, 1H, J=45 Hz), 3.90 (t, 2H, J=9.0 Hz), 2.83-2.80 (m, 2H), 2.68-2.65 (m, 4H), 2.31 (s, 3H); ^{19}F NM R (DMSO-d_6): δ−82.18 (d, J=48 Hz); ESI-MS (m/z, %): 269 (MH$^+$, 100).

Example 18: (R)-3-(2-(3-(Difluoromethoxy)pyrrolidin-1-yl)ethyl)-5-methoxy-1H-indole ((R) I-67) and (R)-5-methoxy-3-(2-(3-methoxypyrrolidin-1-yl)ethyl)-1H-indole ((R) I-66)



(R) I-67

-continued



(R) I-66

Synthesis of (R)-1-(3-(difluoromethoxy)pyrrolidin-1-yl)-2-(5-methoxy-1H-indol-3-yl)ethane-1,2-dione (13)

[0672] A solution of 5-methoxy-1H-indole (1.28 g, 8.75 mmol) in dry THF (30 mL) was treated with oxalyl chloride (0.74 mL, 8.75 mmol) at 0° C. The reaction was brought to room temperature and stirred for additional 5 h. The reaction was cooled to O ° C., treated with (R)-3-(difluoromethoxy) pyrrolidine hydrochloride (3.8 g, 21.89 mmol, free based with Et_3N in TH F) over a period of 5 min. The reaction was brought to room temperature and stirred for overnight (16 h). The reaction was worked-up and purified as described for compound I-128 to obtain the title compound 13 (2.2 g, 75%) as a gray solid. ^{1}H NMR (DMSO-d_6): δ 12/19 (s, 1H), 8.13-8.10 (m, 1H), 7.64 (s, 1H), 7.43 (d, 1H, J=6.0 Hz), 7.00-6.54 (m, 2H), 4.92-4.84 (m, 1H), 3.81 (s, 3H), 3.74-3.47 (m, 4H), 2.17-2.09 (m, 2H); ^{19}F NMR (DMSO-d_6): δ−80.77 (d, J=60 Hz), −80.80 (dd, J=3.0, 60 Hz); ES I-MS (m/z, %): 361 (M+Na, 100), 339 (MH^+).

Synthesis of (R)-3-(2-(3-(difluoromethoxy)pyrrolidin-1-yl)ethyl)-5-methoxy-1H-indole ((R) I-67) and (R)-5-methoxy-3-(2-(3-methoxypyrrolidin-1-yl) ethyl)-1H-indole ((R) I-66)

[0673] A solution of (R)-1-(3-(difluoromethoxy)pyrrolidin-1-yl)-2-(5-methoxy-1H-indol-3-yl)ethane-1,2-dione (1.7 g, 5.02 mmol) in dry TH F (50 mL) was treated with $LiAlH_4$ (1.52 g, 40.20 mmol) at 0° C. over a period of 10 min. The reaction was brought to room temperature and then refluxed for overnight (16 h). The reaction was worked-up and purified as described for compound I-128 to obtain the title compound (R) I-67 (0.75 g, 48%) as a pale-yellow glue. ^{1}H NMR (DMSO-d_6): δ 10.61 (s, 1H), 7.22 (d, 1H, J=6.0 Hz), 7.10 (d, 1H, J=3.0 Hz), 6.98 (d, 1H, J=3.0 Hz), 6.72-6.49 (m, 2H), 4.73-4.68 (m, 1H), 3.76 (s, 3H), 2.83-2.66 (m, 7H), 2.50-2.44 (m, 1H), 2.19-2.15 (m, 1H), 1.81-1.77 (m, 1H); ^{19}F NMR (DMSO-de): 6-80.37 (dd, J=3.0, 60 Hz); ES I-MS (m/z, %): 311 (MH^+, 100).

[0674] De-fluorinated, (R)-5-methoxy-3-(2-(3-methoxypyrrolidin-1-yl)ethyl)-1H-indol, compound (R) I-66 (0.64 g): ^{1}H NMR (DMSO-de): δ 10.60 (s, 1H), 7.22 (d, 1H, J=9.0 Hz), 7.09 (d, 1H, J=3.0 Hz), 6.97 (d, 1H, J=3.0 Hz), 6.70 (dd, 1H, J=3.0, 6.0 Hz), 3.90-3.85 (m, 1H), 3.76 (s, 3H), 3.18 (s, 3H), 2.82-2.46 (m, 8H), 2.00-1.96 (m, 1H), 1.66-1.55 (m, 1H); ESI-MS (m/z, %): 275 (MH^+, 100).

B. Biological Testing

Example 19: Human 5-HT_{2A}: Functional FLIPR Assay

Objective:

[0675] The potential excitatory effects of compounds targeting human 5-hydroxytryptamine receptor 2A (5-HT_{2A}) under agonist mode was assessed.

1. Materials and Instrumentation

TABLE 36

1.1 Cell line

Cell line Name	Target	Host cell
HTR2A&Gα15-HEK293	5-HT_{2A}	Flp-In-293

TABLE 37

1.2 Materials

Regents	Vendor	Cat#
DMEM	Gibco	10569-010
Dialyzed FBS	BIOSUN	BS-0005-500
Penicillin-Streptomycin	Invitrogen	15140
Hygromycin B	Invivogen	Ant-hg-5
Tetracycline hydrochloride	Abcam	ab141223
TrypLE ™ Express	Gibco	12604-013
DPBS	Gibco	14190250
DMSO	Millipore	1029312500
Probenecid	Sigma	P8761
FLIPR Calcium 6 Assay Kit	Molecular Device	R8191
HEPES	Invitrogen	15630
Hank's Buffered Saline Solution	Invitrogen	14025
Serotonin HCl	Selleck	S4244

TABLE 38

1.3 Instrumentation and consumables

Item	Supplier	Cat#
Fluorometric Imaging Plate Reader (FLIPR)	Molecular Device	Tetra
Countess Automated Cell Counter	Invitrogen	Countess
Cell Counting Chamber Slides	Invitrogen	C10312
STERI-CYCLE CO2 Incubator	Thermo	371
1300 Series Class II Biological Safety Cabinet	Thermo	1389
Table-type Large Capacity Low Speed Centrifuge	Cence	L550
Centrifuge	Eppendorf	5702
Echo	Labcyte	550
Echo	Labcyte	655
Electro-thermal incubator	Shanghai Yiheng	DHP-9031
plate shaker	IKA	MS3 digital
Water Purification System	ULUPURE	UPH-III-20T
Versatile and Universal pH and Conductivity Meters	Mettler Toledo	S220

TABLE 38-continued

1.3 Instrumentation and consumables		
Item	Supplier	Cat#
384-Well plate	Corning	3764
384-Well LDV Clear microplate	LABCYTE	LP-0200
384-Well Polypropylene microplate	LABCYTE	PP-0200
384-well compound plate	Corning	3657
T25 cell culture flask	Corning	430639
50 mL Polypropylene Centrifuge Tube	JET	CFT011500
15 mL Polypropylene Centrifuge Tube	JET	CFT011150

2. Experimental Methods

2.1 Cell Culture

[0676] HTR2A&Gα15-HEK293 cells were cultured in DMEM medium containing 10% dialyzed FBS and 1×penicillin-streptomycin, 100 μg/mL Hygromycin B and 300 μg/mL G418. The cells were passaged about three times a week, maintained between ~30% to ~90% confluence.

2.2 Cell Plating

[0677] 1. The cell culture medium (DMEM medium containing 10% dialyzed FBS and 1×penicillin-streptomycin, 100 μg/mL Hygromycin B and 300 μg/mL G418), TrypLE™ Express and DPBS to R.T. was warmed in advance.

[0678] 2. For induction, 1 μg/ml tetracycline (final concentration) was added to cell culture medium and incubated for 48 hours prior to seeding cells into plate at 37° C., 5% (v/v) CO2. The cell culture medium was removed from flask. Cells were washed with DPBS.

[0679] 3. 2 mL TrypLE™ Express was added to the flask, mixed well by gentle shaking and cells were incubated at 37° C. for a few minutes.

[0680] 4. The cells were checked for morphological change under microscope, the digestion was stopped by adding 4 mL cell culture medium to the flask when most of cells turned to round.

[0681] 5. The cell suspension was transferred into a 15 mL centrifuge tube, and then centrifuged at 1,200 rpm for 5 minutes.

[0682] 6. The supernatant was removed. The cell pellet was resuspended with 2 mL cell culture medium.

[0683] 7. The cell density was counted using cell counter. Only cells with >85% viability were used for the assay.

[0684] 8. Cells were diluted to 6.67×10^5/mL with cell culture medium.

[0685] 9. 30 μL/well cell suspensions added into a 384-well cell plate (The cell density was 20,000 cells/well).

[0686] 10. The cell plate was incubated overnight at 37° C., 5% (v/v) CO_2.

2.3 Cell Handling

[0687] 1. On the day of experiments, culture medium was removed from the cell plate.

[0688] 2. 10 μL of assay buffer (20 mM HEPES, in 1×HBSS, pH 7.4) was added to each well of the cell plate.

[0689] 3. 2×dye solution was prepared following the manual of the FLIPR® Calcium 6 Assay Kit:

[0690] i. The dye was diluted with assay buffer.

[0691] ii. Probenecid was added to the final concentration of 5 mM.

[0692] iii. Vortexed vigorously for I-2 minutes.

[0693] 4. 10 μL of 2x dye solution was added to each well of the cell plate.

[0694] 5. The cell plate was placed on plate shaker, followed by shaking at 600 rpm for 2 minutes.

[0695] 6. The plate was incubated at 37° C. for 2 hours followed by an additional 15-minute incubation at 25° C. 2.4 Prepare 3×compound.

[0696] 1. Serotonin HCl was prepared to the concentration of 10 mM with DMSO.

[0697] 2. The test compounds were prepared to the concentration of 10 mM with DMSO.

[0698] 3. The compounds were added to a 384-well compound source plate.

[0699] 4. 3-folds serial dilutions were performed with DMSO.

[0700] 5. 90 nL/well of serial diluted compounds was transferred from source plate to a 384-well compound plate by using an Echo.

[0701] 6. 30 μL/well of assay buffer (20 mM HEPES in 1×HBSS, pH 7.4) was added to the compound plate.

[0702] 7. The plate was mixed on-plate shaker for 2 minutes.

2.5 FLIPR Assay

[0703] 1. After the cells were incubated with dye solution, the cell plate, compound plate containing 3×compounds and F LIP R tips were placed into F LIP R.

[0704] 2. 10 μL of 3×compounds transferred from the compound plate to the cell plate by FLIP R.

[0705] 3. The plate was read for 160 sec with 1 sec interval and the data of agonist mode was obtained.

3. Data Analysis

[0706] 1. The normalized fluorescence reading (RFU) was calculated as shown below, wherein F_{max} and F_{min} stand for maximum and minimum of calcium signal during defined time window:

$$RFU=F_{max}-F_{min}$$

[0707] 2. EC_{50} by fitting RFU against log of compound concentrations with Hill equation was calculated using XLfit.

Results and Discussion

[0708] The results of potential competition binding properties of the exemplary compounds of the disclosure targeting the human 5-hydroxytryptamine receptor 2A (5-HT_{2A}) are summarized in Table 39. The results of exemplary compounds of the disclosure are presented as EC_{50} is provided in Table 39.

TABLE 39

Effect of exemplary compounds of Formula (I) using FLIPR functional assay on human 5-HT_{2A} receptor		
Example	h5-HT_{2A}, EC_{50} [nM]	RFU@10 μM (1)
5-MeO-DMT	63	5,667
DMT	163	3,493
(R) I-66	ND(2)	752

TABLE 39-continued

Effect of exemplary compounds of Formula (I) using FLIPR functional assay on human 5-HT_{2A} receptor		
Example	h5-HT_{2A}, EC_{50} [nM]	RFU@10 μM [(1)]
(S) I-67	994	2,147
(R) I-67	ND	225
I-71	257	1,094
I-128	1,209	2,159
I-130	ND	247

[(1)] Curve fitting with activation (%) @ 10 mM with RFU
[(2)]Not detected

II. Results and Discussion

[0709] Exemplary compounds of Formula (I) were evaluated using FLIP R functional assay on human 5-HT_{2A} receptor. EC_{50} (nM) concentrations are illustrated in Table 39. This assay confirms that compounds of the disclosure are effective agonists of the target human 5-HT_{2A} receptors.

Example 20: Human 5-HT_{2A}: Radioligand Binding Assay

Objective

[0710] The objective of this study was to evaluate the binding properties of exemplary compounds of Formula (I) on 5-hydroxytryptamine receptor 2A (5-HT_{2A}).

1 Materials and Instrumentation

1.1 Regents (Table 40)		
Items	Vendor	Cat#
Ketanserin Hydrochloride, [Ethylene-3H]-	PerkinElmer	NET791250UC
Ketanserin	MedChemExpress	HY-10562
Bovine Serum Albumin (BSA)	Sigma	A1933
Calcium chloride ($CaCl_2$)	Sigma	C5670
Tris(hydroxymethyl)aminomethane (Tris)	Alfa Aesar	A18494
Polyethylenimine, branched (PEI)	Sigma	408727

TABLE 41

1.2 Instrumentation and Consumables		
Item	Supplier	Cat#
Microbeta[2] Microplate Counter	PerkinElmer	2450-0060
UniFilter-96 GF/B	PerkinElmer	6005177
TopSeal	Biotss	SF-800
MicroBeta Filtermate-96	PerkinElmer	D961962
Seven Compact pH meter	Mettler Toledo	S220
Ultrapure Water Meter	Sichuan Ulupure	UPH-III-20T
Benchtop Centrifuge	Hunan Xiangyi	L550
Microplate Shaker	Allsheng	MX100-4A
384-Well Polypropylene Microplate	Labcyte	PP-0200
96 Round Well Plate	Corning	3799
96 Round Deep Well Plate	Axygen	P-DW-11-C
Echo	LABCYTE	550

2 Experimental Methods

[0711] 1. The assay buffer was prepared following Table 42 below.

TABLE 42

Reagent	Concentration
Tris	50 mM
$CaCl_2$	4 mM
BSA	0.1% (w/v)

Adjust pH to 7.4 Followed by 0.2 μM Sterile Filtration

[0712] 2. 8 doses of reference and test compounds starting from 10 mM stock solution as required were prepared by 5-fold serial dilutions with 100% (v/v) DMSO.

[0713] 3. UniFilter-96 GF/B plate was pretreated:

[0714] i. 50 μl/well of 0.5% (v/v) PEI was added to UniFilter-96 GF/C plates. The plates were sealed and incubated at 4° C. for 3 hrs.

[0715] ii. After incubation, the plates were washed 3 times with ice-cold wash buffer (50 mM Tris, pH7.4).

[0716] 4. The assay plate was prepared:

[0717] i. Cell membrane was diluted with assay buffer and 330 μl/well was added to 96 round deep well plates to reach a concentration of 20 μg/well.

[0718] ii. 8 concentrations of reference or test compounds were prepared and 110 μl/well was added to 96 round deep well plates.

[0719] iii. [3H]-ketanserin was diluted with assay buffer to 5 nM (5×final concentration) and 110 μl/well was added to 96 round deep well plates.

[0720] 5. The plate was centrifuged at 1000 rpm for 30 secs and then agitated at 600 rpm, R.T. for 5 min.

[0721] 6. The plates were sealed and the plate incubated at 27° C. for 90 min.

[0722] 7. The incubation was stopped by vacuum filtration onto GF/B filter plates followed by 4 times washing with ice-cold wash buffer (50 mM Tris, pH7.4).

[0723] 8. The plates were dried at 37° C. for 45 min.

[0724] 9. The filter plates were sealed and 40 μl/well of scintillation cocktail was added.

[0725] 10. The plate was read by using a Microbeta[2] microplate counter.

3 Data Analysis

[0726] 1. For reference and test compounds, the results were expressed as % Inhibition, using the normalization equation: $N=100-100x(U-C_2)/(C_1-C_2)$, where U is the unknown value, C_1 is the average of high controls, and C_2 is the average of low controls.

[0727] 2. The IC_{50} was determined by fitting percentage of inhibition as a function of compound concentrations with Hill equation using XLfit.

Results and Discussion

[0728] The results of potential competition binding properties of the exemplary compounds of the disclosure targeting the human 5-hydroxytryptamine receptor 2A (5-HT_{2A}) are summarized in Table 43. The results of exemplary compounds of the disclosure are presented as IC_{50} provided in Table 43.

TABLE 43

Effect of exemplary compounds of Formula (I) using Radioligand binding assay on human 5-HT_{2A} receptor	
Compound ID	h5-HT_{2A}, IC_{50} [nM]
5-MeO-DMT	603
DMT	954
(R) I-66	4,249
(S) I-67	4,878
(R) I-67	4,081
I-71	2,303
I-128	7,829
I-130	5,678

II. Results and Discussion

[0729] Exemplary compounds of Formula (I) were evaluated using radioligand binding assay on human 5-HT_{2A} receptor. IC_{50} (nM) concentrations are illustrated in Table 43. This assay confirms that compounds of the disclosure are effective ligands of the target human 5-HT_{2A} receptors.

Example 21: Human 5-HT_{1A}: Functional FLIPR Assay

1 Objective

[0730] The potential excitatory effects of compounds targeting on 5-hydroxytryptamine receptor 1A (5-HT_{1A}) under agonist mode was assessed.

2 Materials and Instrumentation

TABLE 44

2.1 Cell line		
Cell line Name	Target	Host cell
HTR1A&Gα15-CHO	5-HT_{1A}	Flp-in CHO

TABLE 45

2.2 Materials		
Regents	Vendor	Cat#
DMEM/F12	Gibco	11330057
Dialyzed FBS	BIOSUN	BS-0005-500
Penicillin-Streptomycin	Invitrogen	15140
Hygromycin B	Invivogen	Ant-hg-5
TrypLE ™ Express	Gibco	12604-013
DPBS	Gibco	14190250
DMSO	Millipore	1029312500
Probenecid	Sigma	P8761
FLIPR Calcium 6 Assay Kit	Molecular Device	R8191
HEPES	Invitrogen	15630
Hank's Buffered Saline Solution	Invitrogen	14025
Serotonin HCl	Selleck	S4244

TABLE 46

2.3 Instrumentation and consumables		
Item	Supplier	Cat#
Fluorometric Imaging Plate Reader (FLIPR)	Molecular Device	Tetra

TABLE 46-continued

2.3 Instrumentation and consumables		
Item	Supplier	Cat#
Countess Automated Cell Counter	Invitrogen	Countess
Item	Supplier	Cat#
Cell Counting Chamber Slides	Invitrogen	C10312
STERI-CYCLE CO2 Incubator	Thermo	371
1300 Series Class II Biological Safety Cabinet	Thermo	1389
Table-type Large Capacity Low Speed Centrifuge	Cence	L550
Centrifuge	Eppendorf	5702
Echo	Labcyte	550
Echo	Labcyte	655
Electro-thermal incubator	Shanghai Yiheng	DHP-9031
plate shaker	IKA	MS3 digital
Water Purification System	ULUPURE	UPH-III-20T
Versatile and Universal pH and Conductivity Meters	Mettler Toledo	S220
384-Well plate	Corning	3764
384-Well LDV Clear microplate	LABCYTE	LP-0200
384-Well Polypropylene microplate	LABCYTE	PP-0200
384-well compound plate	Corning	3657
T25 cell culture flask	Corning	430639
50 mL Polypropylene Centrifuge Tube	JET	CFT011500
15 mL Polypropylene Centrifuge Tube	JET	CFT011150

3 Experimental Methods

3.1 Cell Culture

[0731] HTR1A&Gα15-C H0 cells were cultured in DMEM/F 12 medium containing 10% dialyzed FBS, 1x penicillin-streptomycin and 600 μg/mL Hygromycin B. The cells were passaged about three times a week, maintained between ~30% to ~90% confluence.

3.2 Cell Plating

[0732] 1. The cell culture medium (DMEM/F 12 medium containing 10% dialyzed FBS, 1x penicillin-streptomycin and 600 μg/mL Hygromycin B), TrypLE™ Express and DPBS was warmed to R.T. in advance.

[0733] 2. The cell culture medium was removed from flask. Washed cells with DPBS.

[0734] 3. 1 mL TrypLE™ Express was added to the flask, mixed well by gentle shaking and cells were incubated at 37° C. for a few minutes.

[0735] 4. The cells were checked for morphological change under microscope, the digestion was stopped by adding 2 mL cell culture medium to the flask when most of cells turned to round.

[0736] 5. The cell suspension was transferred into a 15 mL centrifuge tube, and then centrifuged at 1,200 rpm for 5 minutes.

[0737] 6. The supernatant was removed. The cell pellets were resuspended with 2 mL cell culture medium.

[0738] 7. The cell density was counted using cell counter. Only cells with >85% viability were used for the assay.

[0739] 8. Cells were diluted to 4×10^5/mL with cell culture medium.

[0740] 9. 30 μL/well cell suspensions were added into a 384-well cell plate (The cell density was 12,000 cells/well).

[0741] 10. The cell plate was incubated overnight at 37° C., 5% (v/v) CO_2.

3.3 Cell Handling

[0742] 1. On the day of experiments, culture medium was removed from the cell plate.

[0743] 2. 10 μL of assay buffer (20 mM HEPES, in 1x HBSS, pH 7.4) was added to each well of the cell plate.

[0744] 3. 2×dye solution was prepared following the manufacture's instruction of the F LIP R® Calcium 6 assay kit:

[0745] i. The dye was diluted with assay buffer.

[0746] ii. probenecid was added to the final concentration of 5 mM.

[0747] iii. Vortexed vigorously for I-2 minutes, adjust pH to 7.4.

[0748] 4. 10 μL of 2x dye solution was added to each well of the cell plate.

[0749] 5. The cell plate was placed on plate shaker, followed by shaking at 600 rpm for 2 minutes.

[0750] 6. The plate was incubated at 37° C. for 2 hours followed by an additional 15-minute incubation at 25° C.

3.4 Prepare 3×compounds.

[0751] 1. Serotonin was prepared to the concentration of 10 mM with DMSO, 3-folds serial dilutions were performed with DMSO.

[0752] 2. Prepare the test compound to the concentration of 10 mM with DMSO, preform 3-folds serial dilutions with DMSO.

[0753] 3. The compounds were added to a 384-well compound source plate.

[0754] 4. 90 nL/well of serial diluted compounds were transferred from source plate to a 384-well compound plate by using an Echo.

[0755] 5. 30 μL/well of assay buffer was added to the compound plate.

[0756] 6. The plate was mixed on-plate shaker for 2 minutes.

3.5 FLIPR Assay

[0757] 1. After the cells incubated with dye solution, the cell plate, compound plate containing 3×compounds and F LIP R tips were placed into F LIP R.

[0758] 2. 10 μL of 3×compounds were transferred from the compound plate to the cell plate by F LIP R.

[0759] 3. The plate was read for 160 sec with 1 sec interval to obtain the data of agonist mode.

4 Data Analysis

[0760] 1. The normalized fluorescence reading (RFU) was calculated as shown below, wherein F_{max} and F_{min} stand for maximum and minimum of calcium signal during defined time window:

$$RFU = F_{max} - F_{min}$$

[0761] 2. EC_{50} was calculated by fitting RFU against log of compound concentrations with Hill equation using XLfit.

Results and Discussion

[0762] The results of potential competition binding properties of the exemplary compounds of the disclosure targeting the human 5-hydroxytryptamine receptor 1A (5-HT1A) are summarized in Table 47. The results of exemplary compounds of the disclosure are presented as EC_{50} provided in Table 47.

TABLE 47

Effect of exemplary compounds of Formula (I) using FLIPR functional assay on human 5-HT_{1A} receptor

Compound ID	h5-HT_{1A}, EC_{50} [nM]	RFU@10 μM [1]
5-MeO-DMT	1,066	3,891
DMT	ND[2]	204
(R) I-66	977	3,690
(S) I-67	187	3,930
(R) I-67	1,601	3,988
I-71	1,845	3,087
I-128	ND	314
I-130	ND	163

[1] Curve fitting with activation (%) @ 10 mM with RFU
[2] Not detected

[0763] Exemplary compounds of Formula (I) were evaluated using functional F LIP R assay on human 5-HT_{1A} receptor. EC_{50} (nM) concentrations are illustrated in Table 47. This assay confirms that compounds of the disclosure are functionally active at the target human 5-HT_{1A}receptors.

Example 22: Human 5-HT_{1A}: Radioligand Binding Assay

1 Objective

[0764] The objective of this study was to evaluate the binding properties of test compounds on 5-hydroxytryptamine receptor 1A (5-HT_A).

2 Materials and Instrumentation

TABLE 48

2.1 Regents

Items	Vendor	Cat#
[3H]-8-Hydroxy-DPAT	PE	NET929250UC
Serotonin HCl	Selleck	S4244
Bovine Serum Albumin (BSA)	Sigma	A1933
Calcium chloride ($CaCl_2$)	Sigma	C5670
$MgCl_2$	Sigma	M1028
Tris(hydroxymethyl)aminomethane (Tris)	Alfa Aesar	A18494
Polyethylenimine, branched (PEI)	Sigma	408727

2.2 Instrumentation and Consumables (Table 49)

Item	Supplier	Cat#
Microbeta^2 Microplate Counter	PerkinElmer	2450-0060
UniFilter-96 GF/B	PerkinElmer	6005177
TopSeal	Biotss	SF-800
MicroBeta Filtermate-96	PerkinElmer	D961962
Seven Compact pH meter	Mettler Toledo	S220
Ultrapure Water Meter	Sichuan Ulupure	UPH-III-20T
Benchtop Centrifuge	Hunan Xiangyi	L550
Microplate Shaker	Allsheng	MX100-4A
384-Well Polypropylene Microplate	Labcyte	PP-0200
96 Round Well Plate	Corning	3799
96 Round Deep Well Plate	Axygen	P-DW-11-C
Echo	LABCYTE	550

3 Experimental Methods

[0765] 1. The assay buffer was prepared following Table 50 below.

TABLE 50

Reagent	Concentration
Tris	25 mM
$MgCl_2$	10 mM
$CaCl_2$	1 mM
BSA	0.5% (w/v)

Adjust pH to 7.4 Followed by 0.2 pMV Sterile Filtration

[0766] 2. 8 doses of reference and test compounds were prepared starting from 10 mM stock solution as required by 5-fold serial dilutions with 100% (v/v) DMSO.

[0767] 3. UniFilter-96 G FIB plate was pretreated:

[0768] i. 50 μl/well of 0.5% (v/v) PEI was added to UniFilter-96 G FIB plates. The plates were sealed and incubated at 4° C. for 3 hrs.

[0769] ii. After incubation, the plates were washed 3 times with ice-cold wash buffer (50 mM Tris, pH7.4).

[0770] 4. Assay plate was prepared:

[0771] i. Cell membrane was diluted with assay buffer and 100 μl/well was added to 96 round well plates to reach a concentration of 20 μg/well.

[0772] ii. 8 concentrations of reference or test compounds were prepared and 50 μl/well was added to 96 round deep well plates.

[0773] iii. [3H]-8-Hydroxy-DPAT was diluted with assay buffer to 2 nM (4×final concentration) and 50 μl/well was added to 96 round well plates.

[0774] 5. The plate was centrifuged at 1000 rpm for 30 secs and then agitated at 600 rpm, R.T. for 5 min.

[0775] 6. The plates were sealed and the plate was incubated at 27° C. for 90 min.

[0776] 7. The incubation was stopped by vacuum filtration onto GF/B filter plates followed by 4 times washing with ice-cold wash buffer (50 mM Tris, pH7.4).

[0777] 8. The plates were dried at 37° C. for 45 min.

[0778] 9. The filter plates were sealed and 40 μl/well of scintillation cocktail was added.

[0779] 10. The plate was read by using a Microbeta^2 microplate counter.

4 Data Analysis

[0780] 1. For reference and test compounds, the results were expressed as % Inhibition, using the normalization equation: $N=100-100x(U-C_2)/(C_1-C_2)$, where U is the unknown value, C_1 is the average of high controls, and C_2 is the average of low controls.

[0781] 2. The IC_{50} was determined by fitting percentage of inhibition as a binding of compound concentrations with Hill equation using XLfit.

Results and Discussion

[0782] The results of potential competition binding properties of the exemplary compounds presented as IC_{50} of the disclosure targeting the human 5-hydroxytryptamine receptor (5-HT_{1A}) are summarized in Table 51.

TABLE 51

Effect of exemplary compounds of Formula (I) using Radioligand binding assay on human 5-HT_{1A} receptor

Compound ID	h5-HT_{1A}, IC_{50} [nM]
5-MeO-DMT	6
DMT	689
(R) I-66	22
(S) I-67	5
(R) I-67	22
I-71	51
I-128	87
I-130	NT[(1)]

[(1)]Not tested

Results and Discussion

[0783] Exemplary compounds of Formula (e), thereof were evaluated using radioligand binding assay on human 5-HT_{1A} receptor. C_{50} (nM) concentrations are illustrated in Table 51. This assay confirms that compounds of Formula (a) of the disclosure are effective ligands of the target human 5-HT_{1A} receptors.

Example 22A: Human 5-HT_{2B}: Radioligand Binding Assay

[0784] The objective of this study was to evaluate the binding properties of test compounds on 5-HT2B.

Materials and Instruments (Table 52)

Materials	Vendor	Cat#
[3H]-LSD	PerkinElmer	NET638250UC
Yohimbine	MedChemExpress	HY-N0127
Bovine Serum Albumin (BSA)	Sigma	A1933
Calcium chloride ($CaCl_2$)	Sigma	C5670
Tris(hydroxymethyl)aminomethane (Tris)	Alfa Aesar	A18494
Polyethylenimine, branched (PEI)	Sigma	408727

Instrumentation and Consumables (Table 53)

Item	Supplier	Cat#
Microbeta2 Microplate Counter	PerkinElmer	2450-0060
UniFilter-96 GF/B	PerkinElmer	6005177
TopSeal	Biotss	SF-800
MicroBeta Filtermate-96	PerkinElmer	D961962
Seven Compact pH meter	Mettler Toledo	S220
Ultrapure Water Meter	Sichuan Ulupure	UPH-III-20T
Benchtop Centrifuge	Hunan Xiangyi	L550
Microplate Shaker	Allsheng	MX100-4A
384-Well Polypropylene Microplate	Labcyte	PP-0200
96 Round Well Plate	Corning	3799
96 Round Deep Well Plate	Axygen	P-DW-11-C
Echo	LABCYTE	550

Experimental Methods

[0785] 1) The assay buffer was prepared following Table 54 below.

TABLE 54

Reagent	Concentration
Tris	50 mM
$CaCl_2$	4 mM
BSA	0.1% (w/V)

Adjust pH to 7.4 Followed by 0.2 μM Sterile Filtration

[0786] 2) Eight doses of reference and test compounds starting from 10 mM stock solution as requested by 5-fold serial dilutions with 100% (v/v) DMSO.

[0787] 3) UniFilter-96 GF/B plate was pretreated:

[0788] a. 50 μl/well of 0.5% (v/v) PEI to UniFilter-96 G F/B plates. The plates were sealed and incubated at 4° C. for 3 hrs.

[0789] b. After incubation, the plates were washed 3 times with ice-cold wash buffer (50 mM Tris, pH7.4).

[0790] 4) Assay plate preparation:

[0791] a. Cell membrane was diluted with assay buffer and 330 μl/well added to 96 round deep well plates to reach a concentration of 1 unit/well.

[0792] b. Eight concentrations of reference or test compounds were prepared and 110 μl/well added to 96 round deep well plates.

[0793] c. [3H]-LSD was diluted with assay buffer to 5 nM (5×final concentration) and 110 μl/well was added to 96 round deep well plates.

[0794] 5) The plate was centrifuged at 1000 rpm for 30 secs and then agitate at 600 rpm, R.T. for 5 min.

[0795] 6) The plates were sealed and incubated at 37° C. for 90 min.

[0796] 7) The incubation was stopped by vacuum filtration onto G F/B filter plates followed by 4 times washing with ice-cold wash buffer (50 mM Tris, pH7.4).

[0797] 8) The plates were dried at 37° C. for 45 min.

[0798] 9) The filter plates were sealed and 40 μl/well of scintillation cocktail was added.

[0799] 10) The plate was read using a Microbeta2 microplate counter.

Data Analysis

[0800] For reference and test compounds, the results are expressed as % Inhibition, using the normalization equation: N=100−100×(U−C2)/(C1−C2), where U is the unknown value, C1 is the average of high controls, and C2 is the average of low controls. The IC_{50} is determined by fitting percentage of inhibition as a function of compound concentrations with Hill equation using XLfit.

TABLE 55

Effect of exemplary compounds of Formula (I) using Radioligand binding assay on 5-HT_{2B} receptor

Compound ID	5-HT_{2B}, IC_{50} [nM]	5-HT2B, Ki [nM]
5-MeO-DMT	248.92	128.79
DMT	423.14	218.92
I-71	171.24	88.60

Example 22B: Human-5HT_{1A}-cAMP Assay

Protocol:

[0801] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT1A receptor in stably transfected CHO-K1 cells was determined in a GPCR cell-based cAMP assay.

[0802] Cells were seeded in a total volume of 20 μL into white walled, 384-well microplates and incubated at 37° C. overnight before analysis. Prior to testing, cell plating media was exchanged with 10 μL of Assay buffer (HBSS+10 mM HEPES). Briefly, intermediate dilution of sample stocks was performed to generate 4×sample in assay buffer. 5 μL of 4×sample +5 μL of 4×forskolin was added to cells and incubated at 37° C. for 30 minutes. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 56.

TABLE 56

Effect of exemplary compounds of Formula (I) using cAMP functional assay on human 5-HT_{1A} receptor

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	0.97437	87.1
5MeO-DMT	0.012699	99.98
(S) I-67	0.011563	98.47

Example 22C: h-5HT_{2B} FLIPR Assay

Protocol:

[0803] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT_2B receptor in stably transfected HEK293 cells was determined in a calcium mobilization-based assay.

[0804] Cells were seeded in a total volume of 20 μL into white walled, 384-well microplates and incubated at 37° C. overnight. Prior to testing, cell plating media was exchanged with 20 μL of Dye Loading buffer (HBSS+20 mM HEPES containing 1×Dye, 1×Additive A and 2.5 mM Probenecid). Plates were incubated at 37° C. for 45 mins followed by 15 mins at room temperature.

[0805] 10 μl of assay buffer (HBSS+20 mM HEPES) was added to cells. Intermediate dilution of sample stocks was performed to generate 4×sample in assay buffer. Assay plates, compound plates were loaded into F LIP R instrument. 10 μL of sample was added using F LIP R onboard robotics after 5 seconds of starting calcium measurement. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 57.

TABLE 57

Effect of exemplary compounds of Formula (I) using FLIP R functional assay on human 5-HT_{2B} receptor

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	>10	13.4
5MeO-DMT	0.015452	28.88
(S) I-67	>10	4.23

Example 22D: h-5HT$_{2B}$—Positive Allosteric Modulator (PAM) Assay

Protocol:

[0806] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT2B receptor in stably transfected HEK293 cells was determined in a GPC R cell-based assay.

[0807] For Positive Allosteric Modulator determination, cells were pre-incubated with sample followed by EC20 addition. Intermediate dilution of sample stocks was performed to generate 5×sample in assay buffer. 5 μL of 5×sample was added to cells and incubated at 37° C. for 10 minutes. 5 μL of agonist at 6×EC20 concentration was added and cells were incubated at 37° C. for 120 minutes. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 58.

TABLE 58

Effect of exemplary compounds of Formula (I) using PAM functional assay on human 5-HT2B receptor

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	>10	0
5MeO-DMT	>10	0
(S) I-67	>10	0

Example 22E: h-5-HT$_{2C}$ FLIPR Assay

Protocol:

[0808] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT$_{2C}$receptor in stably transfected U2OS cells was determined in a calcium mobilization-based assay.

[0809] Cells were seeded in a total volume of 20 μL into white walled, 384-well microplates and incubated at 37° C. overnight. Prior to testing, cell plating media was exchanged with 20 μL of Dye Loading buffer (HBSS+20 mM HEPES containing 1×Dye, 1×Additive A and 2.5 mM Probenecid). Plates were incubated at 37° C. for 45 mins followed by 15 mins at room temperature.

[0810] 10 μl of assay buffer (HBSS+20 mM HEPES) was added to cells. Intermediate dilution of sample stocks was performed to generate 4×sample in assay buffer. Assay plates, compound plates were loaded into F LIP R instrument. 10 μL of sample was added using F LIP R onboard robotics after 5 seconds of starting calcium measurement. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 59.

TABLE 59

Effect of exemplary compounds of Formula (I) using FLIP R functional assay on human 5-HT$_{2C}$ receptor

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	0.01112	94.56
5MeO-DMT	0.0027312	95.42
(S) I-67	2.6897	75.3

Example 22F: h-5HT$_{2A}$-p-arrestin Assay

Protocol:

[0811] Compound potency (EC_{50}) and efficacy (Max response) against the human 5-HT$_{2A}$receptor in stably transfected U2OS cells was determined in a GPCR cell based P-arrestin reporter assay. Cells were seeded in a total volume of 20 μL into white walled, 384-well microplates and incubated at 37° C. overnight before analysis. For agonist determination, cells were incubated with sample to induce response. Intermediate dilution of sample stocks was performed to generate 5×sample in assay buffer. 5 μL of 5×sample was added to cells and incubated at 37° C. for 120 minutes. Final assay vehicle concentration was 1%. The results are expressed as a percent efficacy relative to the maximum response of the control ligand (serotonin) in Table 60.

TABLE 60

Effect of exemplary compounds of Formula (I) using a β-arrestin reporter assay on human 5-HT$_{2A}$ receptor:

Compound ID	EC_{50} (μM)	E_{max} (% of serotonin)
DMT	0.1136	38.86
5MeO-DMT	0.02945	72.41
(S) I-67	2.0697	38.02

Example 23: Psychedelic-Like Effect of Exemplary Compounds of Formula (I)

[0812] The effects of different doses of exemplary compounds of Formula (I) were evaluated on head-twitch response (HTR) as a behavior-based model of psychedelic activity.

Mouse Head Twitch Response (HTR) Test:

Protocols:

[0813] Adult C57BL/6J mice (body weight range 20-30 g) were each placed into an open-top test cage made of transparent plastic for 20-30 min of habituation prior to testing. Habituation and testing were both conducted under low light conditions (~100 lux). Mice received a subcutaneous (SC) injection of either vehicle, positive control substance (e.g., 2,5-dimethoxy-4-iodoamphetamine (DOI)), or test compound at appropriate doses and volumes (10 mL/kg). Immediately post-treatment each mouse was placed back in its respective test cage. The cages were placed at approximately 50 cm from each other on a white, adjustable height table/flat surface so that the experimenter could easily monitor fine behaviors of both mice within the testing environment. An opaque divider was placed between the cages to prevent animals from observing each other. Immediately after placing the mice back into the test cages, the experimenter sat directly in front of the two containers, and recorded in real time the number of head twitch responses (HTR, defined as rapid side-to-side rotational shaking of the head) performed by each mouse for 20 min, subdivided in 5 min intervals with the use of a silent timer. To ensure scoring accuracy and consistency, one experienced experimenter performed HTR recording for all mice included in a study. While mice were subjected to HTR testing, another mouse

pair underwent habituation in a separate set of test cages, so that at the end of the HTR scoring period new animals were ready to undergo substance administration and testing. Between individual HTR tests, cages were cleaned with water, disinfected with a 70% ethanol aqueous solution, and dried using paper towels.

Results and Discussion

[0814] FIGS. **6**, **7**, and **8** are graphs showing the effect of various doses of exemplary compounds of Formula (I), specifically (S) I-67, I-71, and I-128, respectively, on head-twitch response (HTR) in male C57BL6 mice. The mice were treated with compound I-71 by SC route (N=6 mice/dose). Data are expressed as mean±SEM. The induction of head twitches elicited by 5-HT_{2A} receptor agonists is believed to represent a behavioral proxy of their psychedelic effects.

Example 24: Pharmacokinetic Studies in Rat

Protocol

Study Details:

[0815] Animals: Male Sprague-Dawley rats (~225-350 g) from Charles River Labs were acclimatized for a minimum of 5 days prior to start of study procedures. Body weights were recorded on the day of dosing.

[0816] Food restriction: None.

[0817] Clinical observations: Animals were observed at the time of dosing and each sample collection. Any abnormalities were documented including presence/absence of wet dog shakes/back muscle contractions (WDS/BMC).

[0818] Dosing: Formulations were administered intravenously (i.v.) via the tail vein using a 25 G needle connected to a 1 cc syringe.

Formulation:

[0819] The Compounds of Formula (I) were freshly prepared at the appropriate concentrations in 5% Tween-80 in saline.

Sample Collection:

[0820] Blood collection time (h): 0.25, 1 and 4.

[0821] Volume/time-point: ~0.25 mL (saphenous vein).

Bioanalytical Method Development and Sample Analysis:

Analytes: Compounds of Formula (I).

[0822] Matrix: Rat plasma.

[0823] Instrumentation: AB Sciex QTRAP 4000 or 6500 MS/MS system equipped with an LC system with a binary pump, a solvent degasser, a thermostatted column compartment and a multiplate autosampler.

[0824] Bioanalytical method(s) development include:

[0825] 1. The ion transition for the test compounds and potential internal standards (i.e., identification of the parent and product ions) were selected.

[0826] 2. The mass spectrometric operating parameters were optimized.

[0827] 3. The chromatographic condition for the analytes were established.

[0828] 4. The appropriate internal standard (IS) was selected.

[0829] 5. The sample clean-up method using protein precipitation was developed.

Method(s) Qualification:

[0830] 1. The quantification dynamic range using non-zero calibration standards (STDs) in singlet was determined. The STDs consisted of a blank matrix sample (without IS), a zero sample (with IS), and at least 6 non-zero STDs covering the expected range and including the lower level of quantitation (LLOQ).

[0831] 2. Triplicate injections of a system suitability sample (neat solution containing the analyte and IS) bracketed the batch.

Method(s) Acceptance Criteria:

[0832] 1. At least 75% of non-zero STDs were included in the calibration curve with all back-calculated concentrations within ±20% deviation from nominal concentrations (±25% for the lower level of quantification, LLOQ).

[0833] 2. The correlation coefficient (r) of the calibration curve was greater than or equal to 0.99 using quadratic regression analysis ($1/x^2$ weighting).

[0834] 3. The area ratio variation between the pre- and post-run injections of the system suitability samples was within ±25%.

Sample Analysis Batch:

[0835] 1. Triplicate injections of a system suitability sample bracketed the batch.

[0836] 2. The STDs were ascending order.

[0837] 3. The study samples and the dosing solutions were diluted as 3 independent dilutions into blank matrix (plasma).

[0838] 4. For more than 40 study samples in a batch, two sets of STDs bracketing the samples were utilized.

[0839] Samples which are 25% greater than the highest calibration standard, were diluted and re-assayed along with a corresponding dilution quality control standard. Dilution standards were acceptable if they are within 25% accuracy of the target concentration.

PK Analysis

[0840] Analysis software: Phoenix® WinNonlin® 8.3 (Pharsight, Certara, Mountainview, CA).

[0841] Analysis methods: non-compartmental analysis, linear up/log down trapezoidal rule.

[0842] PK parameters: $t_{1/2}$ and $AUC_{0\text{-}tlast}$ were estimated.

Results

[0843] Table 61 shows the plasma concentration of exemplary compounds I-71, (S) I-67, and I-128 following i.v. administration.

TABLE 61

Plasma concentrations of I-1 following 1.10 mg/kg i.v. administration (Group 2).

Example ID	Dose (mg/kg)	Experimental time (h)/Rat#	Plasma concentration (ng/mL)			
I-71	1.37		R01	R02	R03	Mean ± SD
		0.25	292	280	287	286 ± 6.03
		1	61.5	87.2	98.9	82.5 ± 19.1
		4	1.27	1.77	2.43	1.82 ± 0.582
(S) I-67	1.33		R04	R05	R06	Mean ± SD
		0.25	413	473	422	436 ± 32.4
		1	172	155	158	162 ± 9.07
		4	5.35	8.41	7.12	6.96 ± 1.54
I-128	1.37		R04	R05	R06	Mean ± SD
		0.25	146	128	139	138 ± 9.07
		1	19.0	13.1	13.4	15.2 ± 3.32
		4	No Peak	No Peak	No Peak	n/a

*Values in italics are below the lower limit of quantitation (BLQ, 0.5 ng/mL) but were included in calculations.
*BLQ denotes below the lower limit of quantitation (0.5 ng/mL).

[0844] Table 62 is a summary of the plasma apparent $t_{1/2}$ and $AUC_{0\text{-}tlast}$ for exemplary compound I-1 following 1.10 mg/kg i.v. administration (Group 2).

TABLE 62

Summary of plasma apparent $t_{1/2}$ and $AUC_{0\text{-}tlast}$ for I-1 following 1.10 mg/kg i.v. administration (Group 2).

Example ID	Dose (mg/kg)	Parameter	Parameter estimate for each animal			
I-71	1.37		R01	R02	R03	Mean ± SD
		Apparent $t_{1/2}$ (h)[a]	0.493	0.519	0.549	0.520 ± 0.0281
		$AUC_{0\text{-}tlast}$ (h*ng/mL)d	253	275	297	275 ± 21.7
(S) I-67	1.33		R04	R05	R06	Mean ± SD
		Apparent $t_{1/2}$ (h)[a]	0.598	0.663	0.646	0.636 ± 0.0336
		$AUC_{0\text{-}tlast}$ (h*ng/mL)	470	508	472	484 ± 21.1
I-128	1.37		R04	R05	R06	Mean ± SD
		Apparent $t_{1/2}$ (h)[a]	0.255	0.228	0.222	0.235 ± 0.0174
		$AUC_{0\text{-}tlast}$ (h*ng/mL)	99.0	85.7	92.9	92.5 ± 6.63

[a]Apparent $t_{1/2}$ was estimated from 2 points only
nc denotes not calculable.

Discussion

[0845] Exemplary compounds of the disclosure were evaluated for their pharmacokinetics profile rat via i.v. administration. Table 61 and Table 62 summarize the results of three representative compounds of formula 1 for plasma concentrations and plasma apparent $t_{1/2}$ and $AUC_{0\text{-}tlast}$, respectively. These results show that the compounds of the disclosure show a spectrum of plasma $t_{1/2}$ and exposure profiles.

Example 25: Human, Rat, and Mouse Liver Microsomes Stability

Objective

[0846] The objective of this study was to estimate in vitro metabolic stability of exemplary compounds of Formula (I) or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof in pooled human, male rat, and male mouse liver microsomes. The concentrations of compounds in reaction systems were evaluated by LC-MS/MS for estimating the stability in pooled human, male rat, and male mouse liver microsomes. The in vitro intrinsic clearances of test compounds were determined as well.

Protocol

[0847] A master solution in the "Incubation Plate" containing phosphate buffer, ultra-pure H_2O, $MgCl_2$ solution and liver microsomes was made according to Table 63. The mixture was pre-warmed at 37° C. water bath for 5 minutes.

TABLE 63

Preparation of master solution

Reagent	Stock Concentration	Volume	Final Concentration
Phosphate buffer	200 mM	200 μL	100 mM
Ultra-pure H_2O	—	106 μL	—

TABLE 63-continued

Preparation of master solution			
Reagent	Stock Concentration	Volume	Final Concentration
$MgCl_2$ solution	50 mM	40 μL	5 mM
Microsomes	20 mg/mL	10 μL	0.5 mg/mL

[0848] 40 μL of 10 mM NADPH solution was added to each well. The final concentration of NADPH was 1 mM. The negative control samples were prepared by replacing NADPH with 40 μL of ultra-pure H_2O. Samples were prepared in duplicate. Negative controls were prepared in singlet.

[0849] The reaction was started with the addition of 4 μL of 200 μM exemplary test compounds of the disclosure or control compounds to each master solution to get the final concentration of 2 μM. This study was performed in duplicate.

[0850] Aliquots of 50 μL were taken from the reaction solution at 0, 15, 30, 45, and 60 minutes. The reaction solutions were stopped by the addition of 4 volumes of cold methanol with IS (100 nM alprazolam, 200 nM imipramine, 200 nM labet alol and 2 μM ketoprofen). Samples were centrifuged at 3,220 g for 40 minutes. Aliquot of 90 μL of the supernatant was mixed with 90 μL of ultra-pure H2O and then was used for LC-MS/MS analysis.

[0851] LC/MS analysis was performed for all samples from this study using a Shimadzu liquid chromatograph separation system equipped with degasser DGU-20A5R; solvent delivery unit LC-30AD; system controller SIL-30AC; column oven CTO-30A; CTC Analytics HTC PAL System. Mass spectrometric analysis was performed using a Triple Quad™ 5500 instrument.

[0852] All calculations were carried out using Microsoft Excel. Peak area ratios of test compound to internal standard (listed in the below table) were determined from extracted ion chromatograms.

[0853] All calculations were carried out using Microsoft Excel. Peak areas were determined from extracted ion chromatograms. The slope value, k, was determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve.

[0854] The in vitro half-life (in vitro $t_{1/2}$) was determined from the slope value:

$$\text{in vitro } t_{1/2} = -(0.693/k)$$

[0855] Conversion of the in vitro $t_{1/2}$(min) into the in vitro intrinsic clearance (in vitro C Lt, in μL/min/mg proteins) was done using the following equation (mean of duplicate determinations):

$$\text{in vitro } CL_{int} = \left(\frac{0.693}{(t_{1/2})}\right) * \left(\frac{\text{volume of incubation } (\mu L)}{\text{amount of proteins (mg)}}\right)$$

[0856] For the exemplary compounds of the disclosure or control compound that showed an initial fast disappearance followed by a slow disappearance, only the time points that were within the initial rate were included in the calculation.

Results and Discussion

[0857] Human, rat, and mouse liver microsomes contain a wide variety of drug metabolizing enzymes and are commonly used to support in vitro ADME (absorption, distribution, metabolism and excretion) studies. These microsomes are used to examine the potential first-pass metabolism by-products of orally administered drugs. Representative compounds of the disclosure were evaluated for their stability in human, rat and mouse liver microsomes.

[0858] A majority of the exemplary compounds of the disclosure in three species, human, rat, and mouse liver microsomes were recovered within a 60-minute time period indicating that the compounds were not rapidly cleared (see Table 64 for Exemplary compounds of Formula (I)).

TABLE 64

Metabolic Stability of Test Compounds in Liver Microsomes of Different Species (a)					
Compound ID	Species	$t_{1/2}$ (min)	CL_{int} (μL/min/mg protein)	Scaled-up CL_{int} (mL/min/Kg)	Predicted hepatic CL (mL/min/kg)
Diclofenac	Human	10.73	129.12	161.94	18.35
	Rat	15.22	91.05	163.16	41.25
	Mouse	43.31	32.00	140.00	54.78
5-MeO-DMT	Human	12.14	114.19	143.22	18.09
	Rat	5.68	244.17	437.56	49.02
	Mouse	44.52	31.13	136.21	54.19
Diclofenac	Human	10.31	134.44	168.61	18.44
	Rat	15.09	91.86	164.62	41.34
	Mouse	38.23	36.25	158.60	57.42
(R) I-66	Human	313.83	4.42	5.54	4.37
	Rat	17.83	77.73	139.29	39.53
	Mouse	98.54	14.07	61.54	36.55
(S) I-67	Human	46.77	29.64	37.17	13.30
	Rat	<4.51	>307.01	>550.16	>50.17
	Mouse	19.99	69.33	303.33	69.41
(R) I-67	Human	29.33	47.26	59.27	15.34
	Rat	10.54	131.56	235.75	44.73
	Mouse	24.15	57.39	251.07	66.25
I-71	Human	13.68	101.33	127.08	17.80
	Rat	9.70	142.94	256.15	45.41
	Mouse	7.80	177.71	777.46	80.66
I-128	Human	22.81	60.77	76.22	16.28
	Rat	7.43	186.57	334.33	47.38
	Mouse	20.78	66.70	291.79	68.78
I-130	Human	9.60	144.43	181.14	18.58
	Rat	<4.51	>307.01	>550.16	>50.17
	Mouse	8.03	172.54	754.88	80.41

Notes:

1. For the compounds that showed an initial fast disappearance followed by a slow disappearance, only the time points that were within the initial rate were included in the calculation.
2. If % remaining at 30 minutes was lower than 1%, then CL_{int} and $t_{1/2}$ will be reported as ">307.01" and "4.51," respectively.

TABLE 65

Metabolic Stability of Test Compounds in Liver Microsomes of Different Species (b)					
			Remaining Percentage (%)		
Compound ID	Species	Assay Format	0 min	30 min	60 min
Diclofenac	Human	With Cofactors	100.00	5.01	1.77
		Without Cofactors	100.00	112.67	96.67
	Rat	With Cofactors	100.00	11.86	6.35
		Without Cofactors	100.00	102.19	100.63

TABLE 65-continued

Metabolic Stability of Test Compounds in Liver Microsomes of Different Species (b)

Compound ID	Species	Assay Format	Remaining Percentage (%) 0 min	30 min	60 min
	Mouse	With Cofactors	100.00	45.55	33.71
		Without Cofactors	100.00	89.49	96.59
5-MeO-DMT	Human	With Cofactors	100.00	19.24	3.25
		Without Cofactors	100.00	18.58	3.00
	Rat	With Cofactors	100.00	2.57	0.36
		Without Cofactors	100.00	49.55	23.82
	Mouse	With Cofactors	100.00	61.84	39.30
		Without Cofactors	100.00	104.76	95.24
I-130	Human	With Cofactors	100.00	11.46	0.75
		Without Cofactors	100.00	99.47	94.15
	Rat	With Cofactors	100.00	0.00	0.00
		Without Cofactors	100.00	105.21	103.65
	Mouse	With Cofactors	100.00	7.52	0.87
		Without Cofactors	100.00	95.65	104.89
I-71	Human	With Cofactors	100.00	26.55	4.78
		Without Cofactors	100.00	98.77	104.91
	Rat	With Cofactors	100.00	10.63	1.37
		Without Cofactors	100.00	96.79	100.64
	Mouse	With Cofactors	100.00	6.96	0.66
		Without Cofactors	100.00	105.81	109.68
(S) I-67	Human	With Cofactors	100.00	66.20	41.10
		Without Cofactors	100.00	98.68	100.00
	Rat	With Cofactors	100.00	0.00	0.00
		Without Cofactors	100.00	99.06	96.86
	Mouse	With Cofactors	100.00	34.21	12.49
		Without Cofactors	100.00	103.46	100.35
(R) I-67	Human	With Cofactors	100.00	47.22	24.23
		Without Cofactors	100.00	79.21	71.91
	Rat	With Cofactors	100.00	15.35	1.93
		Without Cofactors	100.00	91.21	80.30
	Mouse	With Cofactors	100.00	43.11	17.88
		Without Cofactors	100.00	103.14	109.43
(R) I-66	Human	With Cofactors	100.00	98.13	87.59
		Without Cofactors	100.00	100.00	98.15
	Rat	With Cofactors	100.00	22.22	9.71
		Without Cofactors	100.00	102.61	100.00
	Mouse	With Cofactors	100.00	72.95	65.58
		Without Cofactors	100.00	104.20	100.00
I-128	Human	With Cofactors	100.00	41.35	16.15
		Without Cofactors	100.00	39.57	16.12
	Rat	With Cofactors	100.00	6.09	0.56
		Without Cofactors	100.00	70.92	52.18
	Mouse	With Cofactors	100.00	37.09	13.52
		Without Cofactors	100.00	89.52	87.90

Discussion

[0859] Exemplary compounds of the disclosure were evaluated for their stability inhuman, rat, and mouse liver microsomes. Table 64 and Table 65 illustrate the results of the stability studies. These results show that the compounds of the disclosure show a spectrum of stability across different species, including human, rat, and mouse.

Example 26: Human, Rat, Mouse and Dog: Plasma Stability

1. Preparation of Stock Solutions

[0860] The stock solution of test compound was prepared in DMSO and diluted at the final concentration of 200 μM. 1 mM lovastatin and propantheline working solution was prepared in DMSO and acetonitrile, respectively. Lovastatin was used as positive control for rat and dog plasma stability assay. Propantheline was used as positive control in human, mouse and monkey plasma stability assay.

2. Procedures for Plasma Stability

[0861] a. 2.5 μL of 200 μM or 1 mM test compound or control compound solution was spiked to 497.5 μL plasma to reach a final concentration of 1 μM or 5 μM. The final concentration of organic solvents was 0.5%. The assay was performed in duplicate.

[0862] b. The reaction samples were incubated at 37° C. at approximately 60 rpm in a water bath.

[0863] c. Aliquots of 50 μL were taken from the reaction samples at 0, 30, 60, 120, 180, and 240 minutes. The reaction was stopped by the addition of 7 volumes of cold acetonitrile containing internal standards (IS: 100 nM alprazolam, 200 nM imipramine, 200 nM labet alol and 2 μM ketoprofen).

[0864] d. All samples were vortexed for 2 minutes, followed by centrifugation at 3,220 g for 30 minutes to precipitate proteins. 100 μL of the supernatant was transferred to a new plate. The supernatant was diluted with ultrapure water according to the LC-MS signal response and peak shape.

3. Sample Analysis

[0865] Samples were analyzed by LC-MS/MS.

[0866] LC system: Shimadzu

[0867] MS analysis: Triple Quad™ 6500+ from AB Inc (Canada) with an ESI interface

[0868] Column temperature: 40° C.

[0869] Column: Xselect® Hss T3 2.5 p (2.1×30 mm) coupled with preguard column

TABLE 66

Mobile phase: 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B)

Time (min)	0	0.1	0.5	0.8	0.81	1.0
% B	5	5	100	100	5	5

4. Data Analysis

[0870] All calculations were carried out using Microsoft Excel. Remaining percentages of parent compounds at each time point are estimated by determining the peak area ratios from extracted ion chromatograms.

[0871] Additional embodiments described herein include intermediate compounds, including but not limited to those in Table 67 below:

TABLE 67

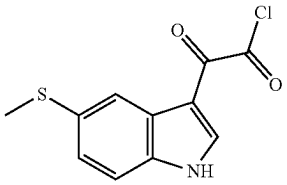
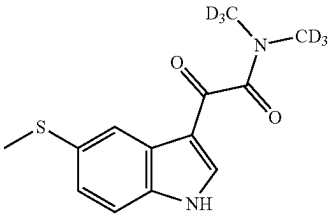
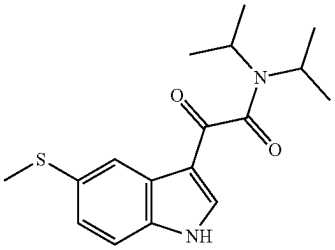
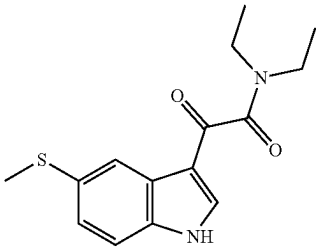
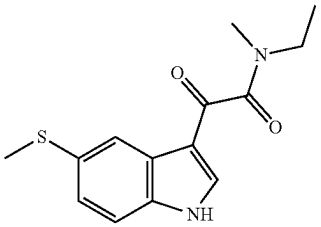
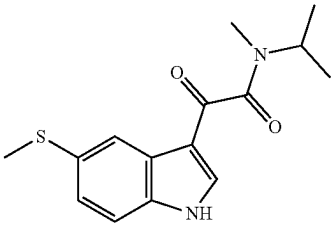
Compound	Structure	IUPAC Name
Intermediate 1; Example 1		(5-(methylthio)-1H-indol-3-yl)-2-oxoacetyl chloride
Intermediate 2; Example 1		N,N-bis(methyl-d_3)-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide
Intermediate 3; Example 2		N,N-diisopropyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide
Intermediate 4; Example 3		N,N-diethyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoacetamide
Intermediate 5; Example 4		N-ethyl-N-methyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoactamide
Intermediate 6; Example 5		N-isopropyl-N-methyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoactamide

TABLE 67-continued

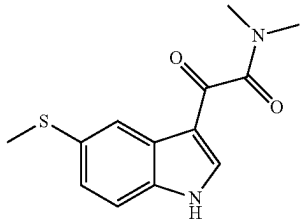
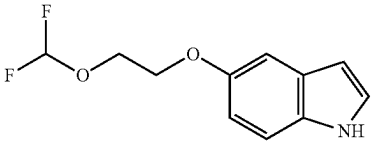
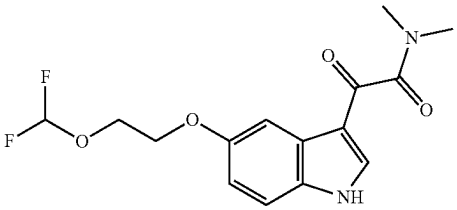
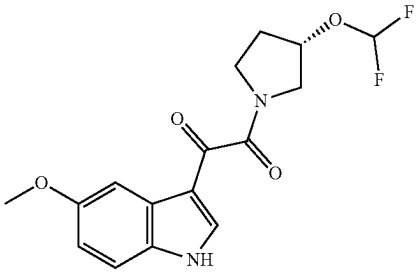
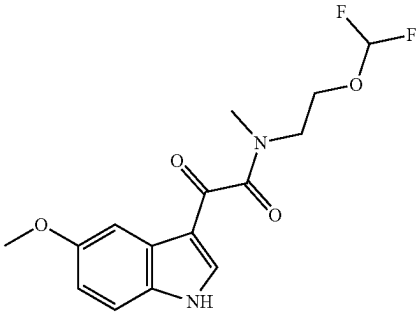
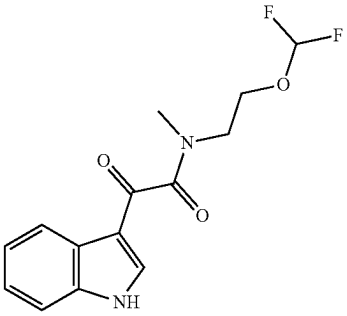
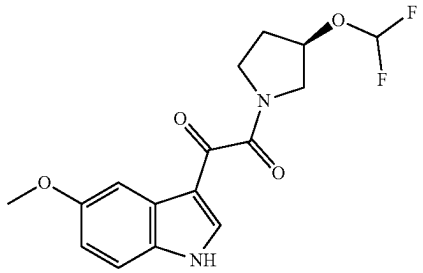
Compound	Structure	IUPAC Name
Intermediate 12A; Example 5A		N,N-dimethyl-2-(5-(methylthio)-1H-indol-3-yl)-2-oxoactamide
Intermediate 7; Example 14		5-(2-(difluoromethoxy)ethoxy)-1H-indole
Intermediate 8; Example 14		2-(5-(2-(difluoromethoxy)ethoxy)-1H-indol-3-yl)-N,N-dimethyl-2-oxoacetamide
Intermediate 9; Example 15		(S)-1-(3-(difluoromethoxy)pyrrolidin-1-yl)-2-(5-methoxy-1H-indol-3-yl)ethane-1,2-dione
Intermediate 10; Example 16		N-(2-(difluoromethoxy)ethyl)-2-(5-methoxy-1H-indol-3-yl)-N-methyl-2-oxoacetamide
Intermediate 11; Example 17		N-(2-(difluoromethoxy)ethyl)-2-(1H-indol-3-yl)-N-methyl-2-oxoacetamide

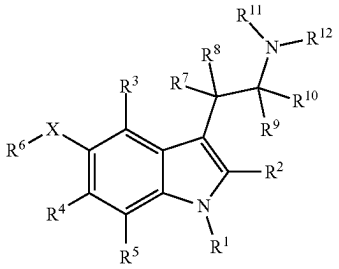
TABLE 67-continued

Compound	Structure	IUPAC Name
Intermediate 12; Example 18		(R)-1-(3-(difluoromethoxy)pyrrolidin-1-yl)-2-(5-methoxy-1H-indol-3-yl)ethane-1,2-dione

Exemplary Embodiments

E1: A Compound of Formula (I):

Formula (I)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

[0872] wherein:

[0873] X is absent or selected from O, S, S(O), and SO_2;

[0874] R^1 is selected from H, C_1-C_6alkyl, C_1-C_6alkyleneP(O)$(OR^{13})_2$, C_1-C_6alkyleneOP(O)$(OR^{13})_2$C(O)R^{13}, CO_2R^{13}, C(O)N$(R^{13})_2$, S(O)R^{13}, and SO_2R^{13};

[0875] R^2 is selected from H, halo, and C_1-C_6alkyl;

[0876] R^3, R^4, and R^5 are independently selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

[0877] R^6 is selected from H, C_1-C_{10}alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15};

[0878] R^7, R^1, R^9, and R^{10} are independently selected from H, halo, and C_1-C_6alkyl;

[0879] R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and C(O)R^{17}; or

[0880] R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl;

[0881] Z is selected from O, C(O), NR^{19}C(O), NR^{18}C(O)O, C(O)NR^{19}, OC(O)NR^{19}, and NR^{19};

[0882] Z' is selected from O, C(O), NR^{20}C(O), NR^{20}C(O)O, C(O)NR^{20}, OC(O)NR^{20}, and NR^{20};

[0883] R^{13}, R^{15}, R^{17}, R^{18}, R^{19}, and R^{20} are independently selected from H and C_1-C_6alkyl;

[0884] R^{14} and R^{16} are independently from H, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and C(O)C_1-C_4alkyl; and

[0885] available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof;

[0886] provided when X is O, R^1 is H, CH_3, or CD_3, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl, then R^{11} and R^{12} are not H, C_1-C_4alkyl, or C_1-C_4deuteroalkyl;

[0887] provided when X is O, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is CH_3 or CHF_2, then R^{11} and R^{12} are not CH_3 or CD_3; and provided when X is absent and R^6 is H, then at least one of R^{11} and R^{12} is not H or C_1-C_6alkyl.

[0888] E2: The compound of E1, provided (1) when X is absent, then R^6 is not H, D, or halogen, and (2) when X is O, S, S(O), or SO_2, then at least one of R^{11} and R^{12} is not selected from H, D, halogen, C_1-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, and C-C_6deuterohaloalkyl.

[0889] E3: The compound of E1, provided (1) when X is absent, then R^6 is not H, D, or halogen, and (2) when X is O, S, S(O), or SO_2, then neither R^{11} nor R^{12} is independently

selected from H, D, halogen, C_1-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, and C_1-C_6deuterohaloalkyl.

[0890] E4: The compound of E1, provided when X is absent, then R^6 is not H, D, or halogen.

[0891] E5: The compound of E1, provided when X is O, S, S(O), or SO_2, at least one of R^{11} and R^{12} is not selected from H, D, halogen, C_1-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, and C_1-C_6deuterohaloalkyl.

[0892] E6: The compound of E1, provided when X is O, S, S(O), or SO_2, neither R^{11} nor R^{12} is independently selected from H, D, C-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, and C_1-C_6deuterohaloalkyl.

[0893] E7: The compound of any one of E1 to E6, wherein available hydrogen atoms are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0894] E8: The compound of any one of E1 to E7, wherein X is S(O) or SO_2.

[0895] E9: The compound of any one of E1 or E7, wherein X is S.

[0896] E10: The compound of any one of E1 or E7, wherein X is absent.

[0897] E11: The compound of any one of E1 or E7, wherein X is O.

[0898] E12: The compound of any one of E1 to E11, wherein R^1 is selected from $S(O)R^{13}$ and SO_2R^{13}

[0899] E13: The compound of any one of E1 to E11, wherein R^1 is selected from H, C_1 C_4alkyl, C_1-C_3alkyleneP(O)$(OR^{13})_2$, C_1-C_4alkyleneOP(O)$(OR^{13})_2$, C(O)R^{13}, CO_2R^{13}, and C(O)N$(R^{13})_2$, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0900] E14: The compound of E13, wherein R^1 is selected from H, C_1-C_3alkyl, $CH_2P(O)(OR^{13})_2$, $CH_2CH_2P(O)(OR^{13})_2$, $CH_2CH(CH_3)P(O)(OR^{13})_2$, $CH(CH_3)CH_2P(O)(OR^{13})_2$, $CH(CH_3)P(O)(OR^{13})_2$, $CH(CH_2CH_3)P(O)(OR^{13})_2$, $(CH_2)OP(O)(OR^{13})_2$, C(O)R^{13}, and CO_2R^{13}, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0901] E15: The compound of any one of E1 to E14, wherein R^2 is selected from H, D, halo, and C_1-C_4alkyl wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0902] E16: The compound of E15, wherein R^2 is selected from H, D, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl.

[0903] E17: The compound of E16, wherein R^2 is selected from H, D, C H_3, CF_3, and CD_3.

[0904] E18: The compound of any one of E1 to E17, wherein R^3 is selected from H, D, halo, CN, C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0905] E19: The compound of E18, wherein R^3 is selected from H, D, CN, halo, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4deuteroalkenyl, C_1-C_4deuterofluoroalkenyl, C_2-C_4alkynyl, C_2-C_4deuteroalkynyl, C_2-C_4fluoroalkynyl, and C_1-C_4deuterofluoroalkynyl.

[0906] E20: The compound of E19, wherein R^3 is selected from H, D, CN, F, Br, Cl, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3, and CD_2CD_3.

[0907] E21: The compound of E20, wherein R^3 is selected from H, F, and Cl.

[0908] E22: The compound of any one of E1 to E21, wherein R^4 and R^5 are independently selected from H, halo, CN, C_1-C_4alkyl, C_2-C_4alkenyl, and C_2-C_4alkynyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0909] E23: The compound of E22, wherein R^4 and R^5 are independently selected from H, D, CN, halo, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, C_2-C_4alkenyl, C_2-C_4fluoroalkenyl, C_2-C_4deuteroalkenyl, C_2-C_4deuterofluoroalkenyl, C_2-C_4alkynyl, C_2-C_4deuteroalkynyl, C_2-C_4fluoroalkynyl, and C_1-C_4deuterofluoroalkynyl.

[0910] E24: The compound of E23, wherein R^4 and R^5 are independently selected from H, D, CN, F, Cl, Br, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3, and CD_2CD_3.

[0911] E25: The compound of E24, wherein R^4 and R^5 are selected from H and D.

[0912] E26: The compound of any one of E1 to E25, wherein R^6 is selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15}, and wherein, available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0913] E27: The compound of E26, wherein R^6 is C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0914] E28: The compound of E27, wherein R^6 is selected from C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_1-C_6deuteroalkyl, and C_1-C_6deuterofluoroalkyl.

[0915] E29: The compound of E28, wherein R^6 is selected from CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3, CD_2CD_3, $CH_2CH_2CH_3$, $CH_2CH_2CHF_2$, $CH_2CH_2CFH_2$, $CH_2CH_2CF_3$, $CH_2CH_2CHD_2$, $CH_2CH_2CDH_2$, $CH_2CH_2CD_3$ $CH(CH_3)_2$, $CH(CF_3)_2$, $CH(CHF_2)_2$, $CH(CFH_2)_2$, $CH(CD_3)_2$, $CH(CHD_2)_2$, $CH(CDH_2)_2$, $C(CH_3)_3$, $C(CF_3)_3$, $C(CHF_2)_3$, $C(CFH_2)_3$, $C(CD_3)_3$, $C(CHD_2)_3$, $C(CDH_2)_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CF_3$, $CH_2CH_2CH_2CD_3$, $CH_2CH(CH_3)_2$, $CH_2CH(CD_3)_2$, $CH_2CH(CF_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)CH_2CF_3$, $CH(CH_3)CH_2CD_3$, CH_2CH

$(CH_3)CH_3$, $CH_2CH(CH_3)CF_3$, $CH_2CH(CH_3)CD_3$, $CH_2C(CH_3)_3$, $CH_2C(CF_3)_3$, $CH_2C(CD_3)_3$, $CH_2CH_2C(CH_3)_3$, $CH_2CH_2C(CF_3)_3$, and $CH_2CH_2C(CD_3)_3$.

[0916] E30: The compound of E29, wherein R^6 is selected from H, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, and $CH_2C(CH_3)_3$.

[0917] E31: The compound of E26, wherein R^6 is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0918] E32: The compound of E31, wherein R^6 is selected from C_4-C_6alkenyl and C_2-C_6alkynyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium

[0919] E33: The compound of E32, wherein R^6 is selected from $CH{=}CH_2$, $CH_2CH{=}CH_2$, $CF_2CH{=}CH_2$, $CD_2CH{=}CH_2$, $CH{=}CH_2CH_3$, $CH{=}CH_2CF_3$, $CH{=}CH_2CHF_2$, $CH{=}CH_2CH_2F$, $CH{=}CH_2CD_3$, $CH{=}CH_2CHD_2$, $CH{=}CH_2CH_2D$, $C{\equiv}CH$, $C{\equiv}CCH_3$, $C{\equiv}CCF_3$, $C{\equiv}CCHF_2$, $C{=}CCFH_2$, $C{\equiv}CCD_3$, $C{\equiv}CCHD_2$, $C{\equiv}CCDH_2$, $CH_2C{\equiv}CH$, $CF_2C{\equiv}CH$, $CD_2C{\equiv}CH$, $CH_2C{\equiv}CCH_3$, $CF_2C{\equiv}CCH_3$, $CD_2C{\equiv}CCH_3$, $CH_2C{\equiv}CCD_3$, $CF_2C{\equiv}CCD_3$, $CD_2C{\equiv}CCD_3$, $CH_2C{\equiv}CCF_3$, $CF_2C{\equiv}CCF_3$, $CD_2C{\equiv}CCF_3$, $CH_2C{\equiv}CCHD_2$, $CF_2C{\equiv}CHD_2$, $CD_2C{\equiv}CHD_2$, $CH_2C{\equiv}CHF_2$, $CF_2C{\equiv}CHF_2$, and $CD_2C{\equiv}CHF_2$.

[0920] E34: The compound of E31, wherein R^6 is selected from C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, and C_2-C_6alkynyleneZR^{14}, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0921] E35: The compound of E34, wherein R^6 is selected from C_1-C_6alkyleneZR^{14}, C_1-C_6fluoroalkyleneZR^{14}, C_1-C_6deuteroalkyleneZR^{14}, C_1-C_6deuterofluoroalkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6fluoroalkenyleneZR^{14}, C_2-C_6deuteroalkenyleneZR^{14}, C_2-C_6deuterofluoroalkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_2-C_6fluoroalkynyleneZR^{14}, C_2-C_6deuteroalkynyleneZR^{14}, and C_2-C_6deuterofluoroalkynyleneZR^{14}

[0922] E36: The compound of E35, wherein R^6 is selected from C_1-C_6alkyleneZR^{14}, C_1-C_6fluoroalkyleneZR^{14}, C_1-C_6deuteroalkyleneZR^{14}, C_1-C_6deuterofluoroalkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, and C_2-C_6alkynyleneZR^{14}

[0923] E37: The compound of E36, wherein R^6 is selected from CH_2ZR^{14}, $CH_2CH_2ZR^{14}$, $CH_2CH_2CH_2ZR^{14}$, $CH_2CH_2CH_2CH_2ZR^{14}$, $CH(CH_3)CH_2ZR^{14}$, $CH(CH_3)CH_2CH_2ZR^{14}$, $CH_2CH(CH_3)ZR^{14}$, CF_2ZR^{14}, $CFHZR^{14}$, CH_2CHFZR^{14}, $CH_2CF_2ZR^{14}$, $CF_2CF_2ZR^{14}$, $CH_2CH_2CF_2ZR^{14}$, $CH_2CH_2CFHZR^{14}$, $CH_2CH_2CF_2ZR^{14}$, $CH(CH_3)CF_2ZR^{14}$, $CH(CH_3)CHFZR^{14}$—$CH_2CH_2CH_2CF_2ZR^{14}$, $CH_2CH_2CH_2CHFZR^{14}$, $CH(CH_3)CH_2CF_2ZR^{14}$, $CH(CH_3)CH_2CHFZR^{14}$, CD_2ZR^{14}, $CDHZR^{14}$, CH_2CHDZR^{14}, $CH_2CD_2ZR^{14}$, $CD_2CD_2ZR^{14}$, $CH_2CH_2CD_2ZR^{14}$, $CH_2CH_2CDHZR^{14}$, $CH_2CH_2CD_2ZR^{14}$, $CH(CH_3)CD_2ZR^{12}$, $CH(CH_3)CHDZR^{14}$—$CH_2CH_2CH_2CD_2ZR^{14}$, $CH_2CH_2CH_2CHDZR^{14}$, $CH(CH_3)CH_2CD_2ZR^{14}$, $CH(CH_3)CH_2CHDZR^{14}$, $CH{=}CHZR^{14}$, $CH_2CH{=}CHZR^{14}$, $C{\equiv}CZR^{14}$, $C{\equiv}CCH_2ZR^{14}$, $CH_2C{\equiv}CZR^{14}$, and $CH_2C{\equiv}CH_2ZR^{14}$.

[0924] E38: The compound of E37, wherein R^6 is selected from CH_2ZR^{14}, $CH_2CH_2ZR^{14}$, $CH_2CH_2CH_2ZR^{14}$, $CH_2CH_2CH_2CH_2ZR^{14}$, $CH(CH_3)CH_2ZR^{14}$, $CH(CH_3)CH_2CH_2ZR^{14}$, $CH_2CH(CH_3)ZR^{14}$, $CH{=}CHZR^{14}$, $CH_2CH{=}CHZR^{14}$, $CH{=}CH_2CHZR^{14}$, $C{\equiv}CCH_2ZR^{14}$, $CH_2C{\equiv}CZR^{14}$, and $CH_2C{\equiv}CH_2ZR^{14}$.

[0925] E39: The compound of E31, wherein R^6 is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, each of which is optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15} and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0926] E40: The compound of E39, wherein R^6 is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_2alkyleneC_3-C_7cycloalkyl, C_1-C_2alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2alkyleneC_6-C_{10}aryl, C_1-C_2alkyleneC_5-C_{10}heteroaryl, C_1-C_2fluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2fluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2fluoroalkyleneC_6-C_{10}aryl, C_1-C_2fluoroalkyleneC_5-C_{10}heteroaryl, C_1-C_2deuteroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuteroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuteroalkyleneC_6-C_{10}aryl, C_1-C_2deuteroalkyleneC_5-C_{10}heteroaryl, C_1-C_2deuterofluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuterofluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuterofluoroalkyleneC_6-C_{10}aryl, and C_1-C_2deuterofluoroalkyleneC_5-C_{10}heteroaryl, in which each of the cyclic groups is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{15}, and $C(O)R^{15}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0927] E41: The compound of E40, wherein the substituents on R^6 are selected from one to four of F, Cl, Br, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, CD_2H, CDH_2, CD_3, CF_3, CHF_2, CH_2F, CH_2CH_2F, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CD_2CD_3, OR^{15}, and $C(O)R^{15}$.

[0928] E42: The compound of any one of E34 to E38, wherein Z is selected from $NR^{19}C(O)$, $NR^{19}C(O)O$, $C(O)NR^{19}$, $OC(O)NR^{19}$, and NR^{19}.

[0929] E43: The compound of any one of E34 to E38, wherein Z is selected from O, C(O), $NR^{19}C(O)$, and $NR^{19}C(O)O$.

[0930] E44: The compound of any one of E1 to E43, wherein R^7, R^8, R^9, and R^{10} are independently selected from H, halo, and C_1-C_4alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0931] E45: The compound of E44, wherein R^7, R^8, R^9, and R^{10} are independently selected from H, D, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl.

[0932] E46: The compound of E45, wherein R^7, R^8, R^9, and R^{10} are independently selected from H, D, F, Br, Cl, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3 CF_2CF_3, CH_2CH_2D, CH_2CD_2H, and CD_2CD_3.

[0933] E47: The compound of E46, wherein R^7, R^8, R^9, and $R^{10}$are independently selected from H, F, and D.

[0934] E48: The compound of any one of E1 to E47, wherein R^{11} and R^{12} are independently selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0935] E49: The compound of any one of E1 to E48, wherein one of R^6, R^{11}, and R^{12} is not H or C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0936] E50: The compound of any one of E1 to E48, wherein one of R^{11} and R^{12} is selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium, and the other of R^{11} and R^{12} is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0937] E51: The compound of any one of E1 to E47, wherein at least one of R^{11} and R^{12} is selected from H and C_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom.

[0938] E52: The compound of E51, wherein at least one of R^{11} and R^{12} is selected from H, C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6fluoroalkyl, and C_1-C_6deuterofluoroalkyl.

[0939] E53: The compound of E52, wherein at least one of R^{11} and R^{12} is selected from H, D, CH_3, CD_2H, CDH_2, CD_3, CF_2H, CFH_2, CF_3, CH_2CH_3, CH_2CH_2F, CH_2CF_2H, CH_2CF_3, CF_2CF_3, CH_2CH_2D, CH_2CD_2H, CH_2CD_3 CD_2CD_3, $CH_2CH_2CH_3$, $CH_2CH_2CHF_2$, $CH_2CH_2CFH_2$, $CH_2CH_2CF_3$, $CH_2CH_2CHD_2$, $CH_2CH_2CDH_2$, $CH_2CH_2CD_3$ $CH(CH_3)_2$, $CH(CF_3)_2$, $CH(CHF_2)_2$, $CH(CFH_2)_2$, $CH(CD_3)_2$, $CH(CHD_2)_2$, $CH(CDH_2)_2$, $C(CH_3)_3$, $C(CF_3)_3$, $C(CHF_2)_3$, $C(CFH_2)_3$, $C(CD_3)_3$, $C(CHD_2)_3$, $C(CDH_2)_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2CH_2CF_3$, $CH_2CH_2CH_2CD_3$, $CH_2CH(CH_3)_2$, $CH_2CH(CD_3)_2$, $CH_2CH(CF_3)_2$, $CH(CH_3)CH_2CH_3$, $CH(CH_3)CH_2CF_3$, $CH(CH_3)CH_2CD_3$, $CH_2CH(CH_3)CH_3$, $CH_2CH(CH_3)CF_3$, $CH_2CH(CH_3)CD_3$, $CH_2C(CH_3)_3$, $CH_2C(CF_3)_3$, $CH_2C(CD_3)_3$, $CH_2CH_2C(CH_3)_3$, $CH_2CH_2C(CF_3)_3$, and $CH_2CH_2C(CD_3)_3$.

[0940] E54: The compound of E48, wherein at least one of R^{11} and R^{12} is selected from C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0941] E55: The compound of E54, wherein at least one of R^{11} and R^{12} is selected from C_4-C_6alkenyl and C_2-C_6alkynyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0942] E56: The compound of E55, wherein at least one of R^{11} and R^{12} is selected from C_2-C_6alkenyl, C_2-C_6fluoroalkenyl, C_2-C_6deuteroalkenyl, C_2-C_6deuterofluoroalkenyl, C_2-C_6alkynyl, C_2-C_6fluoroalkynyl, C_2-C_6deuteroalkynyl, and C_2-C_6deuterofluoroalkynyl.

[0943] E57: The compound of E56, wherein at least one of R^{11} and R^{12} is selected from $CH{=}CH_2$, $CH_2CH{=}CH_2$, $CF_2CH{=}CH_2$, $CD_2CH{=}CH_2$, $CH{=}CH_2CH_3$, $CH{=}CH_2CF_3$, $CH{=}CH_2CHF_2$, $CH{=}CH_2CH_2F$, $CH{=}CH_2CD_3$, $CH{=}CH_2CHD_2$, $CH{=}CH_2CH_2D$, $C{\equiv}CH$, $C{\equiv}CCH_3$, $C{\equiv}CCF_3$, $C{\equiv}CCHF_2$, $C{\equiv}CCFH_2$, $C{\equiv}CCD_3$, $C{\equiv}CCHD_2$, $C{\equiv}CCDH_2$, $CH_2C{\equiv}CH$, $CF_2C{\equiv}CH$, $CD_2C{\equiv}CH$, $CH_2C{\equiv}CCH_3$, $CF_2C{\equiv}CCH_3$, $CD_2C{\equiv}CCH_3$, $CH_2C{\equiv}CCD_3$, $CF_2C{\equiv}CCD_3$, $CD_2C{\equiv}CCD_3$, $CH_2C{\equiv}CCF_3$, $CF_2C{\equiv}CCF_3$, $CD_2C{\equiv}CCF_3$, $CH_2C{\equiv}CCHD_2$, $CF_2C{\equiv}CHD_2$, $CD_2C{\equiv}CHD_2$, $CH_2C{\equiv}CHF_2$, $CF_2C{\equiv}CHF_2$, and $CD_2C{\equiv}CHF_2$.

[0944] E58: The compound of E54, wherein at least one of R^{11} and R^{12} is selected from C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, and C_2-C_6alkynyleneZ'R^{16}, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0945] E59: The compound of E58, wherein at least one of R^{11} and R^{12} is selected from C_1-C_6alkyleneZ'R^{16}, C_1-C_6fluoroalkyleneZ'R^{16}, C_1-C_6deuteroalkyleneZ'R^{16}, C_1-C_6deuterofluoroalkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6fluoroalkenyleneZ'R^{16}, C_2-C_6deuteroalkenyleneZ'R^{16}, C_2-C_6deuterofluoroalkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_2-C_6fluoroalkynyleneZ'R^{16}, C_2-C_6deuteroalkynyleneZ'R^{16}, and C_2-C_6deuterofluoroalkynyleneZ'R^{16}

[0946] E60: The compound of E59, wherein at least one of R^{11} and R^{12} is selected from $CH_2Z'R^{16}$, $CH_2CH_2Z'R^{16}$, $CH_2CH_2CH_2Z'R^{16}$, $CH_2CH_2CH_2CH_2Z'R^{16}$, $CH(CH_3)$

$CH_2Z'R^{16}$, $CH(CH_3)CH_2CH_2Z'R^{16}$, $CH_2CH(CH_3)Z'R^{16}$, $CF_2Z'R^{16}$, CF HZ'R^{16}, $CH_2CHFZ'R^{16}$, $CH_2CF_2Z'R^{16}$, $CF_2CF_2Z'R^{16}$, $CH_2CH_2CF_2Z'R^{16}$, $CH_2CH_2CFHZ'R^{16}$, $CH_2CH_2CF_2Z'R^{16}$, $CH(CH_3)CF_2Z'R^{16}$, $CH(CH_3)CHFZ'R^{16}$—, $CH_2CH_2CH_2CF_2Z'R^{16}$, $CH_2CH_2CH_2CHFZ'R^{16}$, $CH(CH_3)CH_2CF_2Z'R^{16}$, $CH(CH_3)CH_2CHFZ'R^{16}$, $CD_2Z'R^{16}$, $CDHZ'R^{16}$, $CH_2CHDZ'R^{16}$, $CH_2CD_2Z'R^{16}$, $CD_2CD_2Z'R^{16}$, $CH_2CH_2CD_2Z'R^{16}$, $CH_2CH_2CDHZ'R^{16}$, $CH_2CH_2CD_2Z'R^{16}$, $CH(CH_3)CD_2Z'R^{16}$, $CH(CH_3)CHDZ'R^{16}$—, $CH_2CH_2CH_2CD_2Z'R^{16}$, $CH_2CH_2CH_2CHDZ'R^{16}$, $CH(CH_3)CH_2D_2Z'R^{16}$, $CH(CH_3)CH_2CHDZ'R^{16}$, CH═CHZ'R^{16}, CH_2CH═CHZ'R^{16}, C≡CZ'R^{16}, C≡$CCH_2Z'R^{16}$, CH_2C≡CZ'R^{16}, and CH_2C≡$CH_2Z'R^{16}$.

[0947] E61: The compound of E54, wherein at least one of R^{11} and R^{12} is selected from C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_2alkyleneC_3-C_7cycloalkyl, C_1-C_2alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2alkyleneC_6-C_{10}aryl, C_1-C_2alkyleneC_5-C_{10}heteroaryl, C_1-C_2fluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2fluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2fluoroalkyleneC_6-C_{10}aryl, C_1-C_2fluoroaalkyleneC_5-C_{10}heteroaryl, C_1-C_2deuteroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuteroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuteroalkyleneC_6-C_{10}aryl, C_1-C_2deuteroalkyleneC_5-C_{10}heteroaryl, C_1-C_2deuterofluoroalkyleneC_3-C_7cycloalkyl, C_1-C_2deuterofluoroalkyleneC_3-C_{10}heterocycloalkyl, C_1-C_2deuterofluoroalkyleneC_6-C_{10}aryl, and C_1-C_2deuterofluoroalkyleneC_5-C_{10}heteroaryl, in which each of the cyclic groups is optionally substituted with one to four substituents independently selected from F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyl, OR^{17}, and $C(O)R^{17}$, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0948] E62: The compound of any one of E1 to E47, wherein R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a monocyclic 3- to 7-membered heterocyclic ring or a bicyclic 7- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein each said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a halogen atom and/or available atoms are optionally replaced with an alternate isotope thereof.

[0949] E63: The compound of E62, wherein the one to four substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween are independently selected from halo, C_1-C_4alkyl, OH, OC_1-C_4alkyl, C_1-C_4alkyleneOH, and C_1-C_4alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0950] E64: The compound of E63, wherein at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OC_1-C_4alkyl, C_1-C_4alkyleneOH, and C_1-C_4alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0951] E65: The compound of E64, wherein at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OC_1-C_4alkyl, OC_1-C_4deuteroalkyl, OC_1-C_4fluoroalkyl, OC_1-C_4deuterofluoroalkyl, C_1-C_4alkyleneOH, C_1-C_4fluoroalkyleneOH, C_1-C_4deuteroalkyleneOH, C_1-C_4deuterofluoroalkyleneOH, C_1-C_4alkyleneOC_1-C_4alkyl, C_1-C_4alkyleneOC_1-C_4fluoroalkyl, C_1-C_4alkyleneOC_1-C_4deuteroalkyl, C_1-C_4alkyleneOC_1-C_4deuterofluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4alkyl, C_1-C_4deuteroalkyleneOC_1-C_4alkyl, C_1-C_4deuterofluoroalkyleneOC_1-C_4alkyl, C_1-C_4fluoroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4deuteroalkyl, C_1-C_4deuteroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4deuteroalkyleneOC_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4deuterofluoroalkyl, and C_1-C_4deuterofluoroalkyleneOC_1-C_4deuterofluoroalkyl.

[0952] E66: The compound of E65, wherein at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OCH_3, OCF_2H, $OCFH_2$, OCF_3, and OCD_3.

[0953] E67: The compound of any one of E58 to E60, wherein Z' is selected from $NR^{20}C(O)$, $NR^{20}C(O)O$, $C(O)NR^{20}$, $OC(O)NR^{20}$, and NR^{20}.

[0954] E68: The compound of anyone of E58 to E60, wherein Z' is selected from O, C (O), $NR^{20}C(O)$, and $NR^{20}C(O)O$.

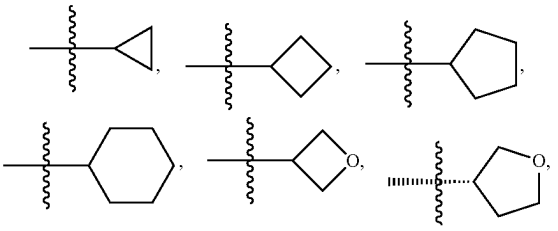
[0955] E69: The compound of any one of E1 to E68, wherein R^{14} and R^{18} are independently selected from H, C_1-C_4alkyl, C_3-C_7cycloalkyl, C_3-C_7heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to three substituents independently selected from F, Cl, C_1-C_4alkyl, and OC_1-C_4alkyl, and wherein available hydrogen atoms are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms are optionally replaced with deuterium.

[0956] E70: The compound of any one of E1 to E25 and E44 to E69, wherein X is selected from S, S(O), and SO_2, and wherein R^6 is selected from

[0957] CH_3, CD_3, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$,

[0958] $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$,

[0959] CH_2F, CHF_2, CH_2CHF_2, CH_2CF_3, $CH_2CH_2CF_3$,



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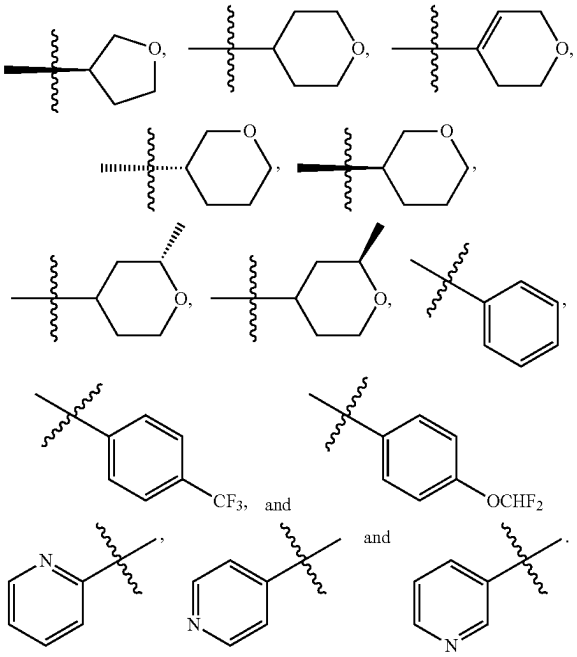


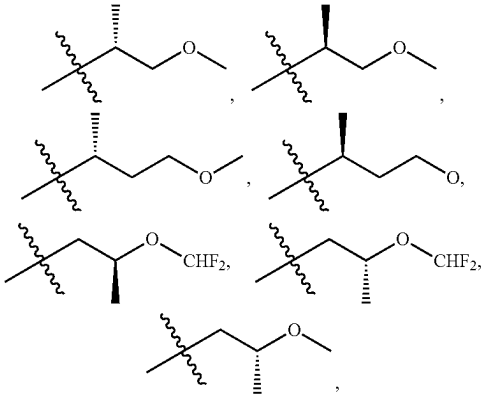
[0960] E71: The compound of any one of E1 to E47, wherein R^{11} and R^{12} are independently selected from

[0961] H, CH_3, CD_3, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$,

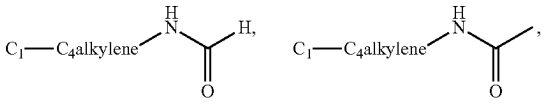
[0962] $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$,

[0963] CH_2F, CHF_2, CH_2CHF_2, CH_2CF_3, $CH_2CH_2CF_3$,

[0964] C_1-C_4alkyleneOCH$_3$, C_1-C_4alkyleneOCHF$_2$, C_1-C_4alkyleneOCH$_2$F,



[0965] C_1-C_4alkyleneC(O)CHF$_2$, C_1-C_4alkyleneC(O)CF$_3$,



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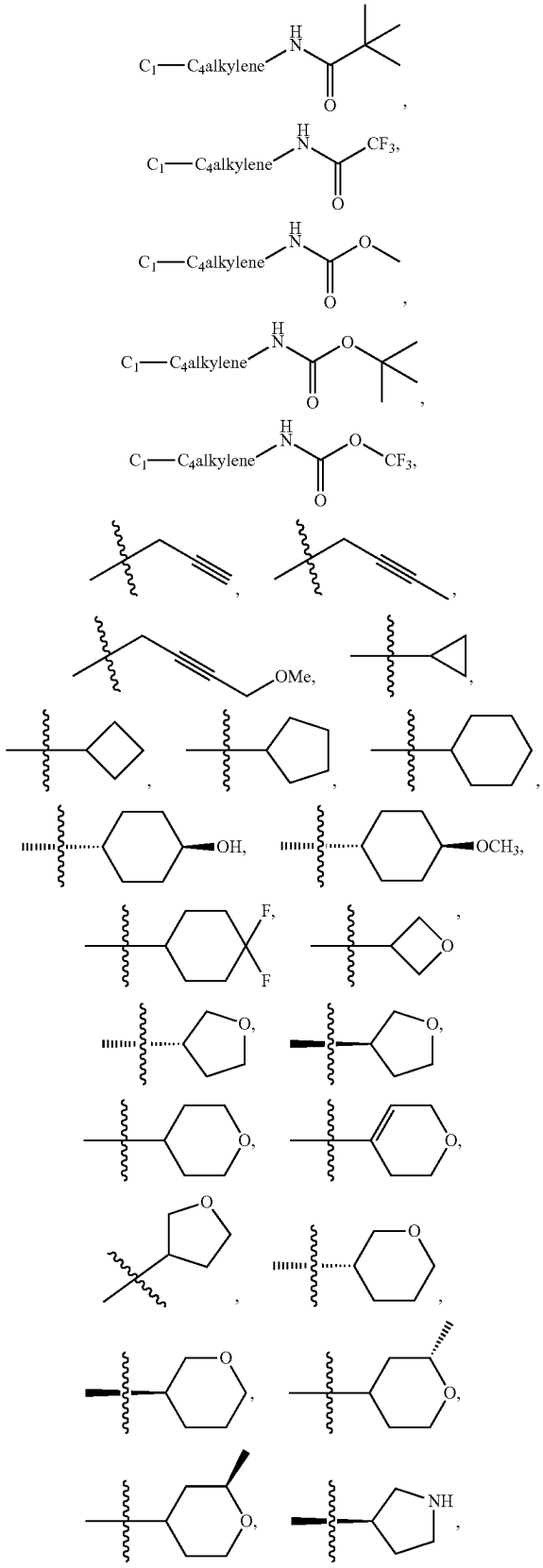

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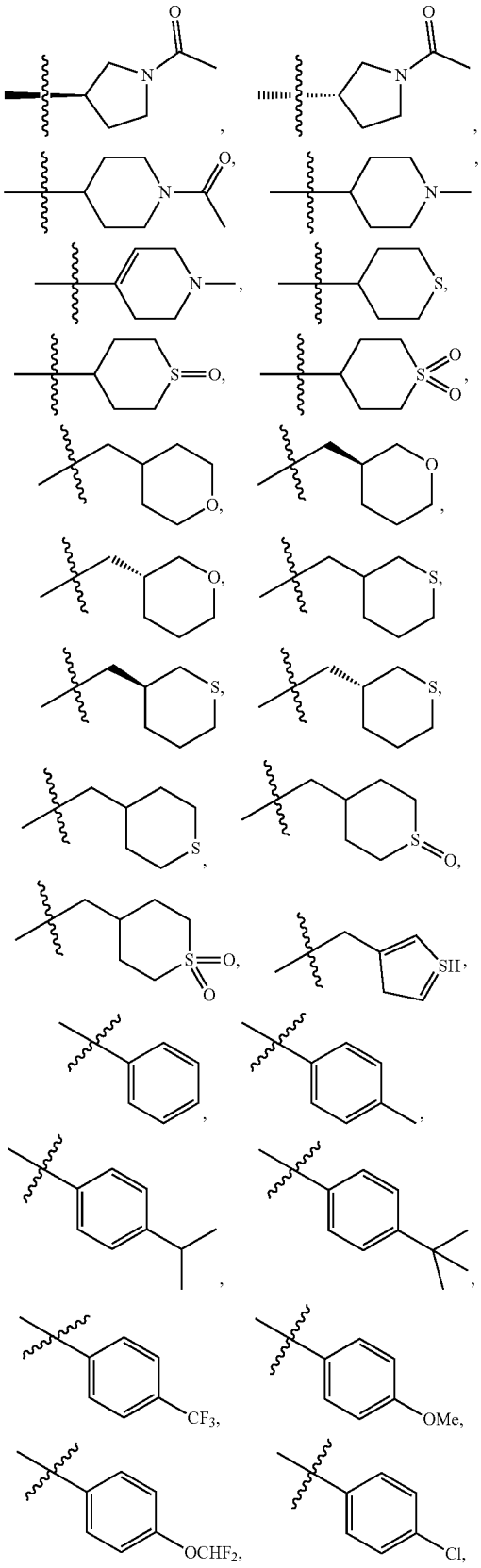

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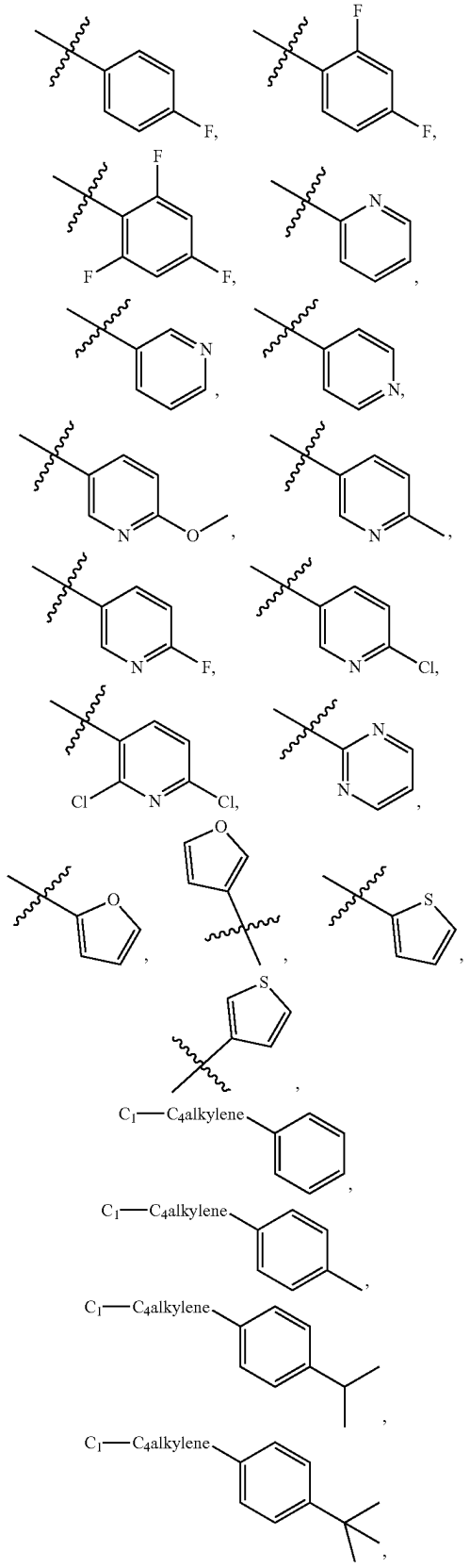

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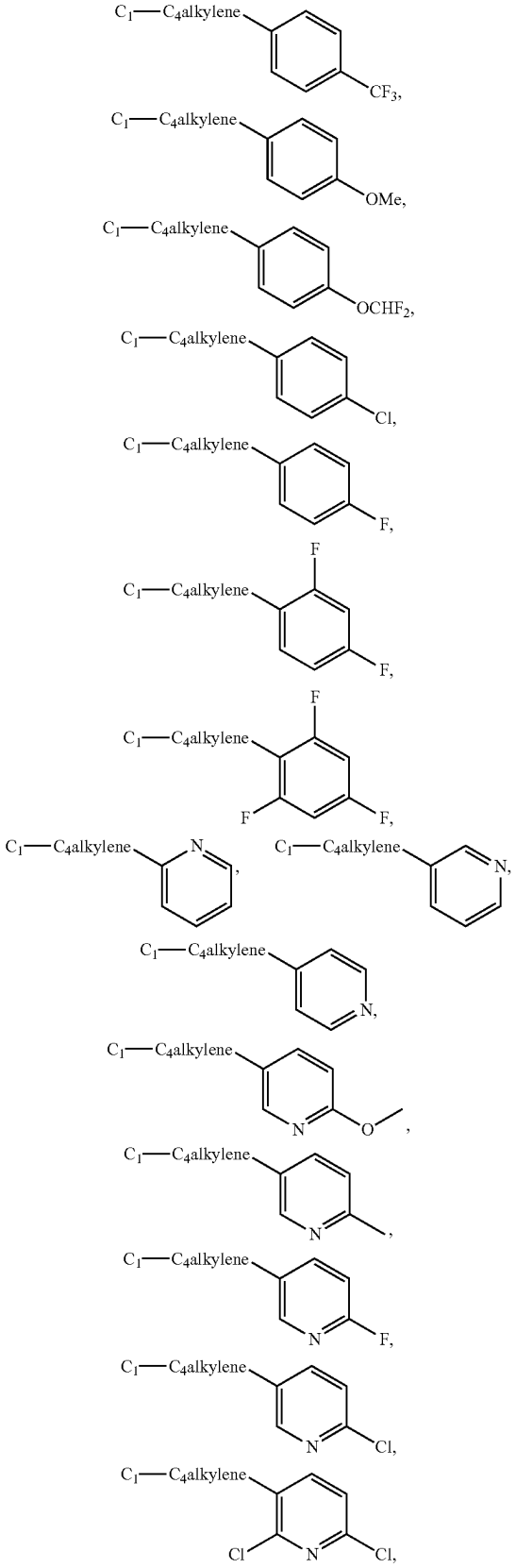

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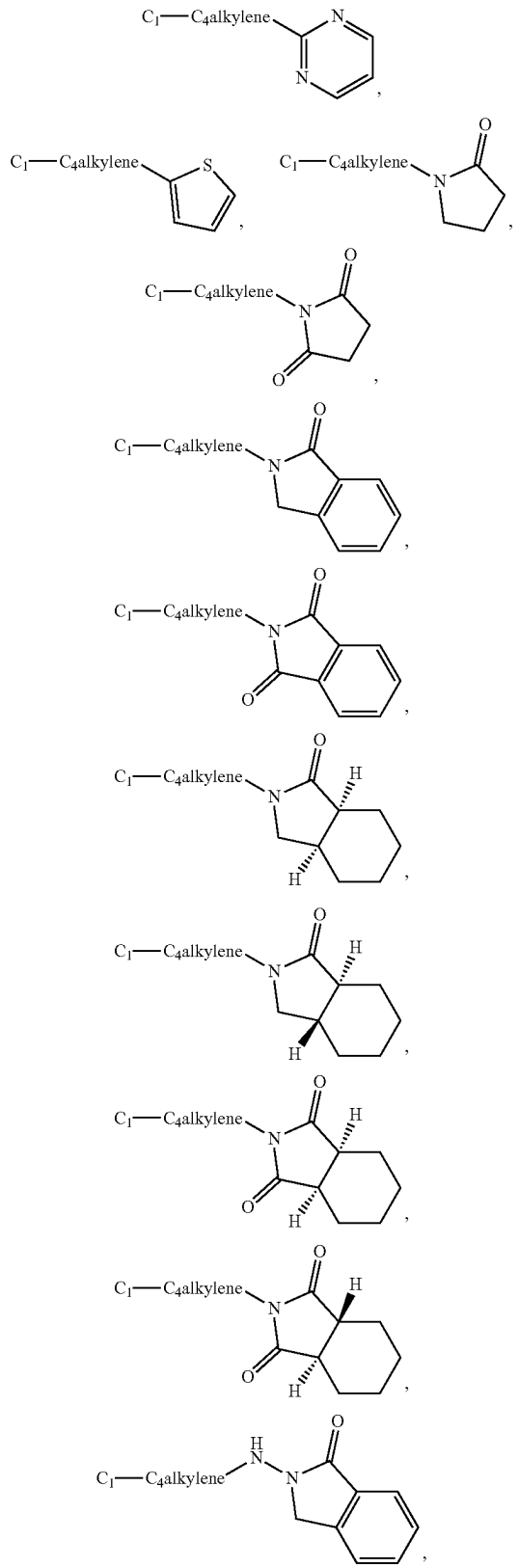

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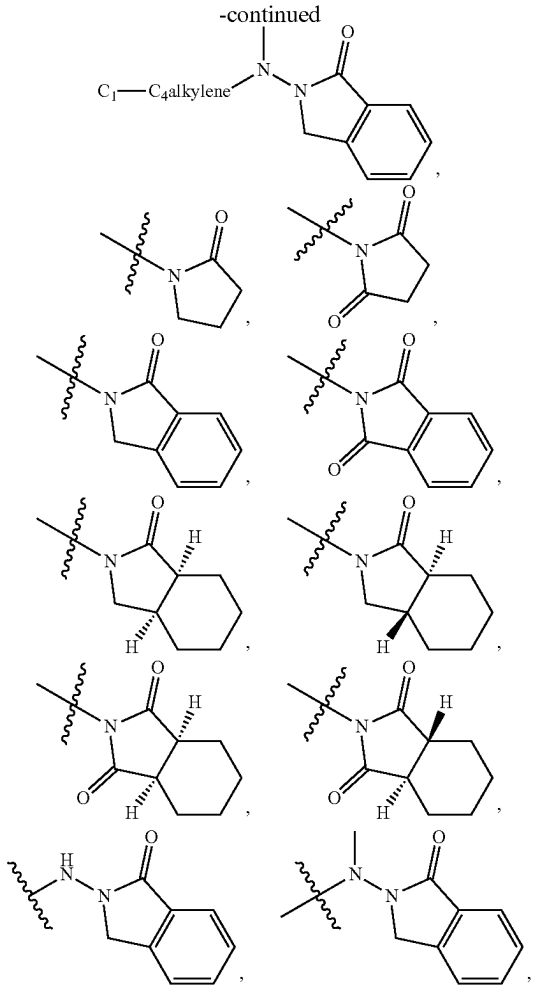
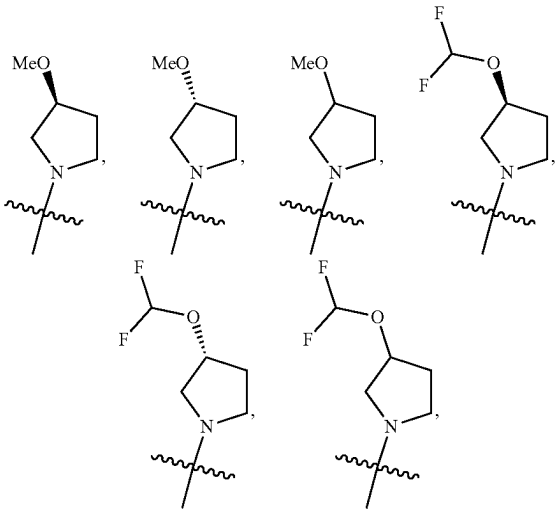


[0966] E72: The compound of any one of E1 to E47, wherein R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a heterocycle selected from:



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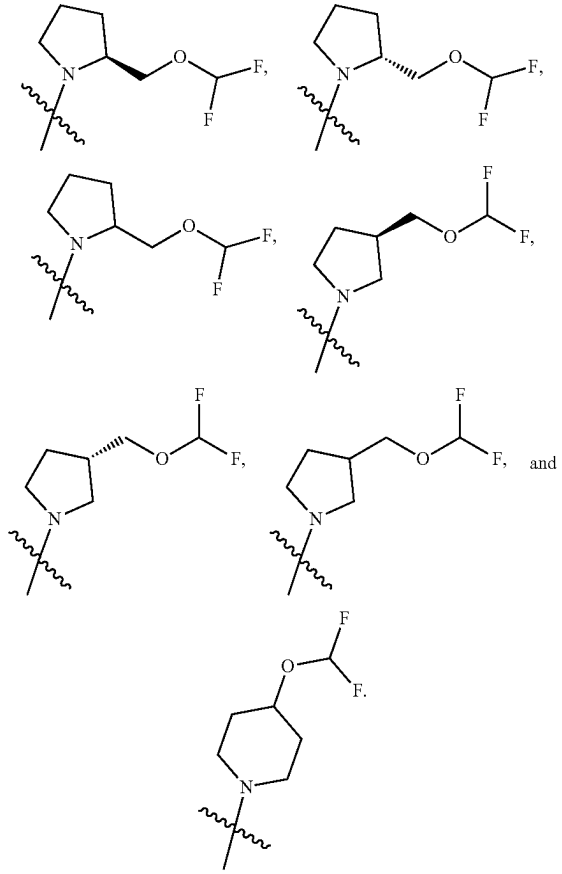

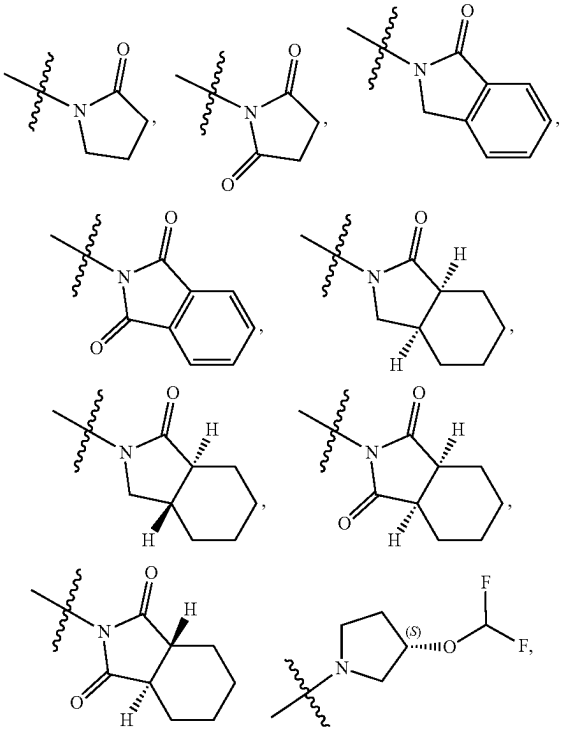

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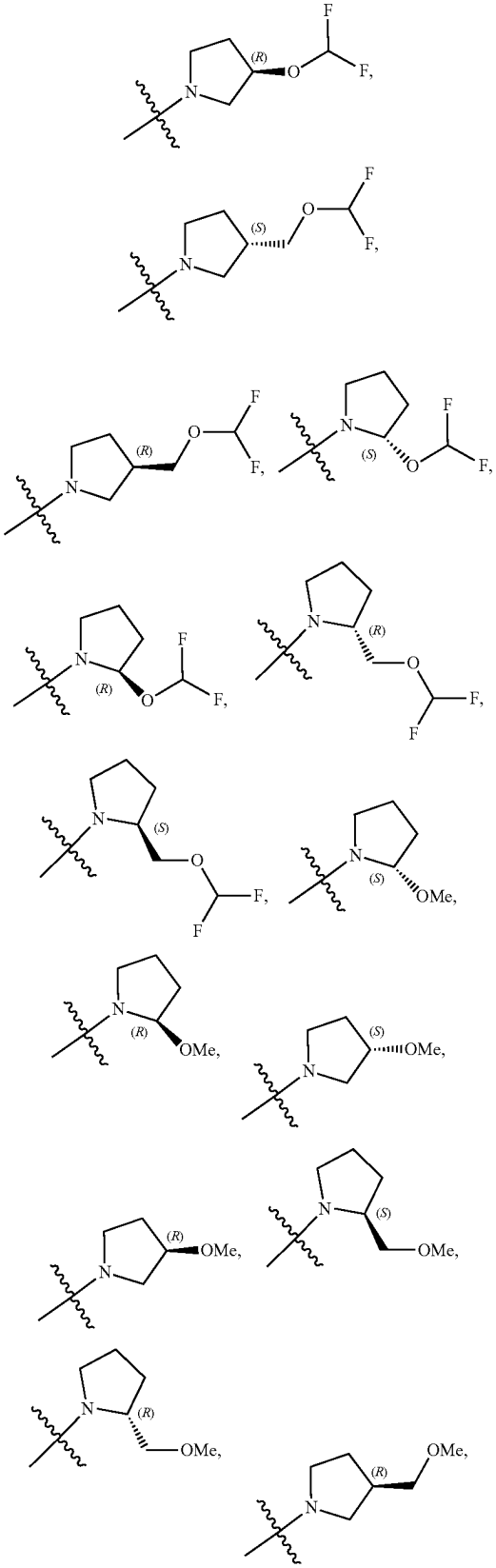

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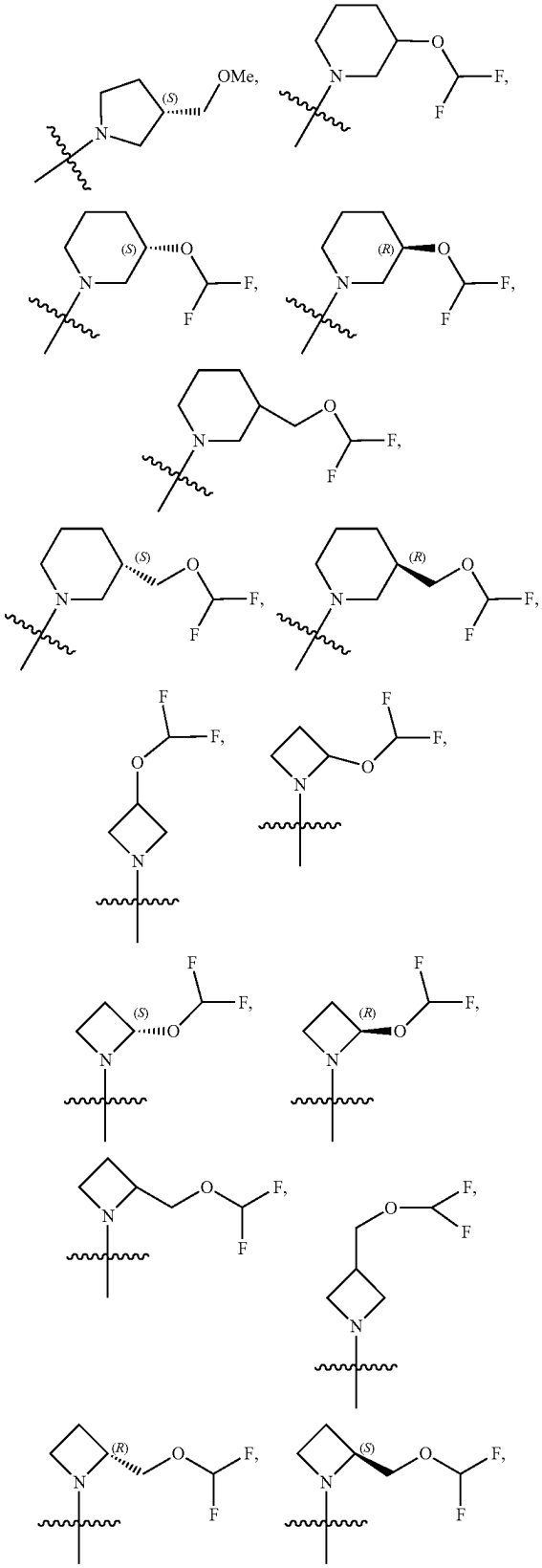

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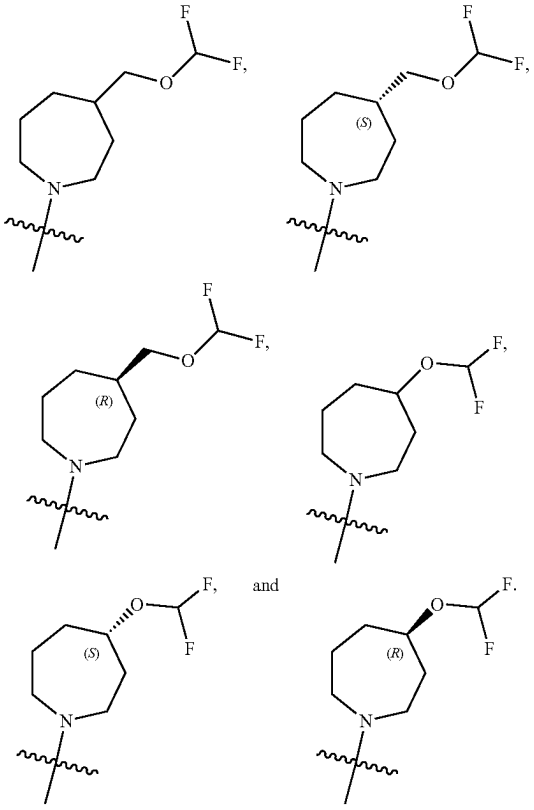
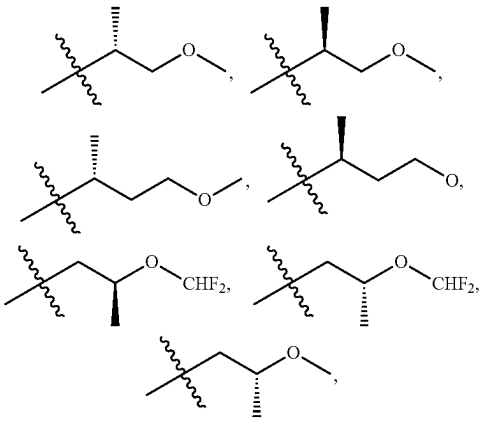
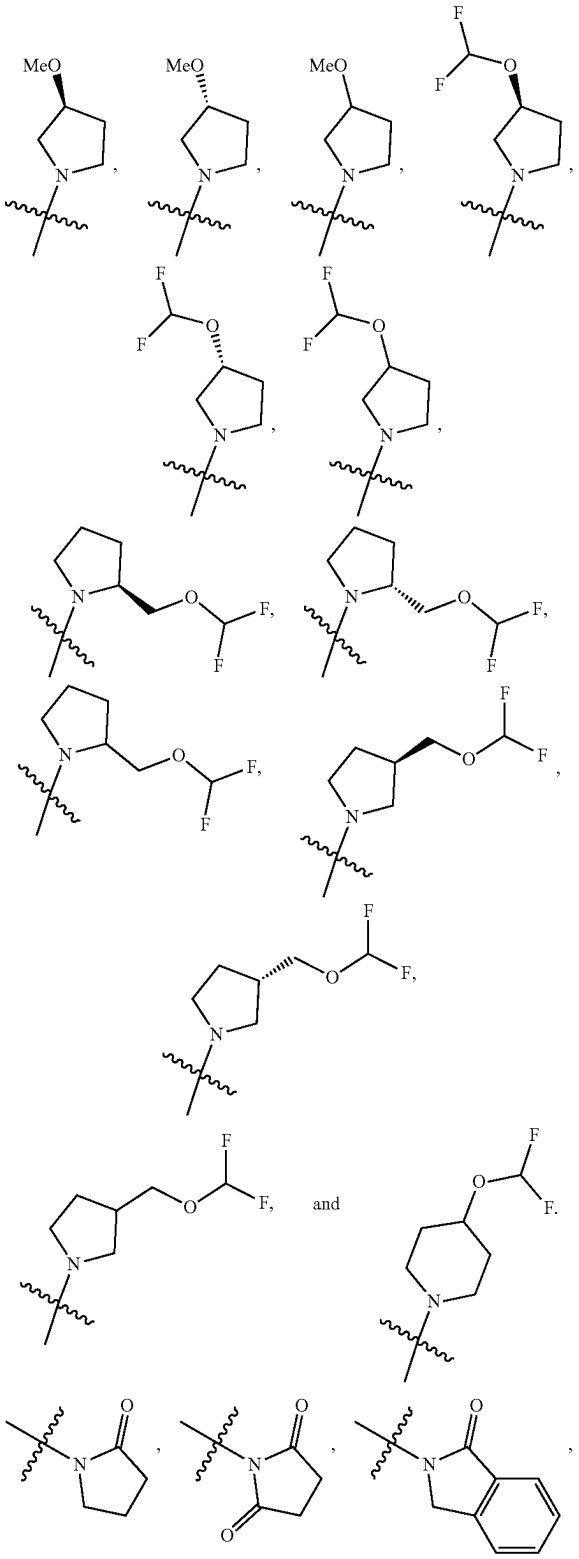


[0967] E73: The compound of any one of E1 to E47, wherein X is absent or O, wherein R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, selected from



[0968] E74: The compound of any one of E1 to E47, wherein R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a heterocycle selected from:



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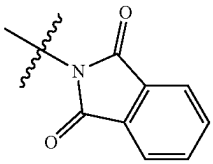
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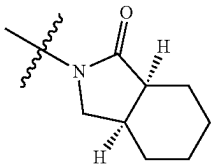
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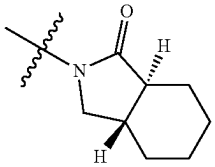
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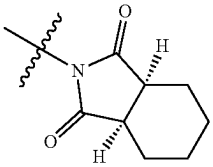
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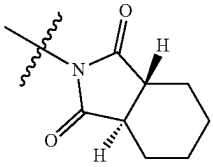
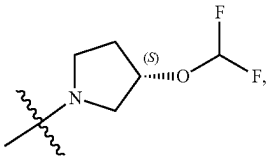
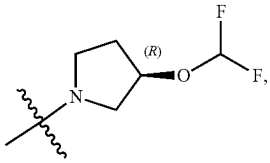
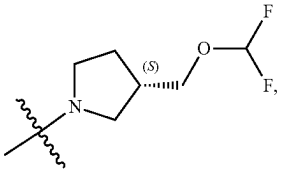
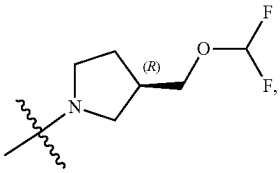
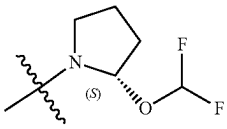
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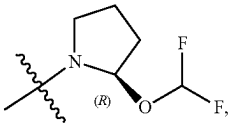
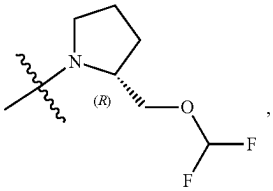
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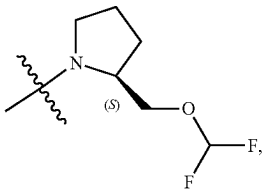
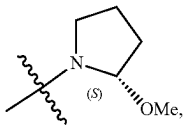
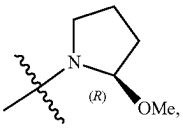
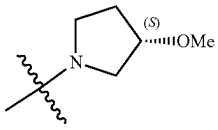
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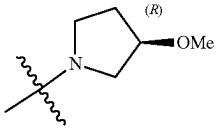
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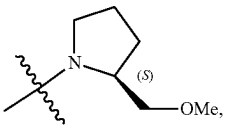

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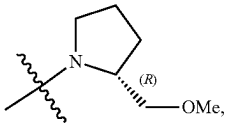
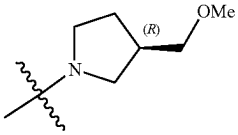
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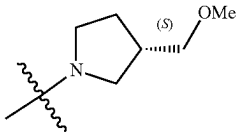
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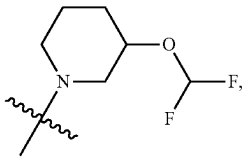
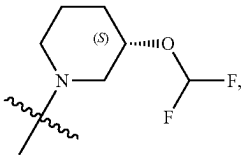
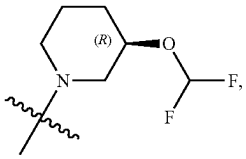
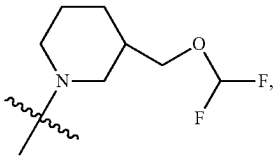
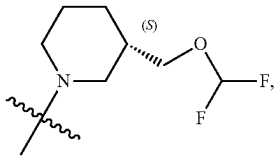
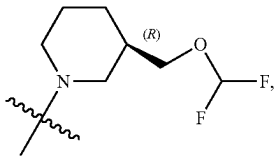
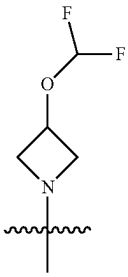
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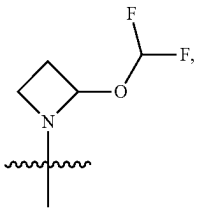
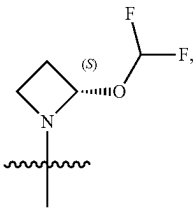
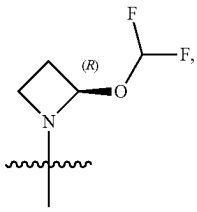
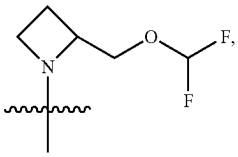
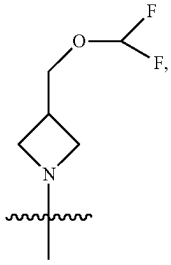
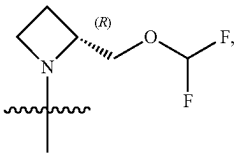

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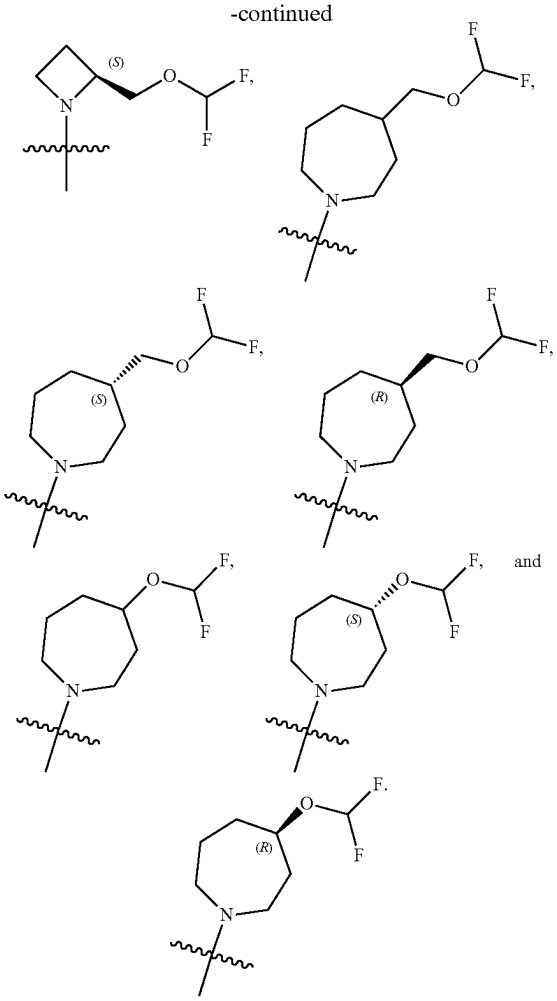
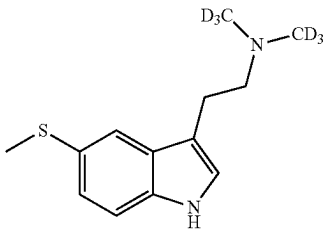
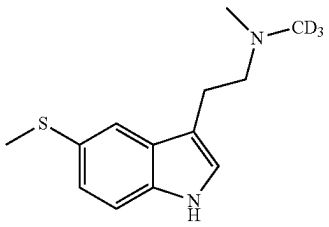


[0969] E75: The compound of any one of E1 to E6, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
I-1	
I-2	

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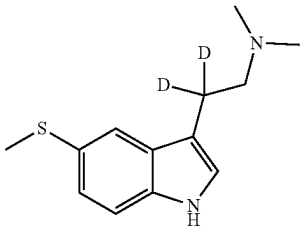
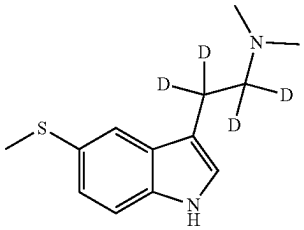
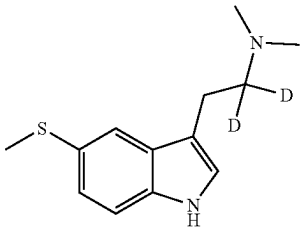
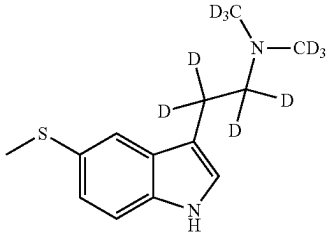
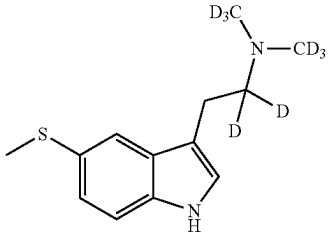
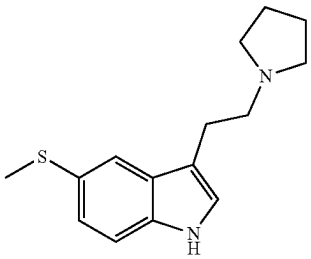
Compound	Structure
I-3	
I-4	
I-5	
I-6	
I-7	
I-8	

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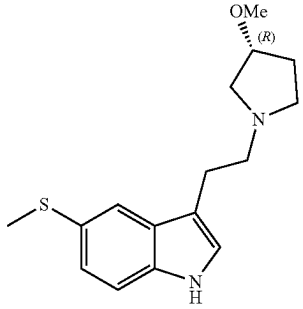
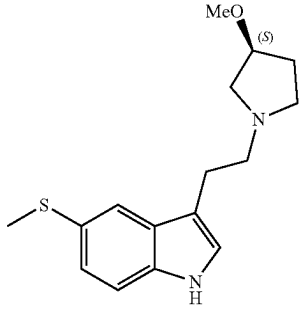
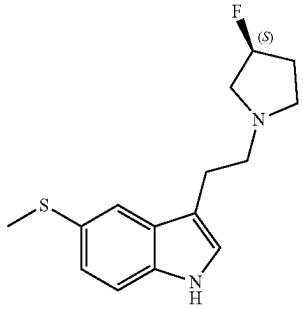
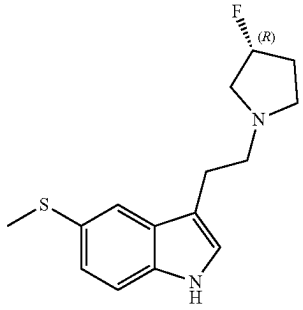
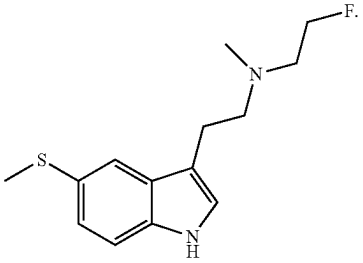
Compound	Structure
(R) I-9	
(S) I-9	
(R) I-10	
(S) I-10	
I-11	

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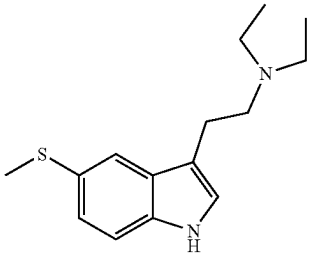
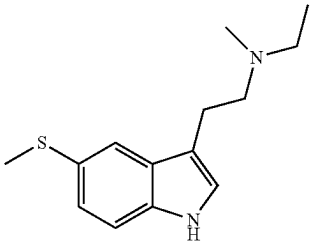
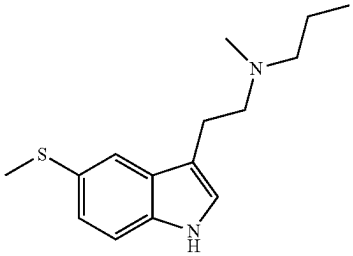
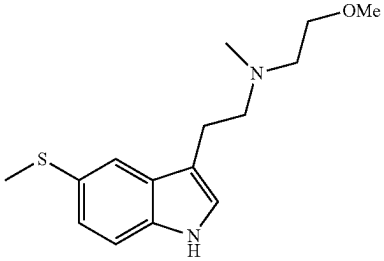
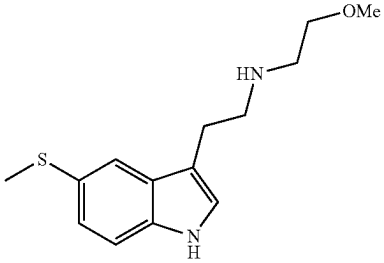
Compound	Structure
I-12	
I-13	
I-14	
I-15	
I-16	

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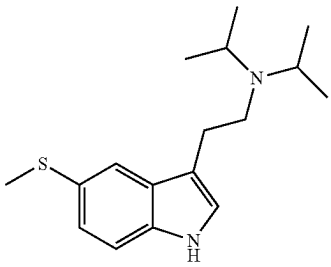
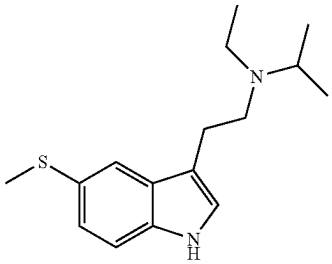
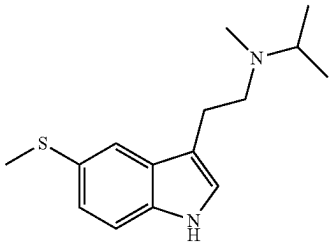
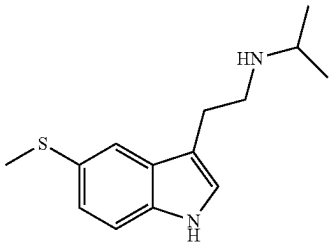
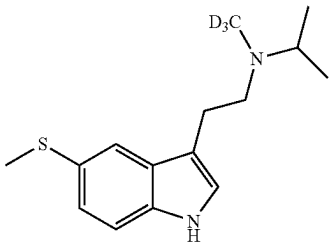
Compound	Structure
I-17	
I-18	
I-19	
I-20	
I-21	

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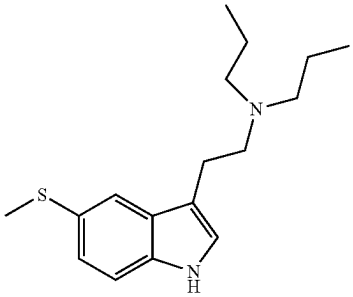
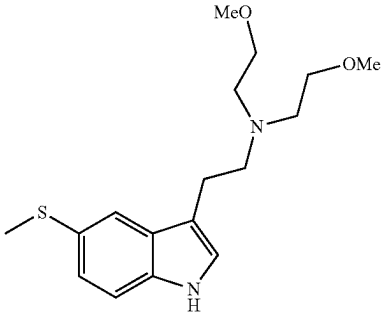
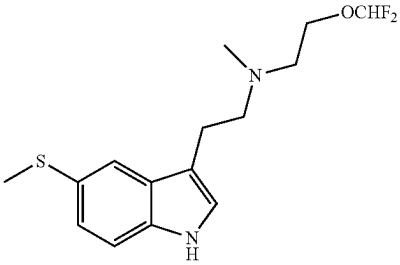
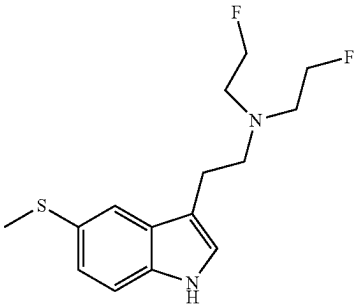
Compound	Structure
I-22	
I-23	
I-24	
I-25	

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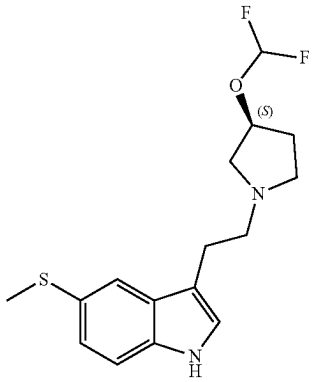
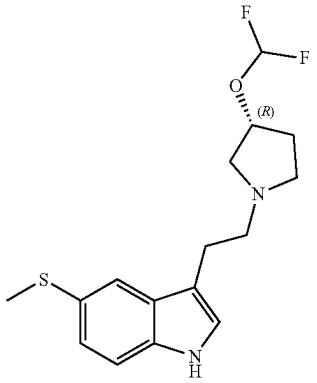
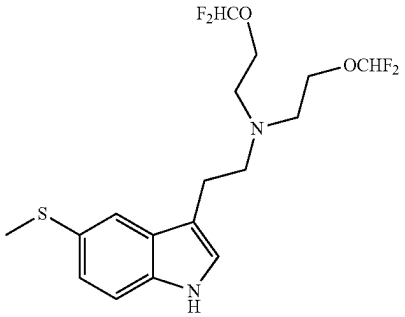
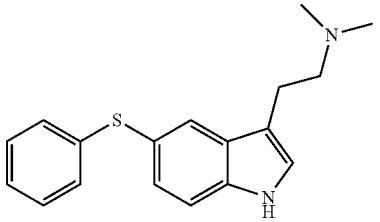
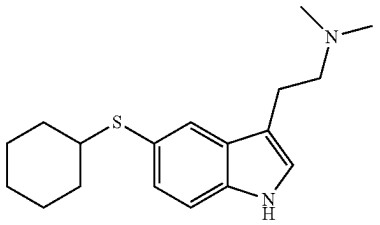
Compound	Structure
(S) I-26	
(R) I-26	
I-27	
I-28	
I-29	

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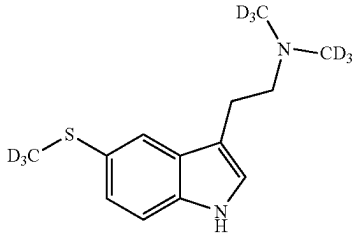
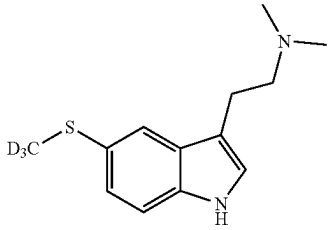
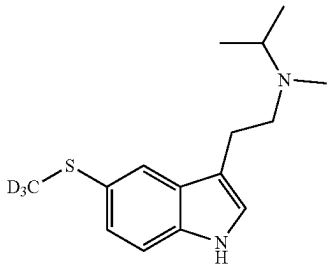
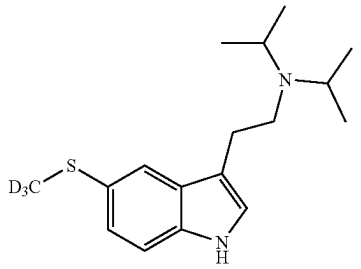
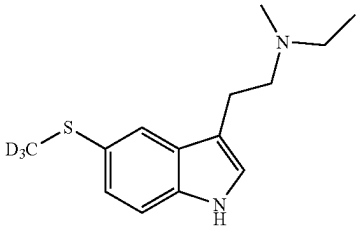
Compound	Structure
I-30	
I-31	
I-32	
I-33	
I-34	

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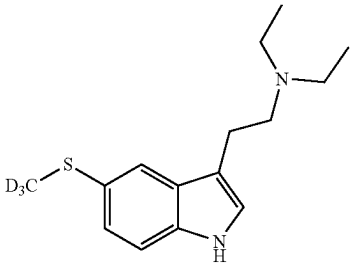
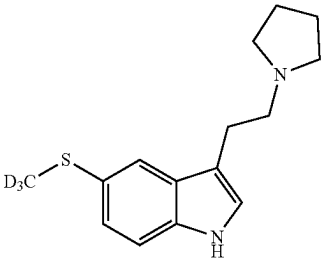
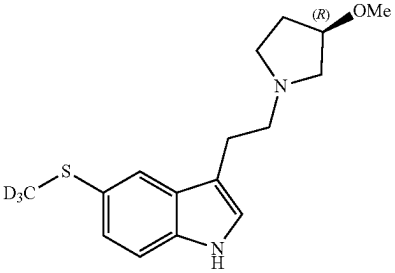
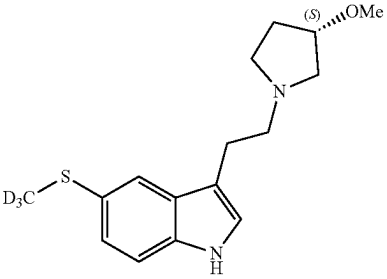
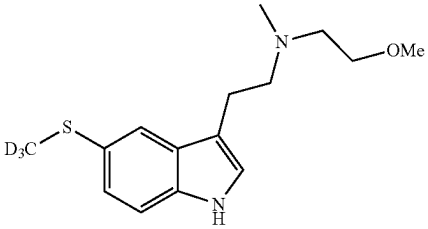
Compound	Structure
I-35	
I-36	
(R) I-37	
(S) I-37	
I-38	

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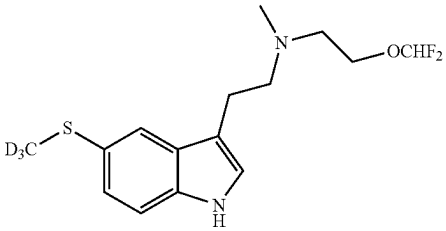
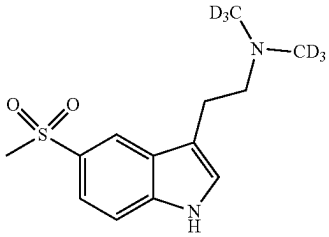
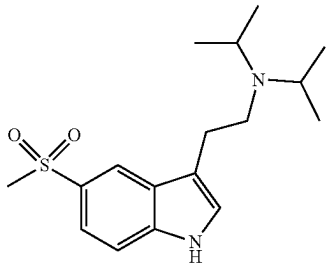
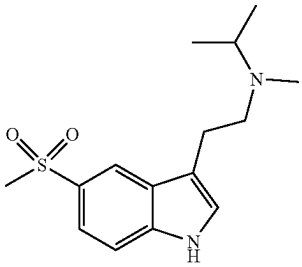
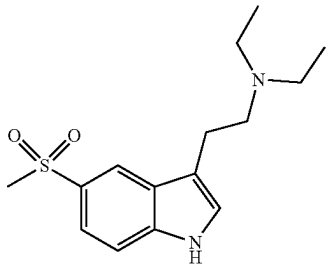
Compound	Structure
I-39	
I-40	
I-41	
I-42	
I-43	

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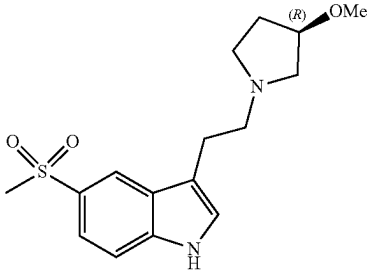
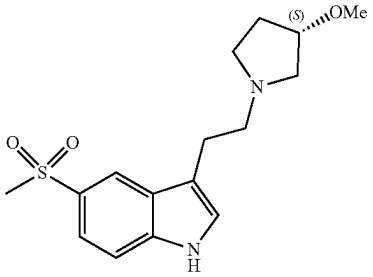
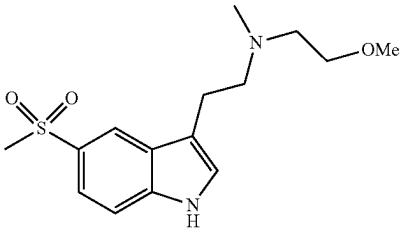
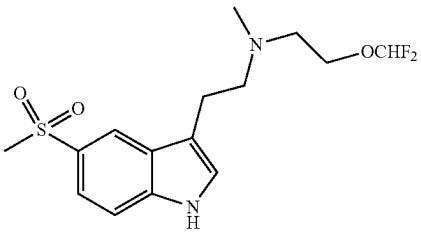
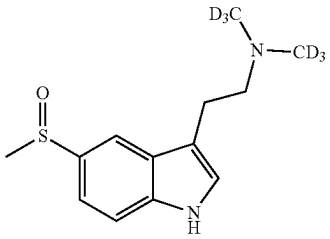
Compound	Structure
(R) I-44	
(S) I-44	
I-45	
I-46	
I-47	

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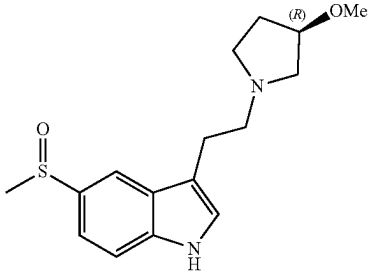
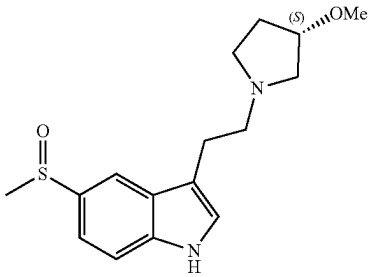
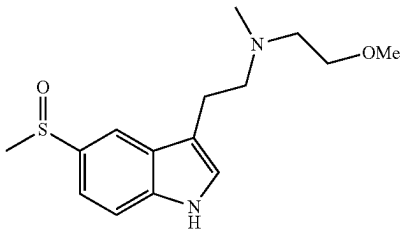
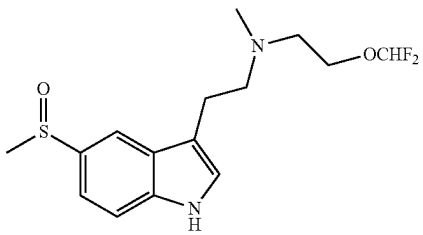
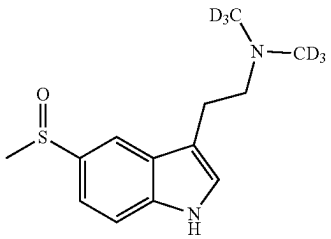
Compound	Structure
(R) I-48	
(S) I-48	
I-49	
I-50	
I-51	

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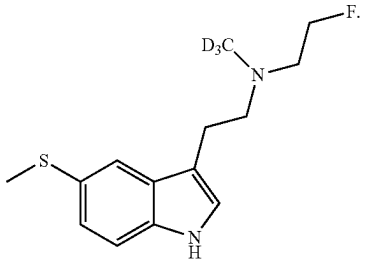
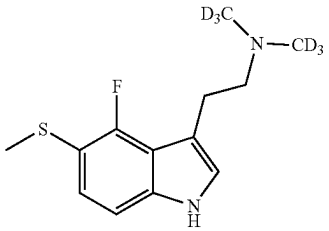
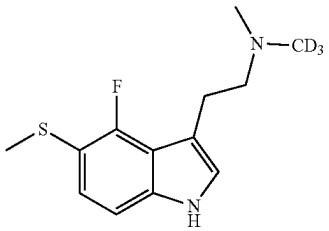
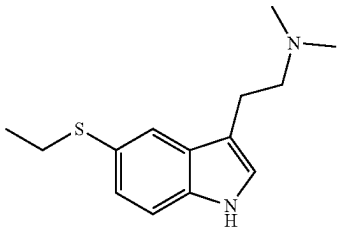
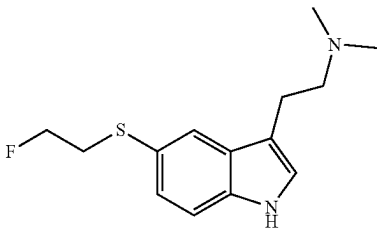
Compound	Structure
I-52	
I-53	
I-54	
I-55	
I-56	

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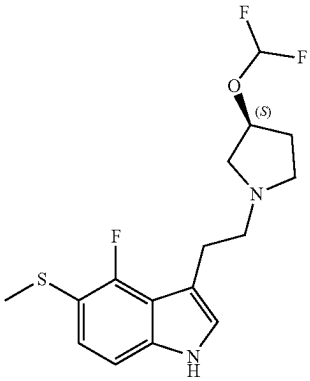
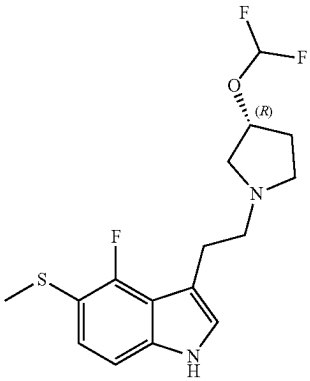
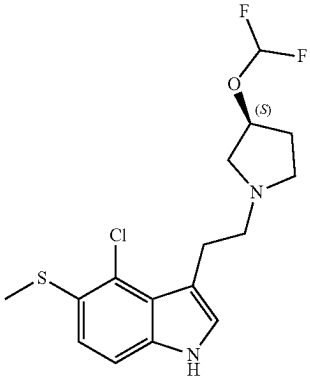
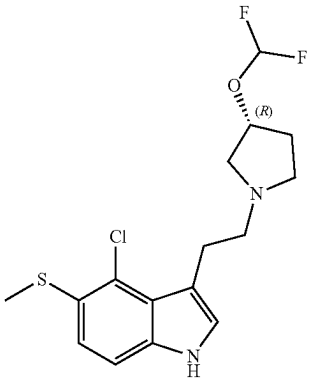
Compound	Structure
(R) I-57	
(S) I-57	
(R) I-58	
(S) I-58	

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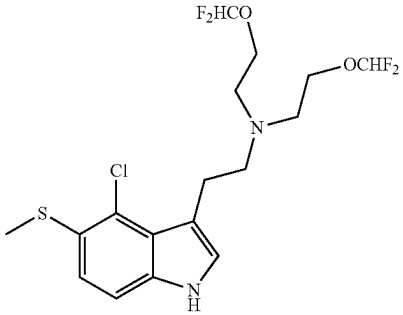
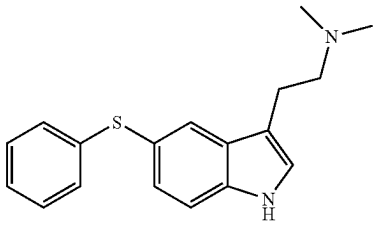
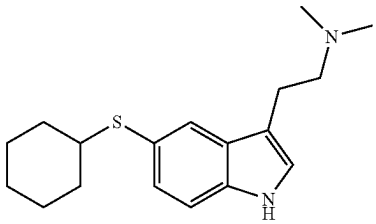
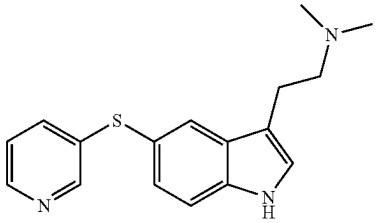
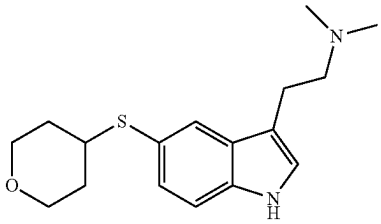
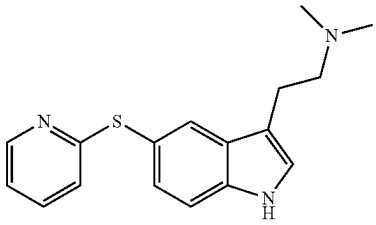
Compound	Structure
I-59	
I-60	
I-61	
I-62	
I-63	
I-64	

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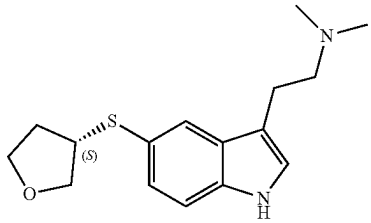
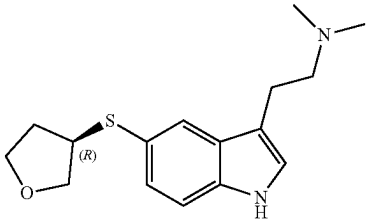
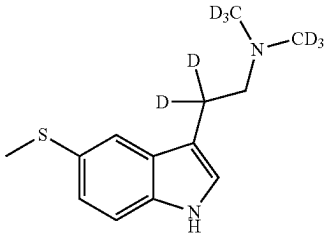
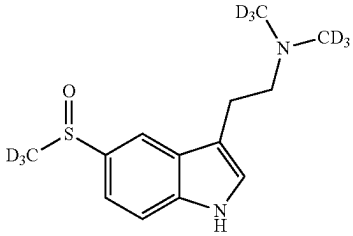
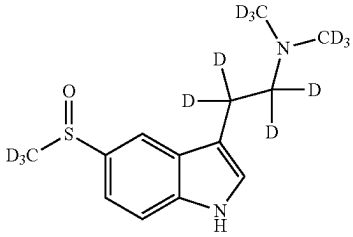
Compound	Structure
(S) I-65	 and
(R) I-65	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0970] E76: The compound of any one of E1 to E6, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
II-01	
II-02	
II-03	

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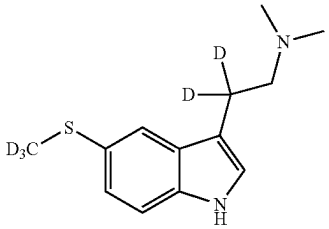
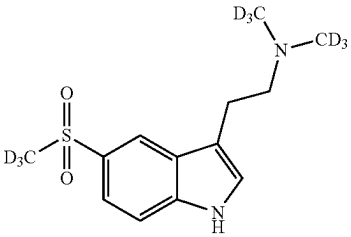
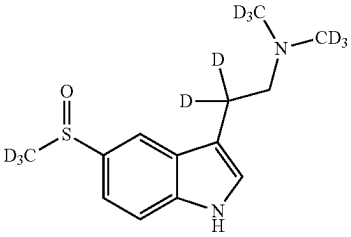
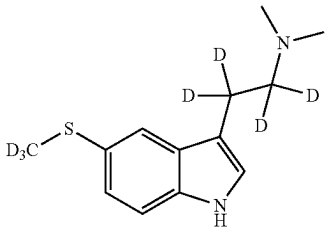
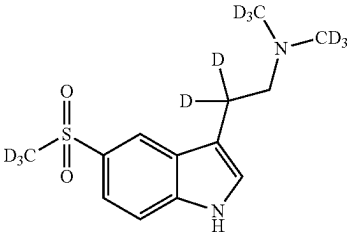
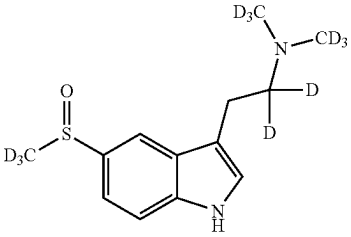
Compound	Structure
II-04	
II-05	
II-06	
II-07	
II-08	
II-09	

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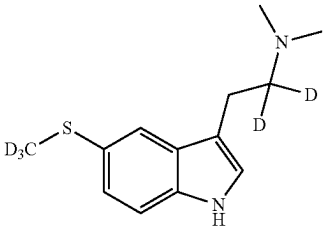
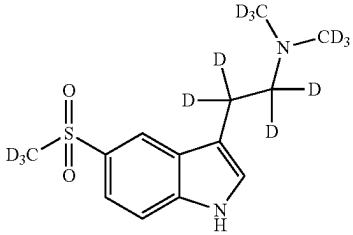
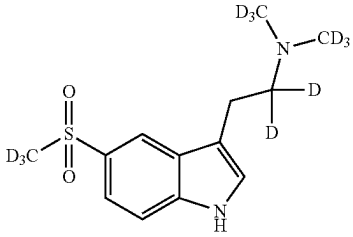
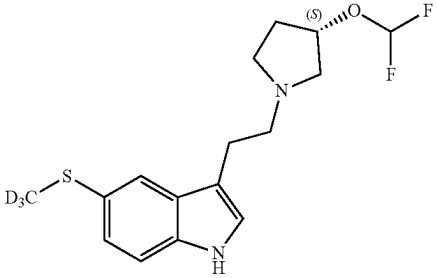
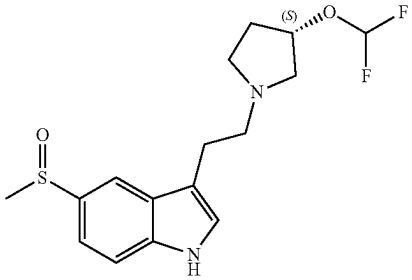
Compound	Structure
II-10	
II-11	
II-12	
(S) II-13	
(S) II-14	

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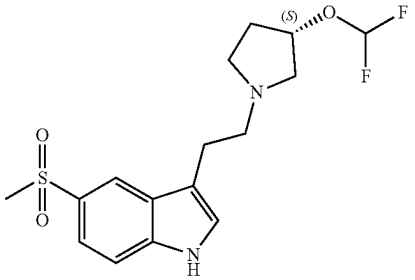
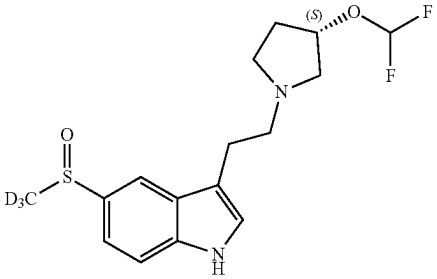
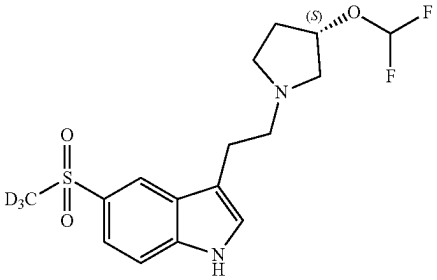
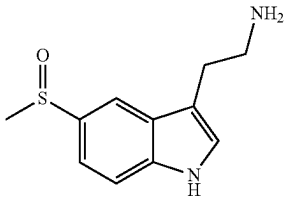
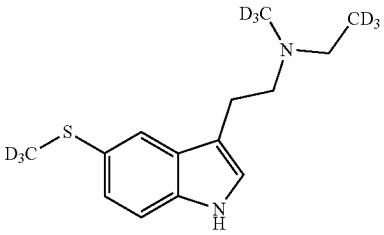
Compound	Structure
(S) II-15	
(S) II-16	
(S) II-17	
II-18	
II-19	

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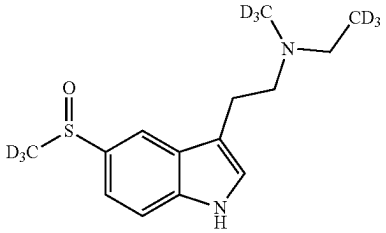
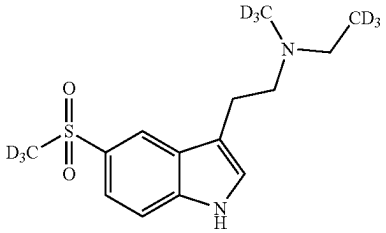
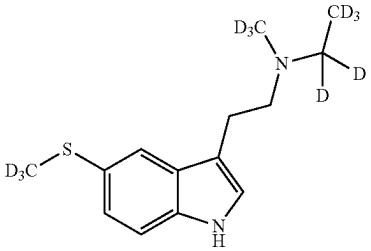
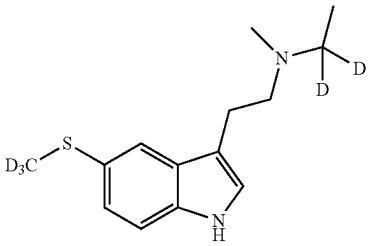
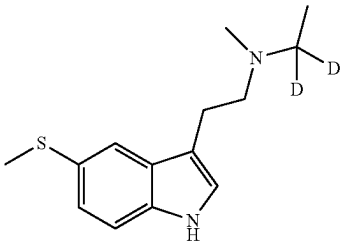
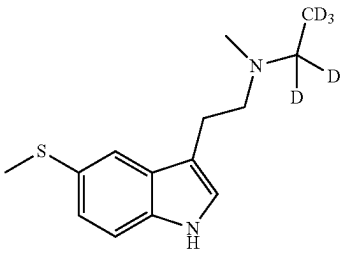
Compound	Structure
II-20	
II-21	
II-22	
II-23	
II-24	
II-25	

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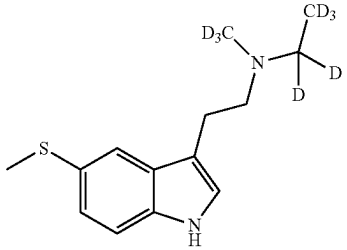
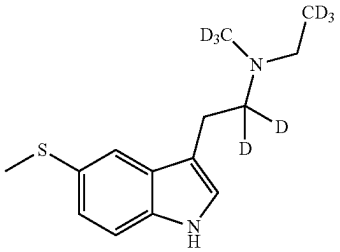
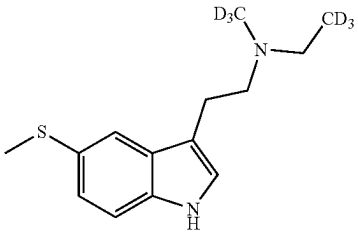
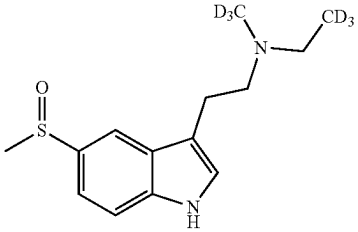
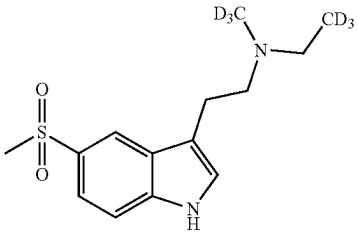
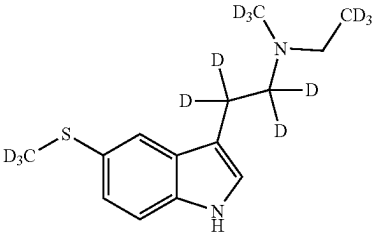
Compound	Structure
II-26	
II-27	
II-28	
II-29	
II-30	
II-31	

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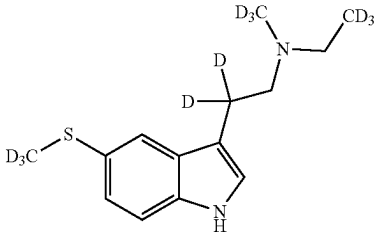
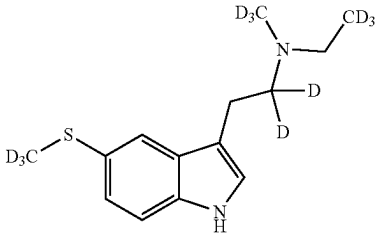
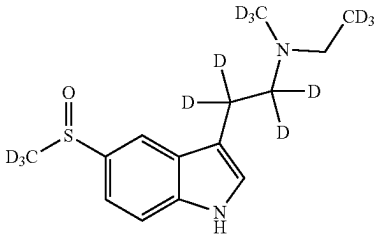
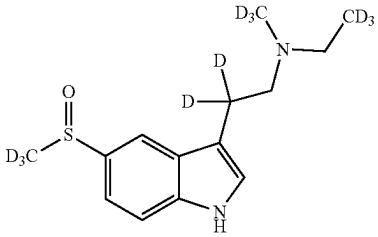
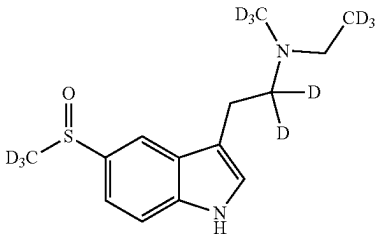
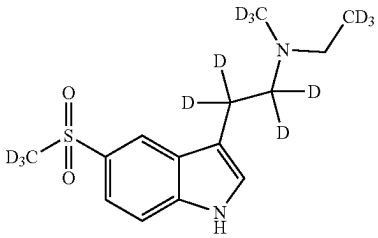
Compound	Structure
II-32	
II-33	
II-34	
II-35	
II-36	
II-37	

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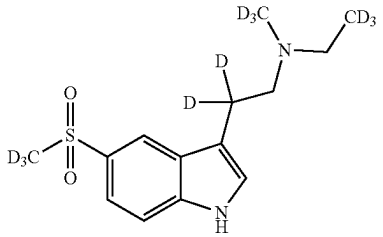
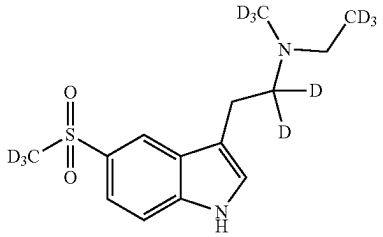
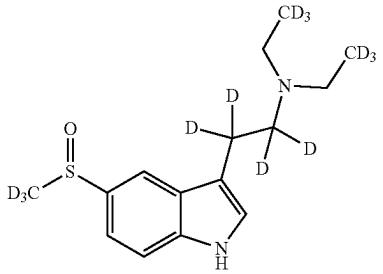
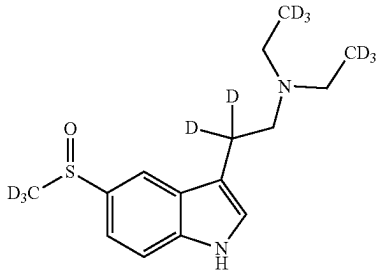
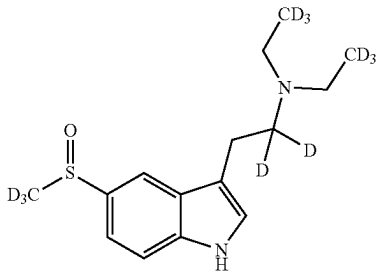
Compound	Structure
II-38	
II-39	
II-40	
II-41	
II-42	

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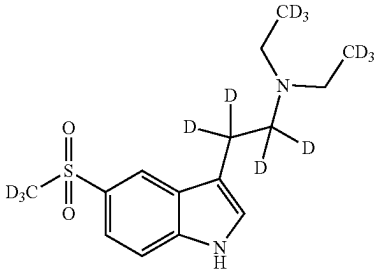
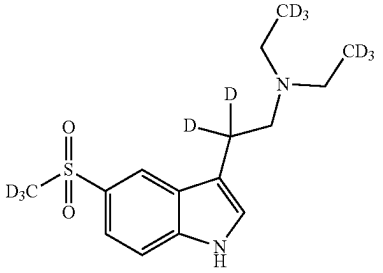
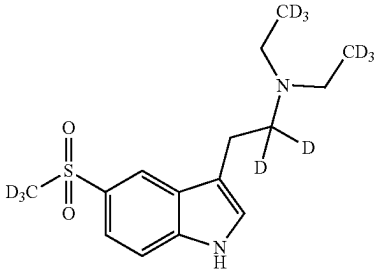
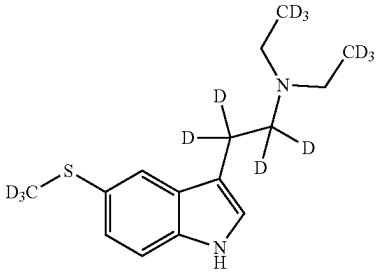
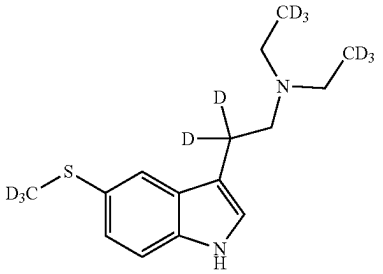
Compound	Structure
II-43	
II-44	
II-45	
II-46	
II-47	

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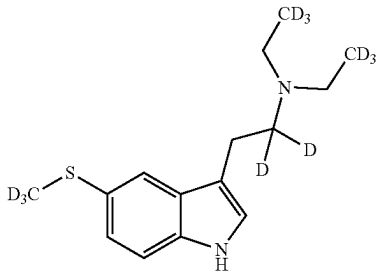
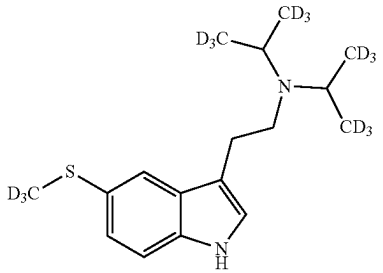
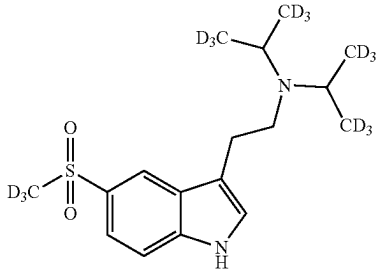
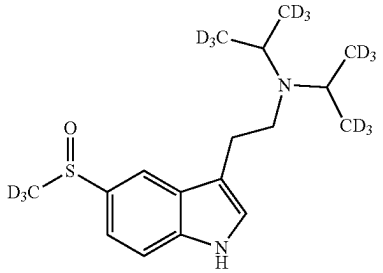
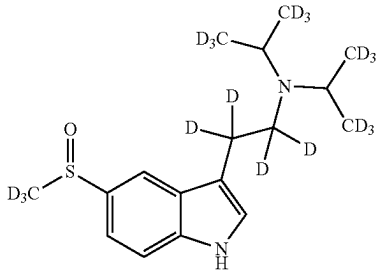
Compound	Structure
II-48	
II-49	
II-50	
II-51	
II-52	

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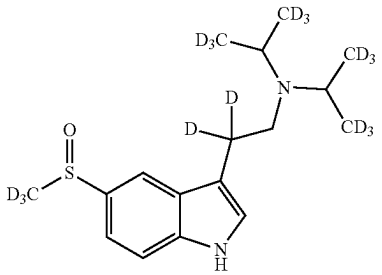
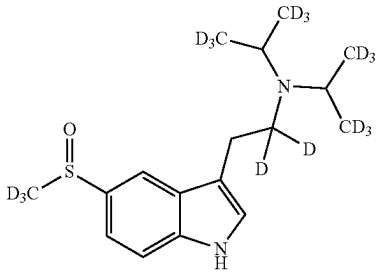
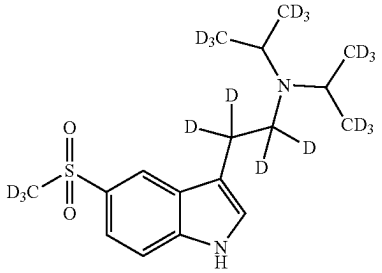
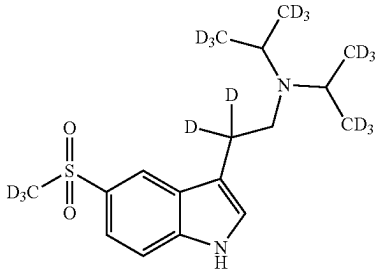
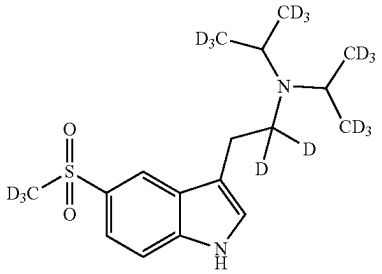
Compound	Structure
II-53	
II-54	
II-55	
II-56	
II-57	

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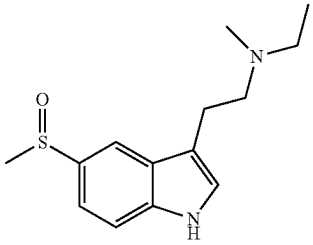
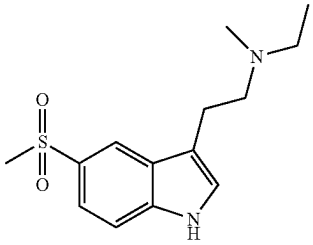
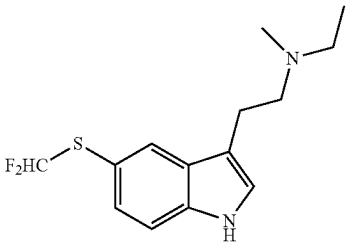
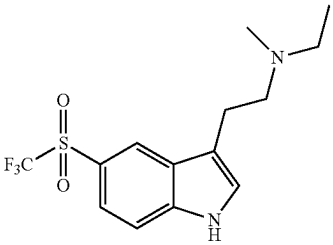
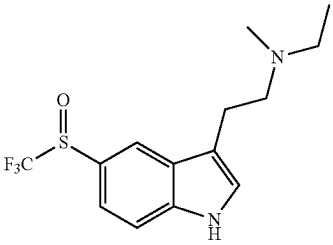
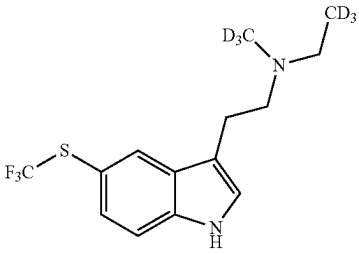
Compound	Structure
II-58	
II-59	
II-60	
II-61	
II-62	
II-63	

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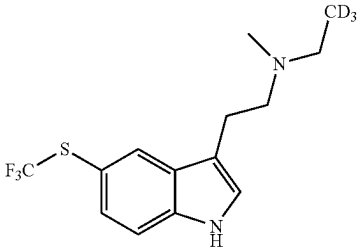
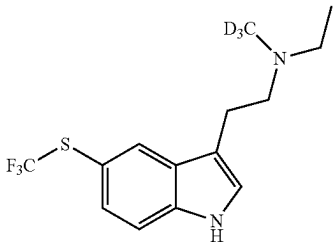
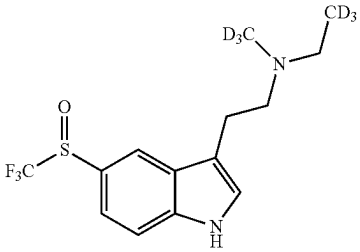
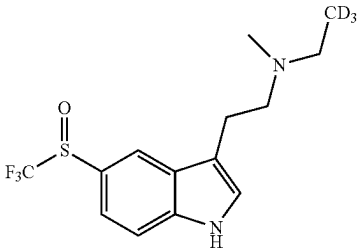
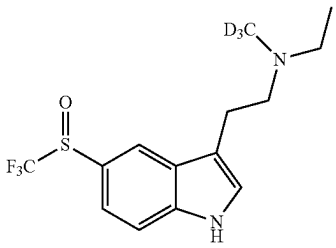
Compound	Structure
II-64	
II-65	
II-66	
II-67	
II-68	

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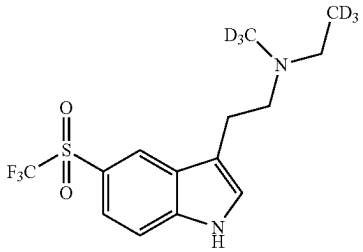
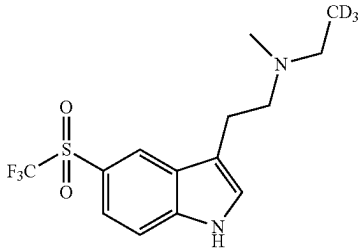
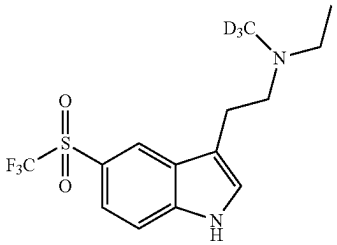
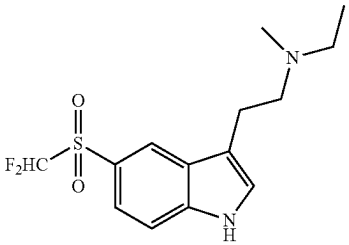
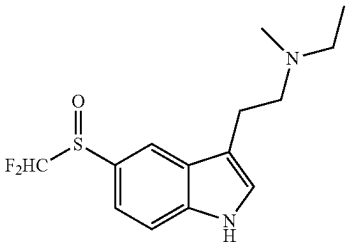
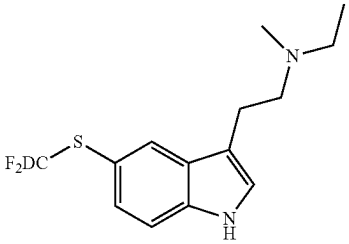
Compound	Structure
II-69	
II-70	
II-71	
II-72	
II-73	
II-74	

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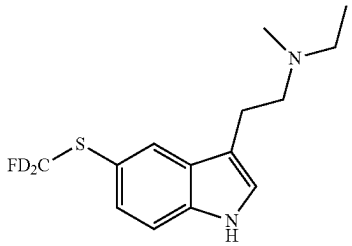
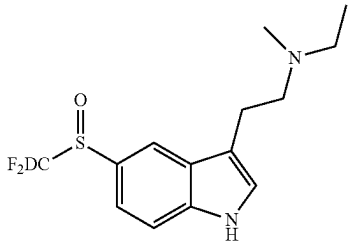
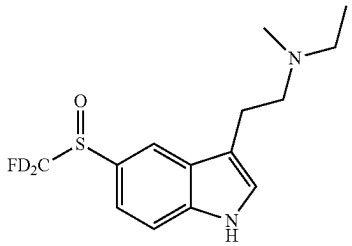
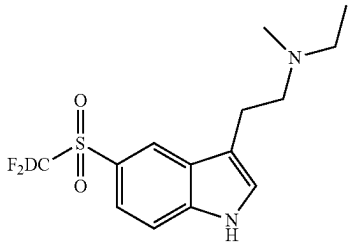
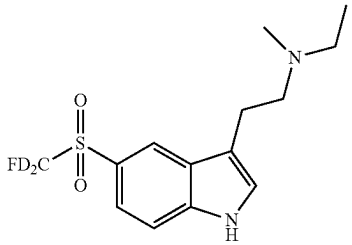
Compound	Structure
II-75	
II-76	
II-77	
II-78	
II-79	

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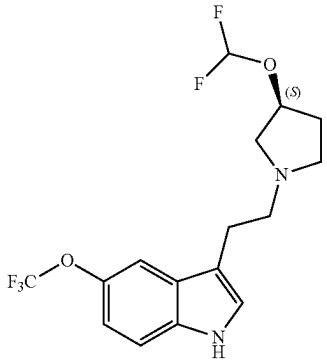
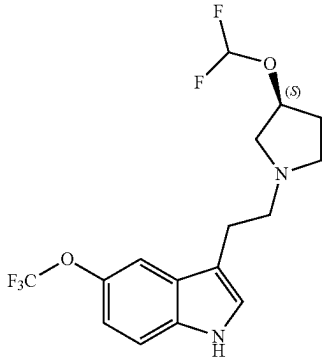
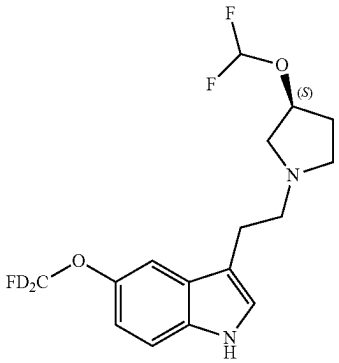
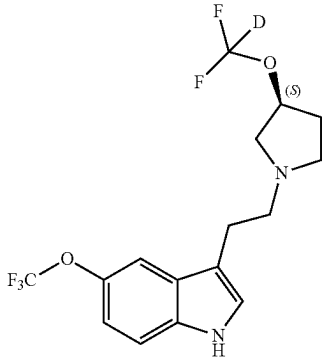
Compound	Structure
II-80	
II-81	
II-82	
II-83	

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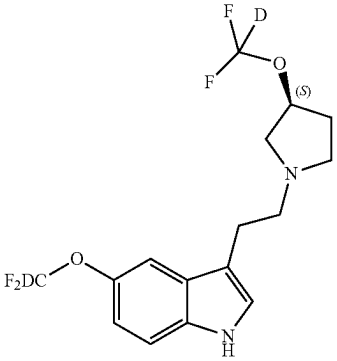
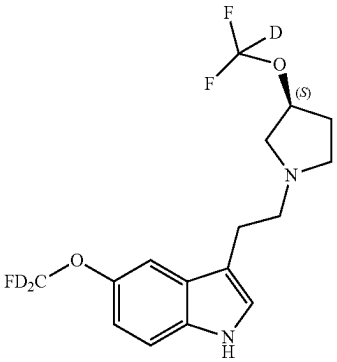
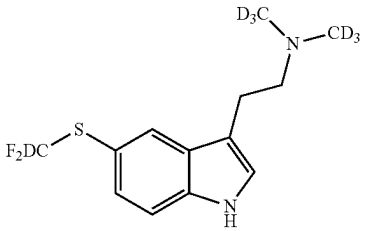
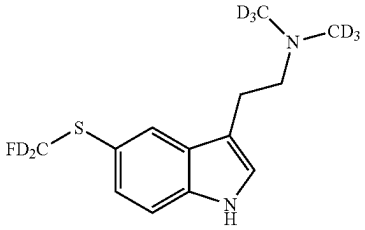
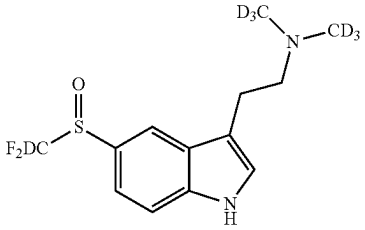
Compound	Structure
II-84	
II-85	
II-86	
II-87	
II-88	

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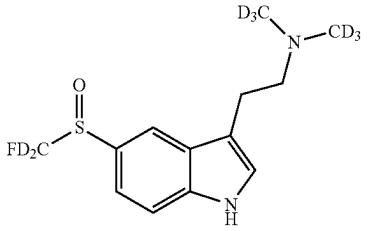
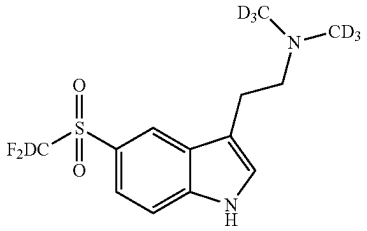
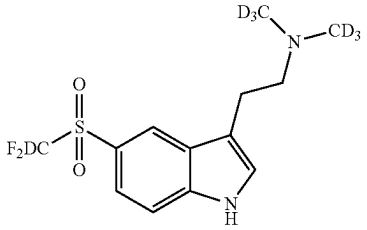
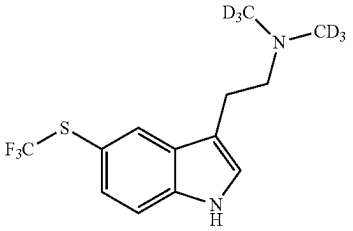
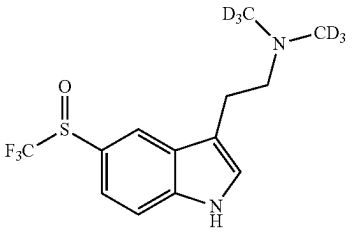
Compound	Structure
II-89	
II-90	
II-91	
II-92	
II-93	

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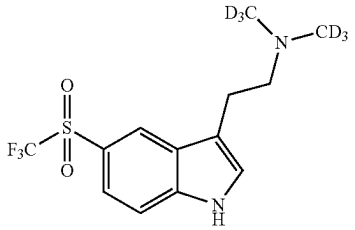
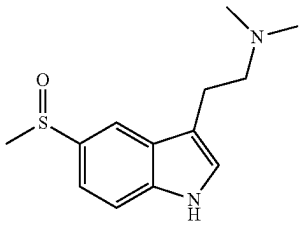
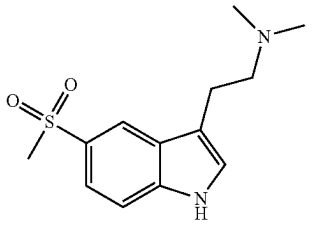
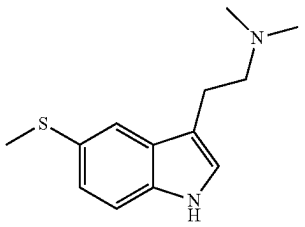
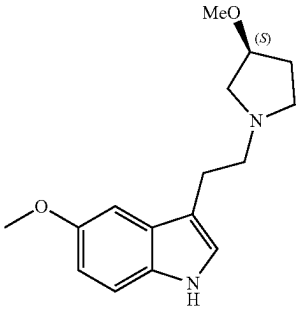
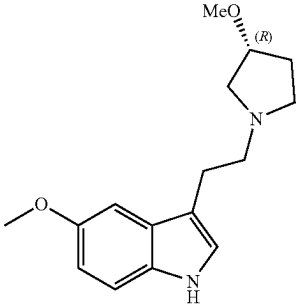
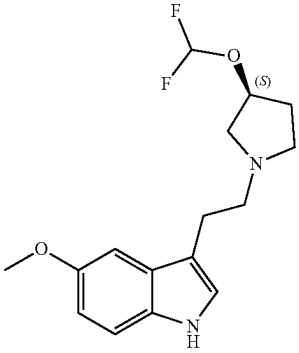
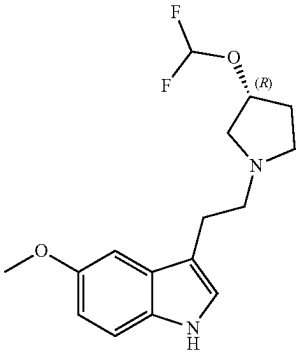
Compound	Structure
II-94	
II-95	
II-96	 and
II-97	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0971] E77: The compound of any one of E1 to E6, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
(S) I-66	
(R) I-66	
(S) I-67	
(R) I-67	

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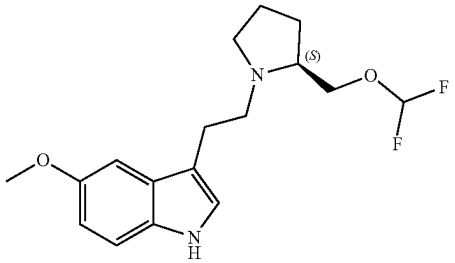
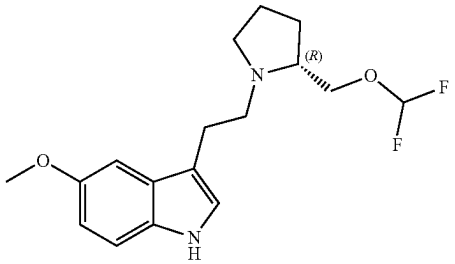
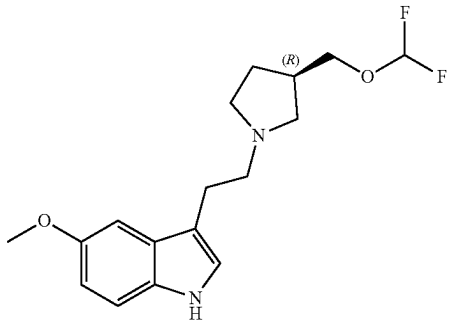
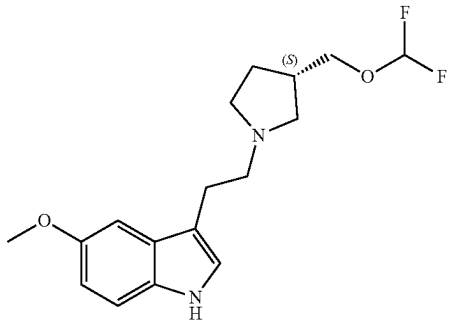
Compound	Structure
(S) I-68	
(R) I-68	
(R) I-69	
(S) I-69	

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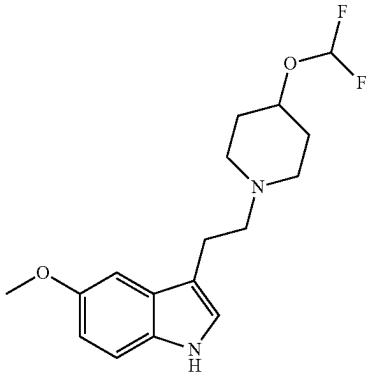
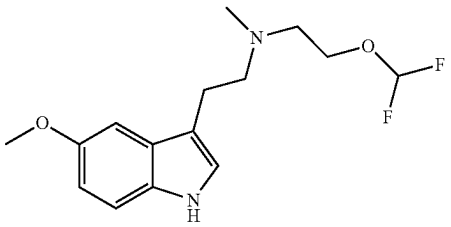
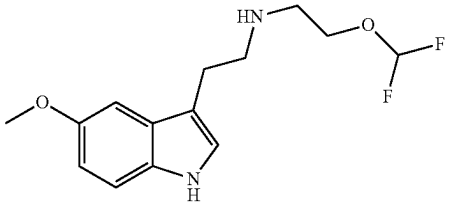
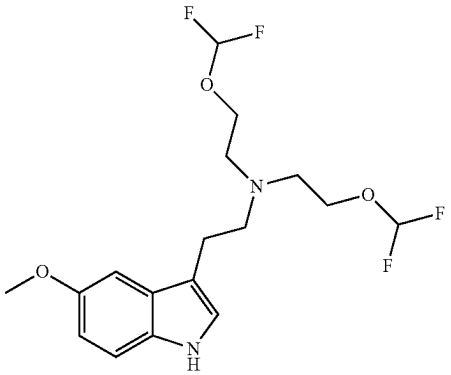
Compound	Structure
I-70	
I-71	
I-72	
I-73	

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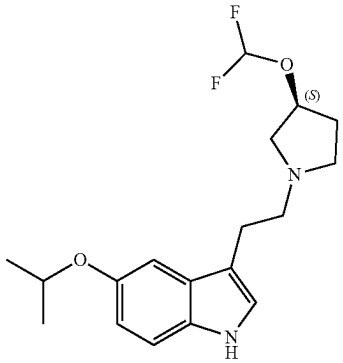
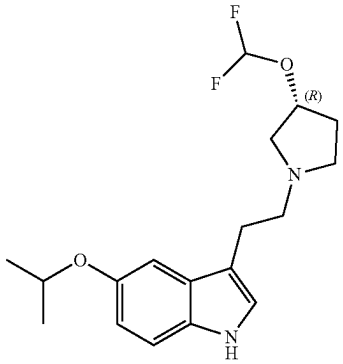
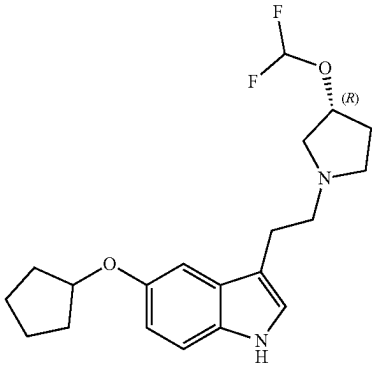
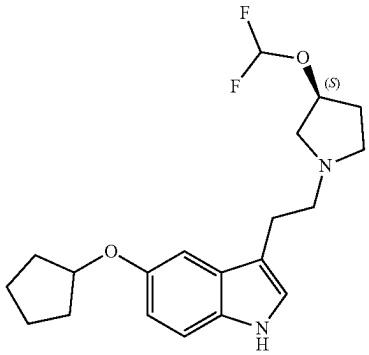
Compound	Structure
(S) I-74	
(R) I-74	
(R) I-75	
(S) I-75	

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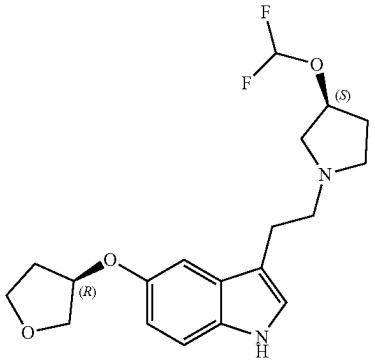
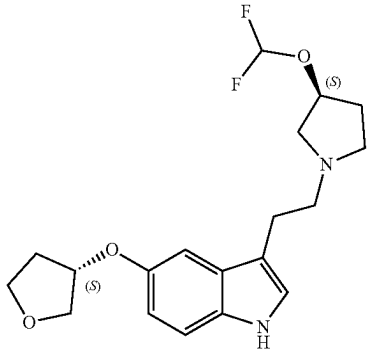
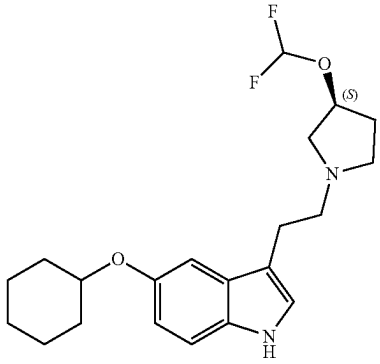
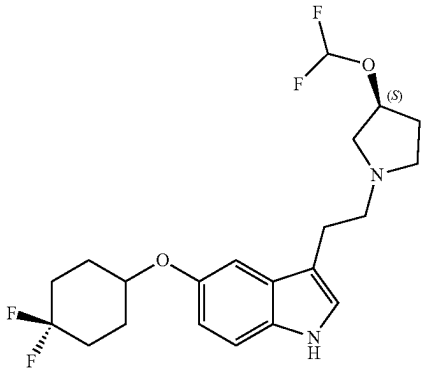
Compound	Structure
(R, S) I-76	
(S, S) I-76	
(S) I-77	
(S) I-78	

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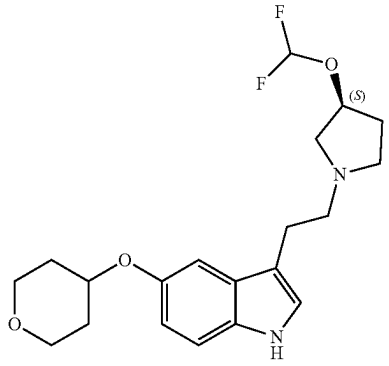
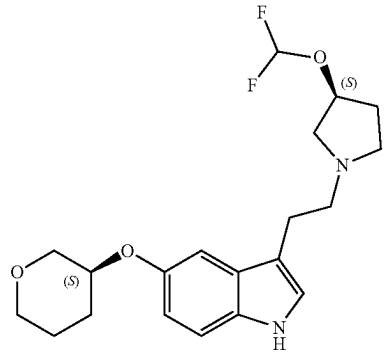
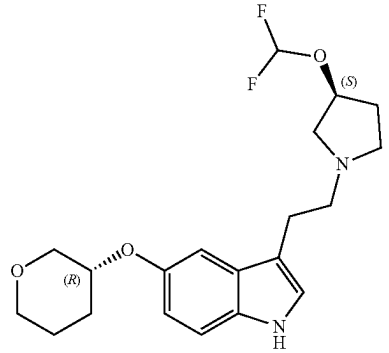
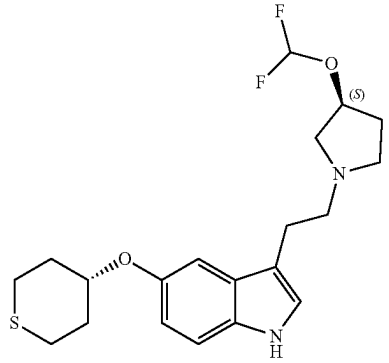
Compound	Structure
(S) I-79	
(S, S) I-80	
(R, S) I-80	
(S) I-81	

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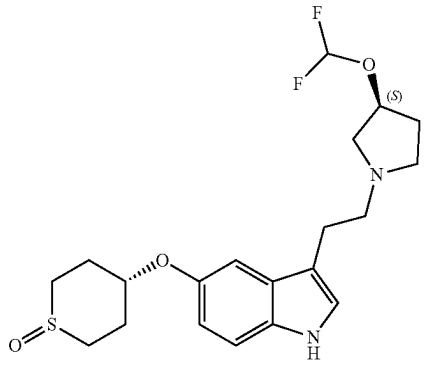
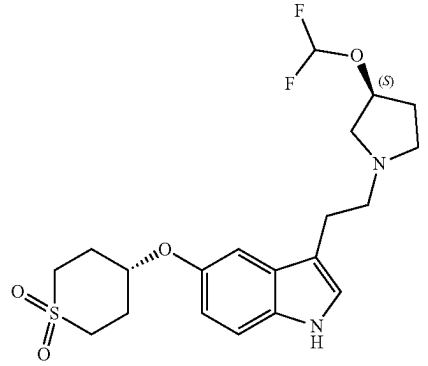
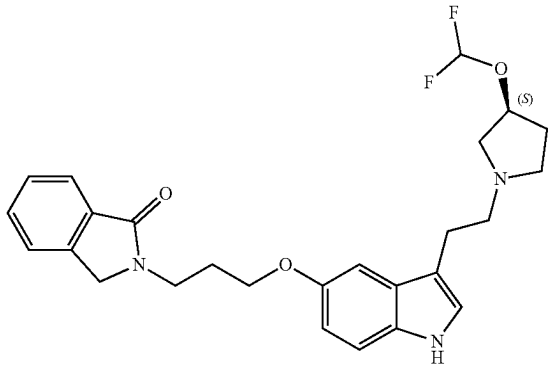
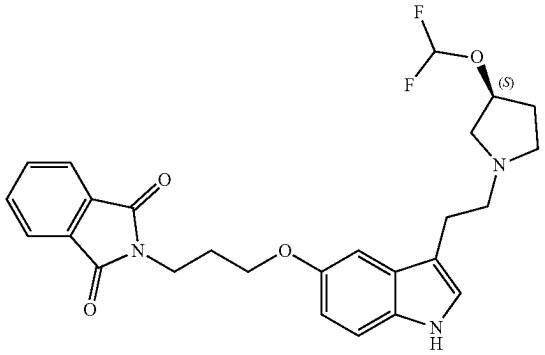
Compound	Structure
(S) I-82	
(S) I-83	
(S) I-84	
(S) I-85	

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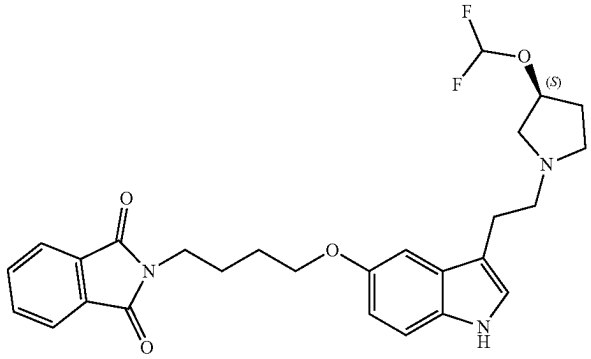
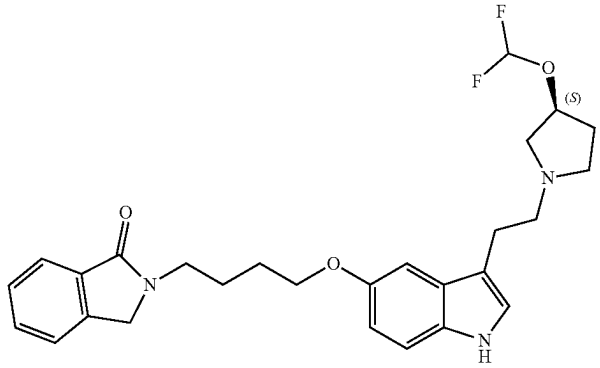
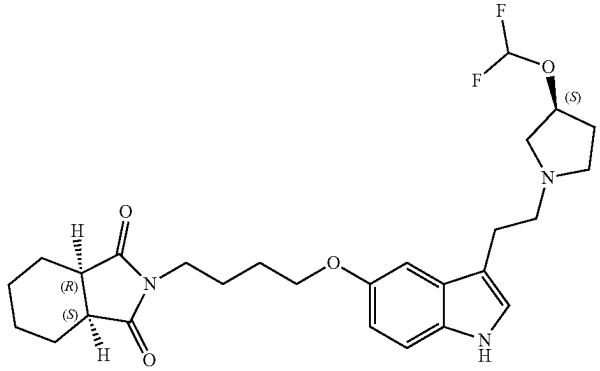
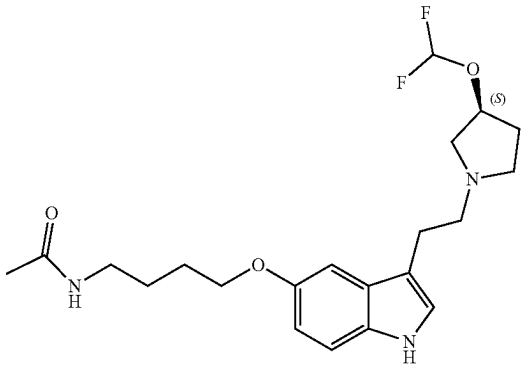
Compound	Structure
(S) I-86	
(S) I-87	
Cis (S) I-88	
(S) I-89	

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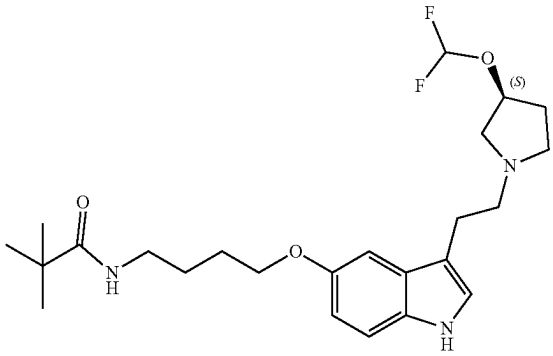
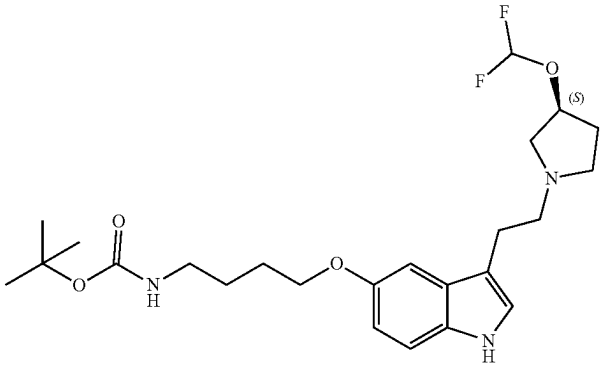
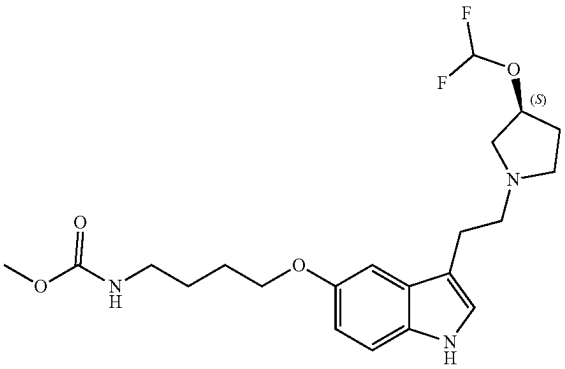
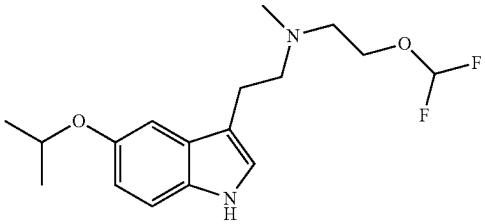
Compound	Structure
(S) I-90	
(S) I-91	
(S) I-92	
I-93	

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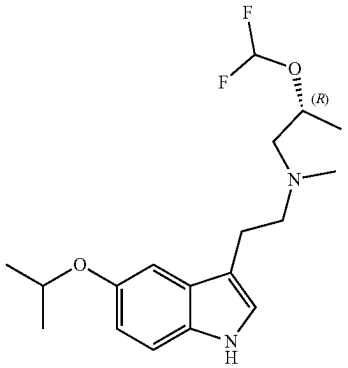
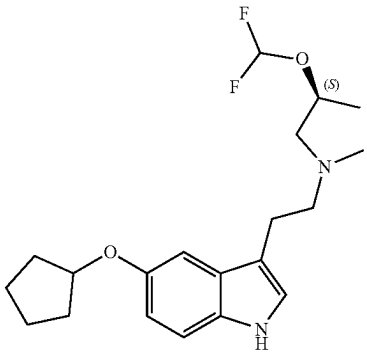
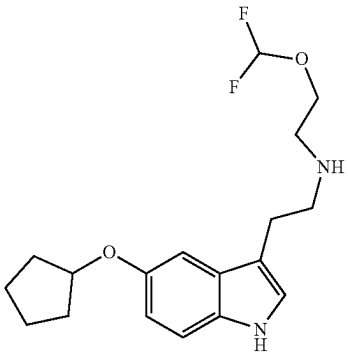
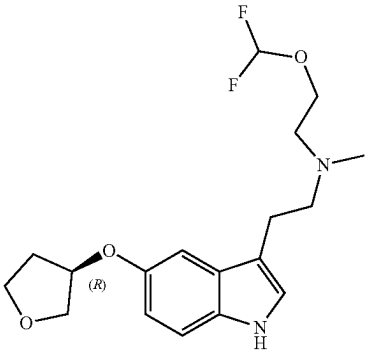
Compound	Structure
(R) I-94	
(S) I-95	
I-96	
(R) I-97	

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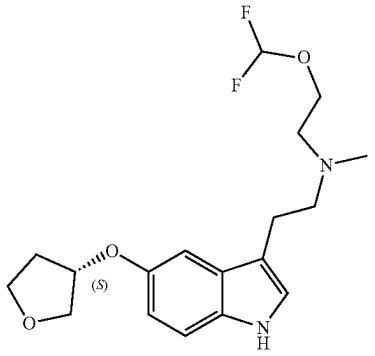
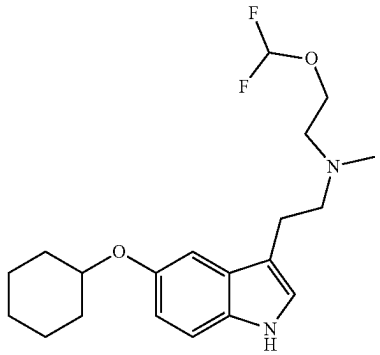
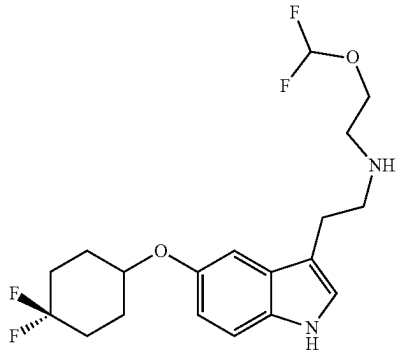
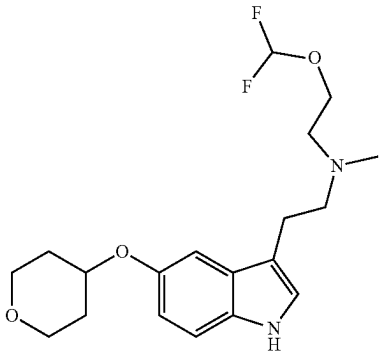
Compound	Structure
(S) I-97	
I-98	
I-99	
I-100	

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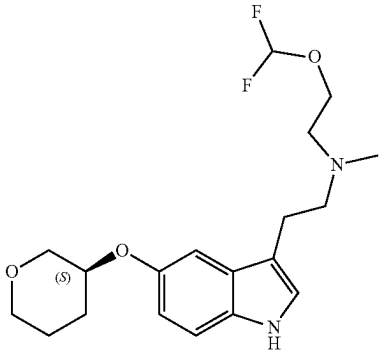
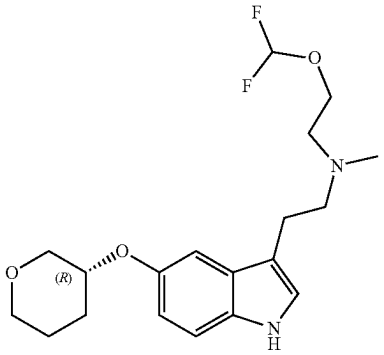
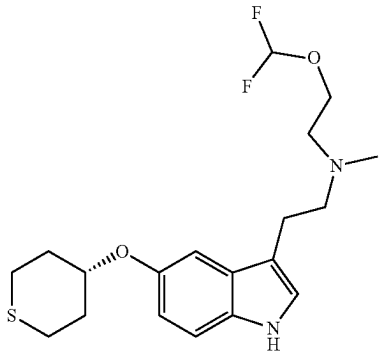
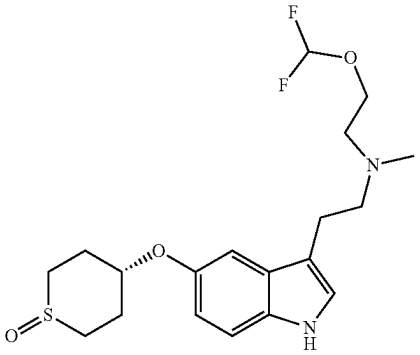
Compound	Structure
(S) I-101	
(R) I-101	
I-102	
I-103	

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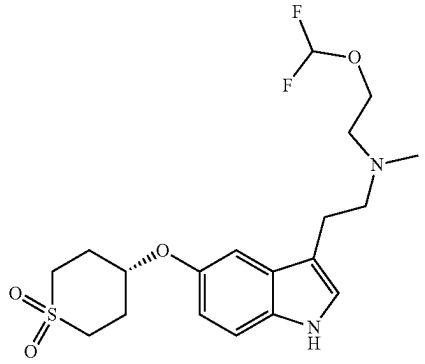
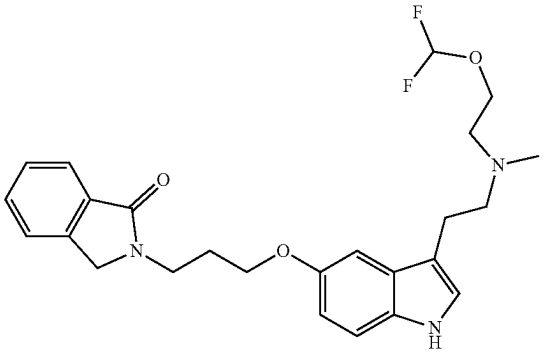
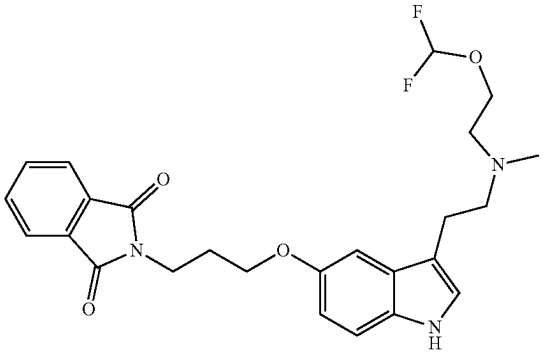
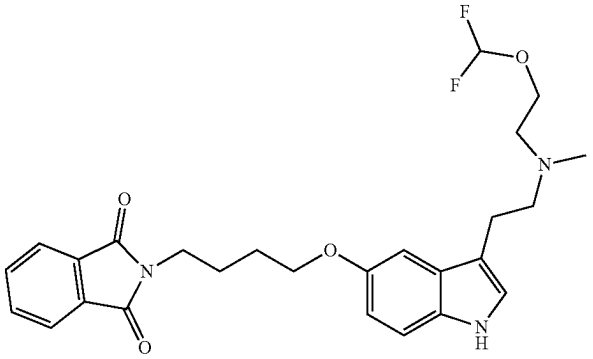
Compound	Structure
I-104	
I-105	
I-106	
I-107	

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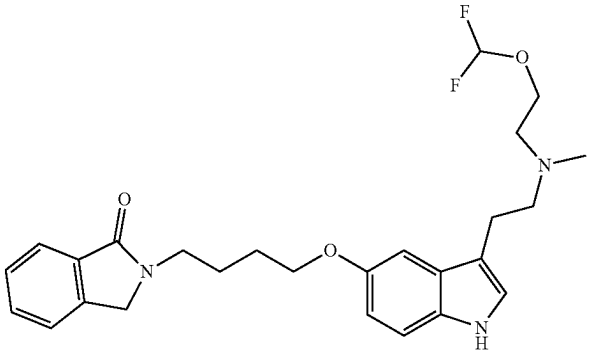
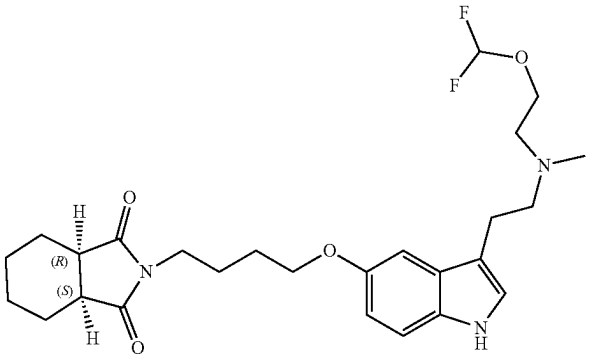
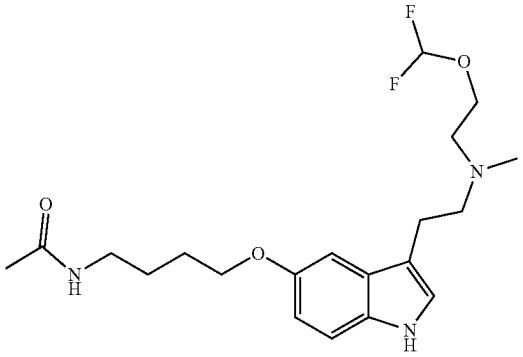
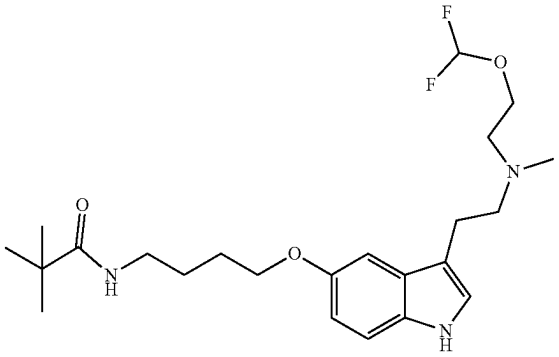
Compound	Structure
I-108	
Cis I-109	
I-110	
I-111	

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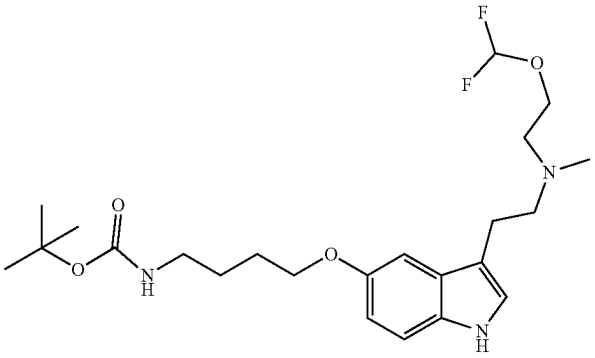
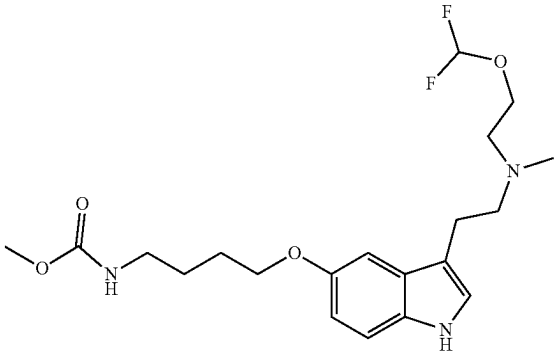
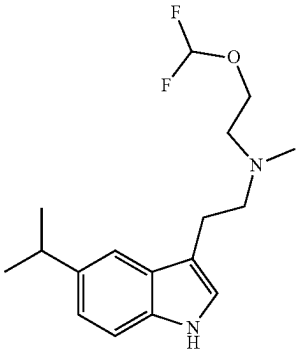
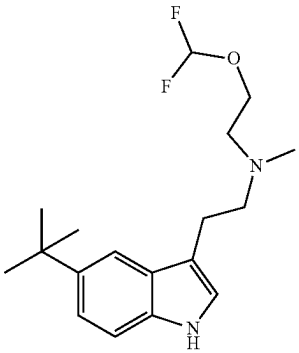
Compound	Structure
I-112	
I-113	
I-114	
I-115	

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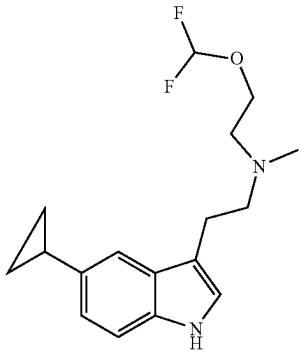
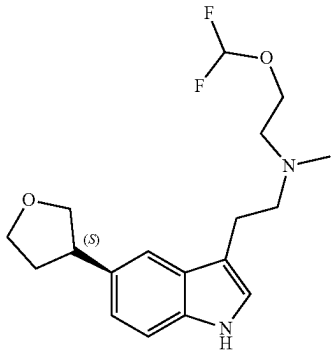
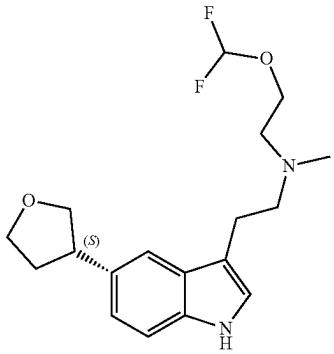
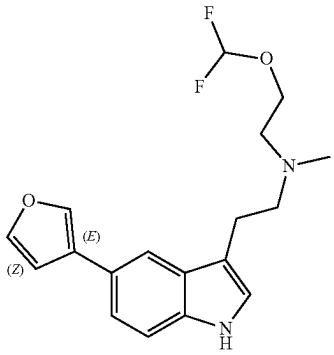
Compound	Structure
I-116	
(S) I-117	
(R) I-117	
I-118	

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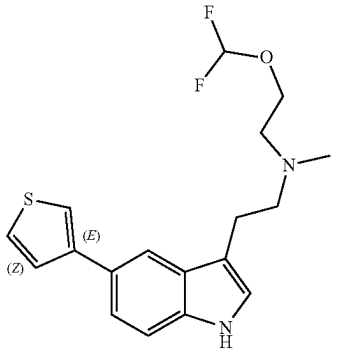
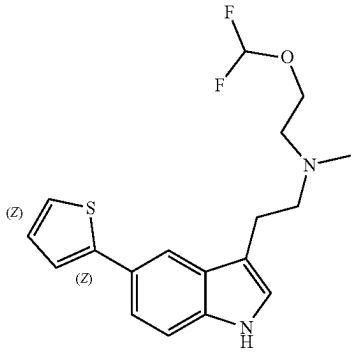
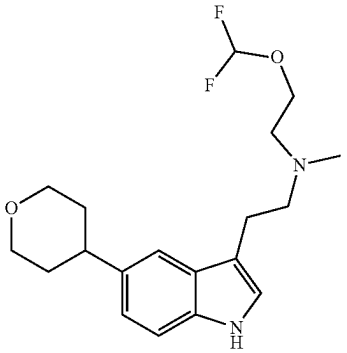
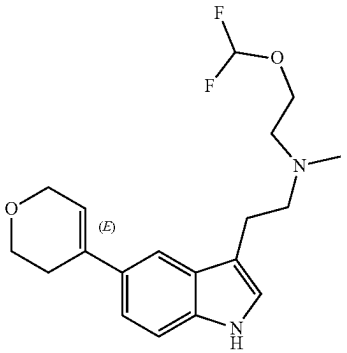
Compound	Structure
I-119	
I-120	
I-121	
I-122	

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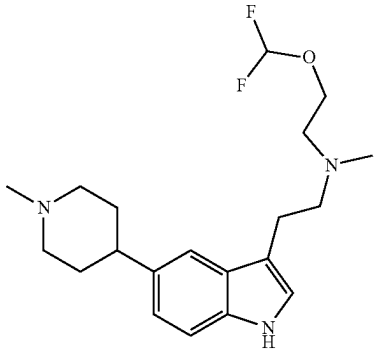
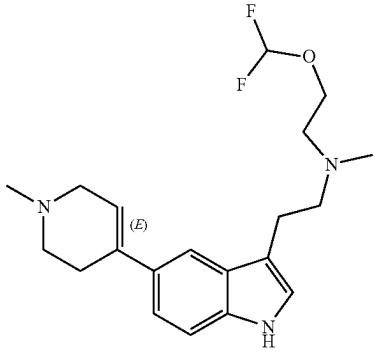
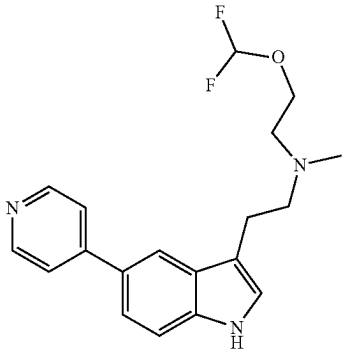
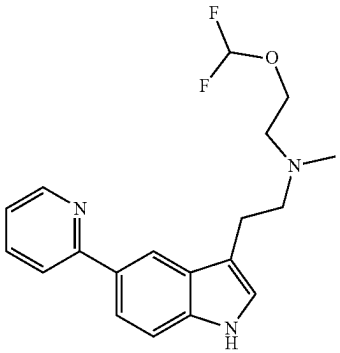
Compound	Structure
I-123	
I-124	
I-125	
I-126	

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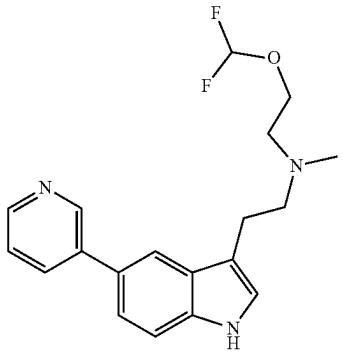
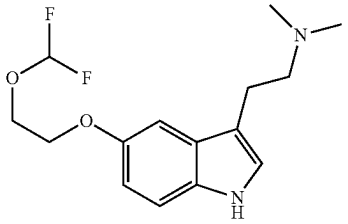
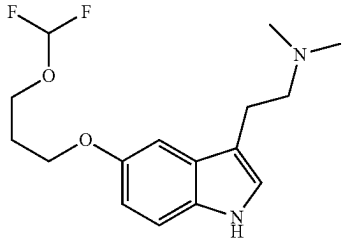
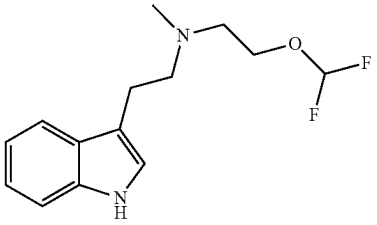
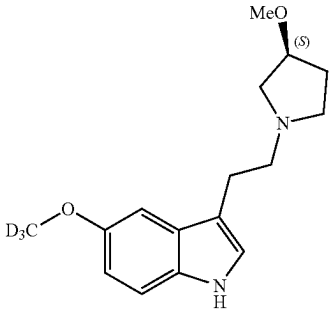
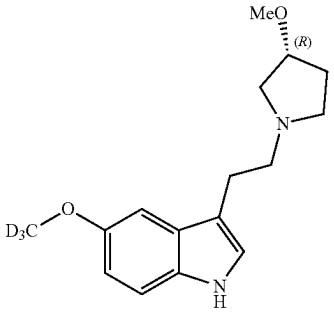
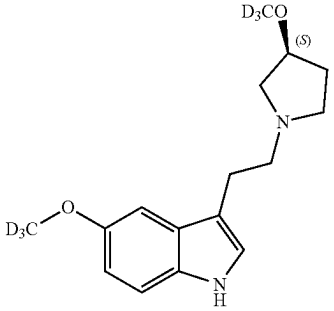
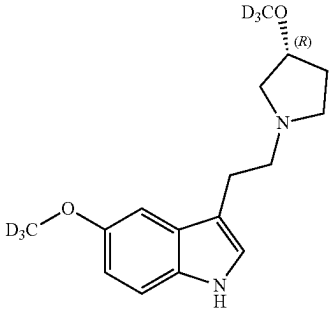
Compound	Structure
I-127	
I-128	
I-129	
	and
I-130	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0972] E78: The compound of any one of E1 to E6, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
(S) I-157	
(R) I-157	
(S) I-158	
(R) I-158	

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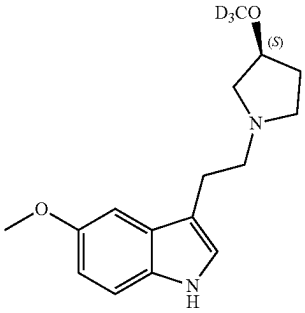
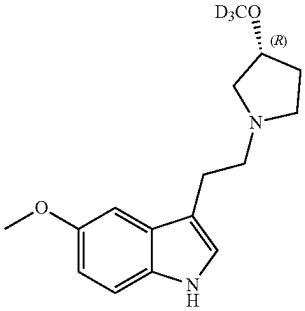
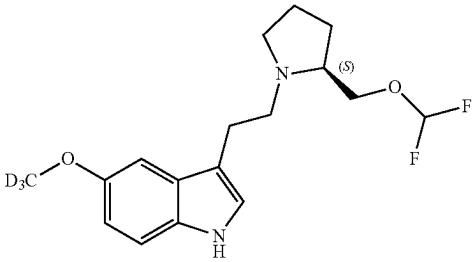
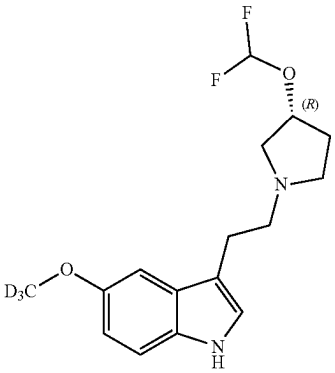
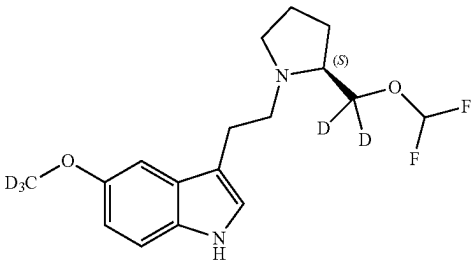
Compound	Structure
(S) I-159	
(R) I-159	
I-160	
(R) I-161	
(S) I-162	

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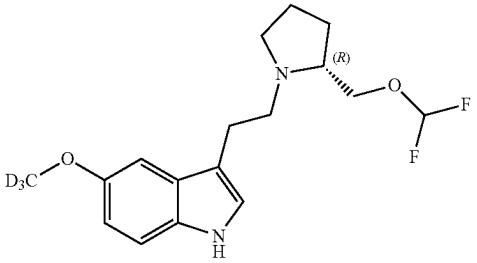
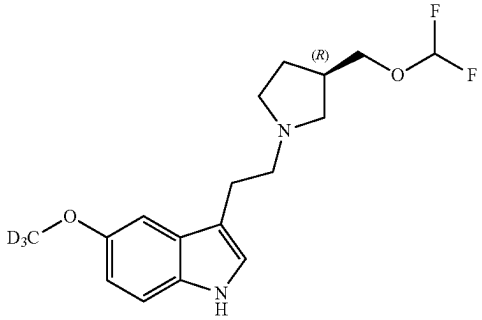
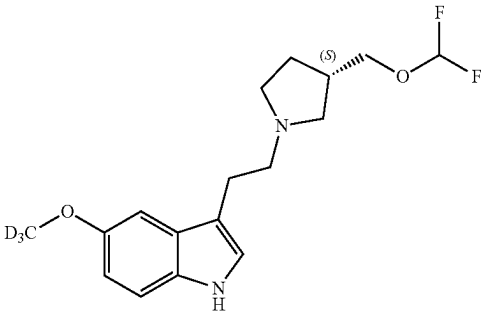
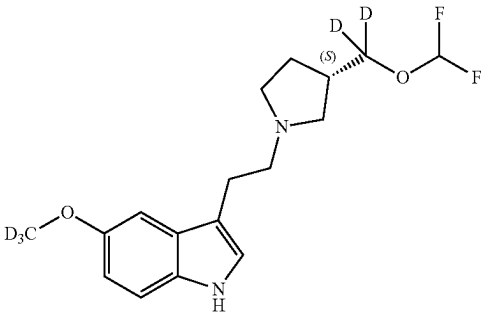
Compound	Structure
(R) I-163	
(R) I-164	
(S) I-164	
(S) I-165	

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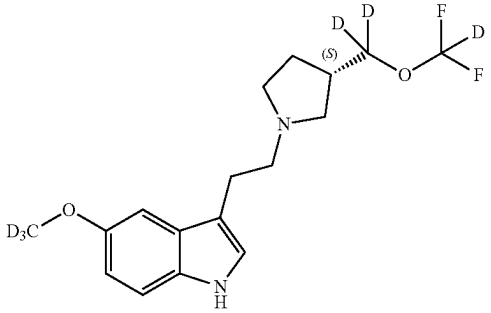
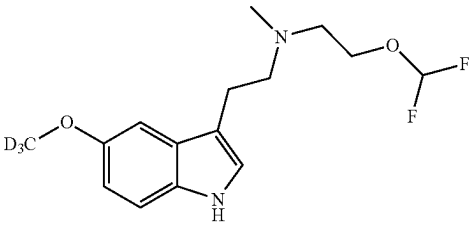
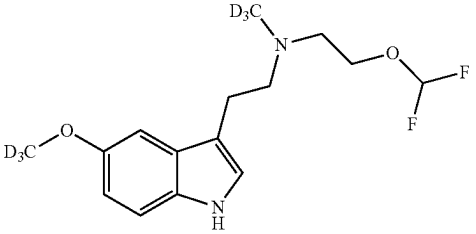
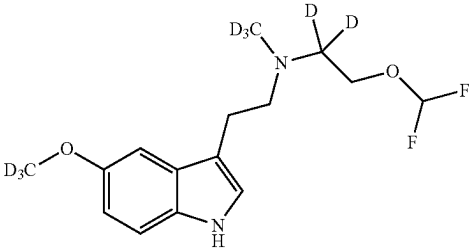
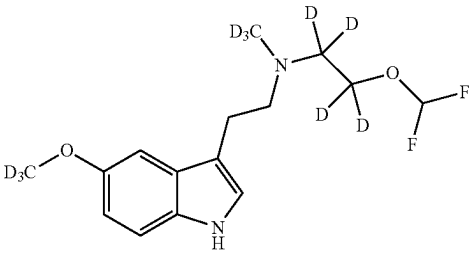
Compound	Structure
((S) I-166	
I-167	
I-168	
I-169	
I-170	

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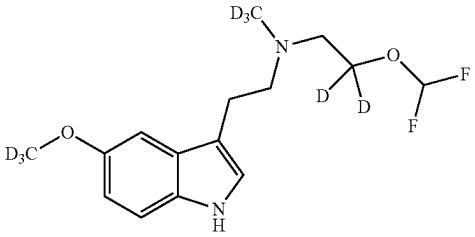
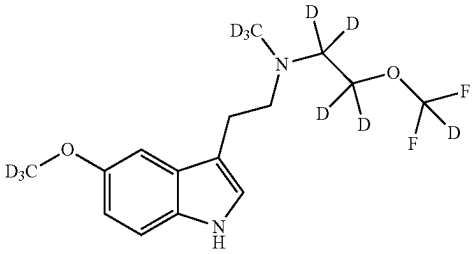
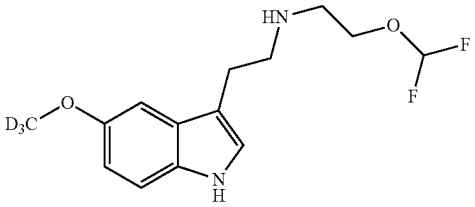
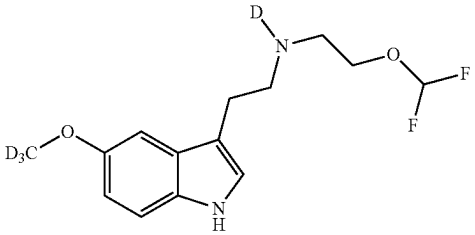
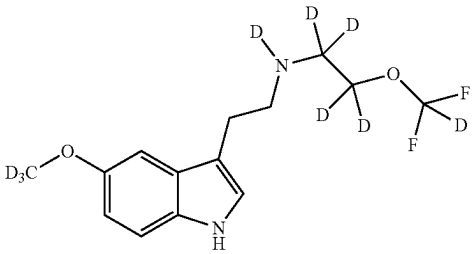
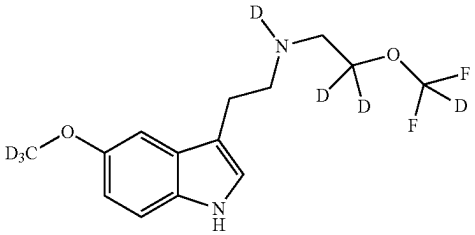
Compound	Structure
I-171	
I-172	
I-173	
I-174	
I-175	
I-176	

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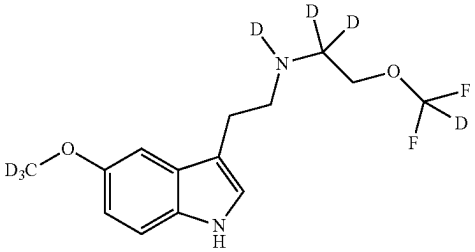
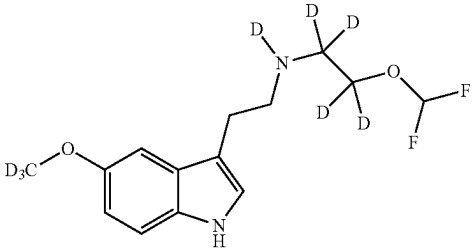
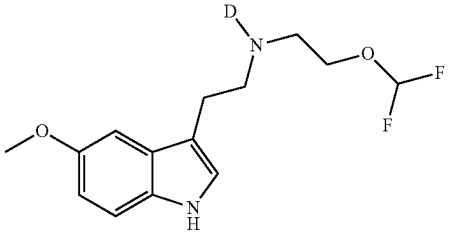
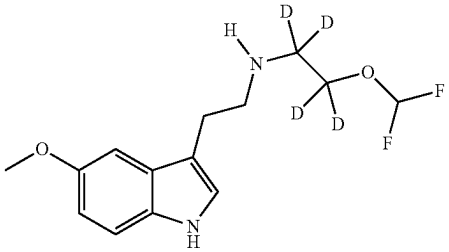
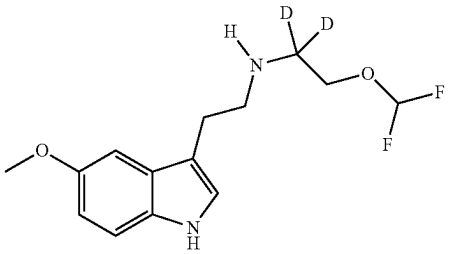
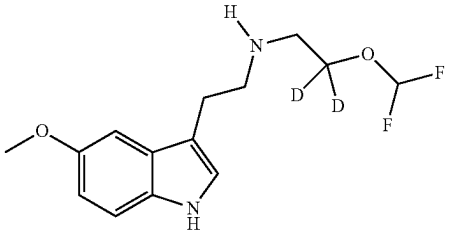
Compound	Structure
I-177	
I-178	
I-179	
I-180	
I-181	
I-182	

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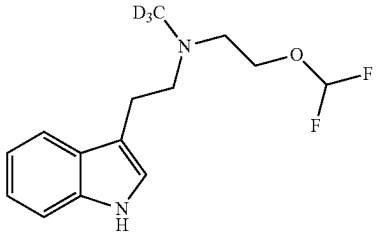
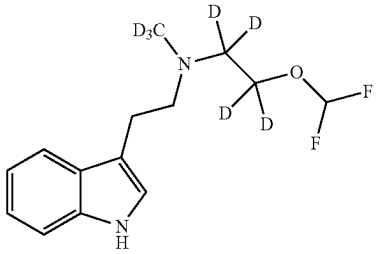
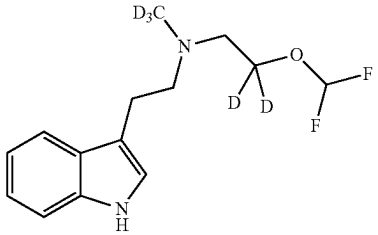
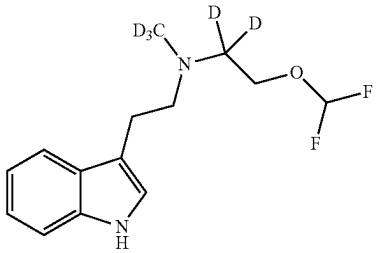
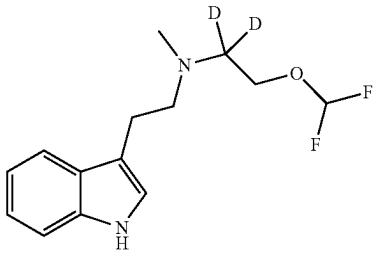
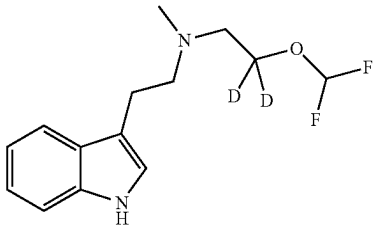
Compound	Structure
I-183	
I-184	
I-185	
I-186	
I-187	
I-188	

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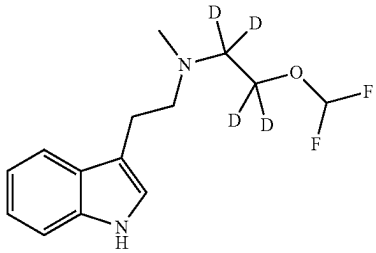
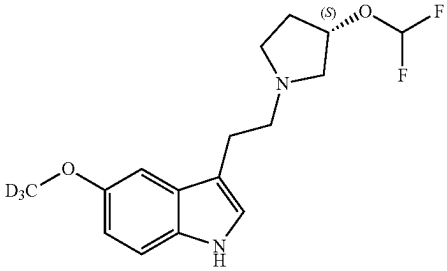
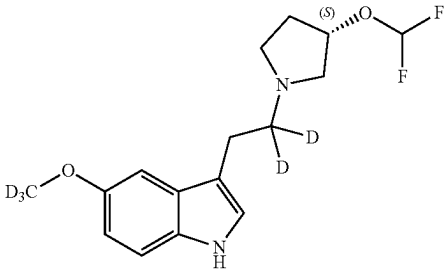
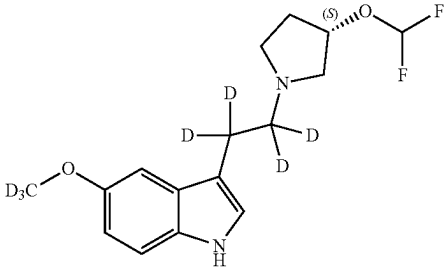
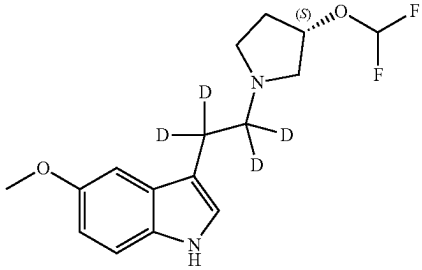
Compound	Structure
I-189	
(S) I-190	
(R) I-190	
I-191	
(S) I-192	

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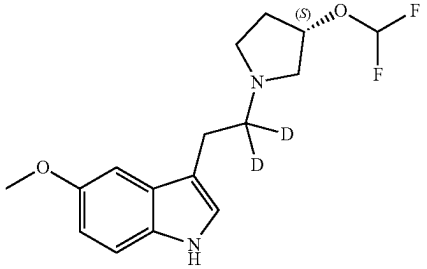
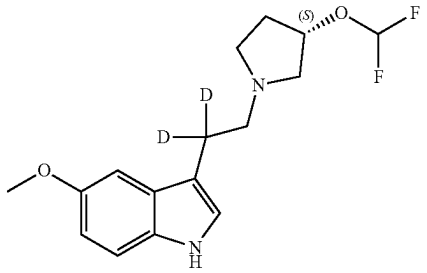
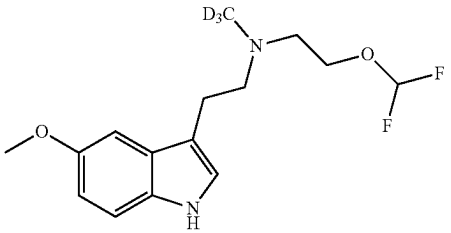
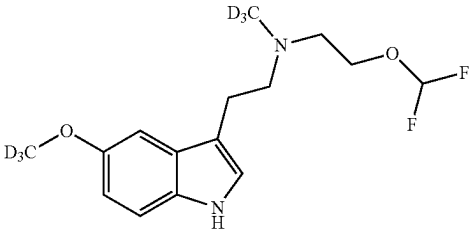
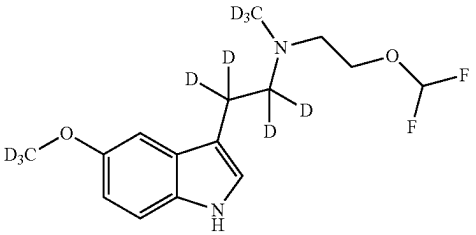
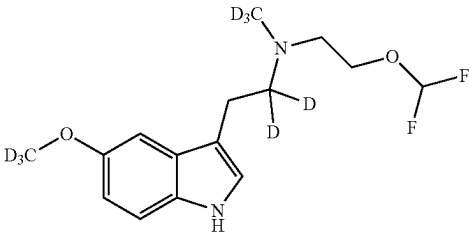
Compound	Structure
(S) I-193	
(S) I-194	
I-195	
I-196	
I-197	
I-198	

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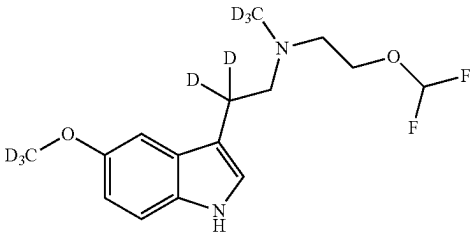
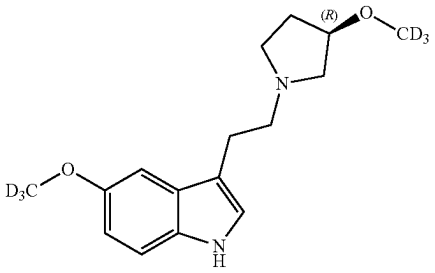
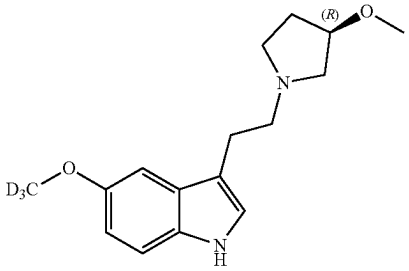
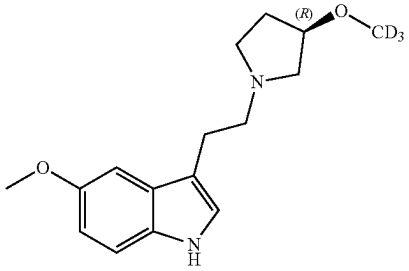
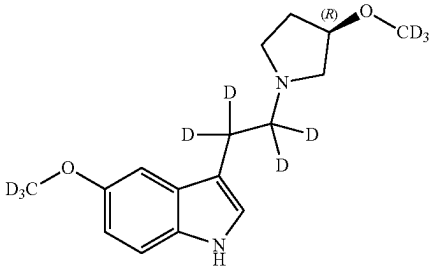
Compound	Structure
I-199	
(R) I-200	
(R) I-201	
(R) I-202	
(R) I-203	

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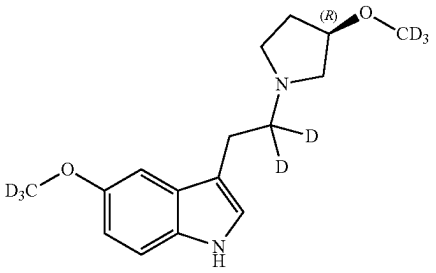
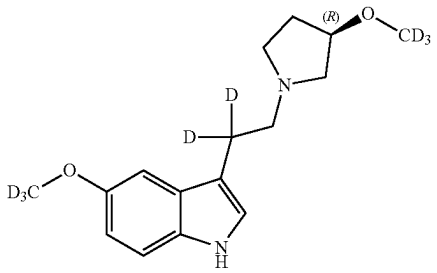
Compound	Structure
(R) I-204	
(R) I-205	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

[0973] E79: A composition comprising one or more compounds of any one of E1 to E78 and a carrier.

[0974] E80: A pharmaceutical composition comprising one or more compounds of any one of E1 to E78 and a pharmaceutically acceptable carrier.

[0975] E81: A method for activating a serotonin receptor in a cell, either in a biological sample or in vivo, comprising administering an effective amount of one or more compounds of any one of E1 to E78 to the cell.

[0976] E82: A method of treating a disease, disorder, or condition by activation of a serotonin receptor comprising administering a therapeutically effective amount of one or more compounds of any one of E1 to E78 to a subject in need thereof.

[0977] E83: A method for activating a 5-HT1A and 5-HT_{2A} in a cell, either in a biological sample or in vivo, comprising administering an effective amount of one or more compounds of any one of E1 to E78 to the cell.

[0978] E84: A method of treating a mental illness comprising administering a therapeutically effective amount of any one of E1 to E78 to a subject in need thereof.

[0979] E85: The method of E84, wherein the mental illness is selected from hallucinations, delusions, and a combination thereof.

[0980] E86: The method of E84, wherein the mental illness is selected anxiety disorders; depression; mood disorders; psychotic disorders; impulse control and addiction disorders and behaviors; drug addiction; obsessive-compulsive disorder (O C D); post-traumatic stress disorder (PTSD); stress response syndromes; dissociative disorders; depersonalization disorder; factitious disorders; sexual and gender disorders; somatic symptom disorders; and combinations thereof.

[0981] E87: A method of treating psychosis or psychotic symptoms comprising administering a therapeutically effective amount of one or more compounds of any one of E1 to E78 to a subject in need thereof.

[0982] E88: A method of treating a central nervous system (CNS) disease, disorder, or condition and/or a neurological disease, disorder, or condition comprising administering a therapeutically effective amount of one or more compounds of any one of E1 to E78 to a subject in need thereof.

[0983] E89: The method of E88, wherein the CNS disease, disorder, or condition and/or neurological disease, disorder, or condition includes neurological diseases including neurodevelopmental diseases and neurodegenerative diseases such as Alzheimer's disease; presenile dementia; senile dementia; vascular dementia; Lewy body dementia; cognitive impairment, Parkinson's disease and Parkinsonian related disorders such as Parkinson dementia, corticobasal degeneration, and supranuclear palsy; epilepsy; CNS trauma; CNS infections; CNS inflammation; stroke; multiple sclerosis; Huntington's disease; mitochondrial disorders; Fragile X syndrome; Angelman syndrome; hereditary ataxias; neuro-otological and eye movement disorders; neurodegenerative diseases of the retina amyotrophic lateral sclerosis; tardive dyskinesias; hyperkinetic disorders; attention deficit hyperactivity disorder and attention deficit disorders; restless leg syndrome; Tourette's syndrome; schizophrenia; autism spectrum disorders; tuberous sclerosis; Rett syndrome; cerebral palsy; disorders of the reward system including eating disorders such as anorexia nervosa ("AN") and bulimia nervosa ("BN"); and binge eating disorder ("BED"); pica; rumination disorder; avoidant/restrictive food intake disorder; trichotillomania; dermotillomania; nail biting; migraine; fibromyalgia; peripheral neuropathy of any etiology; reduction in convergent thinking; increase in spontaneous divergent thinking and goal-oriented divergent thinking; and combinations thereof.

[0984] E90: A method of treating a behavioral problem comprising administering a therapeutically effective amount of one or more compounds of any one of E1 to E78 to a non-human subject in need thereof.

[0985] E91: The method of E90, wherein the non-human subject is a canine or feline suffering from neurological diseases, behavioral problems, trainability problems, and/or a combination thereof.

[0986] E92: The method of E91, wherein and the neurological diseases, behavioral problems, and trainability problems are selected from anxiety, fear and stress, sleep disturbances, cognitive dysfunction, aggression, and a combination thereof.

[0987] E93: A method of treating a disease, disorder, or condition by activation of a serotonin receptor comprising administering a therapeutically effective amount of one or more compounds of any one of E1 to E78 in combination with another known agent useful for treatment of a disease, disorder, or condition by activation of a serotonin receptor to a subject in need thereof.

[0988] E94: A pharmaceutical composition comprising a compound of any one of E1 to E78 and an additional therapeutic agent.

[0989] E95: The composition of E94, wherein the additional therapeutic agent is a psychoactive drug.

[0990] Where a range of values is provided herein, all values inclusive within the range may serve as a lower end value or an upper end value of the range for the purpose of the claims. For example, "C_1-C_6" includes herein the implicit disclosure of ranges inclusive of values within the

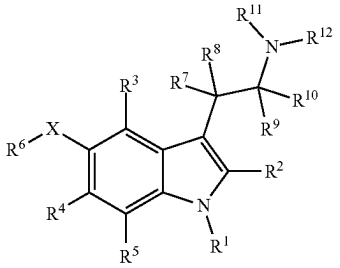
range, including C_1-C_2, C_1-C_3, C_1-C_4, C_1-C_5, C_1-C_6, C_2-C_3, C_2-C_4, C_2-C_5, C_2-C_6, C_3-C_4, C_3-C_5, C_3-C_6, C_4-C_5, C_4-C_6, and C_5-C_6.

[0991] While the present disclosure has been described with reference to examples, it is to be understood that the scope of the claims should not be limited by the embodiments set forth in the examples, but should be given the broadest interpretation consistent with the description as a whole.

[0992] All patents, patent applications and publications cited herein are hereby incorporated by reference in their entirety. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the application described and claimed herein.

1. A compound of Formula (I)

Formula (I)



or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof,

wherein:

X is absent or selected from O, S, S(O), and SO_2;

R^1 is selected from H, C_1-C_6alkyl, C_{1-6}alkylene P(O)$(OR^{13})_2$, C_1-C_6alkylene $OP(O)(OR^{13})_2$, $C(O)R^{13}$, CO_2R^{13}, $C(O)N(R^{13})_2$, $S(O)R^{13}$, and SO_2R^{13};

R^2 is selected from H, halo, and C_1-C_6alkyl;

R^3 is selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

R^4 is selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

R^5 is selected from H, CN, halo, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl;

R^6 is selected from H, C_1-C_{10}alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and $C(O)R^{15}$;

R^7 is selected from H, halo, and C_1-C_6alkyl;

R^8 is selected from H, halo, and C_1—C alkyl;

R^9 is selected from H, halo, and C_1-C_6alkyl;

R^{10} is selected from H, halo, and C_1-C_6alkyl;

R^{11} is selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$,

R^{12} is selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_6alkyleneC_3-C_7cycloalkyl, C_1-C_6alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_6alkyleneC_6-C_{10}aryl, and C_1-C_6alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and $C(O)R^{17}$; or

R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl;

Z is selected from O, C(O), $NR^{19}C(O)$, $NR^{18}C(O)O$, $C(O)NR^{19}$, $OC(O)NR^{19}$, and NR^{19};

Z' is selected from O, C(O), $NR^{20}C(O)$, $NR^{20}C(O)O$, $C(O)NR^{20}$, $OC(O)NR^{20}$, and NR^{20};

R^{13} is independently selected from H and C_1-C_6alkyl;

R^{14} is selected from H, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl;

R^{15} is selected from H and C_1-C_6alkyl;

R^{16} is independently selected from H, C_1-C_6alkyl, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, and C_5-C_{10}heteroaryl, the latter four groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_4alkyl, OC_1-C_4alkyl, and $C(O)C_1$-C_4alkyl;

R^{17} is independently selected from H and C_1-C_6alkyl;

R^{18} is independently selected from H and C_1-C_6alkyl;

R^{19} is selected from H and C_1-C_6alkyl;

R^{20} is selected from H and C_1-C_6alkyl; and

available hydrogen atoms of R^1, R^2, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with a halogen atom and/or available atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with an alternate isotope thereof

provided when X is O, R^1 is H, CH_3, or CD_3, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is H, C_{1-4}alkyl, or C_1-4deuteroalkyl, then R^{11} and R^{12} are not H, C_{1-4}alkyl, or C_{1-4}deuteroalkyl;

provided when X is O, R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, and R^{10} are H or D, and R^6 is CH_3 or CHF_2, then R^{11} and R^{12} are not CH_3 or CD_3; and

provided when X is absent and R^6 is H, then at least one of R^{11} and R^{12} is not H or C_1-C_6alkyl.

2. The compound of claim **1**, provided when (1) X is absent, then R^6 is not H, D, or halogen, and (2) X is O, S, S(O), or SO_2, then at least one of R^{11} and R^{12} is none of H, D, halogen, C_1-C_6alky, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, or C_1-C_6deuterohaloalkyl.

3. The compound of claim **1**, wherein available hydrogen atoms of R^1, R^2, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^1, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with an iodine atom, a fluorine atom, and/or a chlorine atom and/or available hydrogen atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with deuterium.

4. The compound of claim **1**, wherein X is SO_2 or S.

5. The compound of claim **4**, wherein R^6 is selected from C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZR^{14}, C_2-C_6alkenyleneZR^{14}, C_2-C_6alkynyleneZR^{14}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15}, and wherein available hydrogen atoms of R^1, R^2, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with deuterium.

6. The compound of claim **4**, wherein R^6 is a member selected from C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl and C_1-C_4alkyleneC_5-C_{10}heteroaryl including one or more heteromoieties selected from O, S, S(O), SO_2, and N, and optionally and independently comprises one or two C═O groups, wherein the member selected from C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl and C_1-C_4alkyleneC_5-C_{10}heteroaryl is optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{15}, and C(O)R^{15}, and wherein the member selected from C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl and C_1-C_4alkyleneC_5-C_{10}heteroaryl is optionally polycyclic or benzofused, wherein available hydrogen atoms of R^1, R^2, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally and independently replaced with a halogen atom and/or available hydrogen atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with an alternate isotope thereof.

7. The compound of claim **4**, wherein:

R^7 is selected from H, D, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl;

R^8 is selected from H, D, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl;

R^9 is selected from H, D, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl; and

R^{10} is selected from H, D, F, Cl, Br, C_1-C_4alkyl, C_1-C_4fluoroalkyl, C_1-C_4deuteroalkyl, and C_1-C_4deuterofluoroalkyl.

8. The compound of claim **4**, wherein:

R^7 is selected from H, F, and D;

R^8 is selected from H, F, and D;

R^9 is selected from H, F, and D; and

R^{10} is selected from H, F, and D.

9. The compound of claim **4**, wherein:

R^{11} is selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and C(O)R^{17}, and wherein available hydrogen atoms of R^1, R^2, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with deuterium; and

R^{12} is selected from H, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkyleneZ'R^{16}, C_2-C_6alkenyleneZ'R^{16}, C_2-C_6alkynyleneZ'R^{16}, C_3-C_7cycloalkyl, C_3-C_{10}heterocycloalkyl, C_6-C_{10}aryl, C_5-C_{10}heteroaryl, C_1-C_4alkyleneC_3-C_7cycloalkyl, C_1-C_4alkyleneC_3-C_{10}heterocycloalkyl, C_1-C_4alkyleneC_6-C_{10}aryl, and C_1-C_4alkyleneC_5-C_{10}heteroaryl, the latter eight groups being optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OR^{17}, and C(O)R^{17}, and wherein available hydrogen atoms of R^1, R^2, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with a fluorine atom and/or a chlorine atom and/or available hydrogen atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with deuterium.

10. The compound of claim **9**, wherein one of R^6, R^{11}, and R^{12} is not H or C_1-C_6alkyl, wherein available hydrogen atoms of R^1, R^2, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with a halogen atom and/or available atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with an alternate isotope thereof.

11. The compound of claim **4**, wherein at least one of R^{11} and R^{12} is selected from C_1-C_6alkyleneZ'R^{16}, C_1-C_6fluoroalkyleneZ'R^{16}, C_1-C_6deuteroalkyleneZ'R^{16}, and C_1-C_6deuterofluoroalkyleneZ'R^{16}.

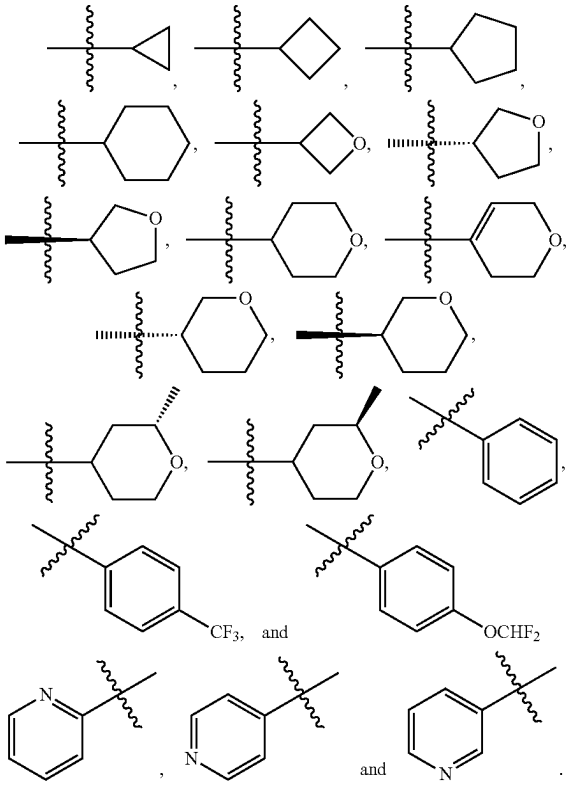
12. The compound of claim **11**, wherein Z' is O and R^{16} is selected from C_1-C_6alkyl, C_1-C_6deuteroalkyl, C_1-C_6haloalkyl, and C_1-C_6deuterohaloalkyl.

13. The compound of claim **4**, wherein R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a monocyclic 3- to 7-membered heterocyclic ring or a bicyclic 7- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, wherein each said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected

from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, wherein available hydrogen atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with a halogen atom and/or available atoms of R^1, R^2, R^3, R^4, R^5, R^6, R^7 R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, and R^{20} are optionally replaced with an alternate isotope thereof.

14. The compound of claim **4**, wherein at least one of the substituents on the 3- to 10-membered heterocyclic ring formed when R^{11} and R^{12} are taken together with the nitrogen atom therebetween is selected from OH, OC_1-C_4alkyl, OC_1-C_4deuteroalkyl, OC_1-C_4fluoroalkyl, OC_1-C_4deuterofluoroalkyl, C_1-C_4alkyleneOH, C_1-C_4fluoroalkyleneOH, C_1-C_4deuteroalkyleneOH, C_1-C_4deuterofluoroalkyleneOH, C_1-C_4alkyleneOC_1-C_4alkyl, C_1-C_4alkyleneOC_1-C_4fluoroalkyl, C_1-C_4alkyleneOC_1-C_4deuteroalkyl, C_1-C_4alkyleneOC_1-C_4deuterofluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4alkyl, C_1-C_4deuteroalkyleneOC_1-C_4alkyl, C_1-C_4deuterofluoroalkyleneOC_1-C_4alkyl, C_1-C_4fluoroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4deuteroalkyl, C_1-C_4deuteroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4deuteroalkyleneOC_1-C_4deuteroalkyl, C_1-C_4deuterofluoroalkyleneOC_1-C_4fluoroalkyl, C_1-C_4fluoroalkyleneOC_1-C_4deuterofluoroalkyl, and C_1-C_4deuterofluoroalkyleneOC_1-C_4deuterofluoroalkyl.

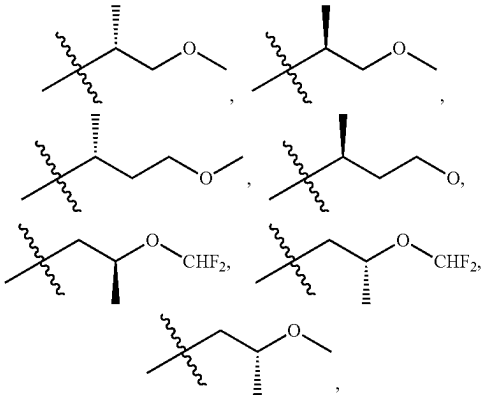
15. The compound of claim **4**, wherein R^6 is selected from CH_3, CD_3, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$, CH_2F, CHF_2, CH_2CHF_2, CH_2CF_3, $CH_2CH_2CF_3$,



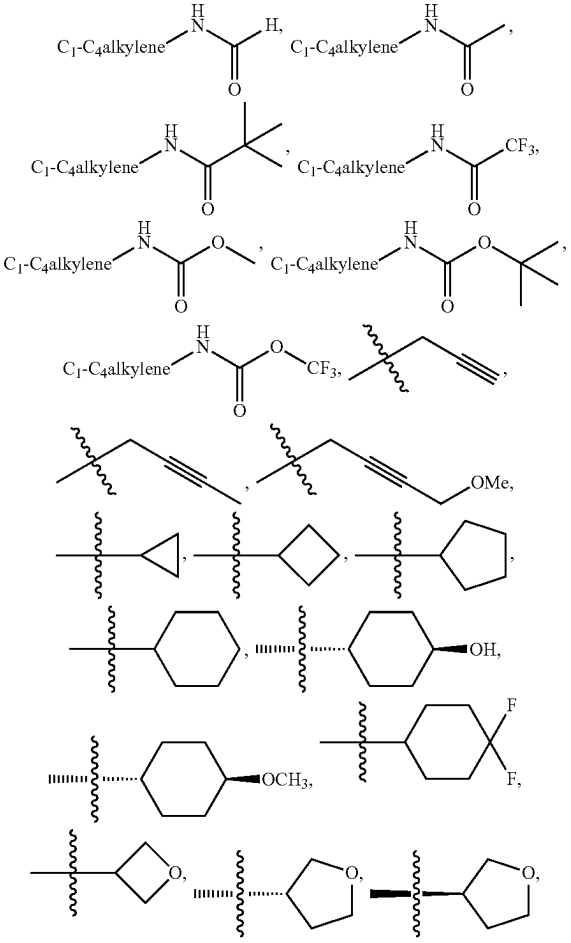
16. The compound of claim **4**, wherein:

R^{11} is selected from

H, CH_3, CD_3, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$, CH_2F, CHF_2, CH_2CHF_2, CH_2CF_3, $CH_2CH_2CF_3$, C_1-C_4alkyleneOCH$_3$, C_1-C_4alkyleneOCHF$_2$, C_1-C_4alkyleneOCH$_2$F,



C_1-C_4alkleneC(O)CHF$_2$, C_1-C_4alkleneC(O)CF$_3$,



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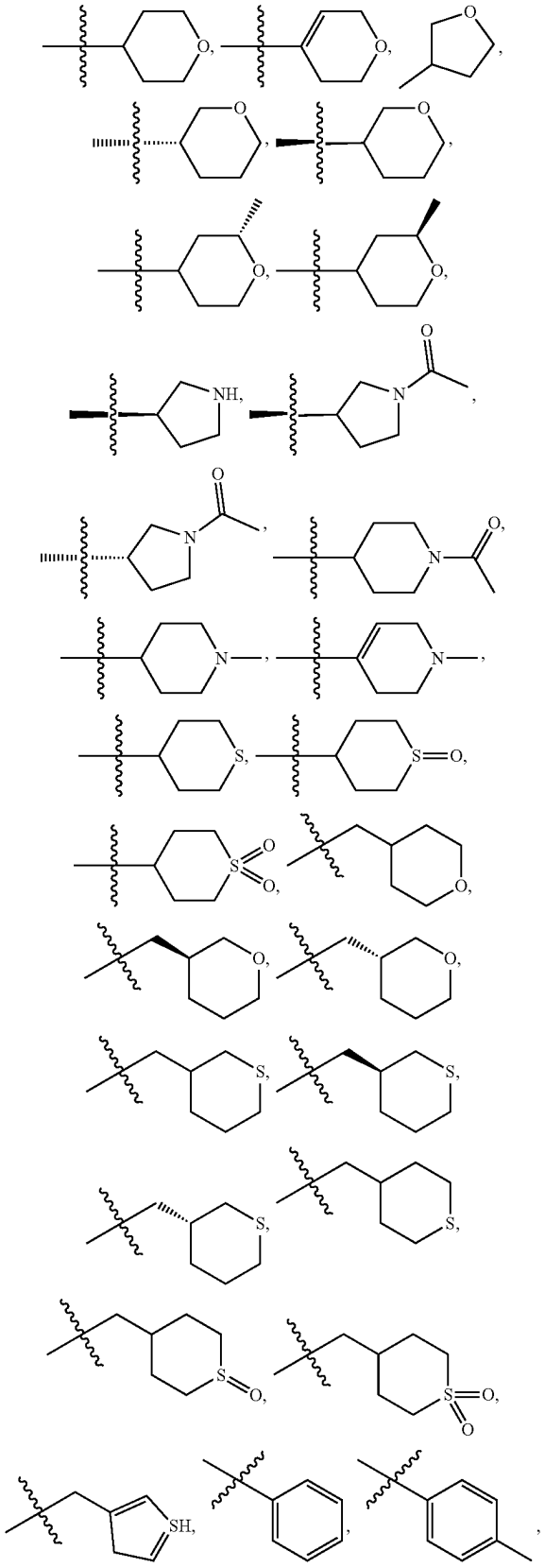

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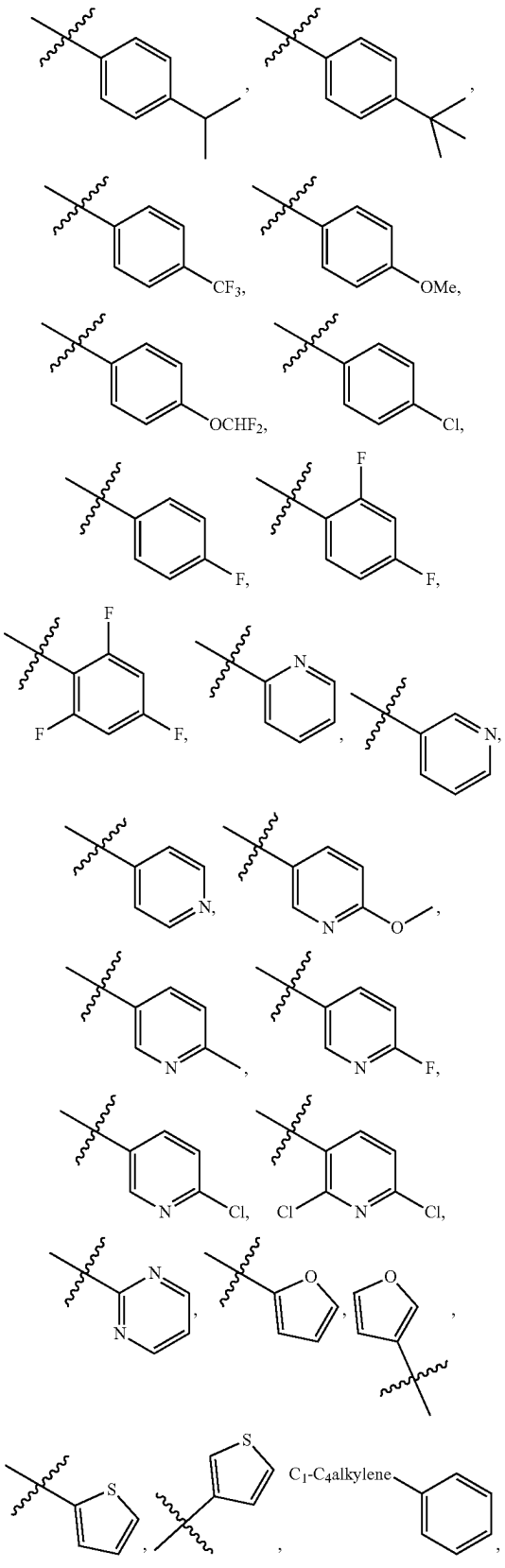

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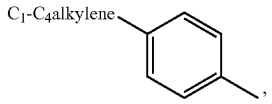

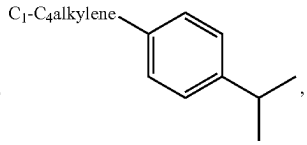

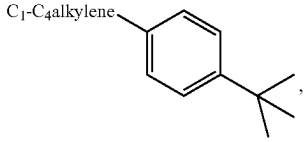

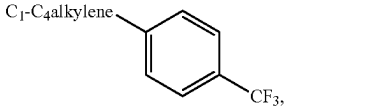

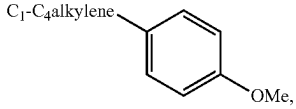

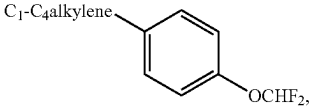

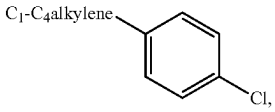

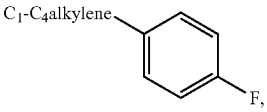

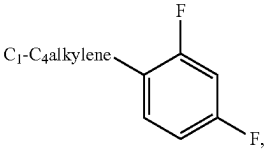

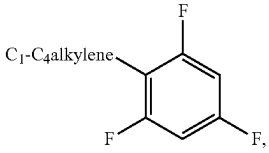

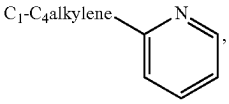

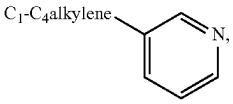

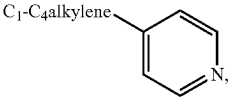

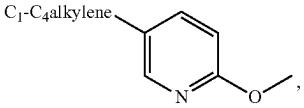

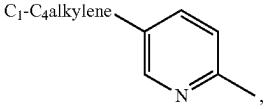

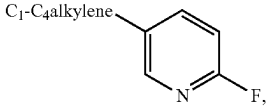

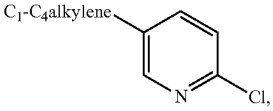

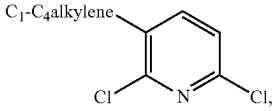

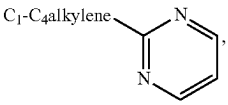

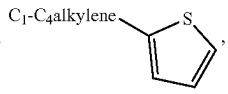

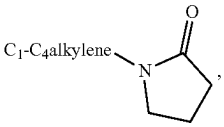

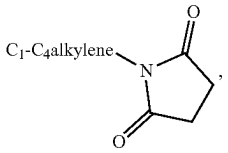

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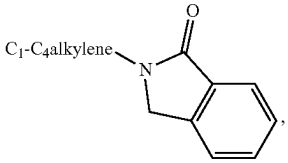

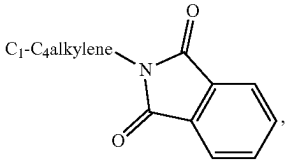

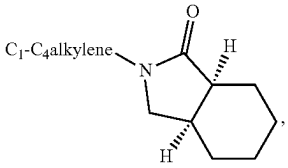

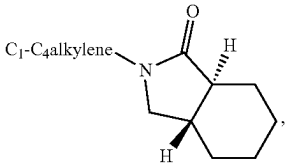

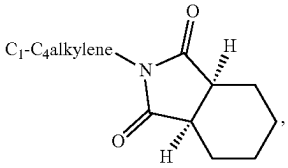

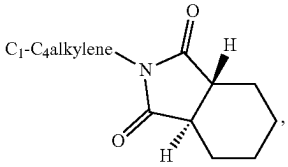

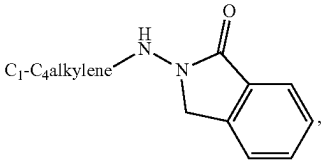

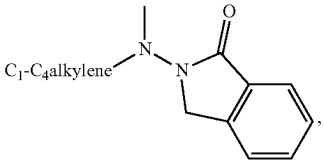

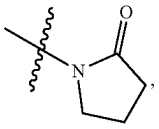

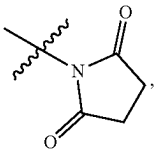

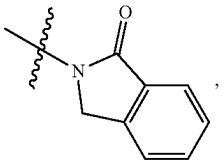

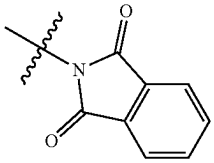

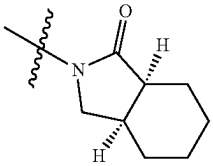

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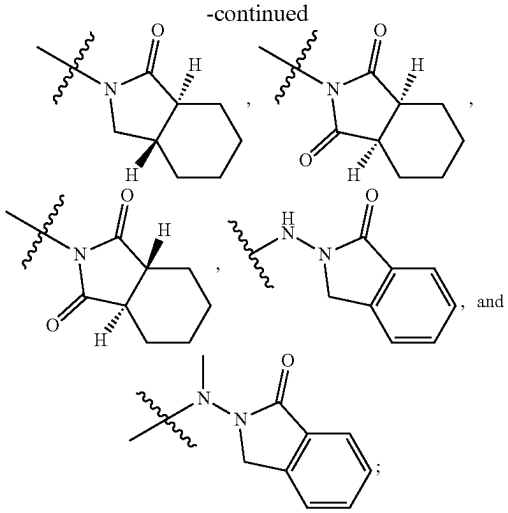
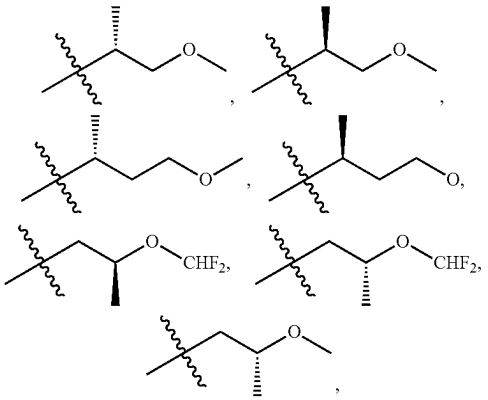


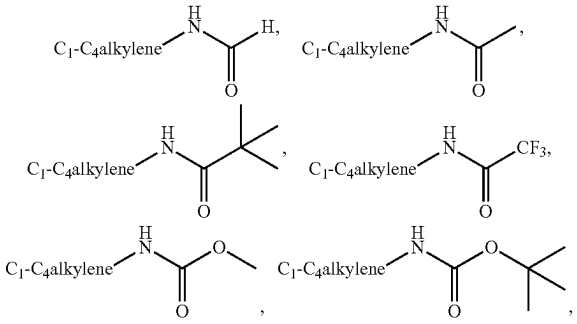
and

R^{12} is selected from

H, CH_3, CD_3, CF_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2C(CH_3)_3$, $CH_2CH_2C(CH_3)_3$, CH_2F, CHF_2, CH_2CHF_2, CH_2CF_3, $CH_2CH_2CF_3$, C_1-C_4alkyleneOCH$_3$, C_1-C_4alkyleneOCHF$_2$, C_1-C_4alkyleneOCH$_2$F,



C_1-C_4alkleneC(O)CHF$_2$, C_1-C_4alkleneC(O)CF$_3$,



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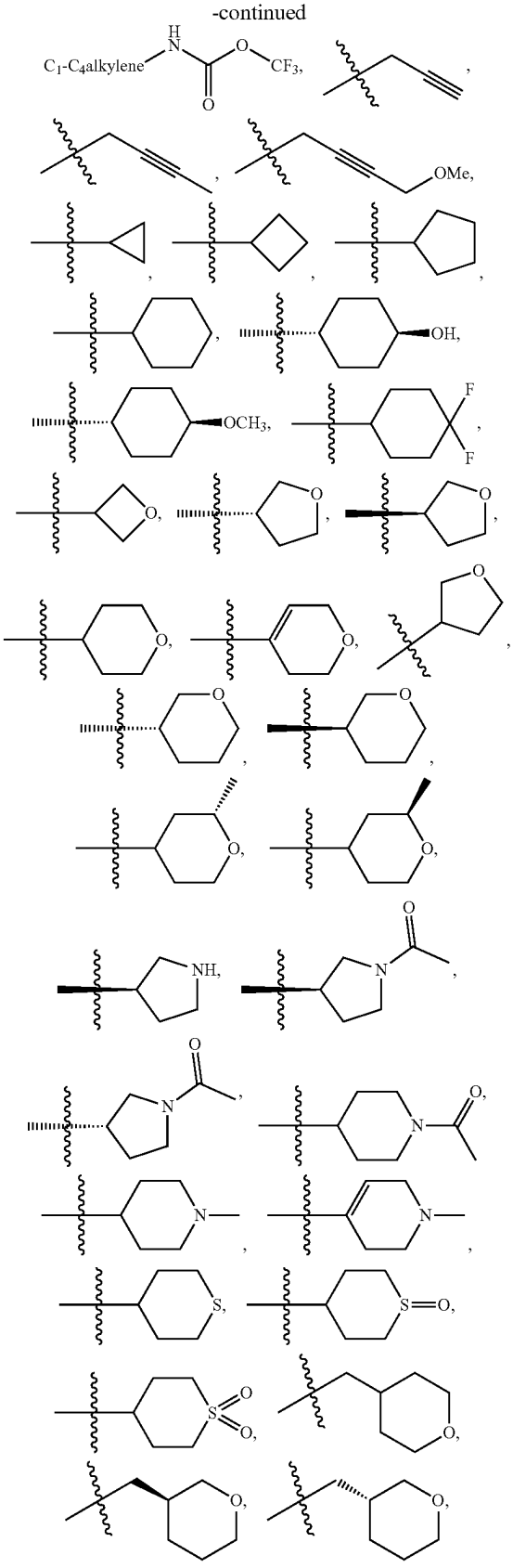

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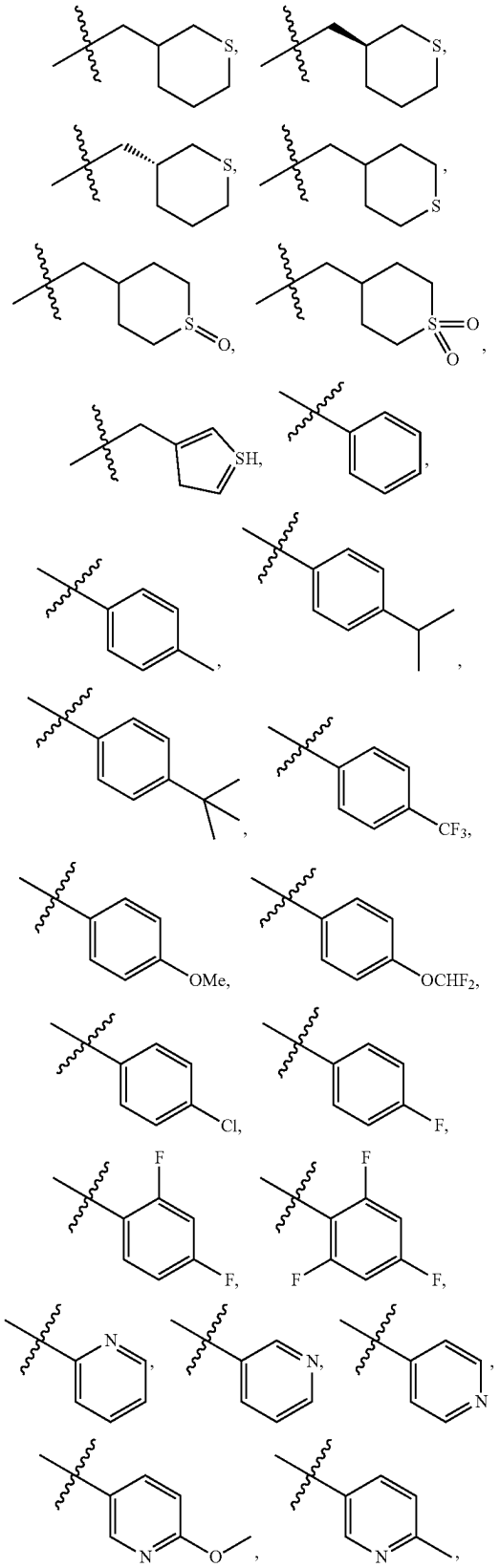

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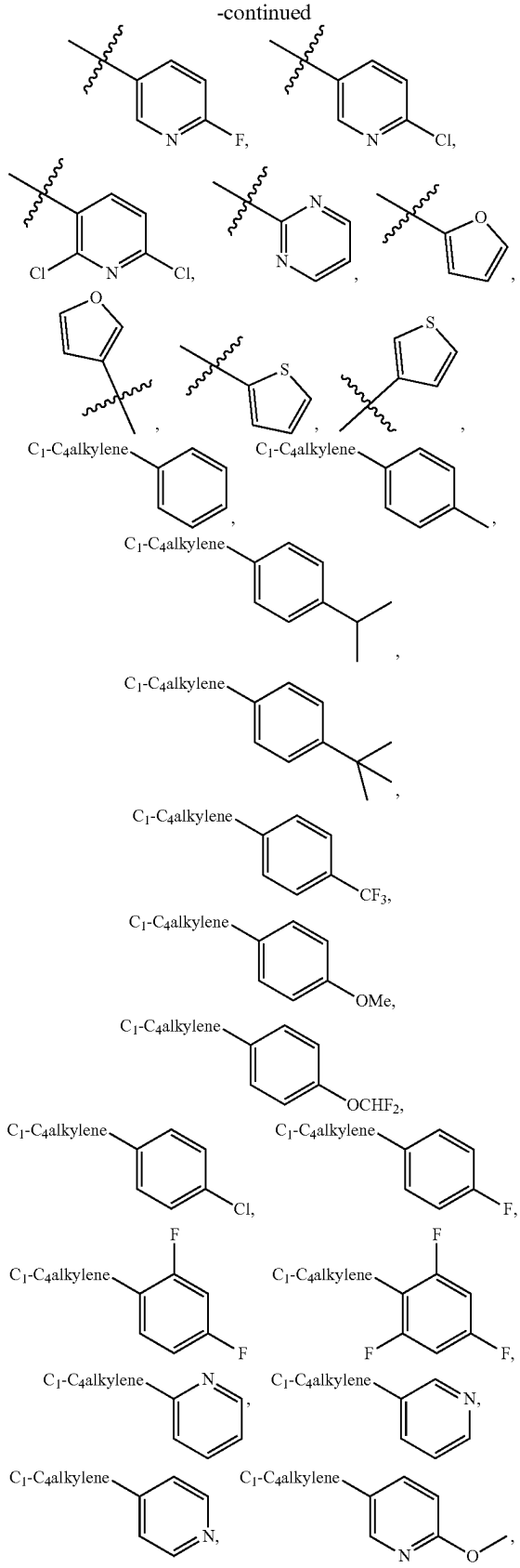

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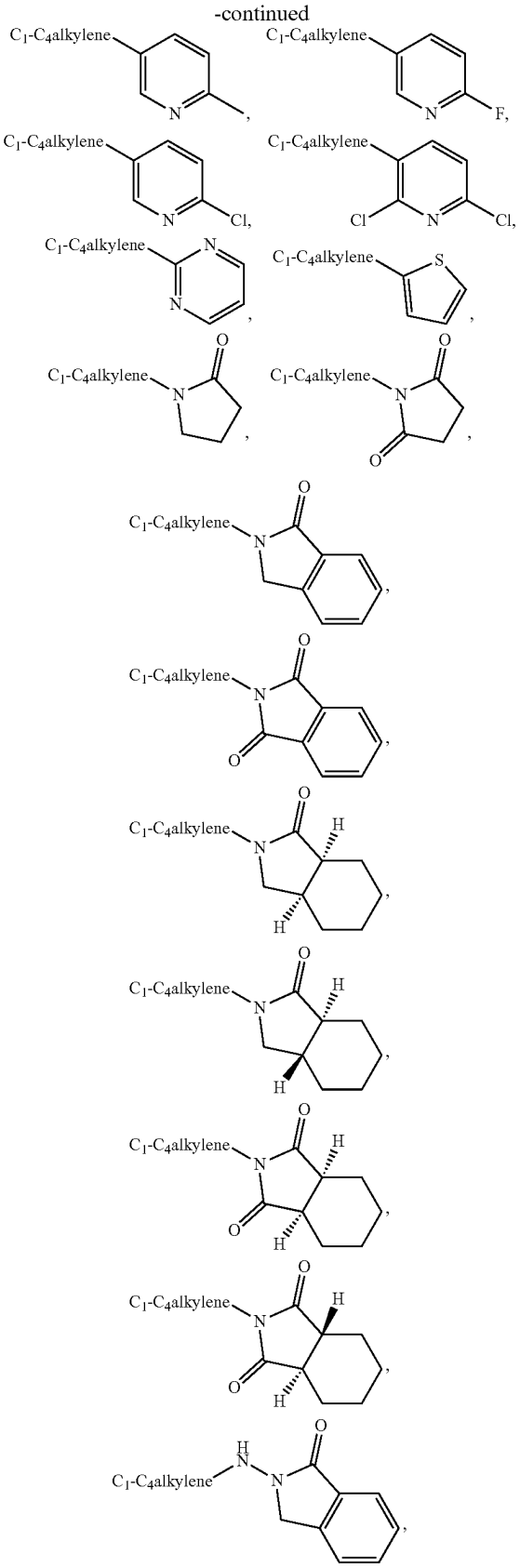

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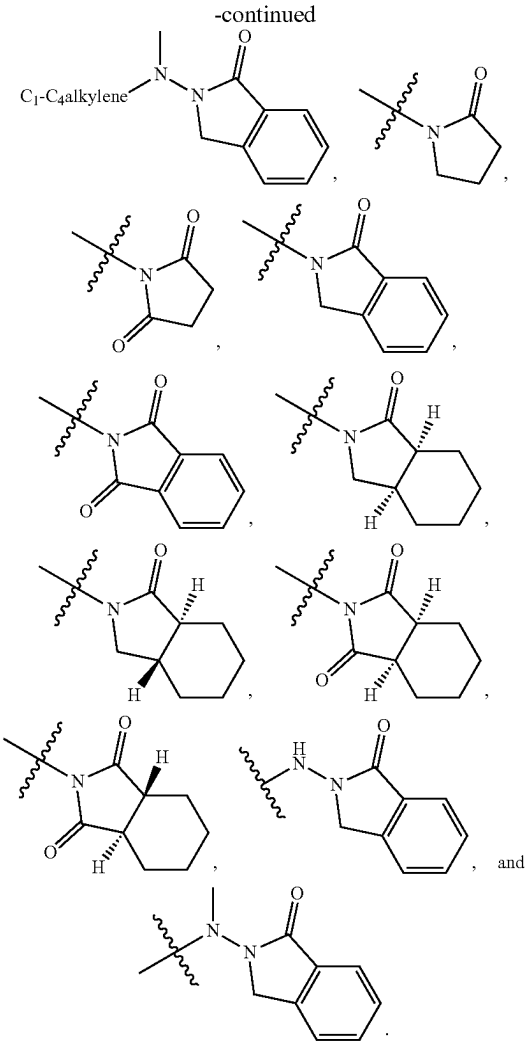
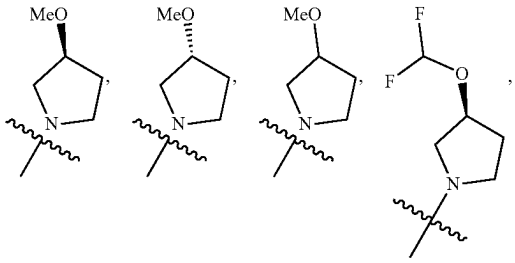


17. The compound of claim **1**, wherein R^{11} and R^{12} are taken together with the nitrogen atom therebetween to form a 3- to 10-membered heterocyclic ring optionally comprising 1 to 3 additional ring heteromoieties selected from O, S, S(O), SO_2, N, and NR^{18} and/or optionally comprising one or two C═O groups, and said 3- to 10-membered heterocyclic ring is further optionally substituted with one to four substituents independently selected from halo, C_1-C_6alkyl, OH, OC_1-C_6alkyl, C_1-C_6alkyleneOH, and C_1-C_6alkyleneOC_1-C_6alkyl, selected from



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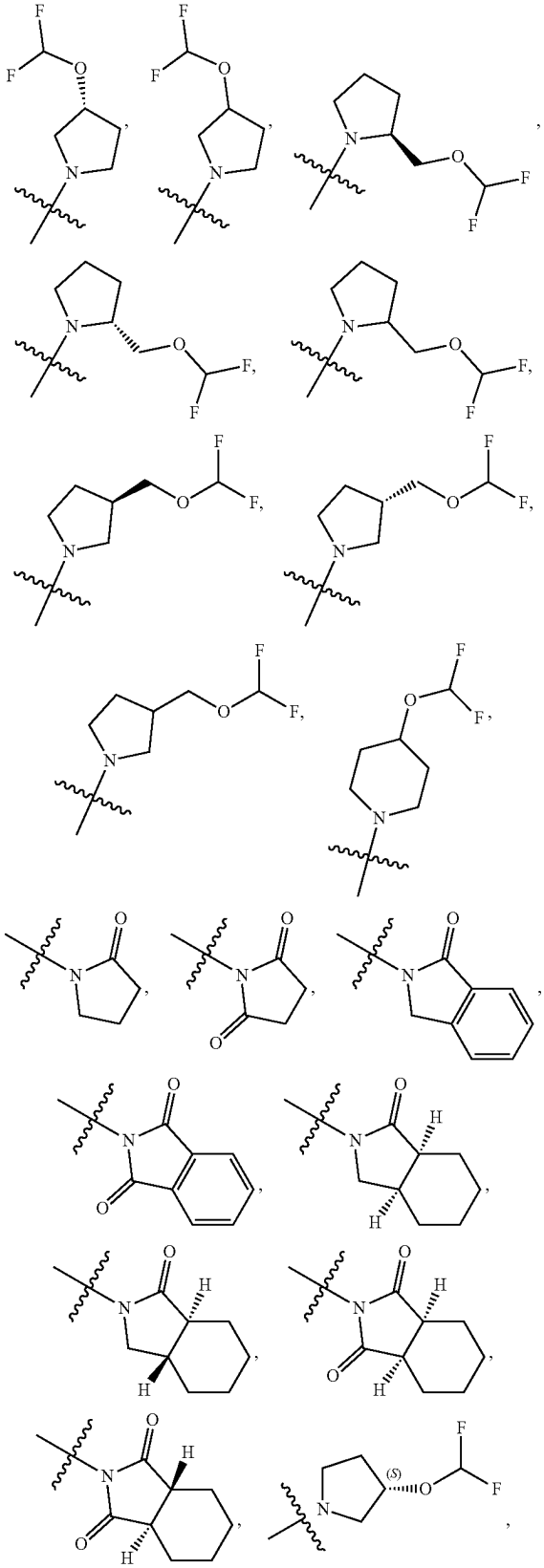

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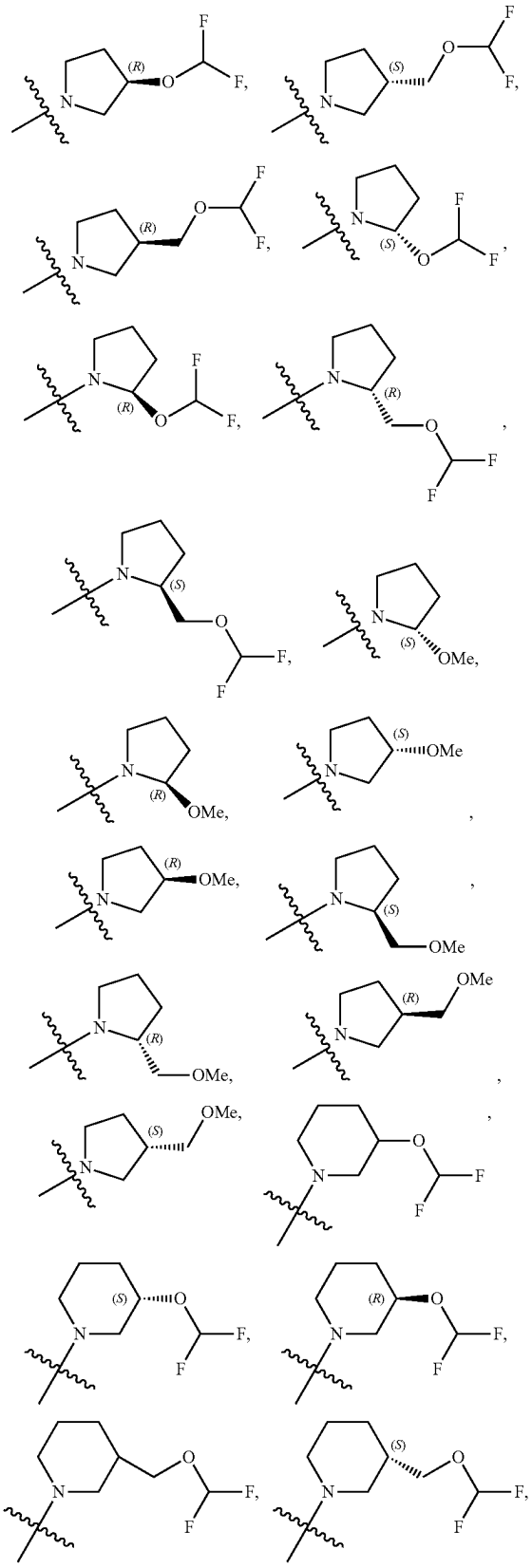

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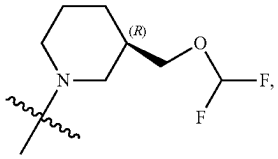

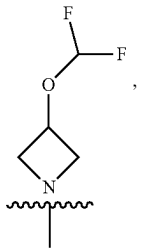

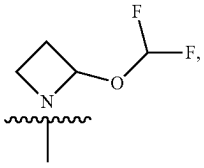

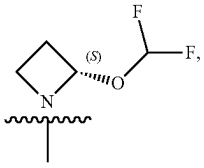

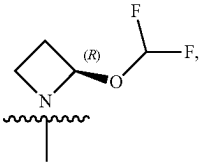

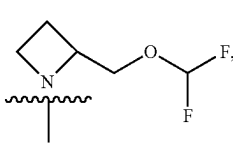

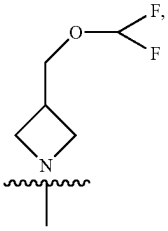

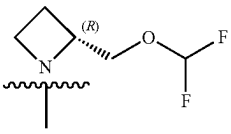

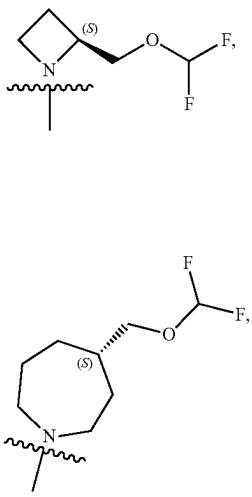

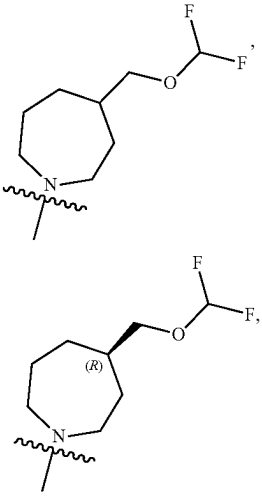

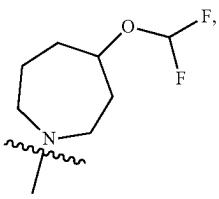

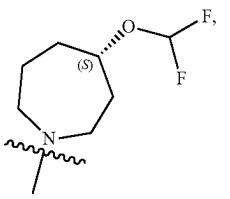

and

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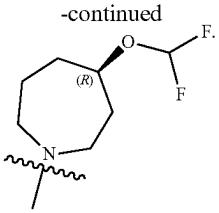
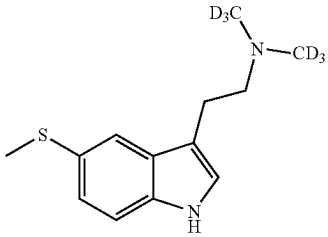
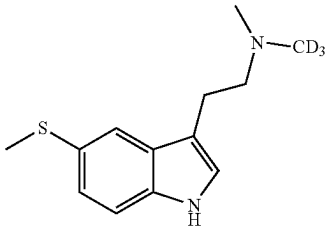
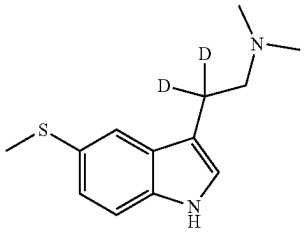
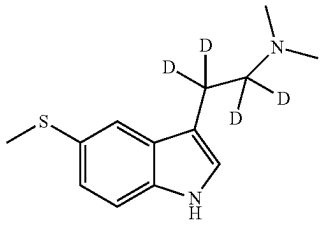
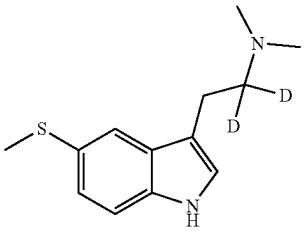


18. The compound of claim **1**, wherein R^3 is selected from H, CN, C_1-C_6alkyl, C_2-C_6alkenyl, and C_2-C_6alkynyl.

19. The compound of claim **4**, wherein the compound of Formula (I) is selected from the

Compound	Structure
I-1	
I-2	
I-3	
I-4	
I-5	

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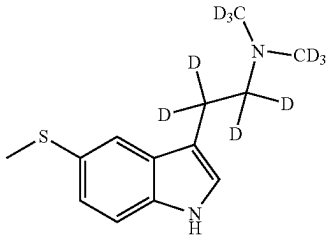
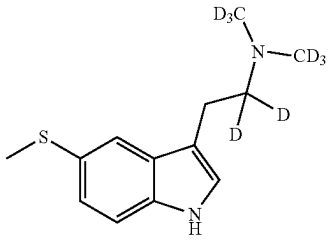
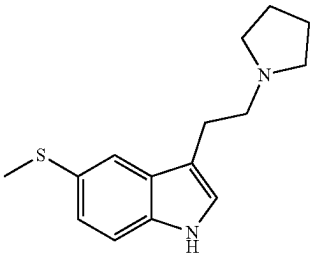
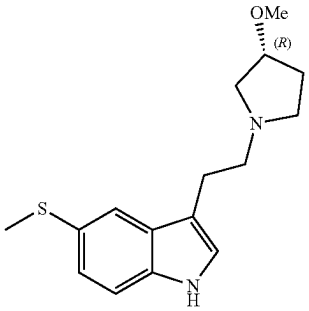
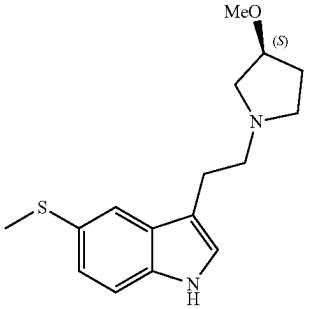
Compound	Structure
I-6	
I-7	
I-8	
(R) I-9	
(S) I-9	

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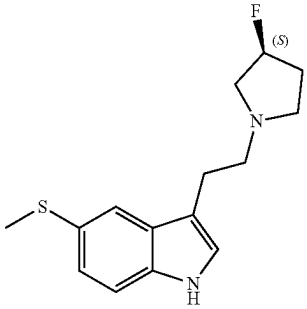
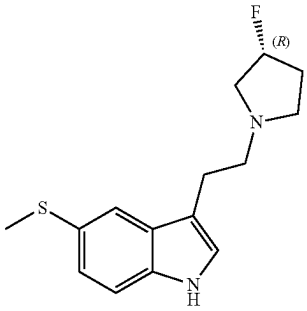
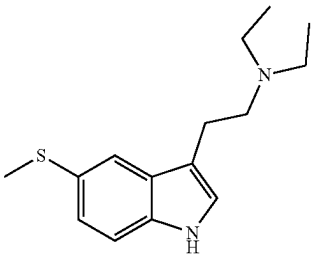
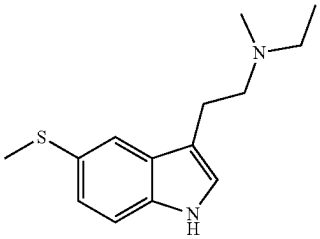
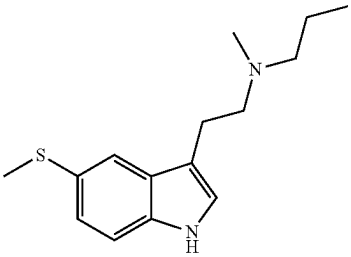
Compound	Structure
(R) I-10	
(S) I-10	
I-12	
I-13	
I-14	

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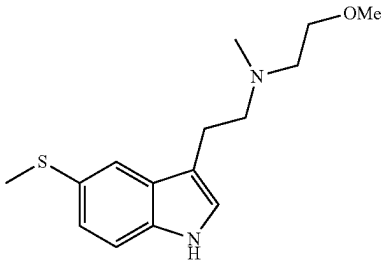
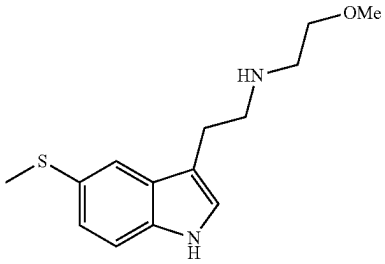
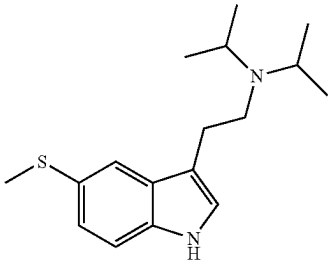
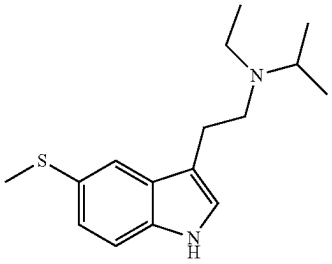
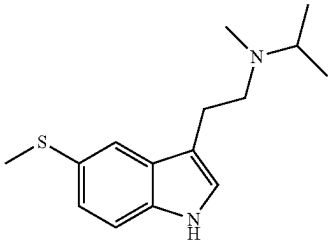
Compound	Structure
I-15	
I-16	
I-17	
I-18	
I-19	

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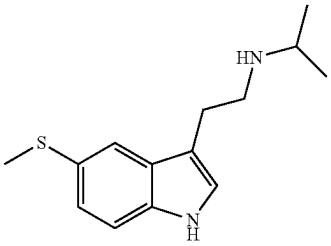
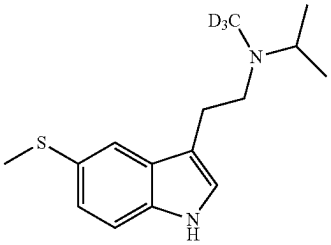
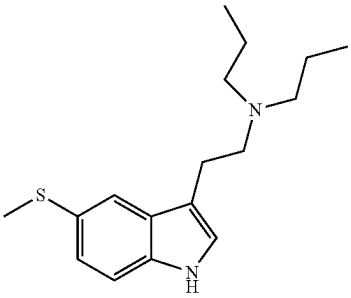
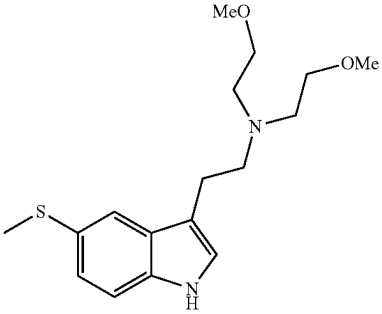
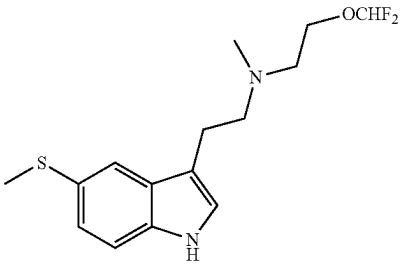
Compound	Structure
I-20	
I-21	
I-22	
I-23	
I-24	

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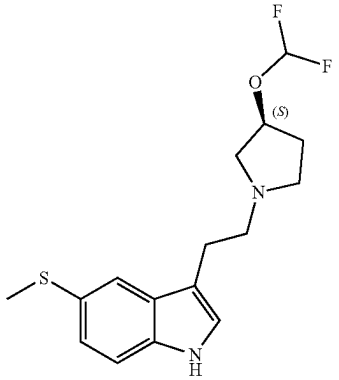
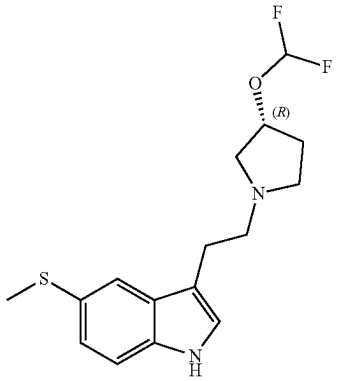
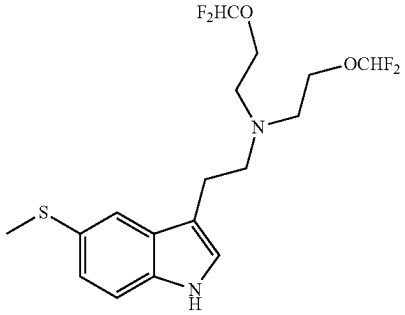
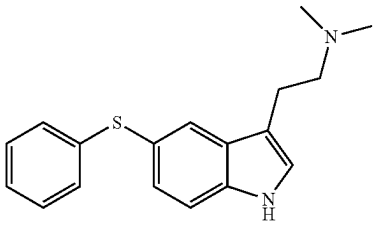
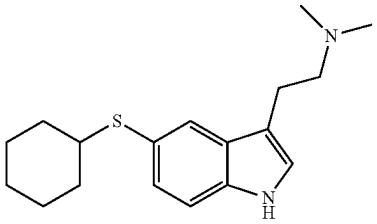
Compound	Structure
(S) I-26	
(R) I-26	
I-27	
I-28	
I-29	

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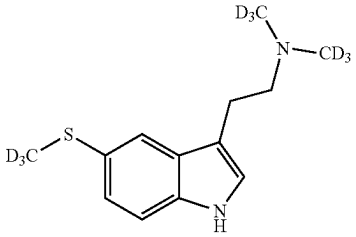
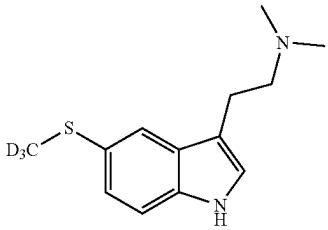
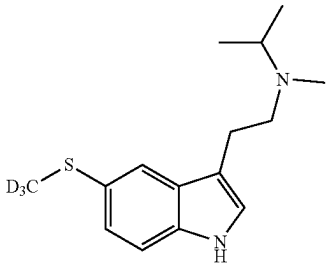
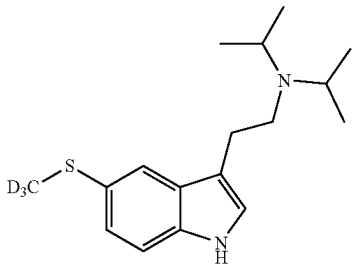
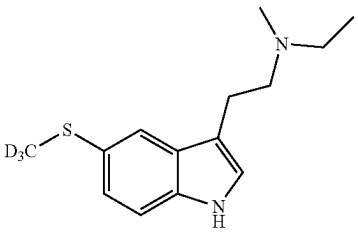
Compound	Structure
I-30	
I-31	
I-32	
I-33	
I-34	

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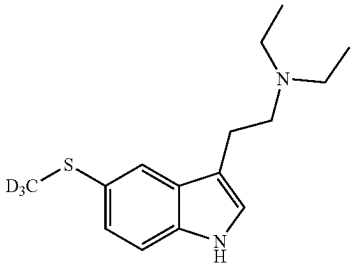
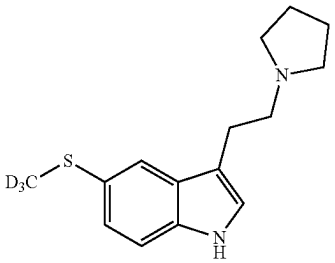
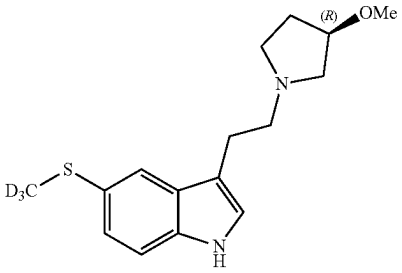
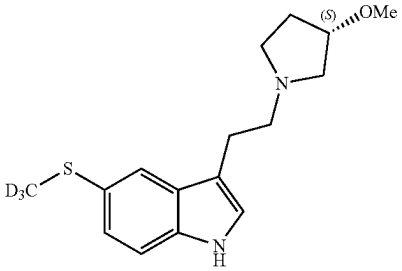
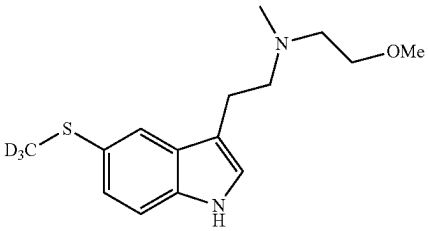
Compound	Structure
I-35	
I-36	
(R) I-37	
(S) I-37	
I-38	

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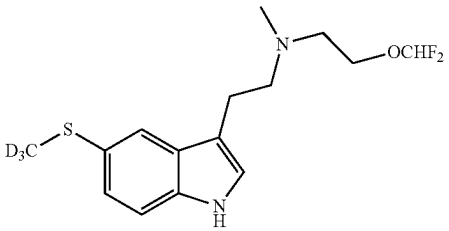
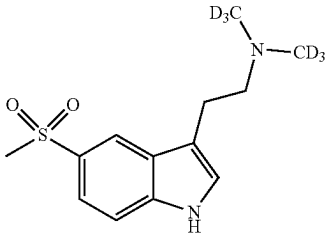
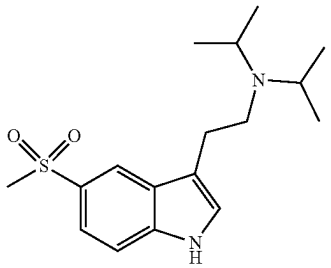
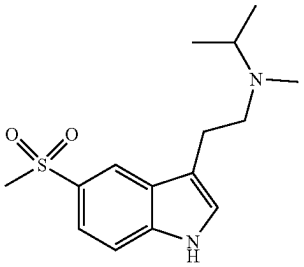
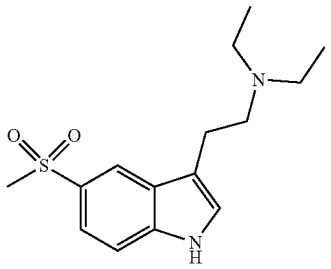
Compound	Structure
I-39	
I-40	
I-41	
I-42	
I-43	

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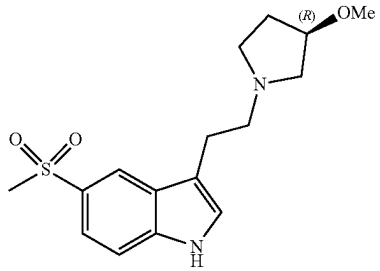
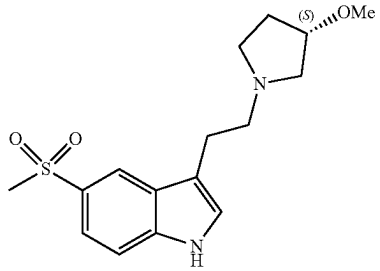
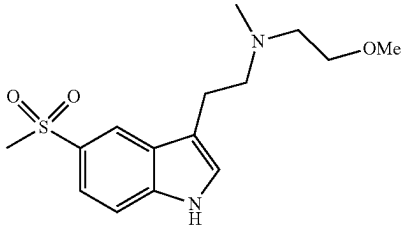
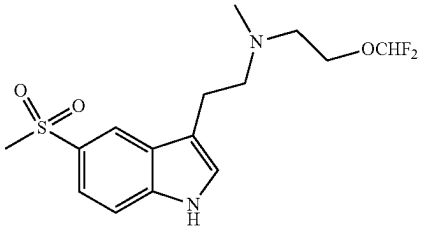
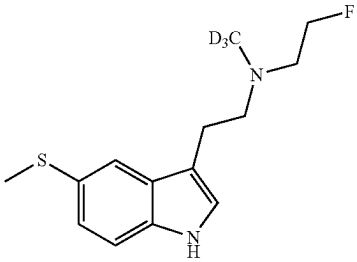
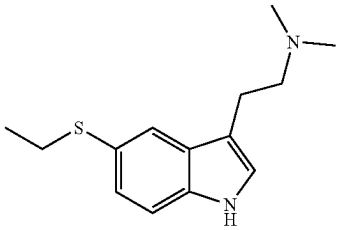
Compound	Structure
(R) I-44	
(S) I-44	
I-45	
I-46	
I-52	
I-55	

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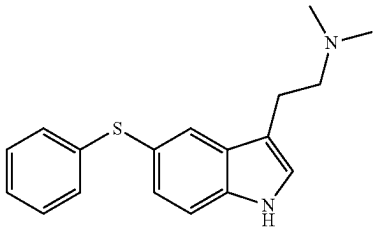
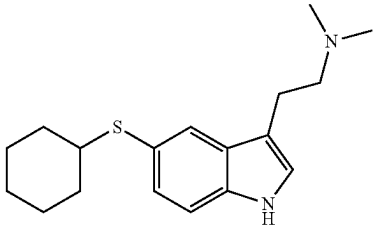
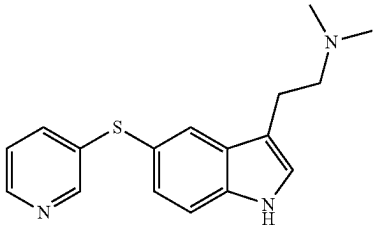
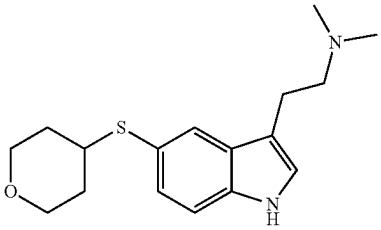
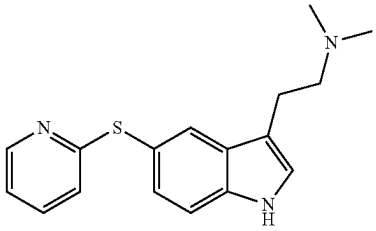
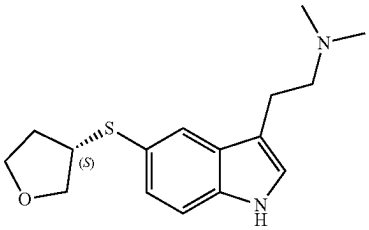
Compound	Structure
I-60	
I-61	
I-62	
I-63	
I-64	
(S) I-65	

and

-continued

Compound	Structure
(R) I-65	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

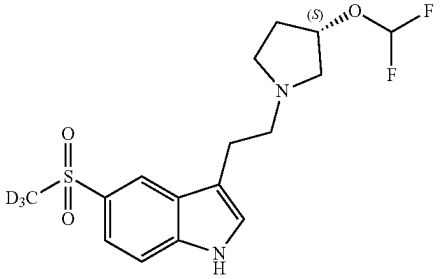
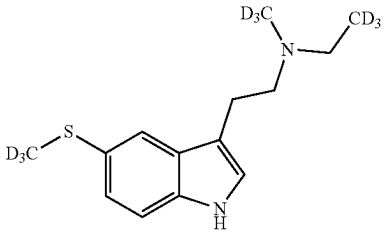
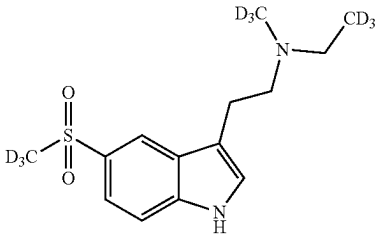
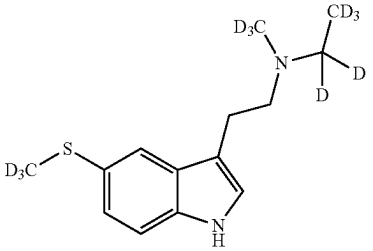
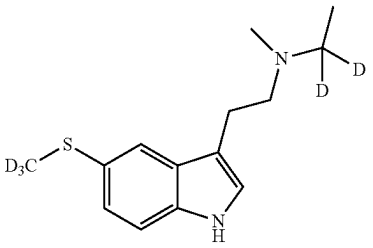
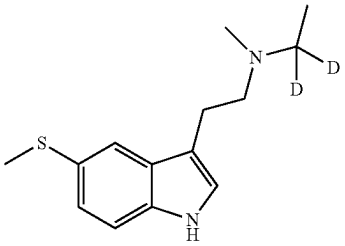
20. The compound of claim **4**, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
II-01	
II-04	
II-05	
II-07	

-continued

Compound	Structure
II-08	
II-10	
II-11	
II-12	
(S) II-13	
(S) II-15	

-continued

Compound	Structure
(S) II-17	
II-19	
II-21	
II-22	
II-23	
II-24	

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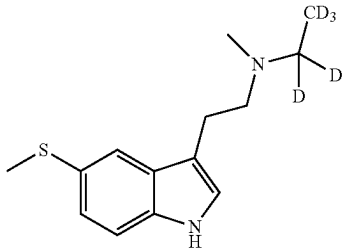
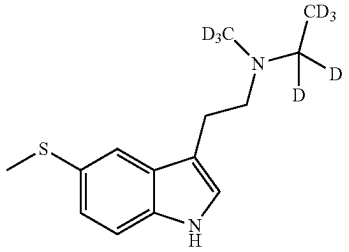
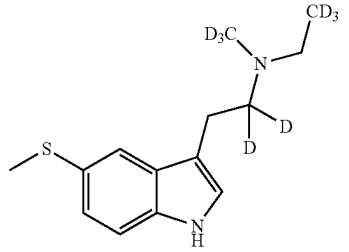
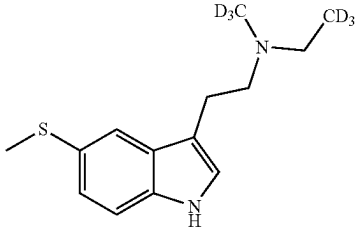
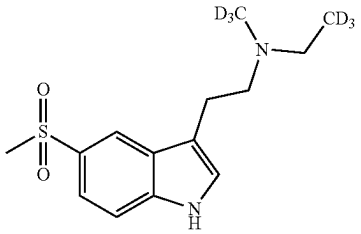
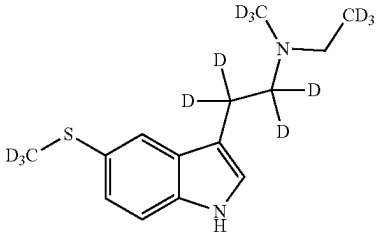
Compound	Structure
II-25	
II-26	
II-27	
II-28	
II-30	
II-31	

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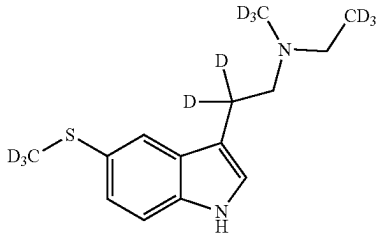
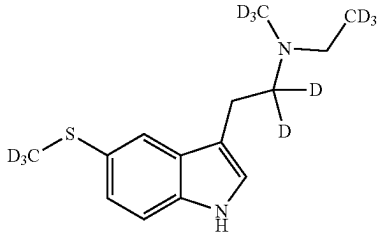
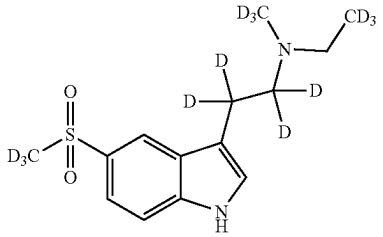
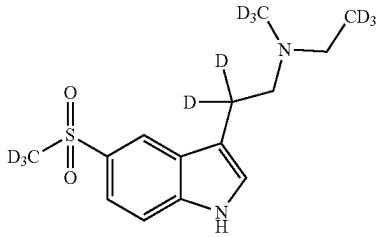
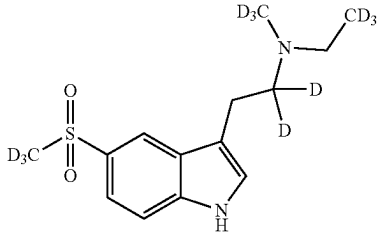
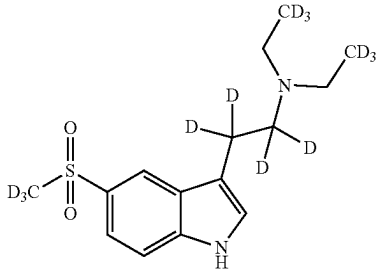
Compound	Structure
II-32	
II-33	
II-37	
II-38	
II-39	
II-43	

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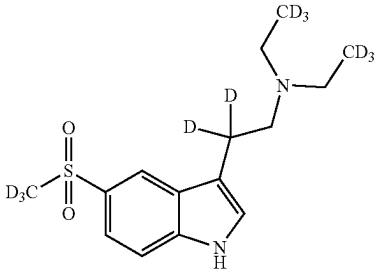
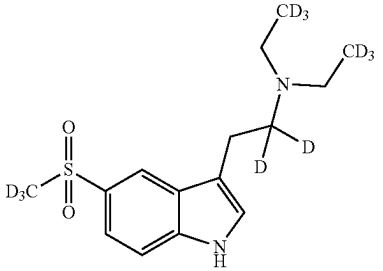
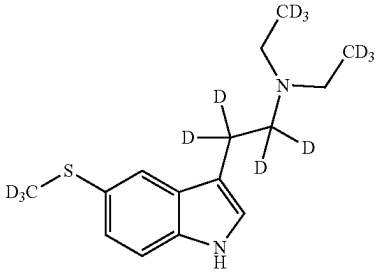
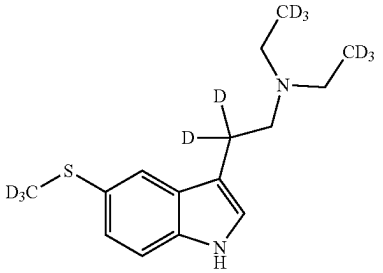
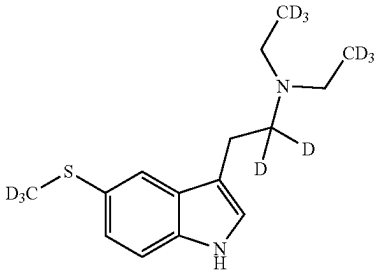
Compound	Structure
II-44	
II-45	
II-46	
II-47	
II-48	

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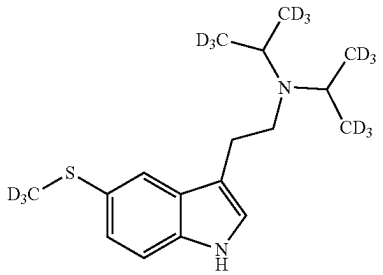
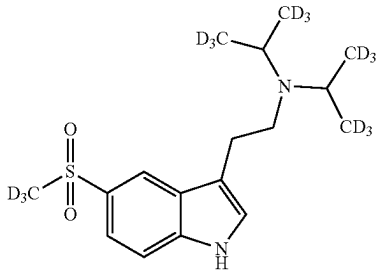
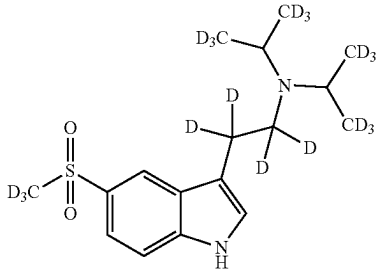
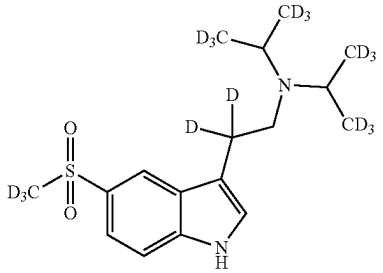
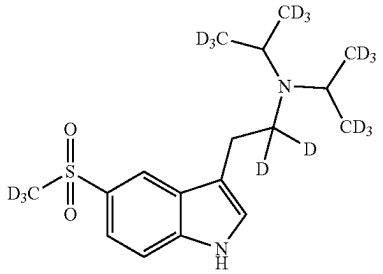
Compound	Structure
II-49	
II-50	
II-55	
II-56	
II-57	

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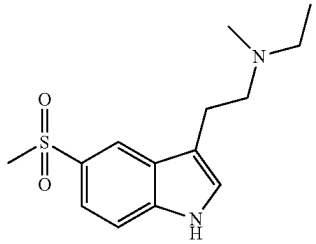
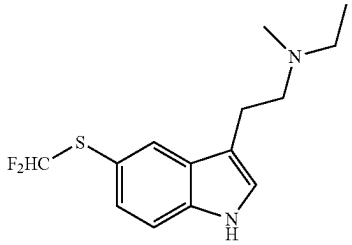
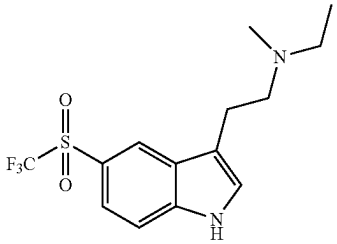
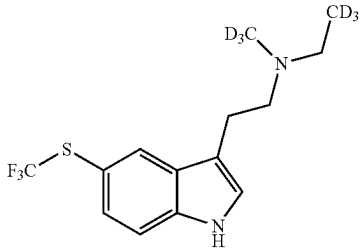
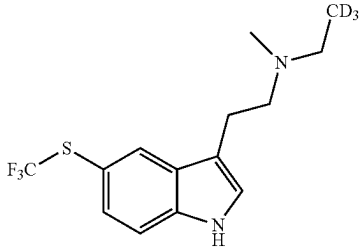
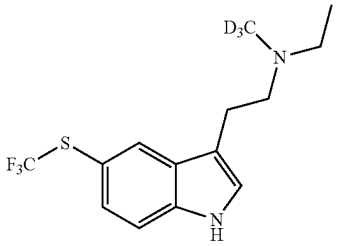
Compound	Structure
II-59	
II-60	
II-61	
II-63	
II-64	
II-65	

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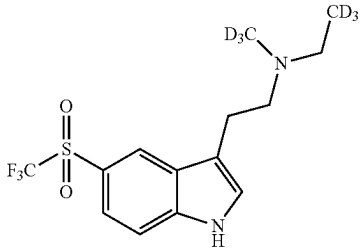
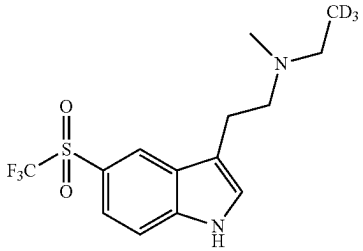
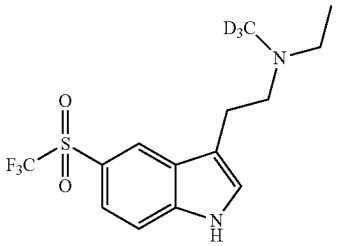
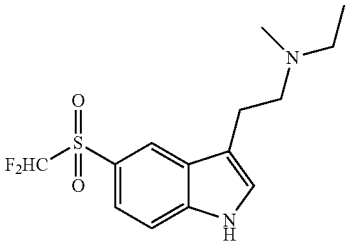
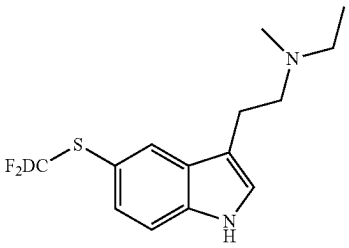
Compound	Structure
II-69	
II-70	
II-71	
II-72	
II-74	

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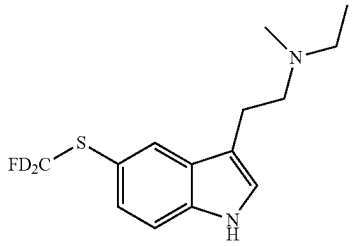
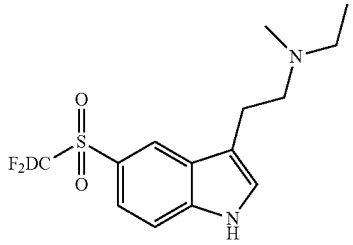
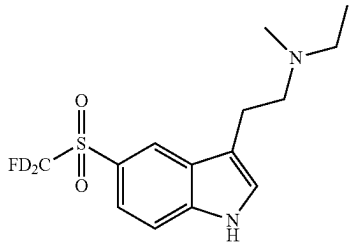
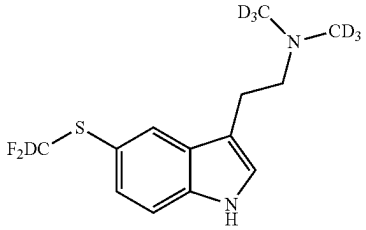
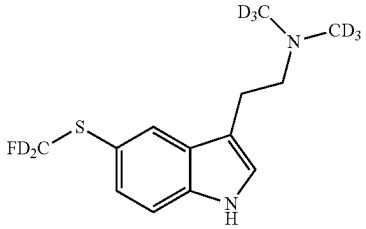
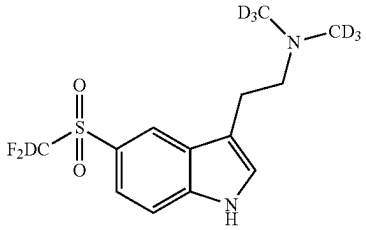
Compound	Structure
II-75	
II-78	
II-79	
II-86	
II-87	
II-90	

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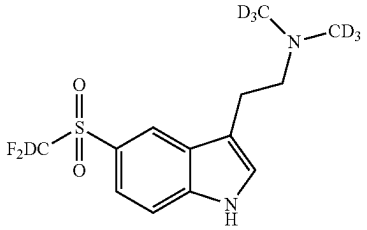
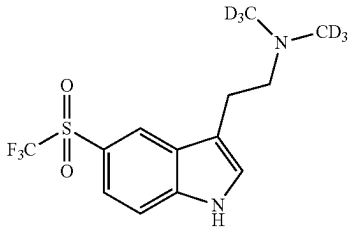
Compound	Structure
II-91	
II-94	

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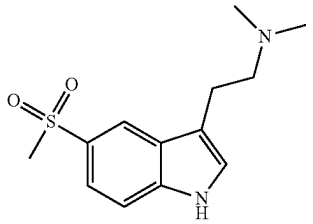
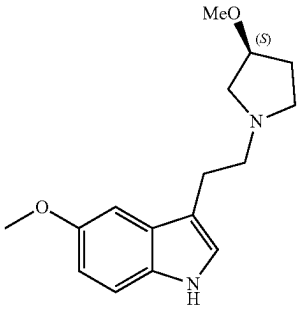
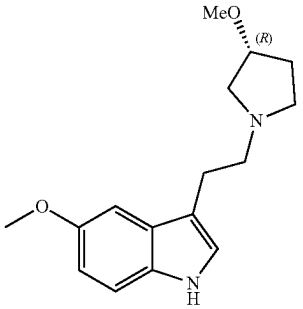
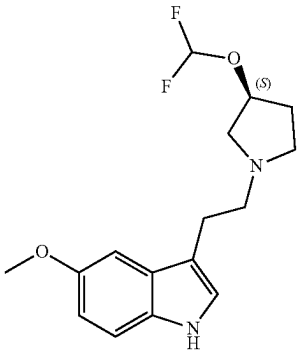
Compound	Structure
II-96	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

21. The compound of claim **1**, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
(S) I-66	
(R) I-66	
(S) I-67	

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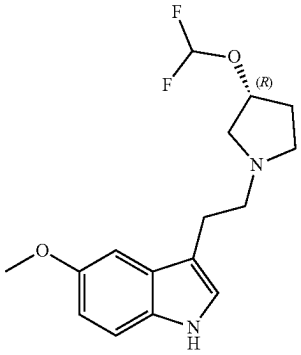
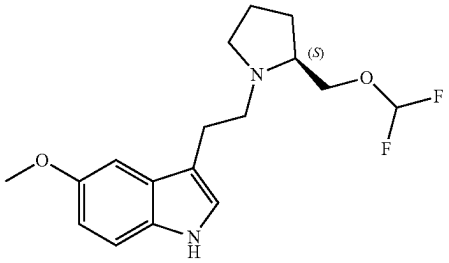
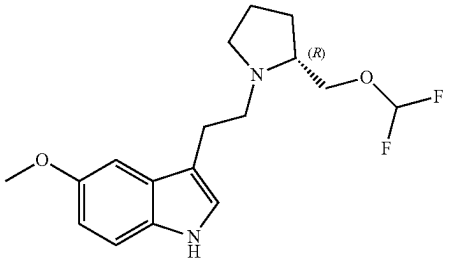
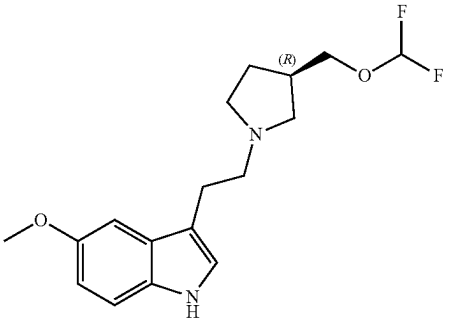
Compound	Structure
(R) I-67	
(S) I-68	
(R) I-68	
(R) I-69	

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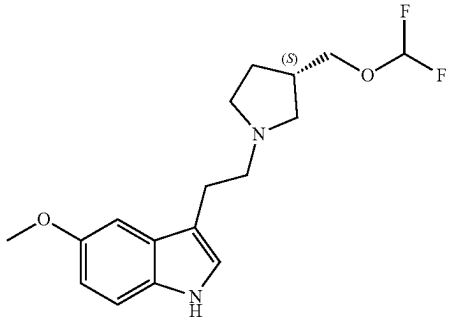
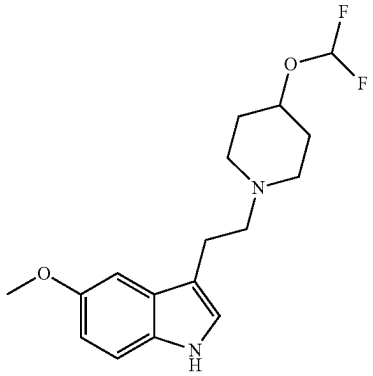
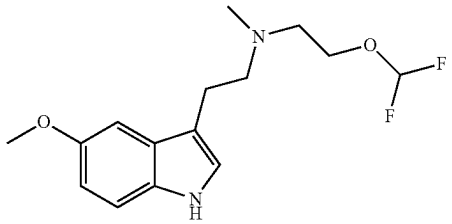
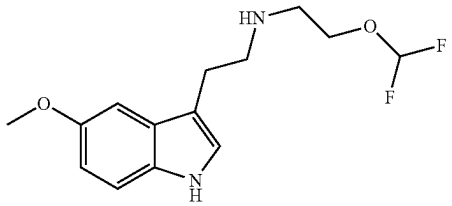
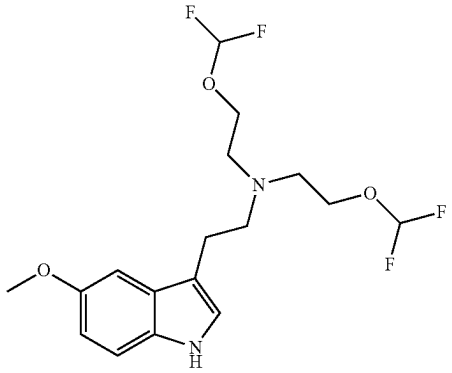
Compound	Structure
(S) I-69	
I-70	
I-71	
I-72	
I-73	

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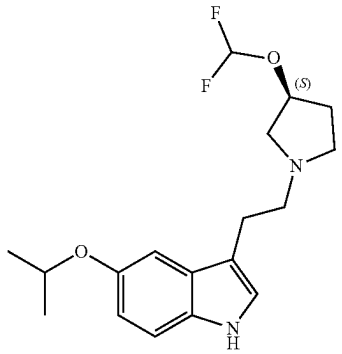
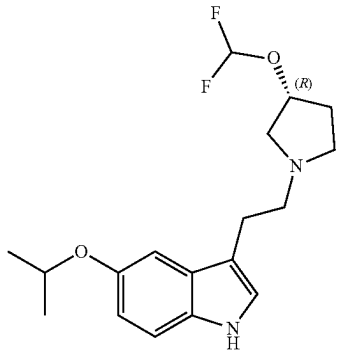
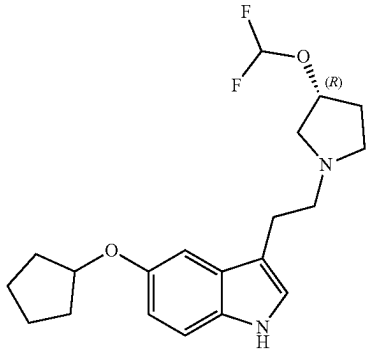
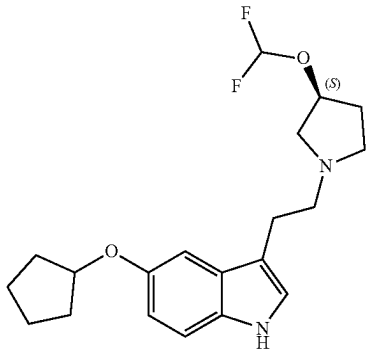
Compound	Structure
(S) I-74	
(R) I-74	
(R) I-75	
(S) I-75	

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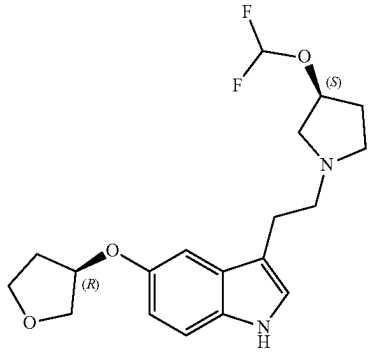
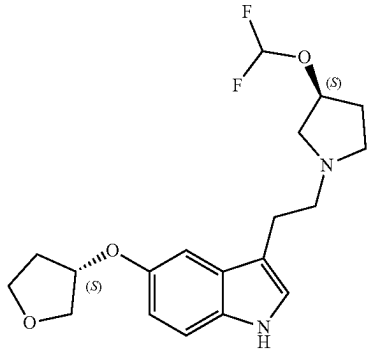
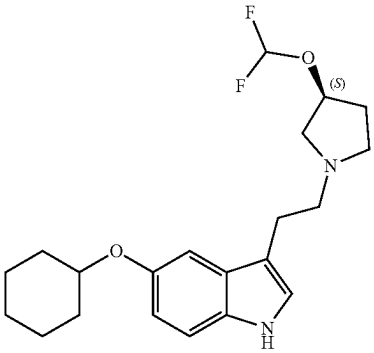
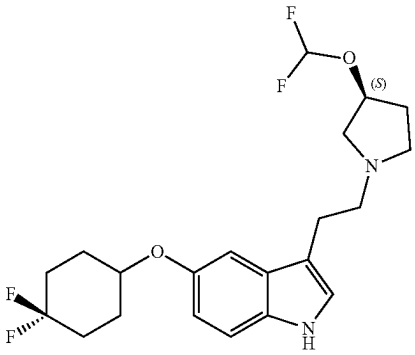
Compound	Structure
(R, S) I-76	
(S, S) I-76	
(S) I-77	
(S) I-78	

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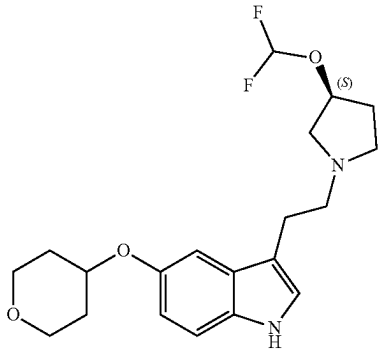
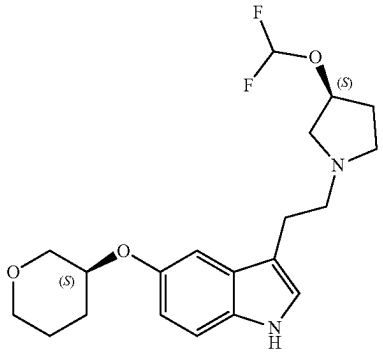
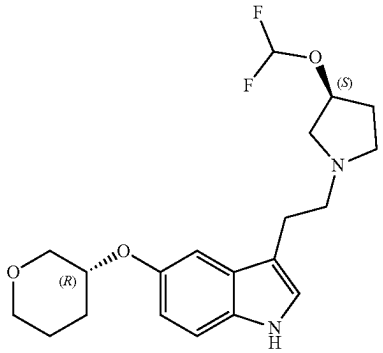
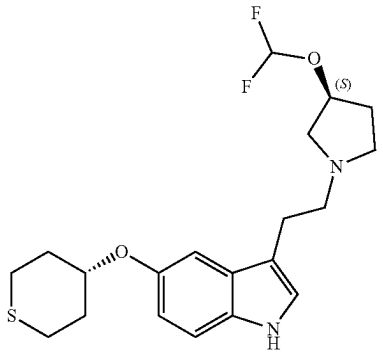
Compound	Structure
(S) I-79	
(S, S) I-80	
(R, S) I-80	
(S) I-81	

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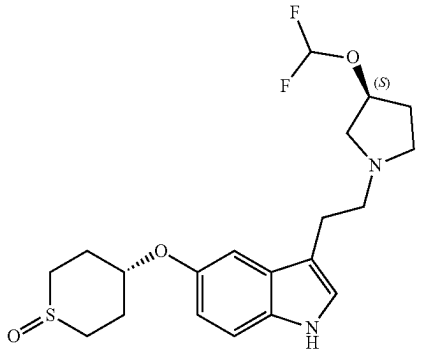
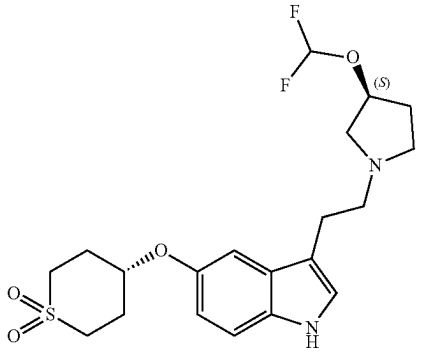
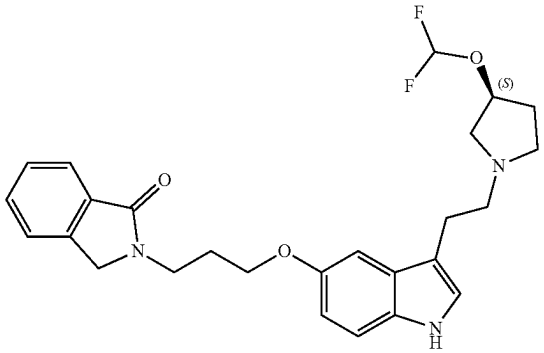
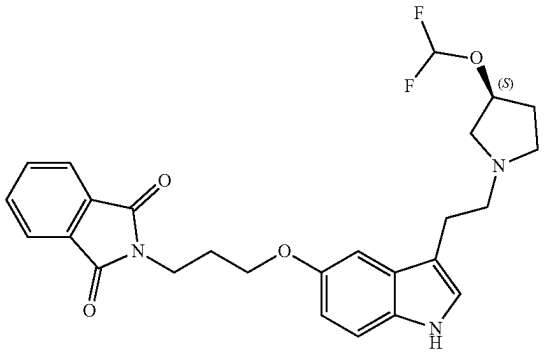
Compound	Structure
(S) I-82	
(S) I-83	
(S) I-84	
(S) I-85	

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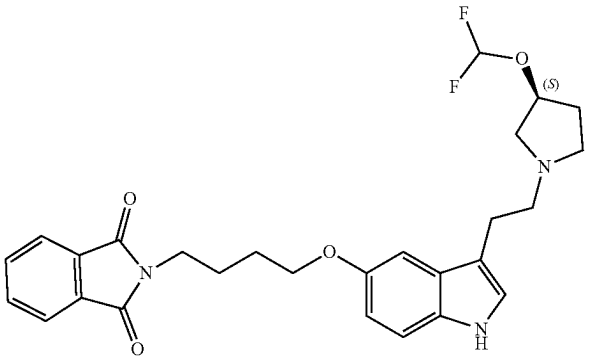
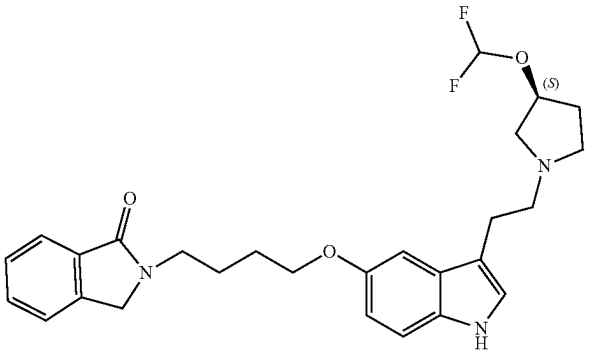
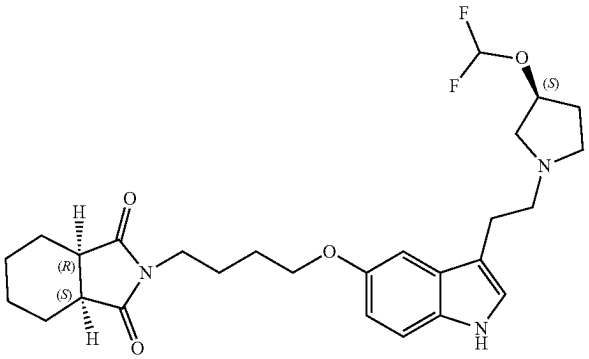
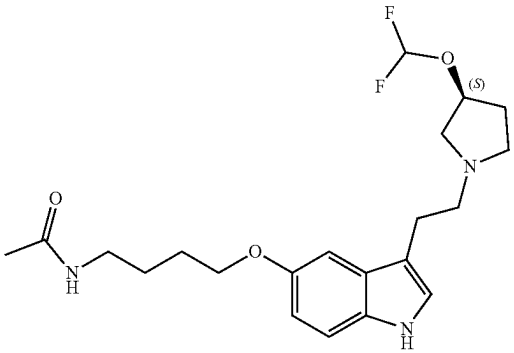
Compound	Structure
(S) I-86	
(S) I-87	
Cis (S) I-88	
(S) I-89	

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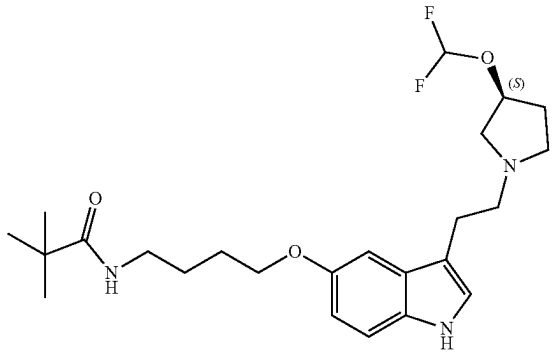
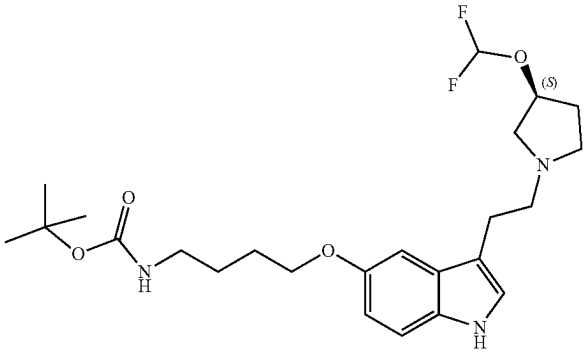
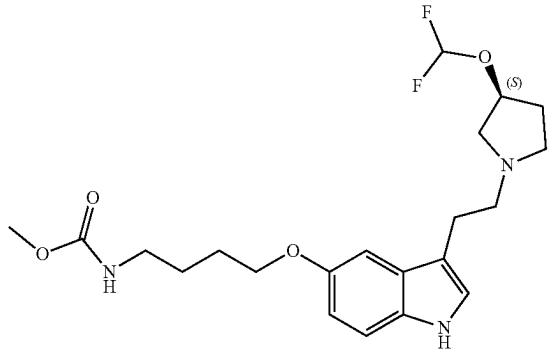
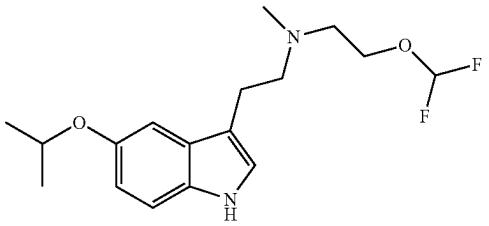
Compound	Structure
(S) I-90	
(S) I-91	
(S) I-92	
I-93	

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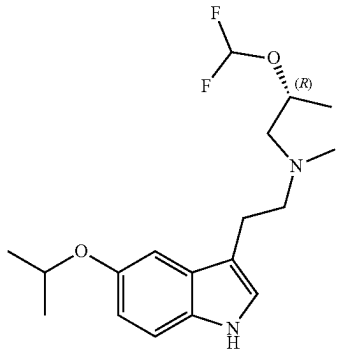
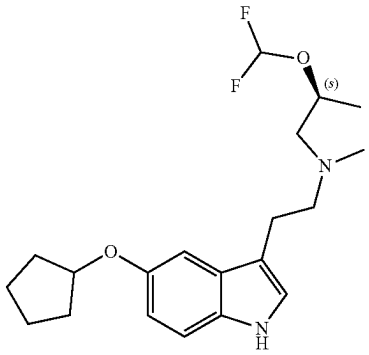
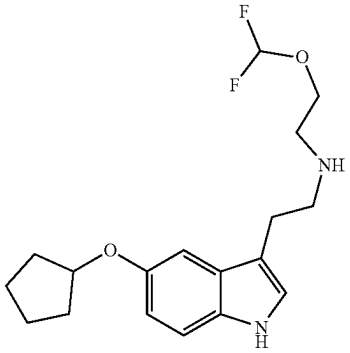
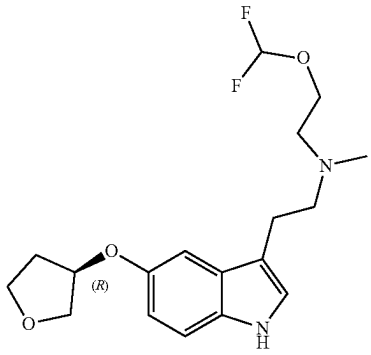
Compound	Structure
(R) I-94	
(S) I-95	
I-96	
(R) I-97	

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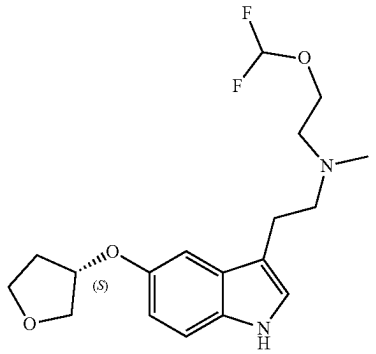
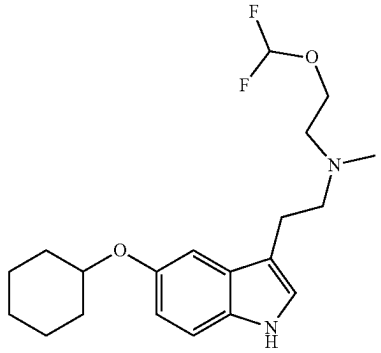
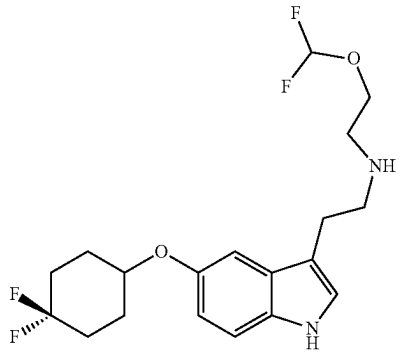
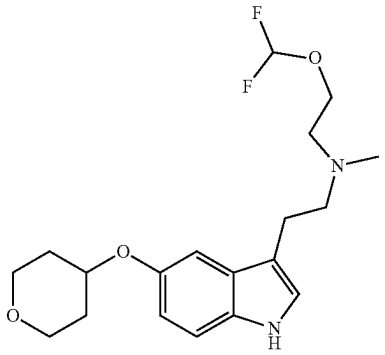
Compound	Structure
(S) I-97	
I-98	
I-99	
I-100	

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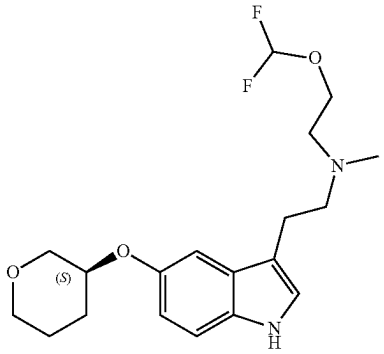
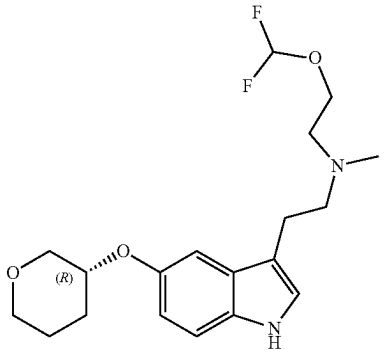
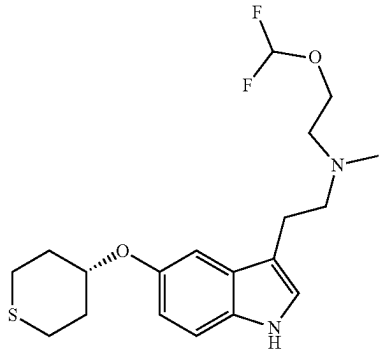
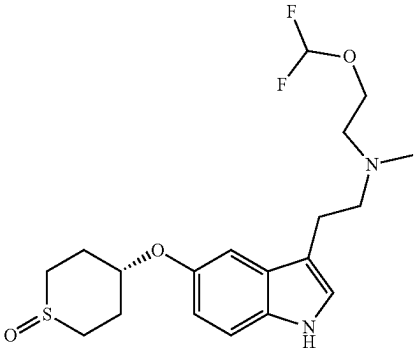
Compound	Structure
(S) I-101	
(R) I-101	
I-102	
I-103	

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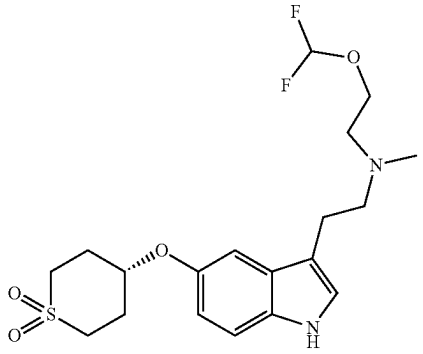
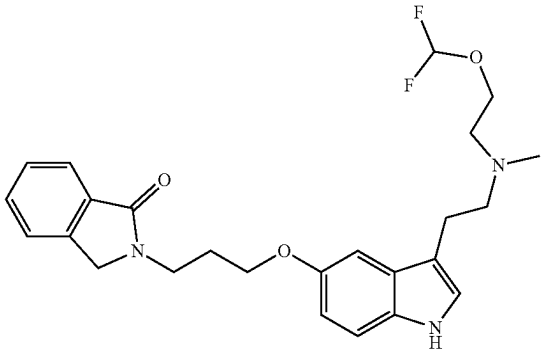
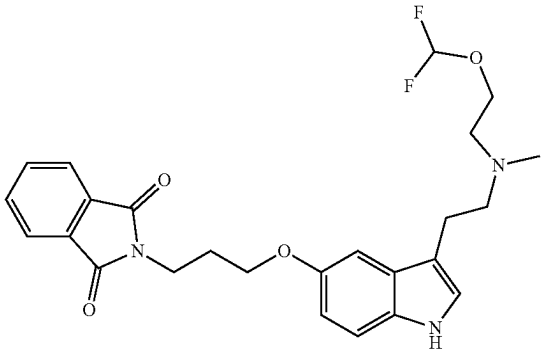
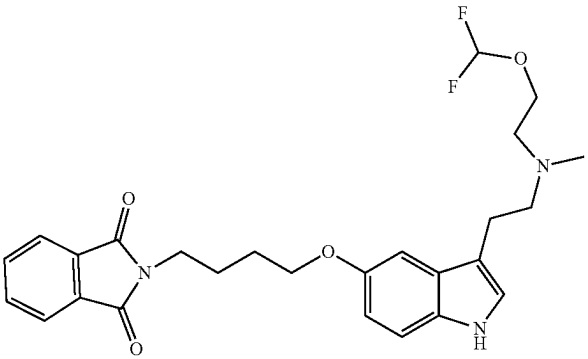
Compound	Structure
I-104	
I-105	
I-106	
I-107	

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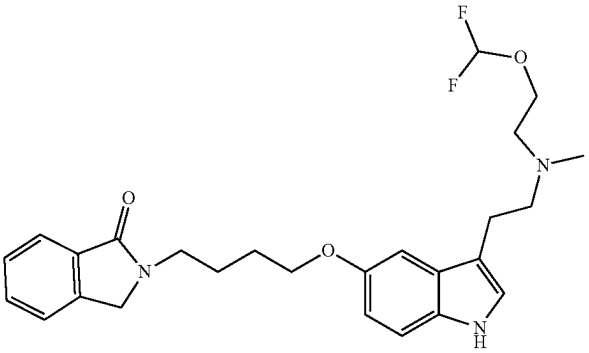
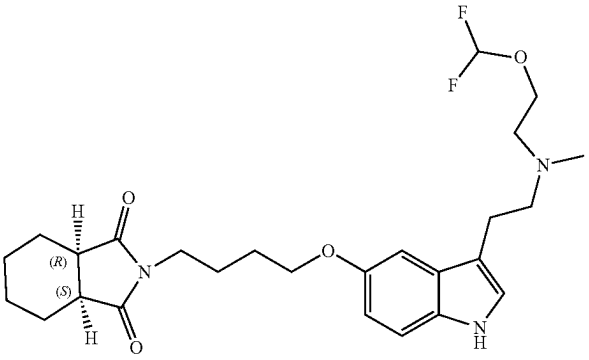
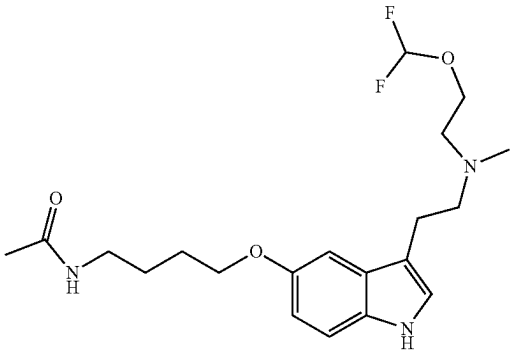
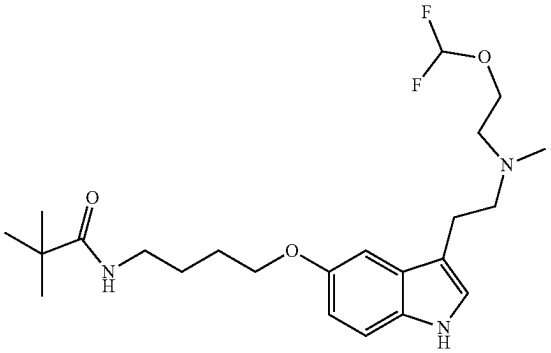
Compound	Structure
I-108	
Cis I-109	
I-110	
I-111	

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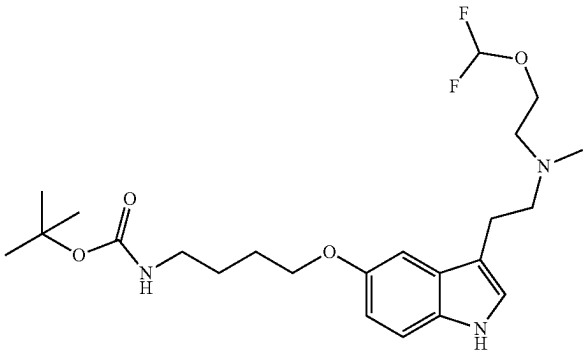
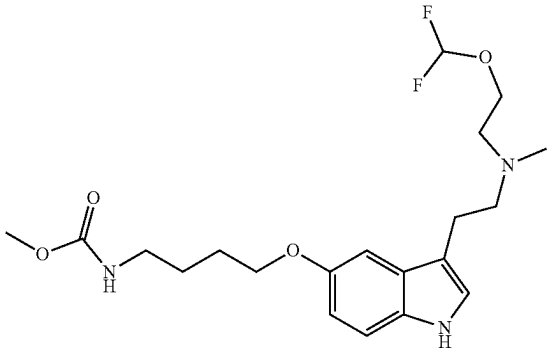
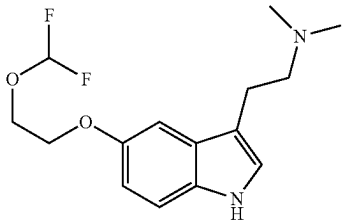
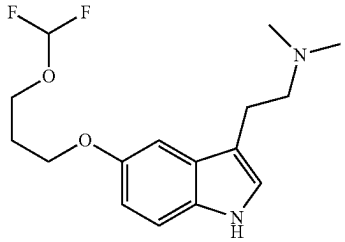
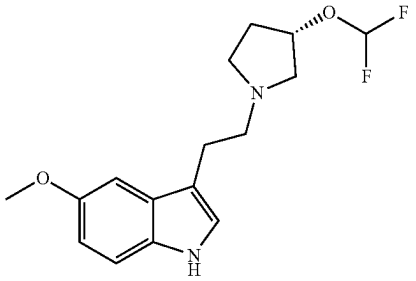
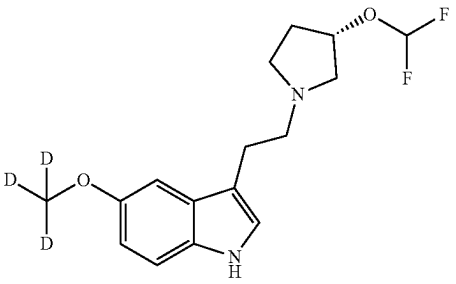
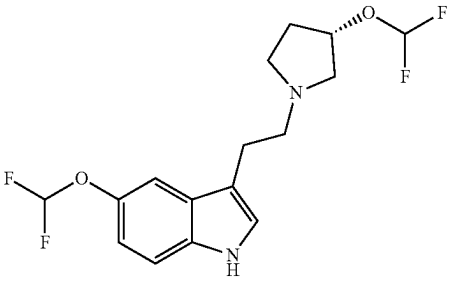
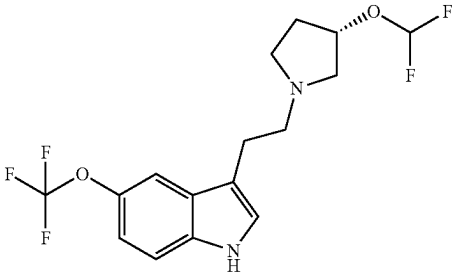
Compound	Structure
I-112	
I-113	
I-128	
I-129	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

22. The compound of claim **1**, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
I-131	
I-132	
I-133	
I-134	

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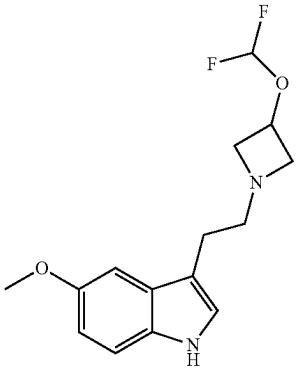
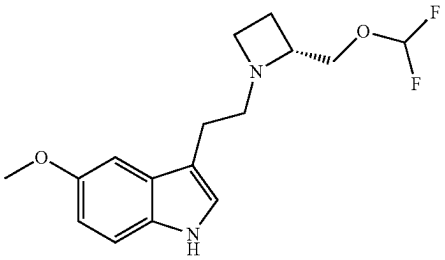
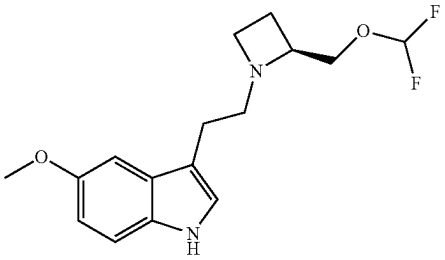
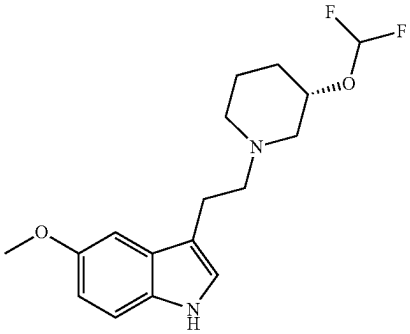
Compound	Structure
I-136	
I-137	
I-138	
I-139	

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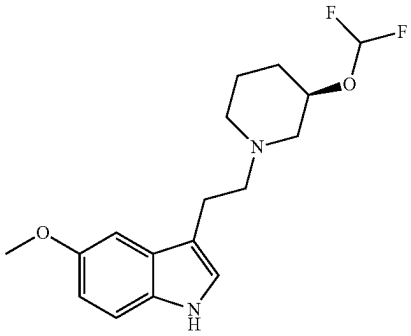
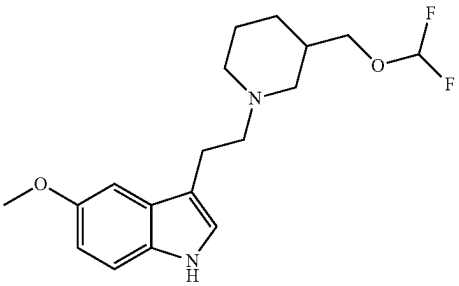
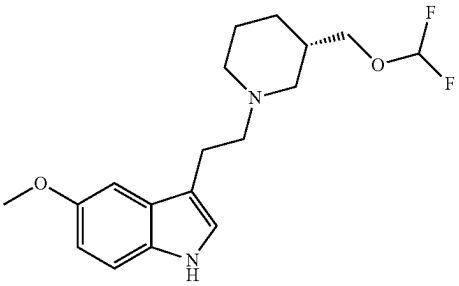
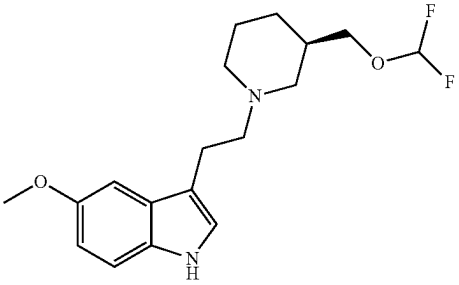
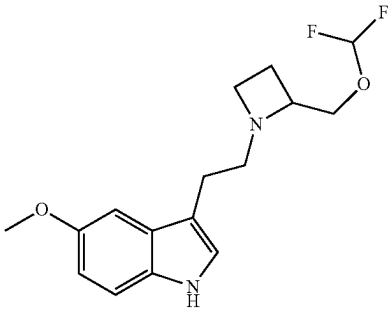
Compound	Structure
I-140	
I-141	
I-142	
I-143	
I-144	

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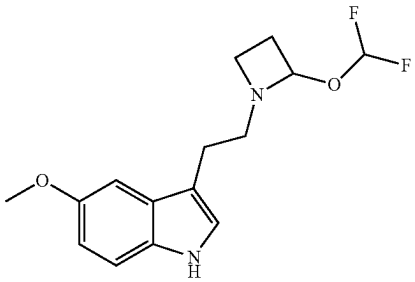
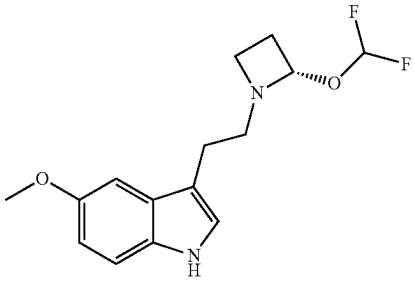
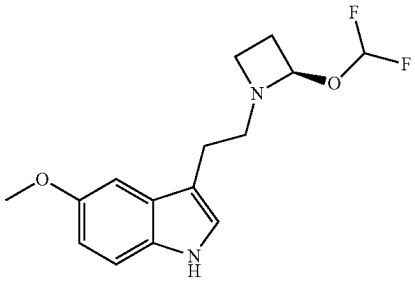
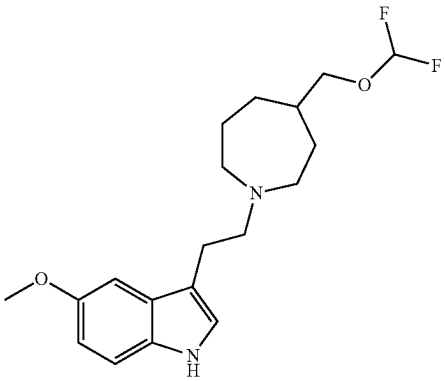
Compound	Structure
I-145	
I-146	
I-147	
I-148	

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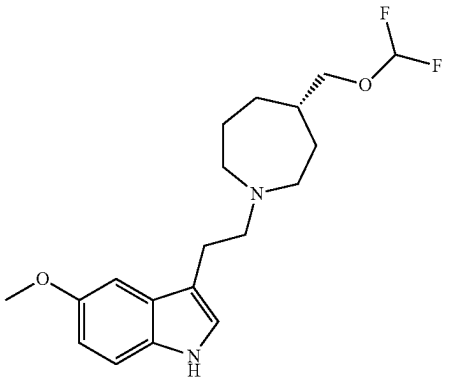
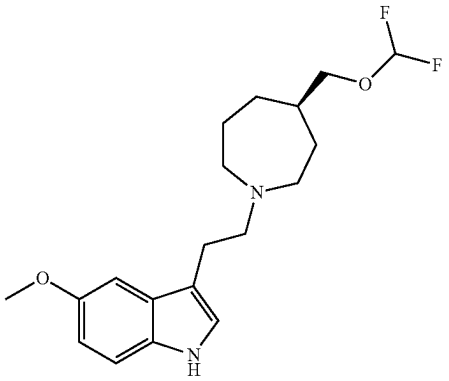
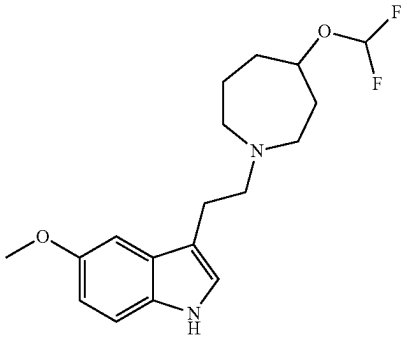
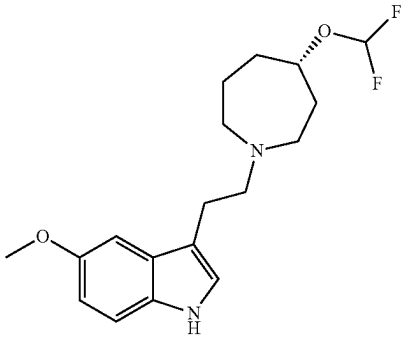
Compound	Structure
I-149	
I-150	
I-151	
I-152	

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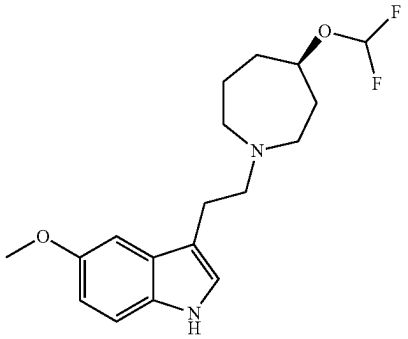
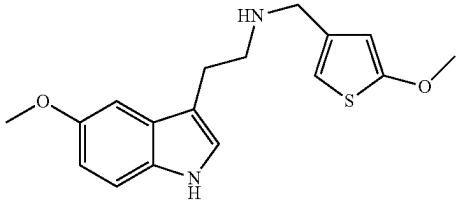
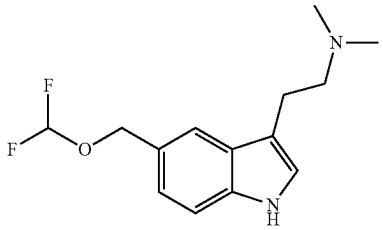
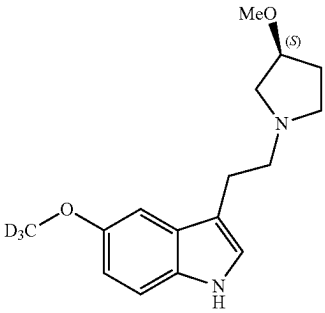
Compound	Structure
I-153	
I-154	
	and
I-155	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

23. The compound of claim **1**, wherein the compound of Formula (I) is selected from the compounds listed below:

Compound	Structure
(S) I-157	

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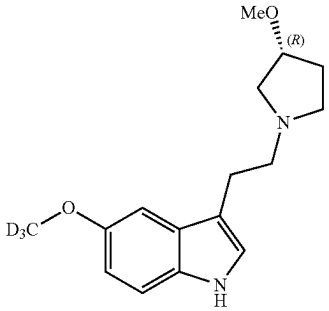
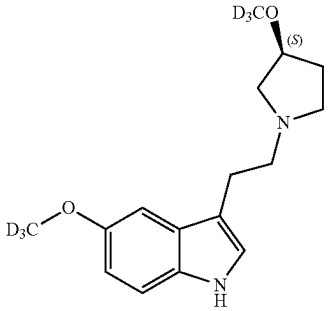
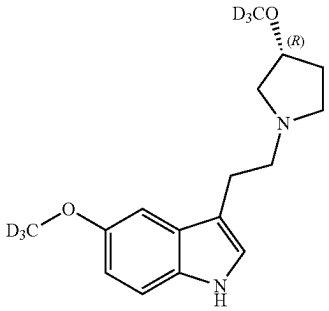
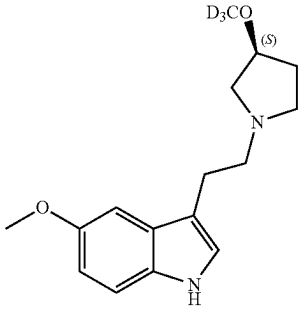
Compound	Structure
(R) I-157	
(S) I-158	
(R) I-158	
(S) I-159	

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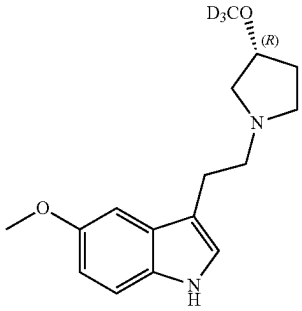
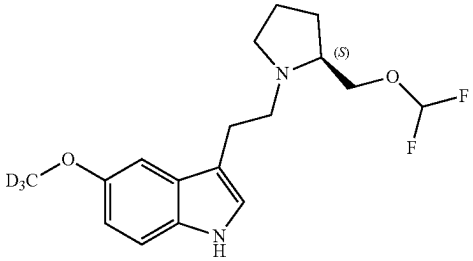
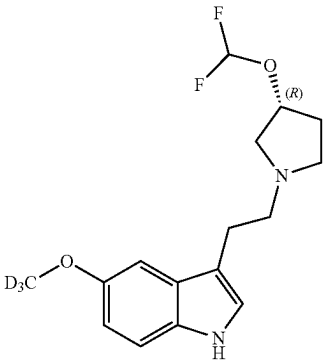
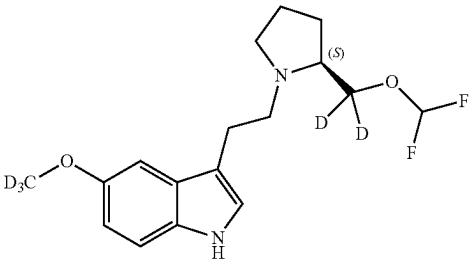
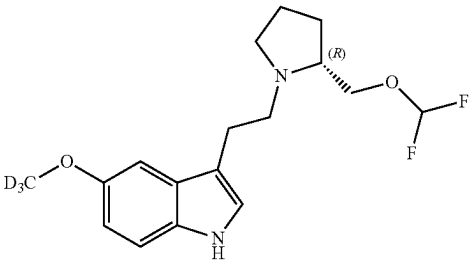
Compound	Structure
(R) I-159	
I-160	
(R) I-161	
(S) I-162	
(R) I-163	

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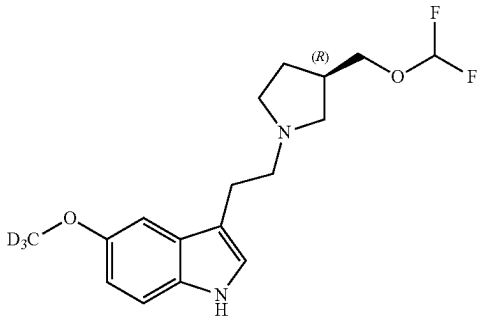
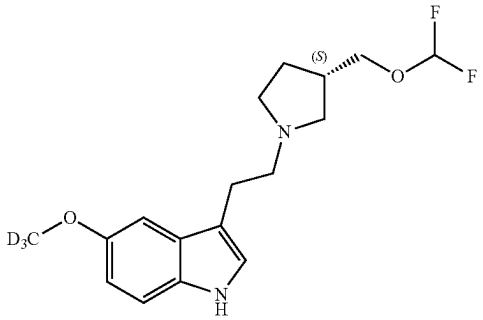
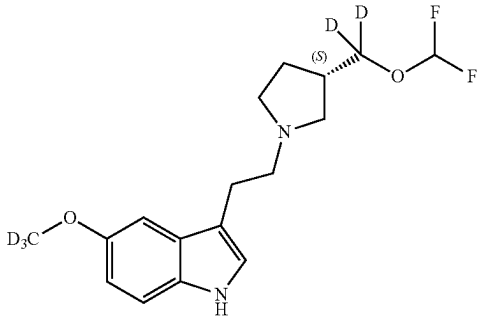
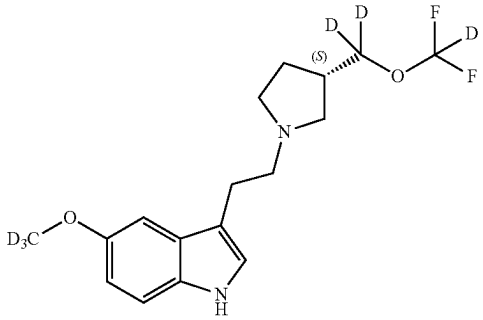
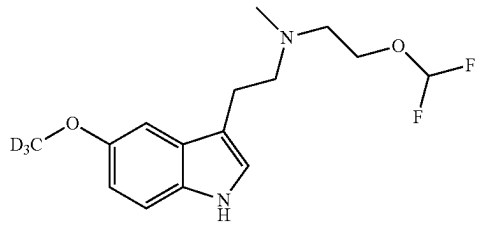
Compound	Structure
(R) I-164	
(S) I-164	
(S) I-165	
((S) I-166	
I-167	

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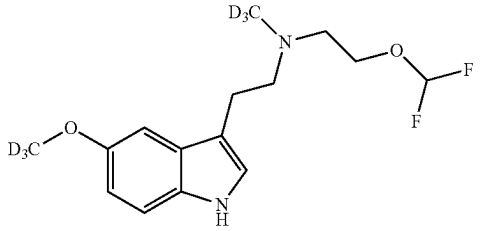
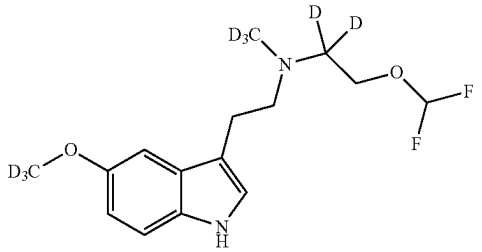
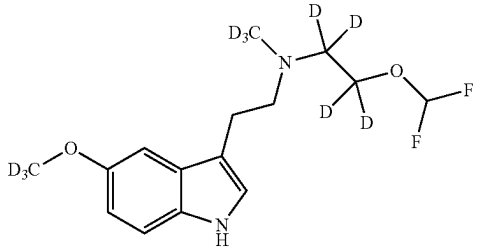
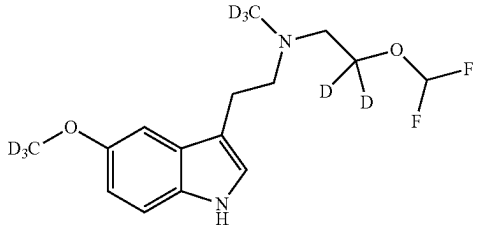
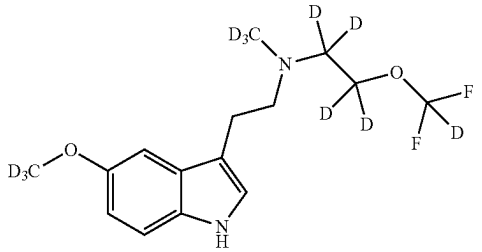
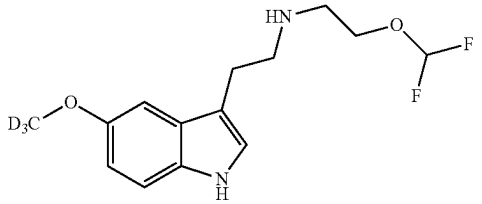
Compound	Structure
I-168	
I-169	
I-170	
I-171	
I-172	
I-173	

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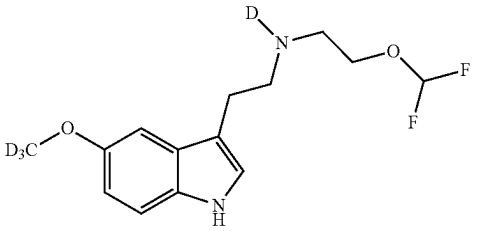
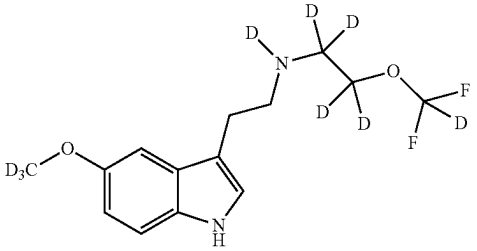
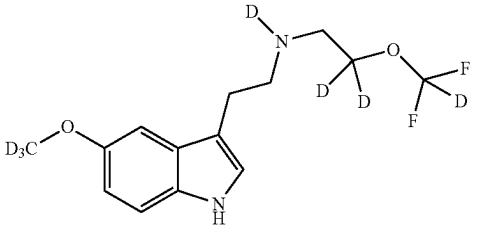
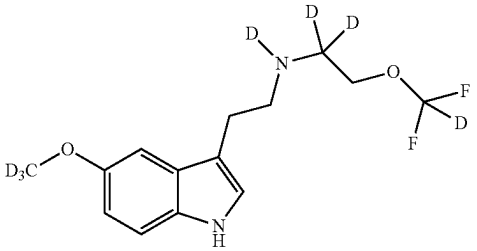
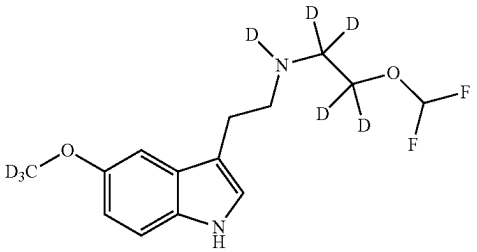
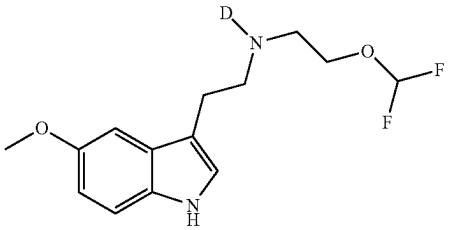
Compound	Structure
I-174	
I-175	
I-176	
I-177	
I-178	
I-179	

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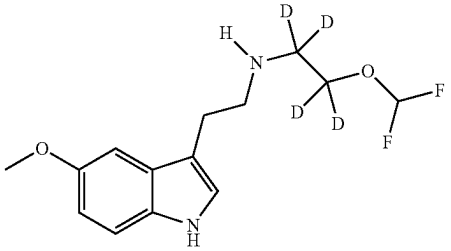
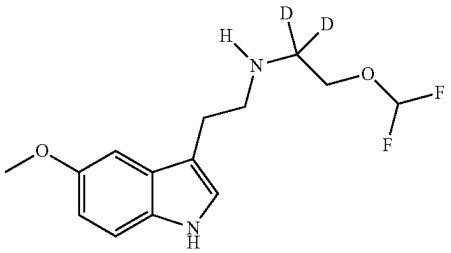
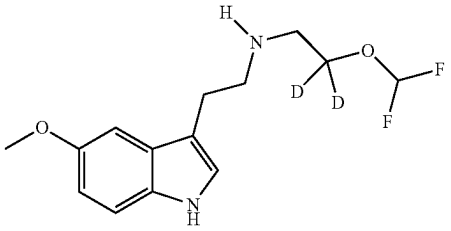
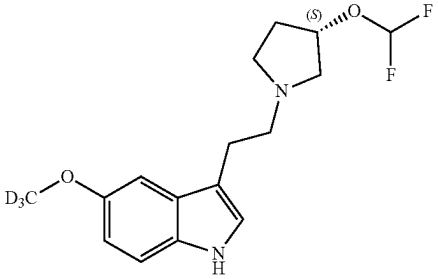
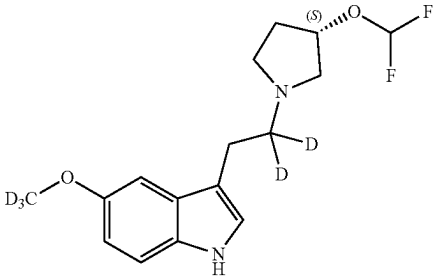
Compound	Structure
I-180	
I-181	
I-182	
(S) I-190	
(R) I-190	

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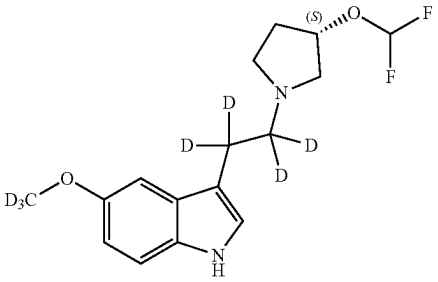
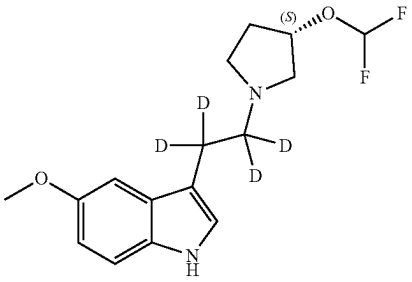
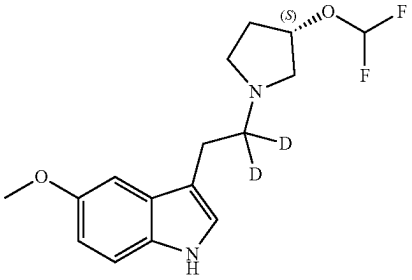
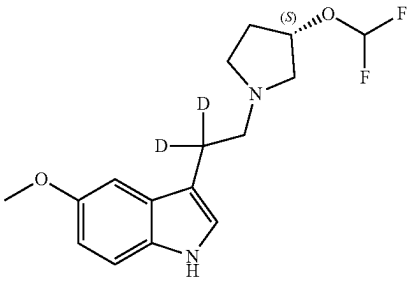
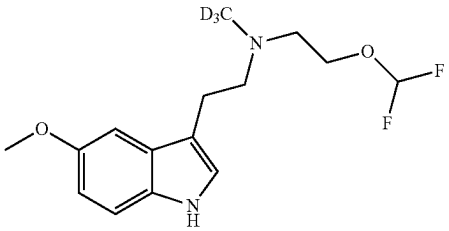
Compound	Structure
I-191	
(S) I-192	
(S) I-193	
(S) I-194	
I-195	

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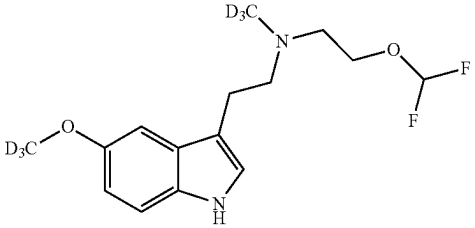
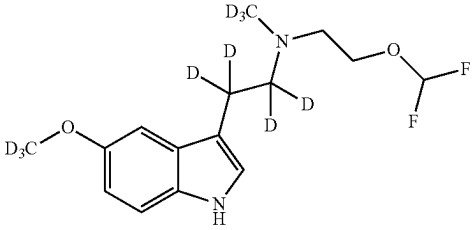
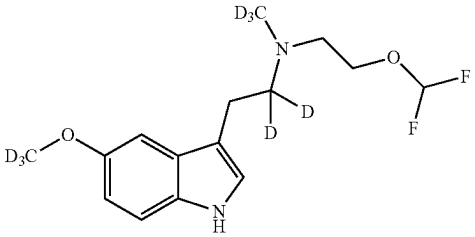
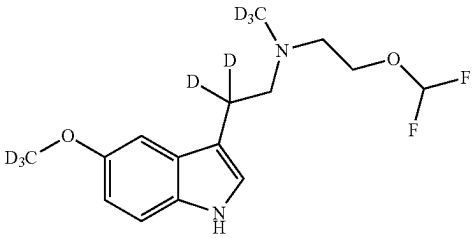
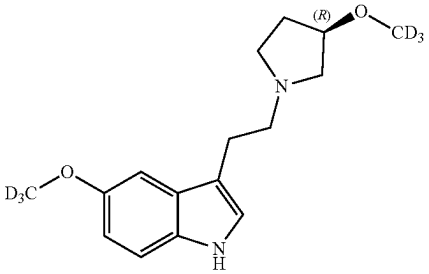
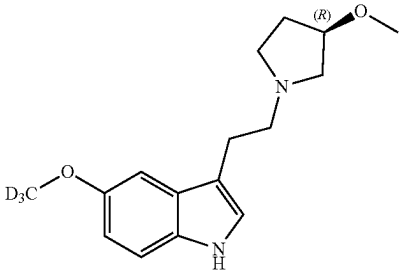
Compound	Structure
I-196	
I-197	
I-198	
I-199	
(R) I-200	
(R) I-201	

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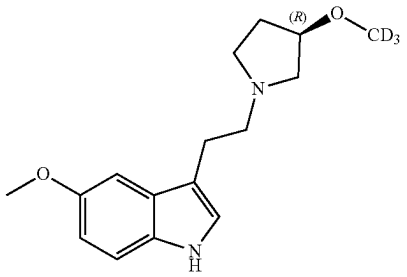
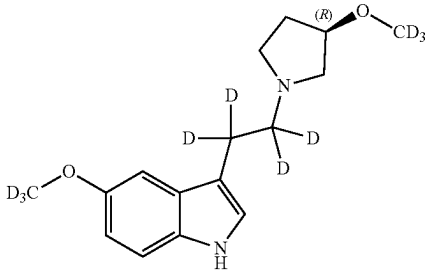
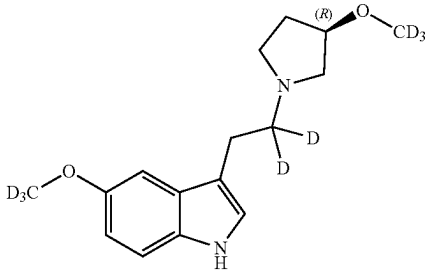
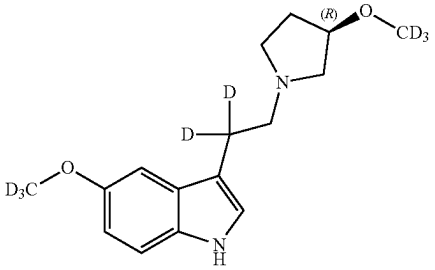
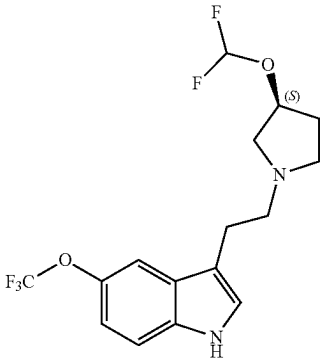
Compound	Structure
(R) I-202	
(R) I-203	
(R) I-204	 and
(R) I-205	
II-80	

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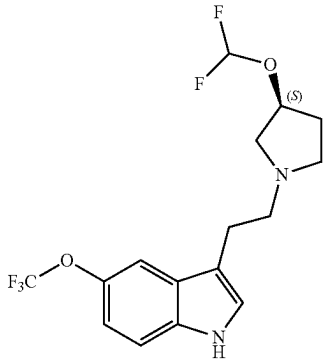
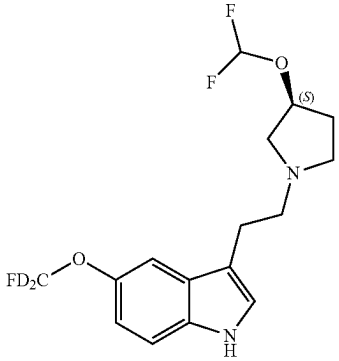
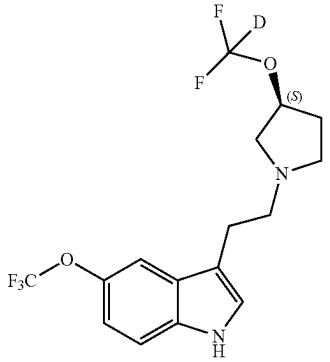
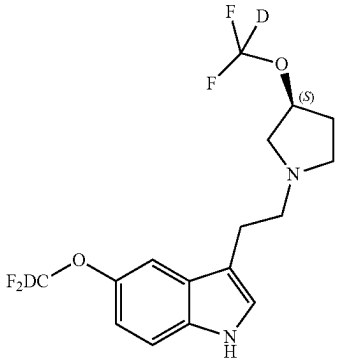
Compound	Structure
II-81	
II-82	
II-83	
II-84	

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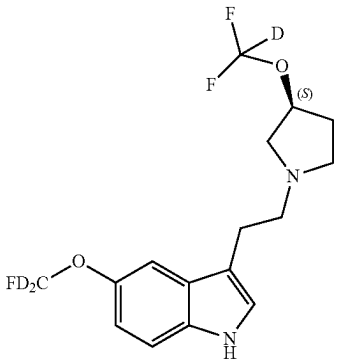
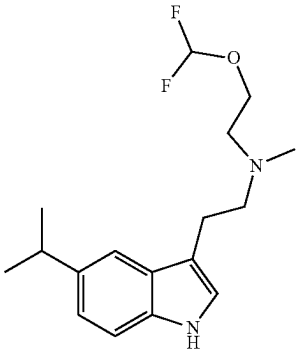
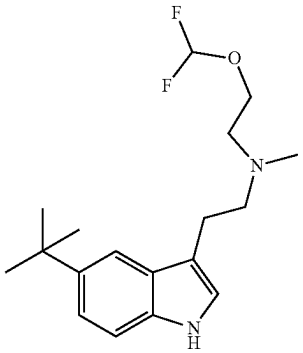
Compound	Structure
II-85	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

24. The compound of claim **1**, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
I-114	
I-115	

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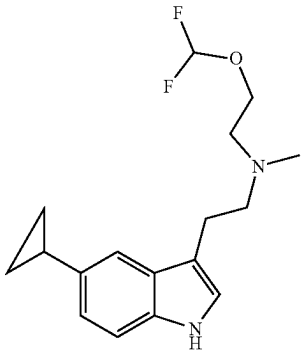
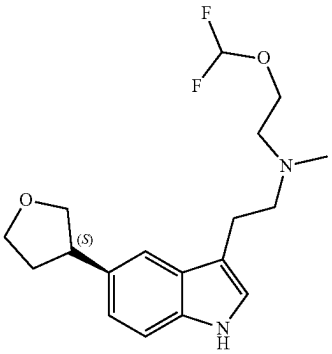
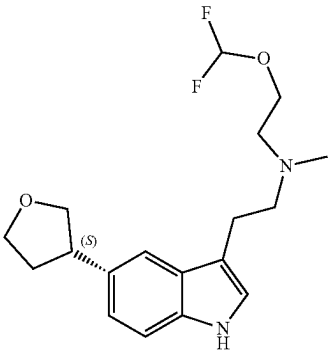
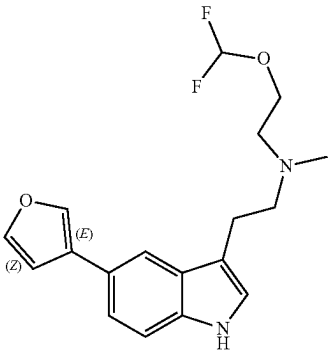
Compound	Structure
I-116	
(S) I-117	
(R) I-117	
I-118	

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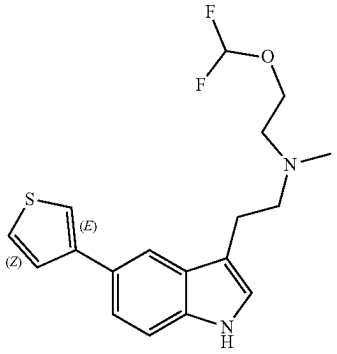
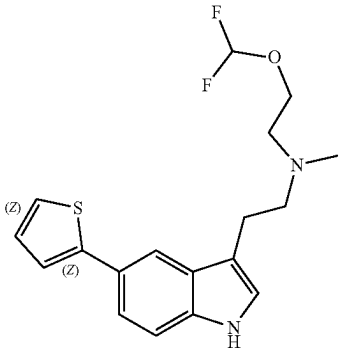
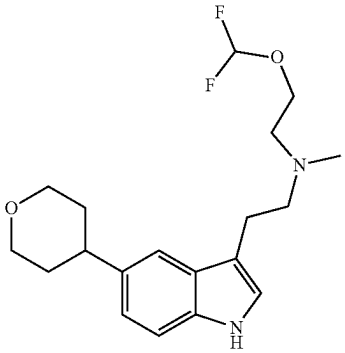
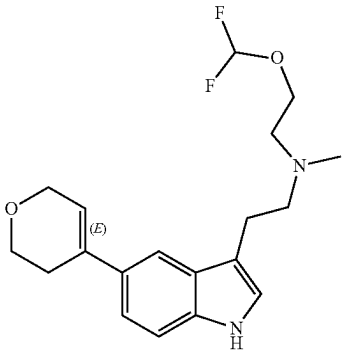
Compound	Structure
I-119	
I-120	
I-121	
I-122	

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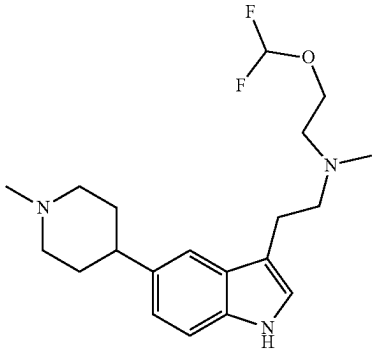
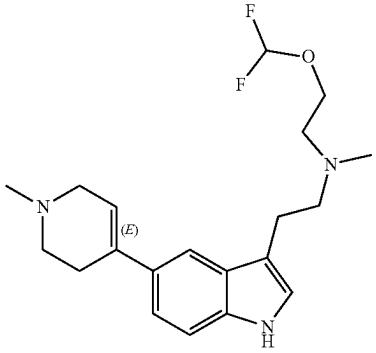
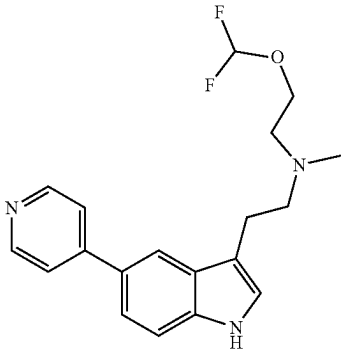
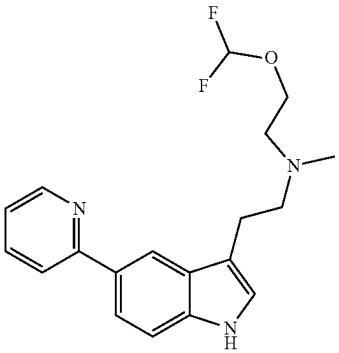
Compound	Structure
I-123	
I-124	
I-125	
I-126	

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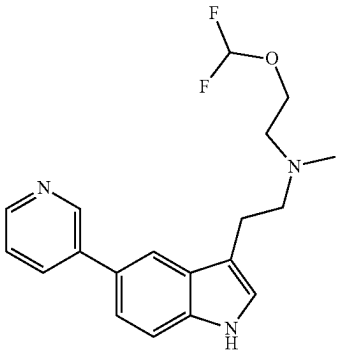
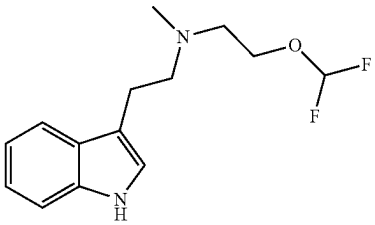
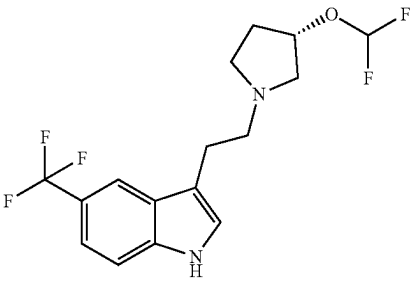
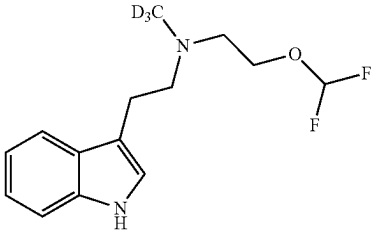
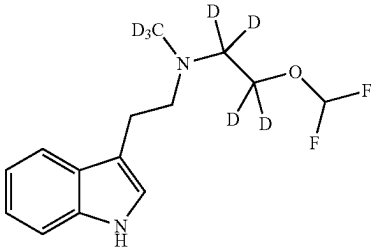
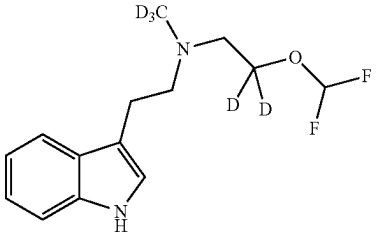
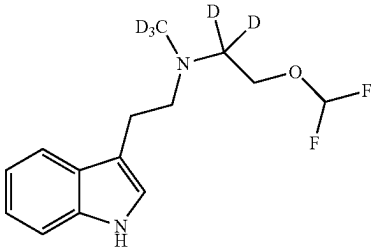
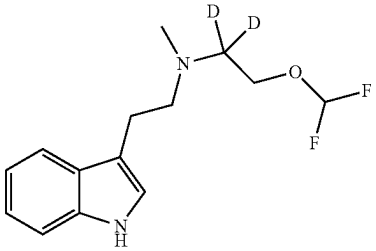
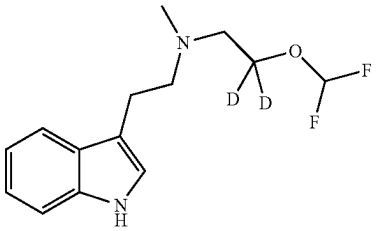
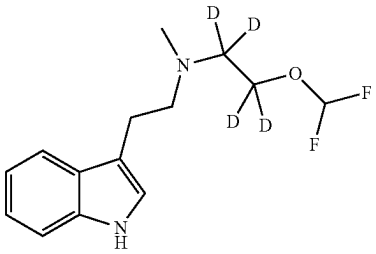
Compound	Structure
I-127	
I-130	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

25. The compound of claim **1**, wherein the compound of Formula (I) is selected from the table below:

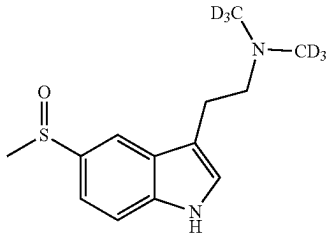
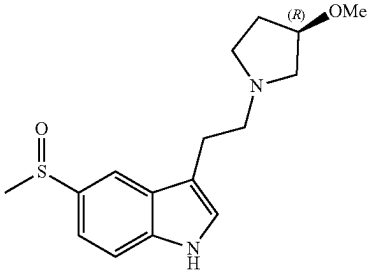
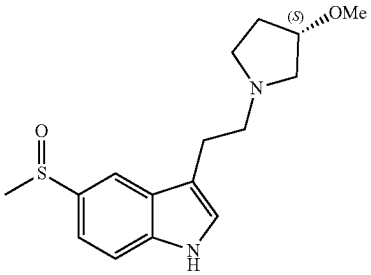
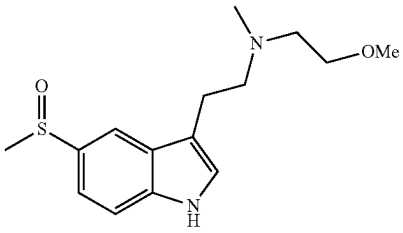
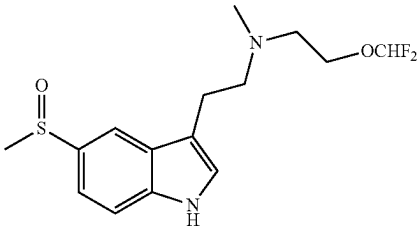
Compound	Structure
I-135	
I-183	

-continued

Compound	Structure
I-184	
I-185	
I-186	
I-187	
I-188	
I-189	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

26. The compound of claim **1**, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
I-47	
(R) I-48	
(S) I-48	
I-49	
I-50	

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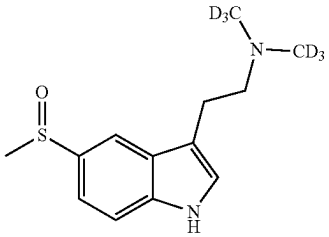
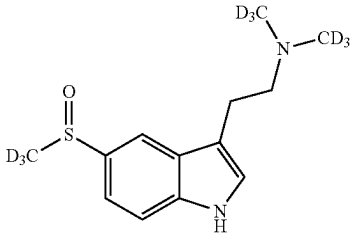
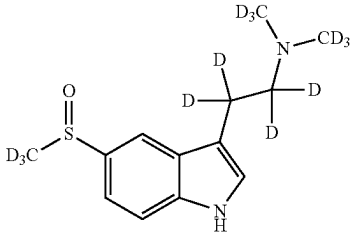
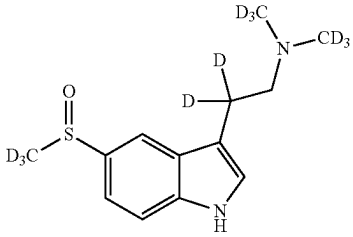
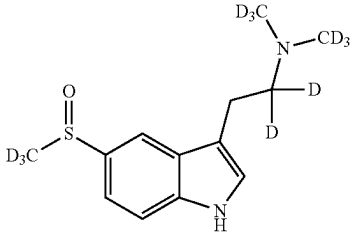
Compound	Structure
I-51	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

27. The compound of claim **1**, wherein the compound of Formula (I) is selected from the table below:

Compound	Structure
II-02	
II-03	
II-06	
II-09	

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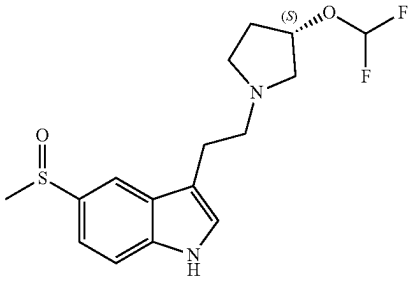
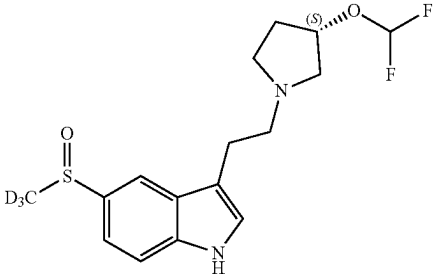
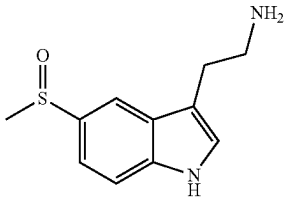
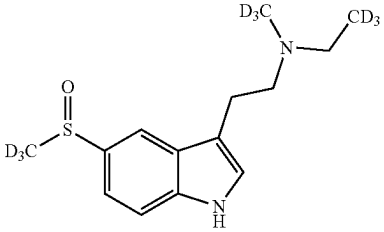
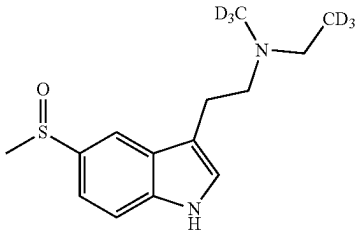
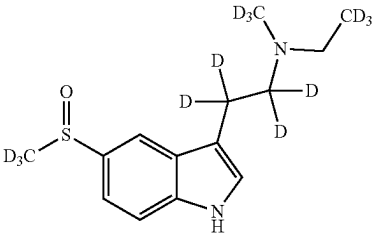
Compound	Structure
(S) II-14	
(S) II-16	
II-18	
II-20	
II-29	
II-34	

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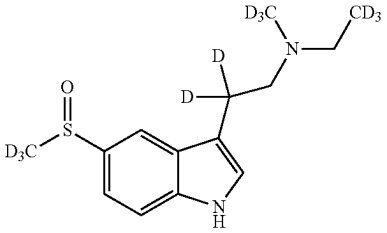
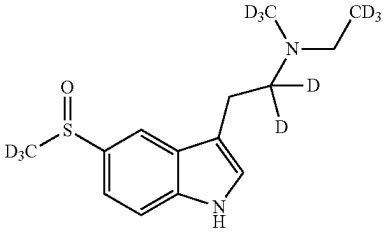
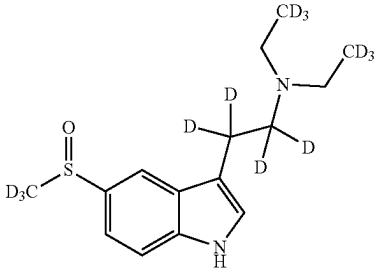
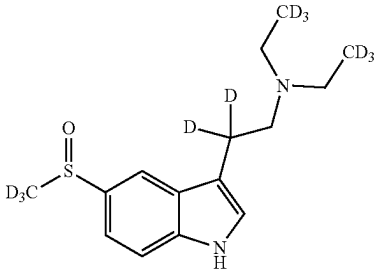
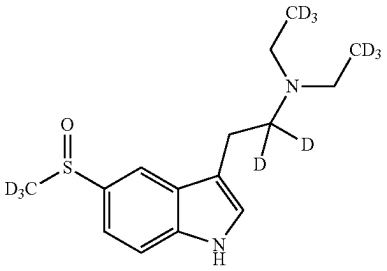
Compound	Structure
II-35	
II-36	
II-40	
II-41	
II-42	

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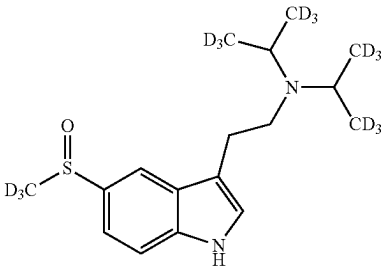
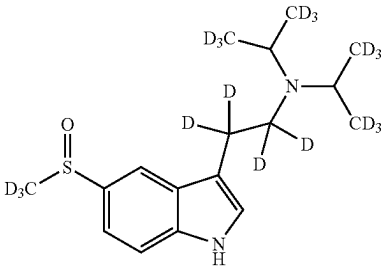
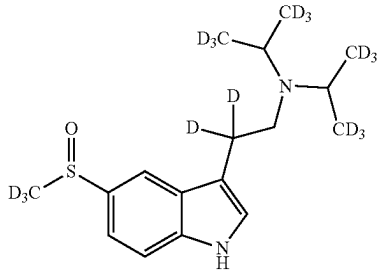
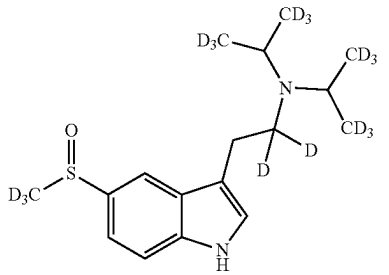
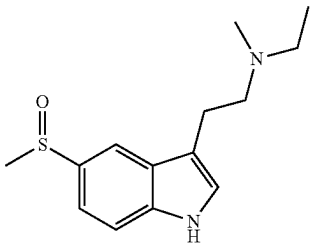
Compound	Structure
II-51	
II-52	
II-53	
II-54	
II-58	

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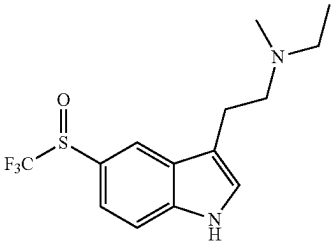
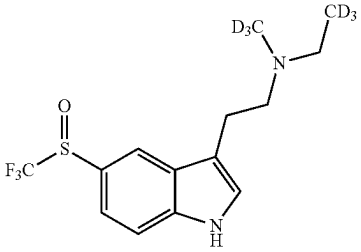
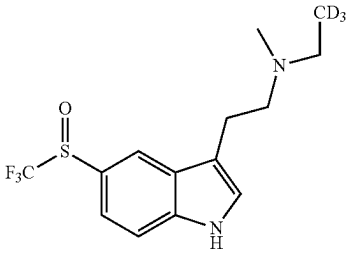
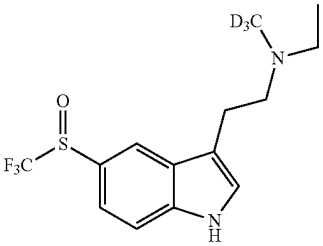
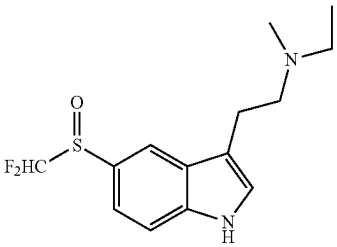
Compound	Structure
II-62	
II-66	
II-67	
II-68	
II-73	

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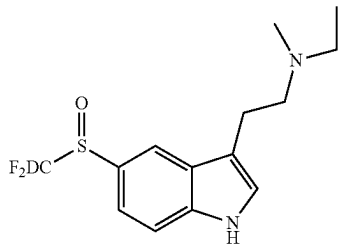
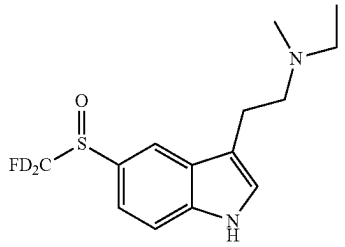
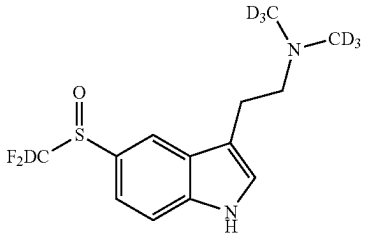
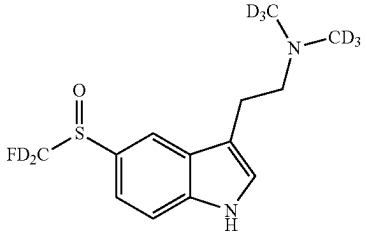
Compound	Structure
II-76	
II-77	
II-88	
II-89	

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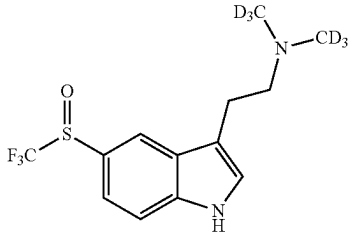
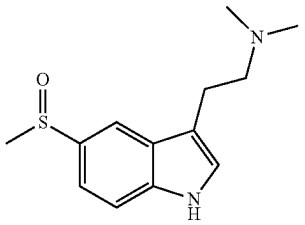
Compound	Structure
II-93	
II-95	

or a pharmaceutically acceptable salt, solvate, and/or prodrug thereof.

28. A pharmaceutical composition comprising one or more compounds of claim **1** and a pharmaceutically acceptable carrier.

29. A method of treating a mental illness, comprising administering a therapeutically effective amount of one or more compounds of claim **1** to a subject in need thereof, wherein the mental illness is selected from anxiety disorders, generalized anxiety disorder, social anxiety disorder, depression, cancer-related depression, major depressive disorder (MDD), treatment-resistant depression (TRD), postpartum depression (PPD), anxiety, alcohol addiction, drug addiction, opioid addiction, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and combinations thereof.

30. A method of treating a central nervous system (CNS) disease, disorder, or condition and/or a neurological disease, disorder, or condition comprising administering a therapeutically effective amount of one or more compounds of claim **1** to a subject in need thereof.

* * * * *