

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

RELATED APPLICATIONS

[0001] The present application claims the benefit of priority of co-pending United States provisional patent application no. 63/401,847 filed on August 29, 2022, the contents of which are incorporated herein by reference in their entirety.

FIELD

[0002] The application relates to methods of activating serotonin receptors in a cell using indoline derivatives of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof as well as to the treatment of different conditions that are treated by activation of serotonin receptors, for example, mental illnesses and neurological disease, in the fields of psychiatry, neurobiology and pharmacotherapy. The present application also relates to indoline derivatives of Formula I-A and to compositions and uses thereof

BACKGROUND OF THE APPLICATION

[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 decades of restricted research due to their legal status. 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 brain 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 are 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 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-HT₂ 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-dimethyltryptamine) has the chemical formula C₁₂H₁₇N₂O₄P. It is a tryptamine 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, and later synthesized by him in 1958 [Passie et al. *Addict Biol.*, 2002, 7(4):357-364], and was used in psychiatric and psychological research and in psychotherapy during the early to mid-1960s up until its controlled drug scheduling in 1970 in the US, 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 4-hydroxy-N,N-dimethyltryptamine. 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 and 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 [Martín-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-HT₂ 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 et 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 5HT_{2A} antagonists, and 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-HT₂ 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 in terminally ill cancer patients, obsessive compulsive disorder, addiction, anxiety, post-traumatic stress disorder and even cluster headaches. It could also be useful as a psychosis model for the development of new treatments for psychotic disorders. [Dubovyk and Monahan-Vaughn, *ACS Chem. Neurosci.* (2018), 9(9):2241–2251].

[0012] Recent developments in the field have occurred in clinical research, where several double-blind placebo-controlled phase 2 studies of psilocybin-assisted psychotherapy in patients with treatment resistant, major depressive disorder and cancer-related psychosocial distress have demonstrated 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 and magnetoencephalography 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 DE. *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 lesser 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 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 anti-depressant 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 no persisting adverse effects. Regarding their mechanisms of action, 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 burgeoning 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-ups. 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 what it may contribute to the opioid crisis response given their potential toxicity. 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 depressive patients with more than 80% of them 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. Moreover, it has been shown that partial or a full night of sleep deprivation can alleviate symptoms of depression suggested by resetting circadian rhythms via modification of clock gene expression. 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

improving 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]. Thus, the use of psychedelics in the fields of oncology and palliative care is intriguing for several reasons. First, 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 those forms of suffering 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, and so on. Not only is this dosing paradigm more consistent with current standards in pharmacological care, but may be particularly beneficial for certain conditions, such as Alzheimer's disease and 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 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, Higgins et al., *Front. Pharmacol.*, 2001, DOI: 10.3389). Similarly, treatment of patients with hallucinogenic doses of 5HT_{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 5HT_{2A} agonists also show similar neuroprotective and increased neuroplasticity effects (neuroplastogens) and reduced neuroinflammation, which could be beneficial in 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.

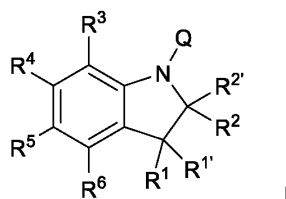
[0021] Psychosis is often referred to as an abnormal state of mind that is characterized by hallucinatory experiences, delusional thinking, and disordered thoughts. Moreover, this state is accompanied by impairments in social cognition, inappropriate emotional expressions, and bizarre behavior. Most often, psychosis develops as part of a psychiatric disorder, of which, it represents an integral part of schizophrenia. It corresponds to the most florid phase of the illness. The very first manifestation of psychosis in a patient 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 OF THE APPLICATION

[0022] The Applicants have found that indoline derivatives modulate the activity of serotonin receptor subtypes, in particular 5-HT_{2A}, by direct binding to these receptors.

[0023] Accordingly, the present application 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 Formula I or a

pharmaceutically acceptable salt, solvate and/or prodrug thereof, to a subject in need thereof,

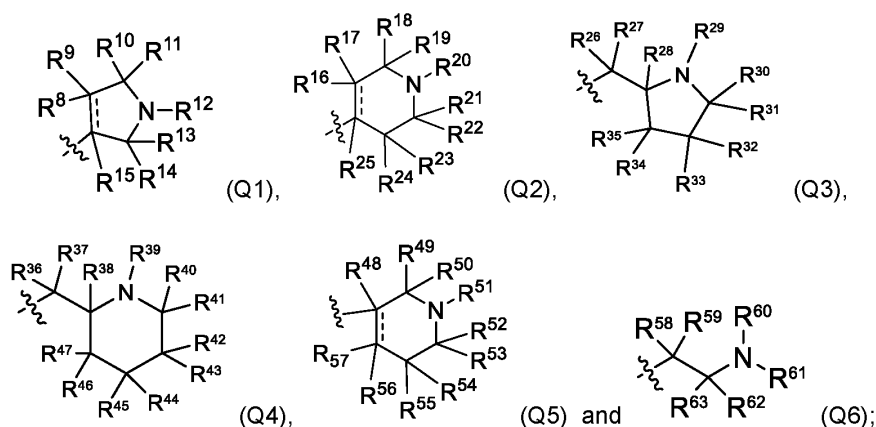


wherein:

R^1 and $R^{1'}$ are independently selected from H, halo, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl) $_2$;

R^2 and $R^{2'}$ are independently selected from H, halo, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl) $_2$;

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



$\equiv$ is a single bond or a double bond provided that when $\equiv$ in Q1 is a double bond then R^9 and R^{15} are not present, when $\equiv$ in Q2 is a double bond then R^{17} and R^{25} are not present, and when $\equiv$ in Q5 is a double bond then R^{48} and R^{57} are not present;

one or both of R^4 and R^5 is independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy, or

R^4 and R^5 are linked together to form $O-(CH_2)_{1-2}O$, or

one of R^4 and R^5 is selected from X-L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy,

X is selected from a direct bond, O, C(O), NR^a, NR^aC(O), C(O)NR^a, OC(O), C(O)O, OC(O)O, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a;

L is selected from a direct bond, C₁₋₆alkylene, C₂₋₆alkenylene, C₁₋₆alkyleneO, C₂₋₆alkenyleneO, C₁₋₆alkyleneC(O), C₂₋₆alkenyleneC(O), C₁₋₆alkyleneNR^bC(O), C₂₋₆alkenyleneNR^bC(O), C₁₋₆alkyleneC(O)NR^b, C₂₋₆alkenyleneC(O)NR^b, C₁₋₆alkyleneOC(O), C₂₋₆alkenyleneOC(O), C₁₋₆alkyleneC(O)O, C₂₋₆alkenyleneC(O)O, C₁₋₆alkyleneOC(O)NR^b, C₂₋₆alkenyleneOC(O)NR^b, C₁₋₆alkyleneNR^bC(O)O, C₂₋₆alkenyleneNR^bC(O)O, C₁₋₆alkyleneOC(O)O, C₂₋₆alkenyleneOC(O)O, C₁₋₆alkyleneNR^bC(O)NR^b and C₂₋₆alkenyleneNR^bC(O)NR^b;

R^a is selected from H and C₁₋₆alkyl;

R^b is selected from H, C₁₋₆alkyl and A;

A is selected from H, C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C₁₋₄alkyl and OC₁₋₄alkyl;

R³ and R⁶ are independently selected from H, halo, OH, C₁₋₆alkyl and C₁₋₆alkoxy;

R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H, halo and C₁₋₆alkyl;

R¹², R²⁰, R²⁹, R³⁹ and R⁵¹ are independently selected from H, C₁₋₆alkyl, C(O)C₁₋₆alkyl and C(O)-A';

R⁶⁰ and R⁶¹ are independently selected from H and C₁₋₆alkyl; or

one of R⁶⁰ and R⁶¹ is C(O)-A' and the other is selected from H and C₁₋₆alkyl;

wherein A' is selected from Y, O-Y and O-C₁₋₄alkylene-O-C(O)-Y; and

Y is selected from C₇₋₃₀alkyl and C₇₋₃₀alkenyl; or

R⁶⁰ and R⁶¹, together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoeities independently selected from O, S, S(O), SO₂, N, and NR⁶⁵ and which is optionally

substituted with one or more substituents independently selected from halo, OH, C₁₋₄alkyl and OC₁₋₄alkyl;

R⁶⁴ and R⁶⁵ are independently selected from H and C₁₋₆alkyl; and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

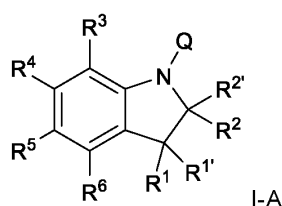
provided when Q is Q6 then the compound of Formula I comprises D.

[0024] The present application also includes a method of treating psychosis or psychotic symptoms comprising administering a therapeutically effective amount of one or more compounds of the application to a subject in need thereof.

[0025] The present application also includes a method of treating a mental illness comprising administering a therapeutically effective amount of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a subject in need thereof.

[0026] The present application also includes a method of treating a CNS disease, disorder or condition and/or a neurological disease comprising administering a therapeutically effective amount of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a subject in need thereof.

[0027] The present application includes one or more compounds of Formula I-A or a pharmaceutically acceptable salt, solvate and/or prodrug thereof

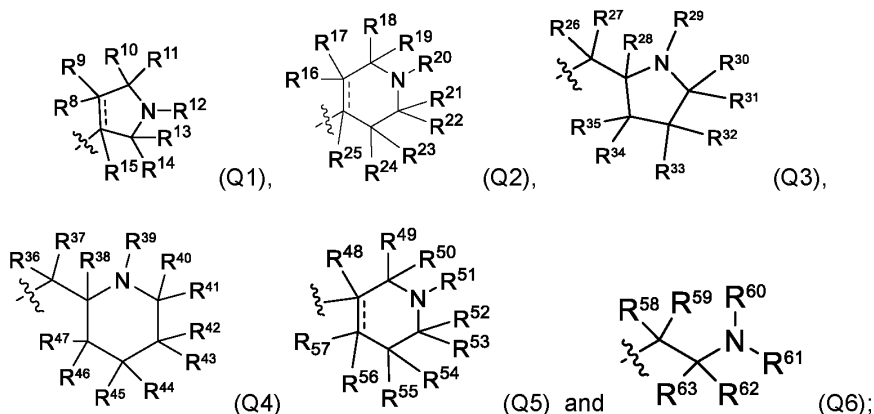


wherein:

R¹ and R^{1'} are independently selected from H, halo, OH, NH₂, C₁₋₆alkyl, C₁₋₆alkoxyl, NH(C₁₋₆alkyl) and N(C₁₋₆alkyl)₂;

R² and R^{2'} are independently selected from H, halo, NH₂, C₁₋₆alkyl, C₁₋₆alkoxyl, NH(C₁₋₆alkyl) and N(C₁₋₆alkyl)₂;

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



--- is a single bond or a double bond provided that when --- in Q1 is a double bond then R⁹ and R¹⁵ are not present, when --- in Q2 is a double bond then R¹⁷ and R²⁵ are not present, and when --- in Q5 is a double bond then R⁴⁸ and R⁵⁷ are not present;

one or both of R⁴ and R⁵ is independently selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy, or

R⁴ and R⁵ are linked together to form O-(CH₂)₁₋₂O, or

one of R⁴ and R⁵ is selected from X-L-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy,

X is selected from a direct bond, O, C(O), NR^a, NR^aC(O), C(O)NR^a, OC(O), C(O)O, OC(O)O, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a;

L is selected from a direct bond, C₁₋₆alkylene, C₂₋₆alkenylene, C₁₋₆alkyleneO, C₂₋₆alkenyleneO, C₁₋₆alkyleneC(O), C₂₋₆alkenyleneC(O), C₁₋₆alkyleneNR^bC(O), C₂₋₆alkenyleneNR^bC(O), C₁₋₆alkyleneC(O)NR^b, C₂₋₆alkenyleneC(O)NR^b, C₁₋₆alkyleneOC(O), C₂₋₆alkenyleneOC(O), C₁₋₆alkyleneC(O)O, C₂₋₆alkenyleneC(O)O, C₁₋₆alkyleneOC(O)NR^b, C₂₋₆alkenyleneOC(O)NR^b, C₁₋₆alkyleneNR^bC(O)O, C₂₋₆alkenyleneNR^bC(O)O, C₁₋₆alkyleneOC(O)O, C₂₋₆alkenyleneOC(O)O, C₁₋₆alkyleneNR^bC(O)NR^b and C₂₋₆alkenyleneNR^bC(O)NR^b;

R^a is selected from H and C₁₋₆alkyl;

R^b is selected from H, C₁₋₆alkyl and A;

A is selected from H, C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 4 heteromoeities independently selected from O, S, S(O),

SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C₁₋₄alkyl and OC₁₋₄alkyl;

R³ and R⁶ are independently selected from H, halo, OH, C₁₋₆alkyl and C₁₋₆alkoxy;

R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H, halo and C₁₋₆alkyl;

R¹², R²⁰, R²⁹, R³⁹ and R⁵¹ are independently selected from H, C₁₋₆alkyl, C(O)C₁₋₆alkyl and C(O)-A';

R⁶⁰ and R⁶¹ are independently selected from H and C₁₋₆alkyl; or

one of R⁶⁰ and R⁶¹ is C(O)-A' and the other is selected from H and C₁₋₆alkyl;

wherein A' is selected from Y, O-Y and O-C₁₋₄alkylene-O-C(O)-Y; and

Y is selected from C₇₋₃₀alkyl and C₇₋₃₀alkenyl; or

R⁶⁰ and R⁶¹, together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoeities independently selected from O, S, S(O), SO₂, N, and NR⁶⁵ and which is optionally substituted with one or more substituents independently selected from halo, OH, C₁₋₄alkyl and OC₁₋₄alkyl;

R⁶⁴ and R⁶⁵ are independently selected from H and C₁₋₆alkyl; and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided when Q is Q6 then the compound of Formula I comprises D,

when Q is Q3 or Q4, R¹, R^{1'}, R², R^{2'}, R³, R⁴, R⁶, R²⁶, R²⁷, R²⁸, R³⁰ to R³⁵, R³⁶, R³⁷, R³⁸ and R⁴⁰ to R⁴⁷ are not all H, when R⁵ is H or OCH₃, and R²⁹ or R³⁹ is CH₃.

when Q is Q4 and R¹, R^{1'}, R², R^{2'}, R³, R⁴, R⁶, R³⁸ and R⁴⁰ to R⁴⁷ are all H, then R³⁶ and R³⁷ are not both D, when R³⁹ is CD₃.

[0028] The application additionally provides a process for the preparation of compounds of the application. General and specific processes are discussed in more detail below and set forth in the examples below.

[0029] Other features and advantages of the present application 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 application, 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.

DETAILED DESCRIPTION

I. Definitions

[0030] 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 application herein described for which they are suitable as would be understood by a person skilled in the art.

[0031] The term "compound(s) of the application" or "compound(s) of the present application" and the like as used herein refers to a compound of Formula I and I-A and includes pharmaceutically acceptable salts, solvates and/or prodrugs thereof as well as all stereoisomers and regioisomers.

[0032] The term "composition(s) of the application" or "composition(s) of the present application" and the like as used herein refers to a composition, such a pharmaceutical composition, comprising one or more compounds of the application.

[0033] 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, solvates and/or prodrugs thereof means that the compounds of the application exist as individual salts, solvates and/or prodrugs, as well as a combination of, for example, a salt of a solvate of a compound of the application.

[0034] As used in the present application, 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 embodiments with one compound, or two or more additional compounds.

[0035] As used in this application 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.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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 $\pm 5\%$ 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.

[0041] 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.

[0042] The term "solvate" as used herein means a compound, or a salt and/or prodrug of a compound, wherein molecules of a suitable solvent are incorporated in the crystal lattice.

[0043] The term "prodrug" as used herein means a compound, or salt of a compound, that, after administration, is converted into an active drug.

[0044] 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-n2} ". Thus, for example, the term " C_{1-6} alkyl" (or " C_1-C_6 alkyl") means an alkyl group having 1, 2, 3, 4, 5, or 6 carbon atoms.

[0045] The term "alkenyl" as used herein, whether it is used alone or as part of another group, means straight or branched chain, saturated alkenyl 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-n2} ". Thus, for example, the term " C_{2-6} alkyl" (or " C_2-C_6 alkyl") means an alkenyl group having 2, 3, 4, 5, or 6 carbon atoms.

[0046] The term "alkenylene" as used herein, whether it is used alone or as part of another group, means a straight or branched chain, unsaturated alkylene group, that is, an unsaturated carbon chain that contains substituents on two of its ends and at least one double bond. The number of carbon atoms that are possible in the referenced alkenylene group are indicated by the prefix " C_{n1-n2} ". For example, the term C_{2-6} alkenylene means an alkenylene group having 2, 3, 4, 5 or 6 carbon atoms.

[0047] As used herein, the term "alkoxy" as used herein, alone or in combination, includes an alkyl group connected to an oxygen-connecting atom.

[0048] The term "cycloalkyl," as used herein, whether it is used alone or as part of another group, means a saturated carbocyclic group containing from 3 to 6 carbon atoms and 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-n2} ". For example, the term C_{3-6} cycloalkyl means a cycloalkyl group having 3, 4, 5 or 6 carbon atoms.

[0049] 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

containing from 3 to 6 atoms in which one or more of the atoms are a heteromoiety selected from O, S, S(O), SO₂, NH, NC₁₋₆alkyl and N and the remaining atoms are C. Heterocycloalkyl groups are either saturated or unsaturated (i.e. contain one or more double bonds). When a heterocycloalkyl group contains the prefix C_{n1-n2} or "n1 to n2" this prefix indicates the number of carbon atoms in the corresponding carbocyclic group, in which one or more, suitably 1 to 4, of the ring atoms is replaced with a heteromoeity as selected from O, S, S(O), SO₂, NH, NC₁₋₆alkyl and N and the remaining atoms are C.

[0050] 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 and contains from 6 to 10 carbon atoms.

[0051] 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 containing 5-6 atoms in which one or more of the atoms are a heteroatom selected from O, S and N 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 4, of the ring atoms is replaced with a heteroatom as defined above.

[0052] 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.

[0053] 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 replaced with a halogen. Thus, for example, "C₁₋₆haloalkyl" refers to a C₁ to C₆ linear or branched alkyl group as defined above with one or more halogen substituents.

[0054] 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 replaced with a deuterium. Thus, for example, "C₁₋₆deuteroalkyl" refers to a C₁ to C₆ linear or branched alkyl group as defined above with one or more deuterium substituents.

[0055] 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.

[0056] As used herein, the term "one or more" item includes a single item selected from the list as well as mixtures of two or more items selected from the list.

[0057] 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. In the compounds of general Formula I and I-A and pharmaceutically acceptable salts, solvates and/or prodrugs 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 application is meant to include all suitable isotopic variations of the compounds of general Formula I and I-A and pharmaceutically acceptable salts, solvates and/or prodrugs 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.

[0058] The term “compound” refers to the compound and, in certain embodiments, to the extent they are stable, any hydrate or solvate thereof. A hydrate is the compound complexed with water and a solvate is the compound complexed with a solvent, which may be an organic solvent or an inorganic solvent. A “stable” compound is a compound that can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic administration to a subject). The compounds of the present application are limited to stable compounds embraced by general Formula (I-A), or pharmaceutically acceptable salts, solvates and/or prodrugs thereof.

[0059] The term “pharmaceutically acceptable” means compatible with the treatment of subjects.

[0060] 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.

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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).

[0065] 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 application are applicable to both human therapy and veterinary applications.

[0066] 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. For example, a subject with early neurological disease can be treated to prevent progression, or alternatively a subject in remission can be treated with a compound or composition of the application to prevent recurrence. Treatment methods comprise administering to a subject a therapeutically effective amount of one or more of the compounds of the application and optionally consist of a single administration, or alternatively comprise a series of administrations.

[0067] As used herein, the term "effective amount" or "therapeutically effective amount" means an amount of one or more compounds of the application 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.

[0068] "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.

[0069] The term "administered" as used herein means administration of a therapeutically effective amount of one or more compounds or compositions of the application to a cell, tissue, organ or subject.

[0070] 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.

[0071] The "disease, disorder or condition" as used herein refers to a disease, disorder or condition treated or treatable by activation a serotonin receptor, for example 5-HT_{2A} and particularly using a serotonin receptor agonist, such as one or more compounds of the application herein described. The disease, disorder or condition may also be treated or treatable via alternative mechanisms, for example by modulation, deactivation, antagonism or reverse agonism of a serotonin receptor, including 5-HT_{2A} and/or 5-HT_{1A}.

[0072] 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 favourably when serotonergic activity associated with the disease, disorder or condition is modulated, for example agonized, by one or more of the compounds or compositions of the application.

[0073] The term "activation" as used herein includes agonism, partial agonist and positive allosteric modulation of a serotonin receptor.

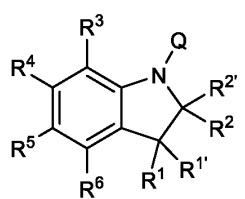
[0074] The terms "5-HT_{1A}" and "5-HT_{2A}" are used herein mean the 5-HT_{1A} and 5-HT_{2A} receptor subtypes of the 5-HT serotonin receptor, respectively.

[0075] 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. Methods and Uses of the Application

[0076] The Applicants have found that indoline derivatives are useful for treating diseases, disorders or conditions by modulating, for example activating, a serotonin receptor. Therefore, the indoline derivatives are useful as medicaments. Accordingly, the application also includes indoline derivatives for use as a medicament.

[0077] Therefore, the present application 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof, to a subject in need thereof,

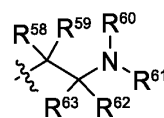
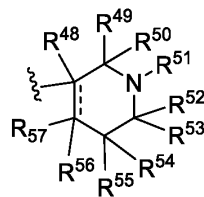
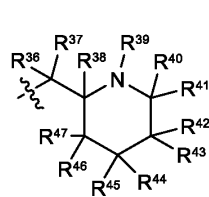
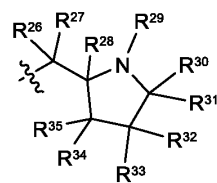
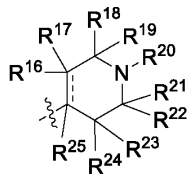
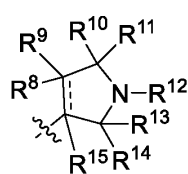


wherein:

R¹ and R^{1'} are independently selected from H, halo, OH, NH₂, C₁₋₆alkyl, C₁₋₆alkoxyl, NH(C₁₋₆alkyl) and N(C₁₋₆alkyl)₂;

R² and R^{2'} are independently selected from H, halo, NH₂, C₁₋₆alkyl, C₁₋₆alkoxyl, NH(C₁₋₆alkyl) and N(C₁₋₆alkyl)₂;

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



--- is a single bond or a double bond provided that when --- in Q1 is a double bond then R⁹ and R¹⁵ are not present, when --- in Q2 is a double bond then R¹⁷ and R²⁵ are not present, and when --- in Q5 is a double bond then R⁴⁸ and R⁵⁷ are not present;

one or both of R⁴ and R⁵ is independently selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy, or

R⁴ and R⁵ are linked together to form O-(CH₂)₁₋₂O, or

one of R⁴ and R⁵ is selected from X-L-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy;

X is selected from a direct bond, O, C(O), NR^a, NR^aC(O), C(O)NR^a, OC(O), C(O)O, OC(O)O, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a;

L is selected from a direct bond, C₁₋₆alkylene, C₂₋₆alkenylene, C₁₋₆alkyleneO, C₂₋₆alkenyleneO, C₁₋₆alkyleneC(O), C₂₋₆alkenyleneC(O), C₁₋₆alkyleneNR^bC(O), C₂₋₆alkenyleneNR^bC(O), C₁₋₆alkyleneC(O)NR^b, C₂₋₆alkenyleneC(O)NR^b, C₁₋₆alkyleneOC(O), C₂₋₆alkenyleneOC(O), C₁₋₆alkyleneC(O)O, C₂₋₆alkenyleneC(O)O, C₁₋₆alkyleneOC(O)NR^b, C₂₋₆alkenyleneOC(O)NR^b, C₁₋₆alkyleneNR^bC(O)O, C₂₋₆alkenyleneNR^bC(O)O, C₁₋₆alkyleneOC(O)O, C₂₋₆alkenyleneOC(O)O, C₁₋₆alkyleneNR^bC(O)NR^b and C₂₋₆alkenyleneNR^bC(O)NR^b;

R^a is selected from H and C₁₋₆alkyl;

R^b is selected from H, C₁₋₆alkyl and A;

A is selected from H, C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C₁₋₄alkyl and OC₁₋₄alkyl;

R³ and R⁶ are independently selected from H, halo, OH, C₁₋₆alkyl and C₁₋₆alkoxy;

R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵²,

R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , R^{59} , R^{62} and R^{63} are independently selected from H, halo and C_{1-6} alkyl;

R^{12} , R^{20} , R^{29} , R^{39} and R^{51} are independently selected from H, C_{1-6} alkyl, $C(O)C_{1-6}$ alkyl and $C(O)-A'$;

R^{60} and R^{61} are independently selected from H and C_{1-6} alkyl; or

one of R^{60} and R^{61} is $C(O)-A'$ and the other is selected from H and C_{1-6} alkyl;

wherein A' is selected from Y, O-Y and O- C_{1-4} alkylene-O- $C(O)-Y$; and

Y is selected from C_{7-30} alkyl and C_{7-30} alkenyl; or

R^{60} and R^{61} , together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoieties independently selected from O, S, $S(O)$, SO_2 , N, and NR^{65} and which is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-4} alkyl and OC_{1-4} alkyl;

R^{64} and R^{65} are independently selected from H and C_{1-6} alkyl; and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided when Q is Q6 then the compound of Formula I comprises D.

[0078] The present application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for treatment of a disease, disorder or condition by activation of a serotonin receptor as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for treatment of a disease, disorder or condition by activation of a serotonin receptor. The application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for use in treating a disease, disorder or condition by activation of a serotonin receptor.

[0079] In some embodiments, the serotonin receptor is 5-HT_{2A}. Accordingly, the present application includes a method for activating 5-HT_{2A} in a cell, either in a biological sample or in a patient, comprising administering an effective amount of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug

thereof to the cell. The application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for activating 5-HT_{2A} in a cell as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for activating 5-HT_{2A} in a cell. The application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for use in activating 5-HT_{2A} in a cell.

[0080] In some embodiments, the serotonin receptor is 5-HT_{1A}. Accordingly, the present application includes a method for activating 5-HT_{1A} receptors in a cell, either in a biological sample or in a patient, comprising administering an effective amount of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to the cell. The application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for activating 5-HT_{1A} receptors in a cell as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for activating 5-HT_{1A} receptors in a cell. The application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for use in activating 5-HT_{1A} receptors in a cell.

[0081] The present application 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a subject in need thereof. The present application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for treatment of a disease, disorder or condition by activation of 5-HT_{2A} as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for treatment of a disease, disorder or condition by activation of 5-HT_{2A}. The application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for use in treating a disease, disorder or condition by activation of 5-HT_{2A}.

[0082] The present application also includes a method of treating a disease, disorder or condition by activation of 5-HT_{1A} comprising administering a therapeutically effective amount of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a subject in need thereof. The present application

also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for treatment of a disease, disorder or condition by activation of 5-HT_{1A} as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for treatment of a disease, disorder or condition by activation of 5-HT_{1A}. The application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for use in treating a disease, disorder or condition by activation of 5-HT_{1A}.

[0083] The disease, disorder or condition may also be treated or treatable via alternative mechanisms, for example by modulation, deactivation, antagonism or reverse agonism of a serotonin receptor, including 5-HT_{2A} and/or 5-HT_{1A}.

[0084] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 application also includes a method of treating a mental illness comprising administering a therapeutically effective amount of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a subject in need thereof. The present application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for treatment a mental illness, as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for treatment of a mental illness. The application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for use in treating a mental illness.

[0085] 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, anxiety and cyclothymic disorder; psychotic disorders, such as hallucinations, delusions, schizophrenia; impulse control and addiction disorders, such as pyromania (starting fires), kleptomania (stealing) and compulsive gambling; alcohol addiction; 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; and combinations thereof.

[0086] In some embodiments, the disease, disorder or condition that is treated by activation of a serotonin receptor comprises cognitive impairment; 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; or a combination thereof.

[0087] In some embodiments, the mental illness is selected from hallucinations and delusions and a combination thereof.

[0088] In some embodiments, the hallucinations are selected from visual hallucinations, auditory hallucinations, olfactory hallucinations, gustatory hallucinations, tactile hallucinations, proprioceptive hallucinations, equilibrioceptive hallucinations, nociceptive hallucinations, thermoceptive hallucinations and chronoceptive hallucinations, and a combination thereof.

[0089] 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 application also includes a method of treating psychosis or psychotic symptoms comprising administering a therapeutically effective amount of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a subject in need thereof.

[0090] The present application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for treatment of psychosis or psychotic symptoms, as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for treatment of psychosis or psychotic symptoms. The application further includes one or more compounds of Formula I or a pharmaceutically

acceptable salt, solvate and/or prodrug thereof for use in treating psychosis or psychotic symptoms.

[0091] In some embodiments, administering to said subject in need thereof a therapeutically effective amount of the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof results in an improvement of psychosis or psychotic symptoms.

[0092] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof are useful for treating a central nervous system (CNS) disorder in a subject in need of therapy, comprising administering a therapeutically effective amount of a compound of general Formula I, or a pharmaceutically acceptable salt thereof to the subject.

[0093] Therefore, 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 application also includes a method of treating a 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a subject in need thereof. The present application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for treatment a CNS disease, disorder or condition and/or a neurological disease, disorder or condition, as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for treatment of a CNS disease, disorder or condition and/or a neurological disease, disorder or condition. The application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for use in treating a CNS disease, disorder or condition and/or a neurological disease, disorder or condition. 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; 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"), trichotillomania, dermatillomania, nail biting; migraine; fibromyalgia; and peripheral neuropathy of any etiology, and combinations thereof.

[0094] In some embodiments, the subject is a mammal. In another embodiment, the subject is human. In some embodiments, 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 application are directed to both human and veterinary diseases, disorders and conditions.

[0095] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof are useful for treating behavioral problems in subjects that are felines or canines.

[0096] 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 application also includes a method of treating a behavioral problem comprising administering a therapeutically effective amount of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a non-human subject in need thereof. The present application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for treatment a behavioral problem in a non-human subject, as well as a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for the preparation of a medicament for

treatment of a behavioral problem in a non-human subject. The application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof for use in treating a behavioral problem in a non-human subject.

[0097] 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.

[0098] In some embodiments, the non-human subject is canine. In some embodiments, the non-human subject is feline.

[0099] The present application 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 application also includes a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 a use of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 application further includes one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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.

[00100] 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.

[00101] 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 carbamazepine, divalproex (valproic acid), lamotrigine, gabapentin and topiramate.

[00102] 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 and a combination thereof are selected from methylphenidate, atomoxetine and amphetamine and a combination thereof.

[00103] 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 acetylcholinesterase inhibitors, NMDA antagonists and muscarinic agonists and antagonists, and nicotinic agonists.

[00104] In some embodiments, the acetylcholinesterase inhibitors are selected from donepezil, galantamine, rivastigmine, and phenserine, and combinations thereof.

[00105] In some embodiments, the NMDA antagonists are selected from MK-801, ketamine, phencyclidine, and memantine, and combinations thereof.

[00106] In some embodiments, the nicotinic agonists is nicotine, nicotinic acid, nicotinic alpha7 agonists or alpha2 beta4 agonists or combinations thereof.

[00107] In some embodiments, the muscarinic agonists is a muscarinic M1 agonist or a muscarinic M4 agonist, or combinations thereof.

[00108] In some embodiments, the muscarinic antagonist is a muscarinic M2 antagonist.

[00109] 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 symptom are selected typical antipsychotics and atypical antipsychotics.

[00110] 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, sulfuridazine, thiopropazate, thioproperazine, thioridazine, thiothixene, timiperone, trifluoperazine, trifluoperidol, triflupromazine and zuclopenthixol and combinations thereof.

[00111] 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 and zotepine, and combinations thereof.

[00112] 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

Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 typical antipsychotics and atypical antipsychotics.

[00113] 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.

[00114] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof are administered one, two, three or four times a year. In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof are administered at least once a week. However, in another embodiment, the compounds are administered to the subject from about one time per 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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.

[00115] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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.

[00116] A compound of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof is either used alone or in combination with other known agents useful for treating diseases, disorders or conditions by activation of a serotonin receptor, such as the compounds of the application. When used in combination with other known agents useful in treating diseases, disorders by activation of a serotonin receptor, it is an embodiment that a compound of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 application that a combination of agents is administered to a subject in a non-contemporaneous fashion. In some embodiments, a compound of the present application 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 application provides a single unit dosage form comprising one or more compounds of the application, an additional therapeutic agent and a pharmaceutically acceptable carrier.

[00117] The dosage of a compound of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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

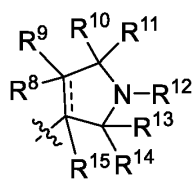
or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof from about 0.01 µg/cc to about 1000 µg/cc, or about 0.1 µg/cc to about 100 µg/cc. As a representative example, oral dosages of one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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. For 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 application, 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 application) per tablet. In some embodiments of the application the one or more compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof are administered in a single daily, weekly or monthly dose or the total daily dose is divided into two, three or four daily doses.

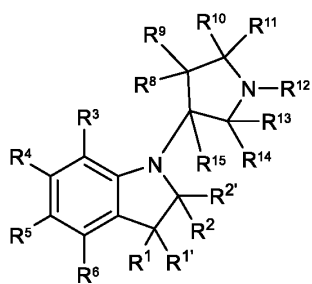
[00118] In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof are used or administered in an effective amount which comprises administration of doses or dosage regimens that are devoid of clinically meaningful psychedelic/ psychotomimetic actions. In some embodiments, the compounds of Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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.

[00119] 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 application” also includes embodiments wherein only one compound is referenced.

[00120] In some embodiments, when all available atoms are optionally replaced with alternate isotope thereof, all available hydrogen atoms in a group are optionally replaced with deuterium.

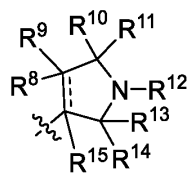
[00121] In some embodiments, Q is Q1, , and  is a single bond and the compound of Formula I has the following structure:

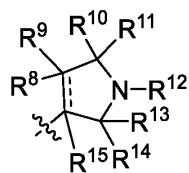


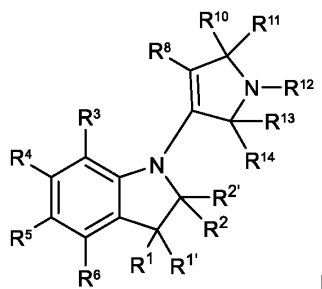
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof, wherein:

R¹, R^{1'}, R², R^{2'}, R³, R⁴, R⁵, R⁶, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴ and R¹⁵ are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



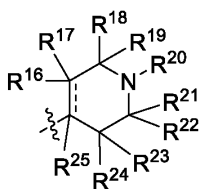
[00122] In some embodiments, Q is Q1, , and  is a double bond and the compound of Formula I has the following structure:

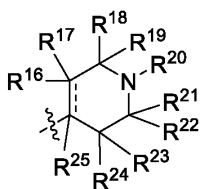


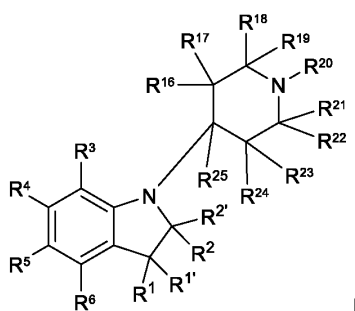
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^8 , R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are as defined for Formula I,
and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00123] In some embodiments, Q is Q2, , and  is a single bond and the compound of Formula I has the following structure:

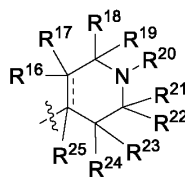


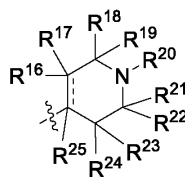
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

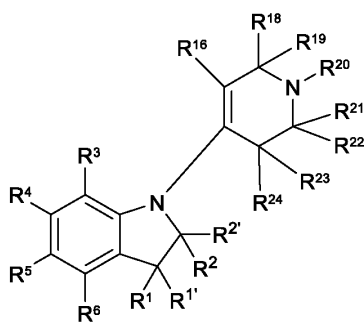
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{16} , R^{17} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} , R^{24} and R^{25} are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00124] In some embodiments, Q is Q2, , and  is a double bond and the compound of Formula I has the following structure:

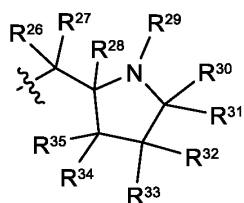


or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

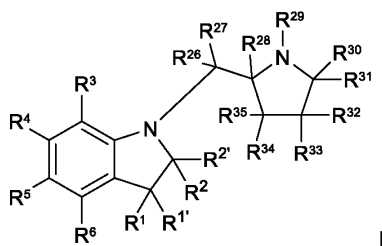
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{16} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} and R^{24} are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00125] In some embodiments, Q is Q3, , and the compound of Formula I has the following structure:

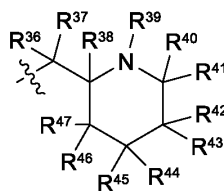


or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

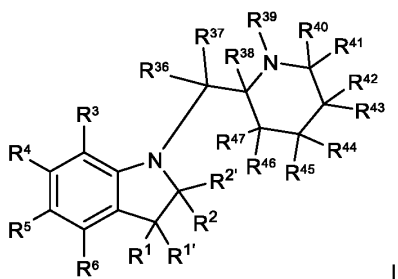
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} and R^{35} are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00126] In some embodiments, Q is Q4 , and the compound of Formula I has the following structure:

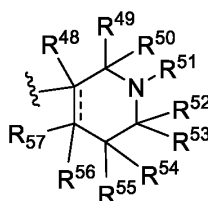


or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

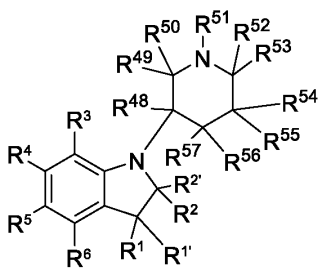
wherein:

$R^1, R^{1'}, R^2, R^{2'}, R^3, R^4, R^5, R^6, R^{36}, R^{37}, R^{38}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}$ and R^{47} are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00127] In some embodiments, Q is Q5, and --- is a single bond and the compound of Formula I has the following structure:

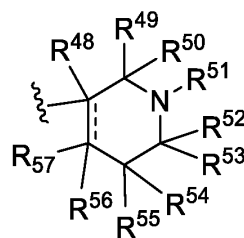


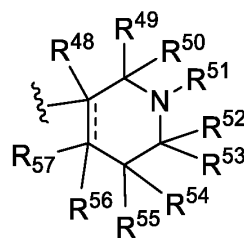
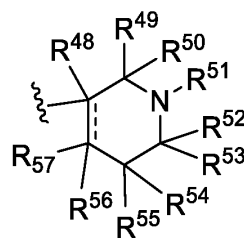
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

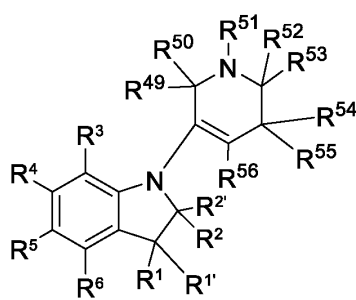
wherein:

$R^1, R^{1'}, R^2, R^{2'}, R^3, R^4, R^5, R^6, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}$ and R^{57} are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00128] In some embodiments, Q is Q5, , and  is a double bond and the compound of Formula I has the following structure:

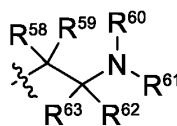


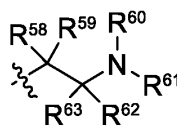
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

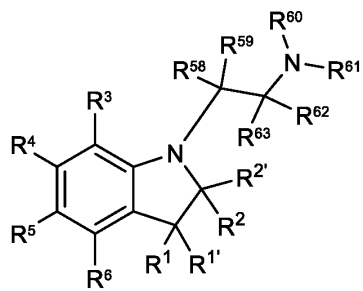
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{48} , R^{50} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} and R^{56} are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00129] In some embodiments, Q is Q6,  (Q6), and the compound of Formula I has the following structure:



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

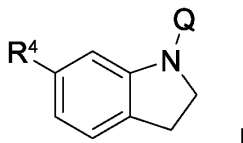
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{58} , R^{59} , R^{60} , R^{61} , R^{62} and R^{63} are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided the compound of Formula I comprises D.

[00130] In some embodiments, R^1 , R^2 , $R^{2'}$, $R^{2''}$, R^3 , R^5 and R^6 are all H and the compound Formula I has the following structure:



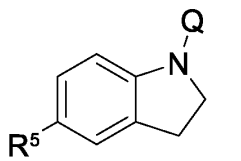
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

R^4 and Q are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.

[00131] In some embodiments, R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 and R^6 are all H and the compound Formula I has the following structure:



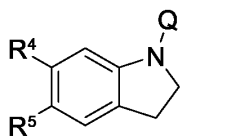
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

R^5 and Q are as defined for Formula I, and

wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.

[00132] In some embodiments, R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 and R^6 are all H and the compound Formula I has the following structure:



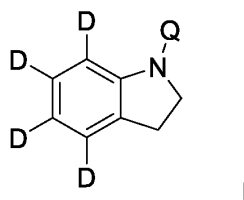
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

R^4 , R^5 and Q are as defined for Formula I, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.

[00133] In some embodiments, R^1 , $R^{1'}$, R^2 and $R^{2'}$ are all H and R^3 , R^4 , R^5 and R^6 are all D and the compound of Formula I has the following structure:



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

wherein:

Q is as defined for Formula I, and

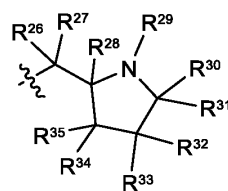
all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.

[00134] In some embodiments, $R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{62}$ and R^{63} are independently selected from H, D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl and C_{1-6} deuteroalkyl. In some embodiments, $R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{62}$ and R^{63} are independently selected from H, F, D, CH_3 , CD_2H , CDH_2 , CD_3 , CF_3 , CHF_2 , CH_2CH_3 , CH_2CH_2D , CH_2CD_2H and CD_2CD_3 . In some embodiments, $R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{62}$ and R^{63} are independently selected from H and D.

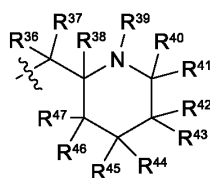
[00135] In some embodiments, $R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}$ and R^{57} are independently selected from H and D.

[00136] In some embodiments, R^{58}, R^{59}, R^{62} and R^{63} are independently selected from H and D. In some embodiments, R^{58}, R^{59}, R^{62} and R^{63} are H. In some embodiments, R^{58}, R^{59}, R^{62} and R^{63} are D. In some embodiments, R^{58} and R^{59} are H and R^{62} and R^{63} are D. In some embodiments, R^{58} and R^{59} are D and R^{62} and R^{63} are H.

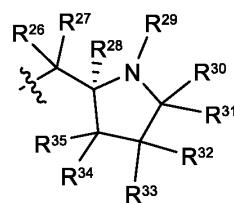
[00137] In some embodiments, when Q is



(Q3) or

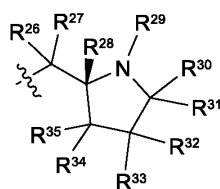


(Q4), the stereochemistry at the carbon to which R^{28} or R^{38} is bonded

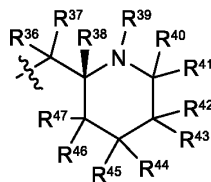


is either R or S. Therefore in some embodiments, Q3 is

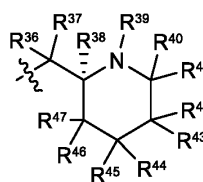
or



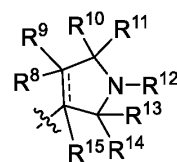
and Q4 is



or

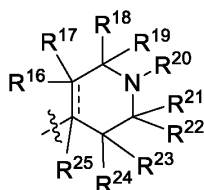


[00138] In some embodiments, the stereochemistry at the carbon to which R^{28} or R^{38} is bonded is R. In some embodiments, the stereochemistry at the carbon to which R^{28} or R^{38} is bonded is S.

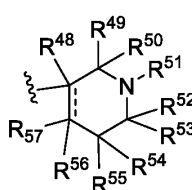


[00139] In some embodiments, when Q is

(Q1),



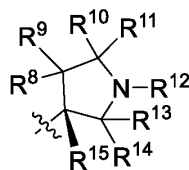
(Q2) or



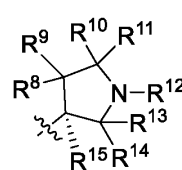
(Q5) and

== is a single bond, the

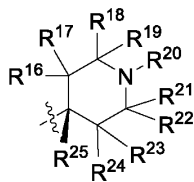
stereochemistry at the carbon to which R^{15} , R^{25} or R^{48} is bonded is either R or S. Therefore



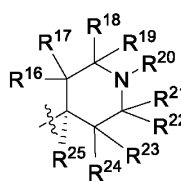
or



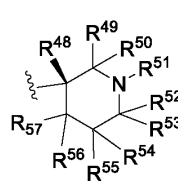
, Q2 is



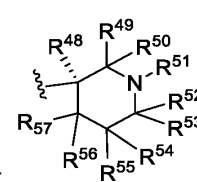
or



, and Q5 is

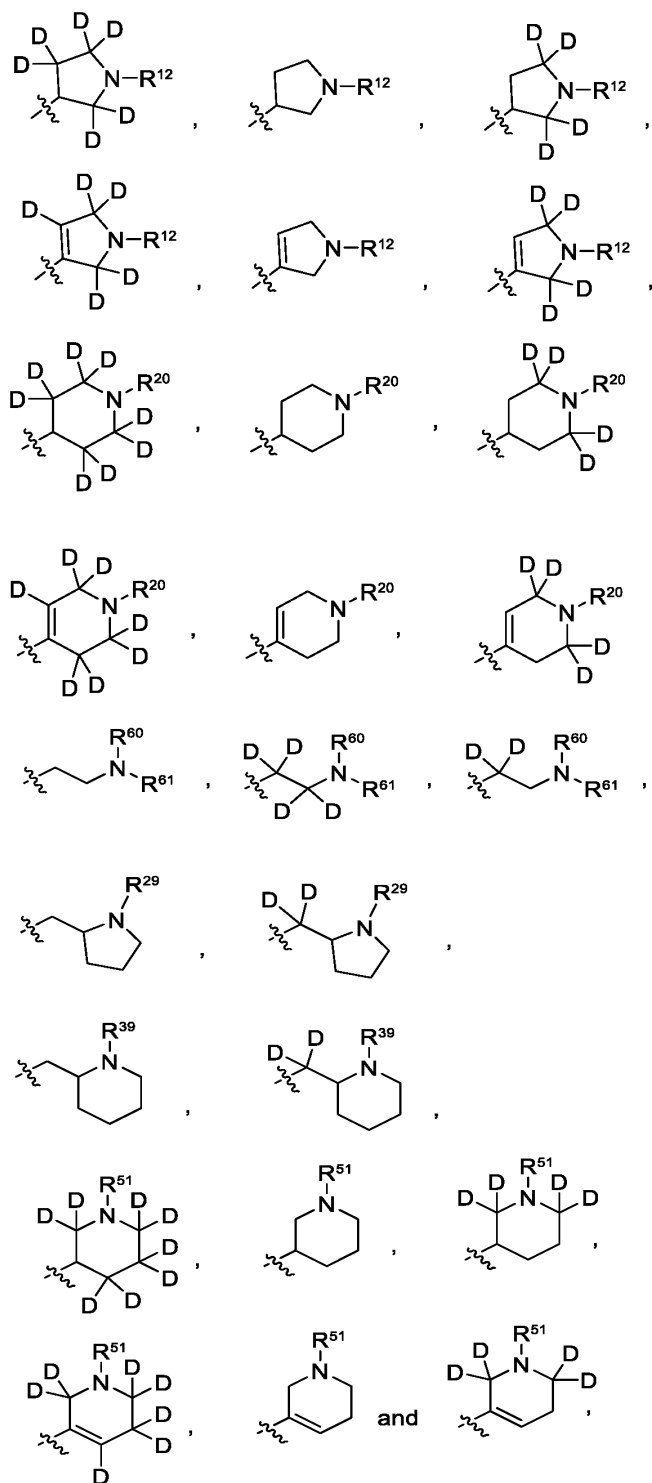


or



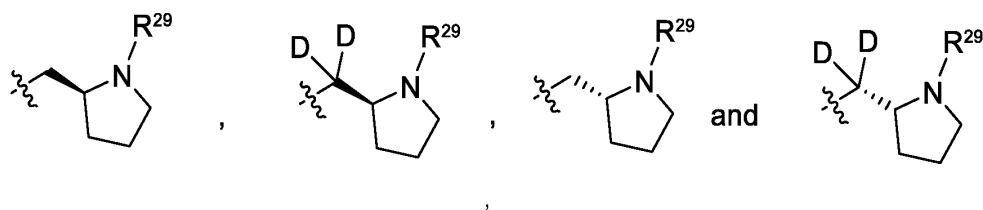
[00140] In some embodiments, the stereochemistry at the carbon to which R^{15} , R^{25} or R^{48} is bonded is R. In some embodiments, the stereochemistry at the carbon to which R^{15} , R^{25} or R^{48} is bonded is S.

[00141] In some embodiments Q is selected from one of the following groups:



wherein R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from H, D, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl and $C(O)-A'$. In some embodiments, R^{12} , R^{20} , R^{29} and R^{39} are independently selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4} deuteroalkyl and $C(O)-A'$. In some embodiments, R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from H, CH_3 , CD_3 , CD_2H , CF_2H and CF_3 . In some embodiments, R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from H, CH_3 and CD_3 . In some embodiments, R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from CH_3 and CD_3 .

[00142] In some embodiments Q is selected from one of the following groups:



wherein R^{29} is selected from H, D, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl and $C(O)-A'$. In some embodiments, R^{29} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4} deuteroalkyl and $C(O)-A'$. In some embodiments, R^{29} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl. In some embodiments, R^{29} is selected from H, CH_3 , CD_3 , CD_2H , CF_2H and CF_3 . In some embodiments, R^{29} is selected from H, CH_3 and CD_3 . In some embodiments, R^{29} is selected from CH_3 and CD_3 .

[00143] In some embodiments, R^{60} and R^{61} , together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoiety independently selected from O, N and NR^{65} and which is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-4} alkyl and OC_{1-4} alkyl.

[00144] In some embodiments, R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from $C(O)-A'$.

[00145] In some embodiments, one of R^{60} and R^{61} is $C(O)-A'$ and the other is selected from H and C_{1-6} alkyl. In some embodiments, one of R^{60} and R^{61} is $C(O)-A'$ and the other is selected from H and C_{1-4} alkyl.

[00146] In some embodiments, A' is selected from Y, O-Y and $O-C_{1-2}$ alkylene-O- $C(O)-Y$, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A' is selected from Y, O-Y

and O-C₁alkylene-O-C(O)-Y, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00147] In some embodiments, Y is C₁₀₋₂₅alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, Y is C₁₃₋₂₁alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00148] In some embodiments, Y is C₁₀₋₂₅alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, Y is C₁₃₋₂₁alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, Y is C₁₀₋₂₅alkenyl and comprises 1, 2, 3, 4, 5 or 6 double bonds.

[00149] In some embodiments, the alkyl or alkene group of Y is an alkyl or alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium. In some embodiments, Y is an alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium. In some embodiments, the fatty acid is an omega-6 fatty acid (i.e. an unsaturated or polyunsaturated fatty acid wherein the double bond that is closest to the methyl end of the molecule is located at carbon numbered 6 starting from the end methyl group) or an omega-3 fatty acid (i.e. an unsaturated or polyunsaturated fatty acid wherein the double bond that is closest to the methyl end of the molecule is located at carbon numbered 3 starting from the end methyl group), wherein all available H atoms are optionally replaced with deuterium. In some embodiments, Y is an alkyl group present in a fatty acid wherein all available H atoms are optionally replaced with deuterium. In some embodiments, the alkyl or alkene group of Y is an alkyl or alkene group present in a fatty acid selected from the list of fatty acids in Table 1 :

Table 1

Common Name	Lipid Number	Chemical Name
linoleic acid (LA)	18:2 (n-6)	<i>all-cis</i> -9,12-octadecadienoic acid,
rumenic acid (conjugated linoleic acid)	18:2 (n-6)	9Z,11E-octadecadienoic acid,
conjugated linoleic acid	18:2 (n-6)	10E,12Z-octadecadienoic acid,

conjugated linoleic acid	18:2 (<i>n</i> -6)	9Z,12E-octadecadienoic acid,
gamma-linolenic acid (GLA)	18:3 (<i>n</i> -6)	<i>all-cis</i> -6,9,12-octadecatrienoic acid,
calendic acid	18:3 (<i>n</i> -6)	8E,10E,12Z-octadecatrienoic acid,
eicosadienoic acid	20:2 (<i>n</i> -6)	<i>all-cis</i> -11,14-eicosadienoic acid,
dihomo-gamma-linolenic acid (DGLA)	20:3 (<i>n</i> -6)	<i>all-cis</i> -8,11,14-eicosatrienoic acid,
arachidonic acid (AA, ARA)	20:4 (<i>n</i> -6)	<i>all-cis</i> -5,8,11,14-eicosatetraenoic acid
docosadienoic acid	22:2 (<i>n</i> -6)	<i>all-cis</i> -13,16-docosadienoic acid,
adrenic acid	22:4 (<i>n</i> -6)	<i>all-cis</i> -7,10,13,16-docosatetraenoic acid,
osbond acid	22:5 (<i>n</i> -6)	<i>all-cis</i> -4,7,10,13,16-docosapentaenoic acid,
tetracosatetraenoic acid	24:4 (<i>n</i> -6)	<i>all-cis</i> -9,12,15,18-tetracosatetraenoic acid,
tetracosapentaenoic acid	24:5 (<i>n</i> -6)	<i>all-cis</i> -6,9,12,15,18-tetracosapentaenoic acid,
α -linolenic acid (ALA)	18:3 (<i>n</i> -3)	<i>all-cis</i> -9,12,15-octadecatrienoic acid,
stearidonic acid (SDA)	18:4 (<i>n</i> -3)	<i>all-cis</i> -6,9,12,15-octadecatetraenoic acid,
hexadecatrienoic acid (HTA)	16:3 (<i>n</i> -3)	<i>all-cis</i> -7,10,13-hexadecatrienoic acid,
eicosatrienoic acid (ETE)	20:3 (<i>n</i> -3)	<i>all-cis</i> -11,14,17-eicosatrienoic acid,

eicosatetraenoic acid (ETA)	20:4 (<i>n</i> -3)	<i>all-cis</i> -8,11,14,17-eicosatetraenoic acid,
eicosapentaenoic acid (EPA)	20:5 (<i>n</i> -3)	<i>all-cis</i> -5,8,11,14,17-eicosapentaenoic acid,
heneicosapentaenoic acid (HPA)	21:5 (<i>n</i> -3)	<i>all-cis</i> -6,9,12,15,18-heneicosapentaenoic acid,
docosapentaenoic acid (DPA)	22:5 (<i>n</i> -3)	<i>all-cis</i> -7,10,13,16,19-docosapentaenoic acid,
docosahexaenoic acid (DHA)	22:6 (<i>n</i> -3)	<i>all-cis</i> -4,7,10,13,16,19-docosahexaenoic acid,
tetracosapentaenoic acid	24:5 (<i>n</i> -3)	<i>all-cis</i> -9,12,15,18,21-tetracosapentaenoic acid,
tetracosahexaenoic acid (Nisinic acid)	24:6 (<i>n</i> -3)	<i>all-cis</i> -6,9,12,15,18,21-tetracosahexaenoic acid,
myristoleic acid	14:1 (<i>n</i> -5)	9Z-tetradecenoic acid,
palmitoleic acid	16:1 (<i>n</i> -7)	(9Z)-hexadecenoic acid,
sapienic acid	16:1 (<i>n</i> -10)	(6Z)-hexadecenoic acid,
oleic acid	18:1 (<i>n</i> -9)	(9Z)-octadecenoic acid,
elaidic acid	18:1 (<i>n</i> -9)	(<i>E</i>)-octadecenoic acid,
vaccenic acid	18:1 (<i>n</i> -7)	(11 <i>E</i>)-octadecenoic acid,
eruric acid	22:1 (<i>n</i> -9)	(13Z)-Docosenoic acid,
caprylic acid	8:0	octanoic acid,
capric acid	10:0	decanoic acid,
lauric acid	12:0	dodecanoic acid,
myristic acid	14:0	tetradecanoic acid,
palmitic acid	16:0	hexadecenoic acid,
stearic acid	18:0	octadecanoic acid,
arachidic acid	20:0	icosanoic acid,

behenic acid	22:0	docosanoic acid,
lignoceric acid	24:0	tetracosanoic acid, and
cerotic acid	26:0	hexacosanoic acid,

wherein all available H atoms are optionally replaced with deuterium.

[00150] In some embodiments, the alkene group of Y is an alkyl or alkenyl group present in linoleic acid, eicosadienoic acid or decosahexanoic acid.

[00151] In some embodiments, Y is the alkyl or alkenyl group of a fatty acid wherein 1-10, 2-8, 2-6 or 2-4 H atoms are replaced with deuterium.

[00152] In some embodiments, Y is $(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_8\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$. Therefore, in some embodiments, Y is $(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$, $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$, $(\text{CH}_2)_8\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$, $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$, $(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$, or $(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$.

[00153] In some embodiments, A' is Y.

[00154] In some embodiments, A' is -O-Y.

[00155] In some embodiments, A' is -O-C₃alkylene-O-C(O)-Y.

[00156] In some embodiments, R¹ and R^{1'} are independently selected from H, OH, halo, NH₂, C₁₋₄alkyl, C₁₋₄alkoxy, NH(C₁₋₄alkyl) and N(C₁₋₄alkyl). In some embodiments, R¹ and R^{1'} are independently selected from H, D, Cl, F, OH, NH₂, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkyl, C₁₋₄deuteroalkyl, NH(C₁₋₄alkyl), NH(C₁₋₄deuteroalkyl), NH(C₁₋₄fluoroalkyl), N(C₁₋₄alkyl)₂, N(C₁₋₄fluoroalkyl)₂, N(C₁₋₄deuteroalkyl)₂, N(C₁₋₄fluoroalkyl)(C₁₋₄alkyl), N(C₁₋₄fluoroalkyl)(C₁₋₄deuteroalkyl) and N(C₁₋₄deuteroalkyl)(C₁₋₄alkyl). In some embodiments, R¹ and R^{1'} are independently selected from H, D, Cl, F, OH, NH₂, C₁₋₂alkyl, C₁₋₂alkoxy, C₁₋₂fluoroalkyl and C₁₋₂deuteroalkyl, NH(C₁₋₂alkyl), NH(C₁₋₂deuteroalkyl), NH(C₁₋₂fluoroalkyl), N(C₁₋₂alkyl)₂, N(C₁₋₂fluoroalkyl)₂, N(C₁₋₂deuteroalkyl)₂, N(C₁₋₂fluoroalkyl)(C₁₋₂alkyl), N(C₁₋₂fluoroalkyl)(C₁₋₂deuteroalkyl) and N(C₁₋₂deuteroalkyl)(C₁₋₂alkyl). In some embodiments R¹

is selected from H, D, F, NH₂, CH₃, CF₂H, CD₂H, CH₃O, CF₃, CD₃, NH(CH₃), NH(CD₃), NH(CF₃), N(CH₃)₂, N(CF₃)₂ and N(CD₃)₂. In some embodiments, R¹ and R^{1'} are independently selected from H, D, F, NH₂, CH₃, CF₂H, CD₂H, CH₃O, CF₃ and CD₃. In some embodiments R¹ and R^{1'} are independently selected from H, D, F, OH, CH₃, CF₂H, CD₂H, CH₃O, CF₃ and CD₃. In some embodiments, R¹ and R^{1'} are independently H, D or F. In some embodiments, R¹ and R^{1'} are all H or are all D. In some embodiments, R¹ and R^{1'} are both H.

[00157] In some embodiments, R² and R^{2'} are independently selected from H, halo, NH₂, C₁₋₄alkyl, C₁₋₄alkoxy, NH(C₁₋₄alkyl) and N(C₁₋₄alkyl). In some embodiments, R² and R^{2'} are independently selected from H, D, Cl, F, NH₂, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkyl, C₁₋₄deuteroalkyl, NH(C₁₋₄alkyl), NH(C₁₋₄deuteroalkyl), NH(C₁₋₄fluoroalkyl), N(C₁₋₄alkyl)₂, N(C₁₋₄fluoroalkyl)₂, N(C₁₋₄deuteroalkyl)₂, N(C₁₋₄fluoroalkyl)(C₁₋₄alkyl), N(C₁₋₄fluoroalkyl)(C₁₋₄deuteroalkyl) and N(C₁₋₄deuteroalkyl)(C₁₋₄alkyl). In some embodiments, R² and R^{2'} are independently selected from H, D, Cl, F, C₁₋₂alkyl, C₁₋₂alkoxy, C₁₋₂fluoroalkyl, C₁₋₂deuteroalkyl, NH(C₁₋₂alkyl), NH(C₁₋₂deuteroalkyl), NH(C₁₋₂fluoroalkyl), N(C₁₋₂alkyl)₂, N(C₁₋₂fluoroalkyl)₂, N(C₁₋₂deuteroalkyl)₂, N(C₁₋₂fluoroalkyl)(C₁₋₂alkyl), N(C₁₋₂fluoroalkyl)(C₁₋₂deuteroalkyl) and N(C₁₋₂deuteroalkyl)(C₁₋₂alkyl). In some embodiments, R² and R^{2'} are independently selected from H, D, F, NH₂, CH₃, CF₂H, CD₂H, CH₃O, CF₃, CD₃, NH(CH₃), NH(CD₃), NH(CF₃), N(CH₃)₂, N(CF₃)₂ and N(CD₃)₂. In some embodiments R¹ is selected from H, D, F, NH₂, CH₃, CF₂H, CD₂H, CH₃O, CF₃ and CD₃. In some embodiments R² and R^{2'} are independently selected from H, D, F, CH₃, CF₂H, CD₂H, CH₃O, CF₃ and CD₃. In some embodiments, R² and R^{2'} are independently H, D or F. In some embodiments, R² and R^{2'} are all H or are all D. In some embodiments, R² and R^{2'} are all H.

[00158] In some embodiments, R¹, R^{1'}, R² and R^{2'} are independently H, D or F. In some embodiments, R¹, R^{1'}, R² and R^{2'} are all H or are all D. In some embodiments, R¹, R^{1'}, R² and R^{2'} are all H.

[00159] In some embodiments, R³ and R⁶ are independently selected from H, D, Cl, F, OH, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkoxy, C₁₋₄deuteroalkoxy, C₁₋₄fluoroalkyl and C₁₋₄deuteroalkyl. In some embodiments, R³ and R⁶ are independently selected from H, D, Cl, F, OH, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkyl and C₁₋₄deuteroalkyl. In some embodiments, R³ and R⁶ are independently selected from H, D, Cl, F, OH, C₁₋₂alkyl, C₁₋₂alkoxy, C₁₋₂fluoroalkoxy, C₁₋₂deuteroalkoxy, C₁₋₂fluoroalkyl and C₁₋₂deuteroalkyl. In some embodiments, R³ and R⁶ are independently selected from H, D, Cl, F, OH, C₁₋₂alkyl, C₁₋₂alkoxy, C₁₋₂fluoroalkyl and C₁₋₂deuteroalkyl. In some embodiments, R³ and R⁶ are

independently selected from H, D, F, OH, CH₃, CH₃O, CF₂HO, CD₂HO, CF₃O, CD₃O, CF₂H, CD₂H, CF₃ and CD₃. In some embodiments, R³ and R⁶ are independently selected from H, D, F, OH, CH₃, CH₃O, CF₂H, CD₂H, CF₃ and CD₃. In some embodiments, R³ and R⁶ are independently selected from H, D, F, OH, CH₃, CH₃O, CF₂HO, CF₃O and CD₃O. In some embodiments, R³ and R⁶ are independently selected from H and D. In some embodiments, at least one of R³ and R⁶ is D. In some embodiments, each of R³ and R⁶ are D. In some embodiments, each of R³ and R⁶ are H.

[00160] In some embodiments, one or both of R⁴ and R⁵ is independently selected from H, D, F, Cl, C₁₋₆alkyl, C₁₋₆fluoroalkyl, C₁₋₆deuteroalkyl, C₁₋₆alkoxy, C₁₋₆fluoroalkoxy and C₁₋₆deuteroalkoxy. In some embodiments both of R⁴ and R⁵ are independently selected from H, D, F, Cl, C₁₋₄alkyl, C₁₋₄fluoroalkyl, C₁₋₄deuteroalkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkoxy and C₁₋₄deuteroalkoxy. In some embodiments, one or both of R⁴ and R⁵ is independently selected from H, D, F, Cl, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CF₃, CF₂H, CH₂CF₂H, CH₂CF₃, CH₂CFH₂, CH(CF₃)₂, CD₃, CH(CH₃)₂O, CH₃CH₂CH₂O, CH₃CH₂O, CH₃O, CF₃O, CHF₂O, CF₂HCH₂O, CF₃CH₂O, (CF₃)₂CHO, and CD₃O. In some embodiments, one or both of R⁴ and R⁵ is independently selected from H, D, F, Cl, CH₃, CH(CH₃)₂, CF₃, CF₂H, CD₃, CH₃O, CH(CH₃)₂O, CF₃O, CHF₂O, and CD₃O.

[00161] In some embodiments both of R⁴ and R⁵ are independently selected from H, D, F, Cl, C₁₋₆alkyl, C₁₋₆fluoroalkyl, C₁₋₆deuteroalkyl, C₁₋₆alkoxy, C₁₋₆fluoroalkoxy and C₁₋₆deuteroalkoxy. In some embodiments both of R⁴ and R⁵ are independently selected from D, F, Cl, C₁₋₆alkyl, C₁₋₆fluoroalkyl, C₁₋₆deuteroalkyl, C₁₋₆alkoxy, C₁₋₆fluoroalkoxy and C₁₋₆deuteroalkoxy. In some embodiments both of R⁴ and R⁵ are independently selected from H, D, F, Cl, C₁₋₄alkyl, C₁₋₄fluoroalkyl, C₁₋₄deuteroalkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkoxy and C₁₋₄deuteroalkoxy. In some embodiments both of R⁴ and R⁵ are independently selected from H, D, F, Cl, CH₃, CH(CH₃)₂, CF₃, CF₂H, CD₃, CH(CH₃)₂O, CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments both of R⁴ and R⁵ are independently selected from D, F, Cl, CH₃, CH(CH₃)₂, CF₃, CF₂H, CD₃, CH(CH₃)₂O, CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments both of R⁴ and R⁵ are independently selected from CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments both of R⁴ and R⁵ are CD₃O or both of R⁴ and R⁵ are CH₃O.

[00162] In some embodiments, R⁴ is H or D and R⁵ is selected from H, D, F, Cl, C₁₋₆alkyl, C₁₋₆fluoroalkyl, C₁₋₆deuteroalkyl, C₁₋₆alkoxy, C₁₋₆fluoroalkoxy and C₁₋₆deuteroalkoxy. In some embodiments, R⁴ is H or D and R⁵ is selected from H, D, F, Cl, C₁₋₄alkyl, C₁₋₄fluoroalkyl, C₁₋₄deuteroalkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkoxy and C₁₋₄deuteroalkoxy. In some embodiments, R⁴ is H or D and R⁵ is selected from H, D, F, Cl, CH(CH₃)₂, CH₃, CF₃, CF₂H,

CD₃, CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, R⁴ is H or D and R⁵ is selected from D, F, Cl, CH(CH₃)₂, CH₃, CF₃, CF₂H, CD₃, CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, R⁴ is H or D and R⁵ is selected from CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, R⁴ is H and R⁵ is selected from CH₃O and CD₃O.

[00163] In some embodiments, R⁵ is H or D and R⁴ is selected from H, D, F, Cl, C₁₋₆alkyl, C₁₋₆fluoroalkyl, C₁₋₆deuteroalkyl, C₁₋₆alkoxy, C₁₋₆fluoroalkoxy and C₁₋₆deuteroalkoxy. In some embodiments, R⁵ is H or D and R⁴ is selected from H, D, F, Cl, C₁₋₄alkyl, C₁₋₄fluoroalkyl, C₁₋₄deuteroalkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkoxy and C₁₋₄deuteroalkoxy. In some embodiments, R⁵ is H or D and R⁴ is selected from D, F, Cl, CH₃, CH(CH₃)₂, CF₃, CF₂H, CD₃, CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, R⁵ is H or D and R⁴ is selected from CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, R⁵ is H and R⁴ is selected from CH₃O and CD₃O.

[00164] In some embodiments, R⁴ and R⁵ are linked together to form O-CH₂O.

[00165] In some embodiments, R³, R⁴, R⁵ and R⁶ are selected from D, F, Cl, CH₃, CH(CH₃)₂, CF₃, CF₂H, CD₃, CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, R³, R⁴, R⁵ and R⁶ are all H or in some embodiments, R³, R⁴, R⁵ and R⁶ are all D. In some embodiments, R³, R⁴, R⁵ and R⁶ are selected from CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, two of R³, R⁴, R⁵ and R⁶ are selected from H or D and the remaining of R³, R⁴, R⁵ and R⁶ are selected from CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, two of R³, R⁴, R⁵ and R⁶ are selected from H or D and the remaining of R³, R⁴, R⁵ and R⁶ are selected from CH₃O and CD₃O. In some embodiments, one of R³, R⁴, R⁵ and R⁶ is selected from H or D and the remaining of R³, R⁴, R⁵ and R⁶ are selected from CH(CH₃)₂O CH₃O, CF₃O, CHF₂O, and CD₃O. In some embodiments, one of R³, R⁴, R⁵ and R⁶ is selected from H or D and the remaining of R³, R⁴, R⁵ and R⁶ are selected from CH₃O and CD₃O.

[00166] In some embodiments, one of R⁴ and R⁵ is selected from X-L-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy.

[00167] In some embodiments, X is a direct bond and one of R⁴ and R⁵ is selected from L-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy. In some embodiments, X is selected from O, C(O), NR^a, NR^aC(O), C(O)NR^a, OC(O), C(O)O, OC(O)O, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, X is selected from O, C(O), OC(O), C(O)O and OC(O)O. In some embodiments, X is selected from O, OC(O) and C(O)O. In some embodiments, X is O. In some embodiments, X is selected

from OC(O) and C(O)O. In some embodiments, X is selected from O, NR^a, NR^aC(O), C(O)NR^a, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, X is selected from NR^aC(O), C(O)NR^a, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, X is selected from NR^aC(O), and C(O)NR^a. In some embodiments, X is selected from NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, X is selected from O, OC(O), C(O)O, NR^aC(O), and C(O)NR^a.

[00168] In some embodiments, L is selected from a direct bond, C₁₋₄alkylene, C₂₋₄alkenylene, C₁₋₄alkyleneO, C₂₋₄alkenyleneO, C₁₋₄alkyleneC(O), C₂₋₄alkenyleneC(O), C₁₋₄alkyleneNR^bC(O), C₂₋₄alkenyleneNR^bC(O), C₁₋₄alkyleneC(O)NR^b, C₂₋₄alkenyleneC(O)NR^b, C₁₋₄alkyleneOC(O), C₂₋₄alkenyleneOC(O), C₁₋₄alkyleneC(O)O, C₂₋₄alkenyleneC(O)O, C₁₋₄alkyleneOC(O)NR^b, C₂₋₄alkenyleneOC(O)NR^b, C₁₋₄alkyleneNR^bC(O)O, C₂₋₄alkenyleneNR^bC(O)O, C₁₋₄alkyleneOC(O)O, C₂₋₄alkenyleneOC(O)O, C₁₋₄alkyleneNR^bC(O)NR^b and C₂₋₄alkenyleneNR^bC(O)NR^b. In some embodiments, L is selected from a direct bond, C₁₋₂alkylene, C₂₋₄alkenylene, C₁₋₂alkyleneO, C₂₋₄alkenyleneO, C₁₋₂alkyleneC(O), C₂₋₄alkenyleneC(O), C₁₋₂alkyleneNR^bC(O), C₂₋₄alkenyleneNR^bC(O), C₁₋₂alkyleneC(O)NR^b, C₂₋₄alkenyleneC(O)NR^b, C₁₋₂alkyleneOC(O), C₂₋₄alkenyleneOC(O), C₁₋₂alkyleneC(O)O, C₂₋₄alkenyleneC(O)O, C₁₋₂alkyleneOC(O)NR^b, C₂₋₄alkenyleneOC(O)NR^b, C₁₋₂alkyleneNR^bC(O)O, C₂₋₄alkenyleneNR^bC(O)O, C₁₋₂alkyleneOC(O)O, C₂₋₄alkenyleneOC(O)O, C₁₋₂alkyleneNR^bC(O)NR^b and C₂₋₄alkenyleneNR^bC(O)NR^b. In some embodiments, L is selected from a direct bond, C₁₋₂alkylene, C₁₋₂alkyleneO, C₁₋₂alkyleneC(O), C₁₋₂alkyleneNR^bC(O), C₁₋₂alkyleneC(O)NR^b, C₁₋₂alkyleneOC(O), C₁₋₂alkyleneC(O)O, C₁₋₂alkyleneOC(O)NR^b, C₁₋₂alkyleneNR^bC(O)O, C₁₋₂alkyleneOC(O)O, and C₁₋₂alkyleneNR^bC(O)NR^b. In some embodiments, L is selected from a direct bond, CH₂, CF₂, CD₂, CH₂-O, CF₂-O, CD₂-O, CH₂-C(O), CF₂-C(O), CD₂-C(O), CH₂-NR^bC(O), CD₂-NR^bC(O), CF₂-NR^bC(O), CH₂-C(O)NR^b, CF₂-C(O)NR^b, CD₂-C(O)NR^b, CH₂-OC(O), CD₂-OC(O), CF₂-OC(O), CH₂-C(O)O, CF₂-C(O)O, CD₂-C(O)O, CH₂-OC(O)NR^b, CD₂-OC(O)NR^b, CF₂-OC(O)NR^b, CH₂-NR^bC(O)O, CF₂-NR^bC(O)O, CD₂-NR^bC(O)O, CH₂-OC(O)O, CF₂-OC(O)O, CD₂-OC(O)O, CH₂-NR^bC(O)NR^b, CF₂-NR^bC(O)NR^b and CD₂-NR^bC(O)NR^b.

[00169] In some embodiments, X is a direct bond and L is a direct bond and one of R⁴ and R⁵ is selected from A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₄alkyl and C₁₋₄alkoxy.

[00170] In some embodiments, X is selected from O, OC(O), C(O)O, NR^aC(O), and C(O)NR^a and one of R⁴ and R⁵ is selected from O-C₁₋₂alkylene-A, O-C₁₋₂alkyleneO-A, O-

$C_{1-2}alkyleneC(O)-A$, $O-C_{1-2}alkyleneNR^bC(O)-A$, $O-C_{1-2}alkyleneC(O)NR^b-A$, $O-C_{1-2}alkyleneOC(O)-A$, $O-C_{1-2}alkyleneC(O)O-A$, $O-C_{1-2}alkyleneOC(O)NR^b-A$, $O-C_{1-2}alkyleneNR^bC(O)O-A$, $O-C_{1-2}alkyleneOC(O)O-A$, $O-C_{1-2}alkyleneNR^bC(O)NR^b-A$, $OC(O)-C_{1-2}alkylene-A$, $OC(O)-C_{1-2}alkyleneO-A$, $OC(O)-C_{1-2}alkyleneC(O)-A$, $OC(O)-C_{1-2}alkyleneNR^bC(O)-A$, $OC(O)-C_{1-2}alkyleneC(O)NR^b-A$, $OC(O)-C_{1-2}alkyleneOC(O)-A$, $OC(O)-C_{1-2}alkyleneC(O)O-A$, $OC(O)-C_{1-2}alkyleneOC(O)NR^b-A$, $OC(O)-C_{1-2}alkyleneNR^bC(O)O-A$, $OC(O)-C_{1-2}alkyleneOC(O)O-A$, $OC(O)-C_{1-2}alkyleneNR^bC(O)NR^b-A$, $C(O)O-C_{1-2}alkylene-A$, $C(O)O-C_{1-2}alkyleneO-A$, $C(O)O-C_{1-2}alkyleneC(O)-A$, $C(O)O-C_{1-2}alkyleneNR^bC(O)-A$, $C(O)O-C_{1-2}alkyleneC(O)NR^b-A$, $C(O)O-C_{1-2}alkyleneOC(O)-A$, $C(O)O-C_{1-2}alkyleneC(O)O-A$, $C(O)O-C_{1-2}alkyleneOC(O)NR^b-A$, $C(O)O-C_{1-2}alkyleneNR^bC(O)O-A$, $C(O)O-C_{1-2}alkyleneOC(O)O-A$, $C(O)O-C_{1-2}alkyleneNR^bC(O)NR^b-A$, $NR^aC(O)-C_{1-2}alkylene-A$, $NR^aC(O)-C_{1-2}alkyleneO-A$, $NR^aC(O)-C_{1-2}alkyleneC(O)-A$, $NR^aC(O)-C_{1-2}alkyleneNR^bC(O)-A$, $NR^aC(O)-C_{1-2}alkyleneC(O)NR^b-A$, $NR^aC(O)-C_{1-2}alkyleneOC(O)-A$, $NR^aC(O)-C_{1-2}alkyleneC(O)O-A$, $NR^aC(O)-C_{1-2}alkyleneOC(O)NR^b-A$, $NR^aC(O)-C_{1-2}alkyleneNR^bC(O)O-A$, $NR^aC(O)-C_{1-2}alkyleneOC(O)O-A$, $NR^aC(O)-C_{1-2}alkyleneNR^bC(O)NR^b-A$, $C(O)NR^a-C_{1-2}alkylene-A$, $C(O)NR^a-C_{1-2}alkyleneO-A$, $C(O)NR^a-C_{1-2}alkyleneC(O)-A$, $C(O)NR^a-C_{1-2}alkyleneNR^bC(O)-A$, $C(O)NR^a-C_{1-2}alkyleneC(O)NR^b-A$, $C(O)NR^a-C_{1-2}alkyleneOC(O)-A$, $C(O)NR^a-C_{1-2}alkyleneC(O)O-A$, $C(O)NR^a-C_{1-2}alkyleneOC(O)NR^b-A$, $C(O)NR^a-C_{1-2}alkyleneNR^bC(O)O-A$, $C(O)NR^a-C_{1-2}alkyleneOC(O)O-A$, and $C(O)NR^a-C_{1-2}alkyleneNR^bC(O)NR^b-A$ and the other of R^4 and R^5 is selected from H, halo, $C_{1-4}alkyl$ and $C_{1-4}alkoxy$ wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, X is selected from O, $OC(O)$, $C(O)O$, $NR^aC(O)$, and $C(O)NR^a$ and one of R^4 and R^5 is selected from $O-C_{1-2}alkylene-A$, $O-C_{1-2}alkyleneO-A$, $O-C_{1-2}alkyleneC(O)-A$, $O-C_{1-2}alkyleneNR^bC(O)-A$, $O-C_{1-2}alkyleneC(O)NR^b-A$, $O-C_{1-2}alkyleneOC(O)-A$, $O-C_{1-2}alkyleneC(O)O-A$, $O-C_{1-2}alkyleneOC(O)NR^b-A$, $O-C_{1-2}alkyleneNR^bC(O)O-A$, $O-C_{1-2}alkyleneOC(O)O-A$, $O-C_{1-2}alkyleneNR^bC(O)NR^b-A$, $OC(O)-C_{1-2}alkylene-A$, $OC(O)-C_{1-2}alkyleneO-A$, $OC(O)-C_{1-2}alkyleneC(O)-A$, $OC(O)-C_{1-2}alkyleneNR^bC(O)-A$, $OC(O)-C_{1-2}alkyleneC(O)NR^b-A$, $OC(O)-C_{1-2}alkyleneOC(O)-A$, $OC(O)-C_{1-2}alkyleneC(O)O-A$, $OC(O)-C_{1-2}alkyleneOC(O)NR^b-A$, $OC(O)-C_{1-2}alkyleneNR^bC(O)O-A$, $OC(O)-C_{1-2}alkyleneOC(O)O-A$, $OC(O)-C_{1-2}alkyleneNR^bC(O)NR^b-A$, $C(O)O-C_{1-2}alkylene$, $C(O)O-C_{1-2}alkyleneO-A$, $C(O)O-C_{1-2}alkyleneC(O)-A$, $C(O)O-C_{1-2}alkyleneNR^bC(O)-A$, $C(O)O-C_{1-2}alkyleneC(O)NR^b-A$, $C(O)O-C_{1-2}alkyleneOC(O)-A$, $C(O)O-C_{1-2}alkyleneC(O)O-A$, $C(O)O-C_{1-2}alkyleneOC(O)NR^b-A$, $C(O)O-C_{1-2}alkyleneNR^bC(O)O-A$, $C(O)O-C_{1-2}alkyleneOC(O)O-A$, $C(O)O-C_{1-2}alkyleneNR^bC(O)NR^b-A$, $NR^aC(O)-C_{1-2}alkylene-A$, $NR^aC(O)-C_{1-2}alkyleneO-A$,

NR^aC(O)-C₁₋₂alkyleneC(O)-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)-A, NR^aC(O)-C₁₋₂alkyleneC(O)NR^b-A, NR^aC(O)-C₁₋₂alkyleneOC(O)-A, NR^aC(O)-C₁₋₂alkyleneC(O)O-A, NR^aC(O)-C₁₋₂alkyleneOC(O)NR^b-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)O-A, NR^aC(O)-C₁₋₂alkyleneOC(O)O-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)NR^b-A, C(O)NR^a-C₁₋₂alkylene-A, C(O)NR^a-C₁₋₂alkyleneO-A, C(O)NR^a-C₁₋₂alkyleneC(O)-A, C(O)NR^a-C₁₋₂alkyleneNR^bC(O)-A, C(O)NR^a-C₁₋₂alkyleneC(O)NR^b-A, C(O)NR^a-C₁₋₂alkyleneOC(O)-A, C(O)NR^a-C₁₋₂alkyleneC(O)O-A, C(O)NR^a-C₁₋₂alkyleneOC(O)NR^b-A, C(O)NR^a-C₁₋₂alkyleneNR^bC(O)O-A, C(O)NR^a-C₁₋₂alkyleneOC(O)O-A, and C(O)NR^a-C₁₋₂alkyleneNR^bC(O)NR^b-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₄alkyl and C₁₋₄alkoxy wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00171] In some embodiments, the other of R⁴ and R⁵ is selected from H, F, Cl, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄deuteroalkyl and C₁₋₄alkoxy wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, the other of R⁴ and R⁵ is selected from D, F, Cl, CH₃, CH(CH₃)₂, CF₃, CF₂H, CD₃, CH(CH₃)₂O, CH₃O, CF₃O, CHF₂O, and CD₃O wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom, and the other of R⁴ and R⁵ is H or D.

[00172] In some embodiments, R⁴ is X-L-A and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy. In some embodiments, of R⁵ is X-L-A and R⁴ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy.

[00173] In some embodiments, R^a is selected from H and C₁₋₄alkyl.

[00174] In some embodiments, R^b is selected from H, C₁₋₄alkyl and A.

[00175] In some embodiments, A is H, and one of R⁴ and R⁵ is selected OH, C(O)H, NHR^a, NHR^aC(O), C(O)NHR^a, OC(O)H, C(O)OH, OC(O)OH, NR^aC(O)OH, OC(O)NHR^a, NHR^aC(O)NR^a, X-C₁₋₄alkylene, X-C₂₋₄alkenylene, X-C₁₋₄alkyleneOH, X-C₂₋₄alkenyleneOH, X-C₁₋₄alkyleneC(O)H, X-C₂₋₄alkenyleneC(O)H, X-C₁₋₄alkyleneNR^bC(O)H, X-C₂₋₄alkenyleneNR^bC(O)H, X-C₁₋₄alkyleneC(O)NHR^b, X-C₂₋₄alkenyleneC(O)NHR^b, X-C₁₋₄alkyleneOC(O)H, X-C₂₋₄alkenyleneOC(O)H, X-C₁₋₄alkyleneC(O)OH, C₂₋₄alkenyleneC(O)H, X-C₁₋₄alkyleneOC(O)NHR^b, X-C₂₋₄alkenyleneOC(O)NHR^b, X-C₁₋₄alkyleneNR^bC(O)OH, X-C₂₋₄alkenyleneNR^bC(O)OH, X-C₁₋₄alkyleneOC(O)OH, X-C₂₋₄alkenyleneOC(O)OH, X-C₁₋₄alkyleneNR^bC(O)NHR^b and X-C₂₋₄alkenyleneNR^bC(O)NHR^b and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₄alkyl and C₁₋₄alkoxy, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom

or deuterium atom. In some embodiments, A is H, and one of R⁴ and R⁵ is selected OH, C(O)H, NHR^a, NHR^aC(O), C(O)NHR^a, OC(O)H, C(O)OH, OC(O)OH, NR^aC(O)OH, OC(O)NHR^a, NHR^aC(O)NR^a, X-C₁₋₂alkylene, X-C₂₋₄alkenylene, X-C₁₋₂alkyleneOH, X-C₂₋₄alkenyleneOH, X-C₁₋₂alkyleneC(O)H, X-C₂₋₄alkenyleneC(O)H, X-C₁₋₂alkyleneNR^bC(O)H, X-C₂₋₄alkenyleneNR^bC(O)H, X-C₁₋₂alkyleneC(O)NHR^b, X-C₂₋₄alkenyleneC(O)NHR^b, X-C₁₋₂alkyleneOC(O)H, X-C₂₋₄alkenyleneOC(O)H, X-C₁₋₂alkyleneC(O)OH, C₂₋₄alkenyleneC(O)H, X-C₁₋₂alkyleneOC(O)NHR^b, X-C₂₋₄alkenyleneOC(O)NHR^b, X-C₁₋₂alkyleneNR^bC(O)OH, X-C₂₋₄alkenyleneNR^bC(O)OH, X-C₁₋₂alkyleneOC(O)OH, X-C₂₋₄alkenyleneOC(O)OH, X-C₁₋₂alkyleneNR^bC(O)NHR^b and X-C₂₋₄alkenyleneNR^bC(O)NHR^b and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₄alkyl and C₁₋₄alkoxy, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00176] In some embodiments, A is H and X is a direct bond. Therefore, in some embodiments, and one of R⁴ and R⁵ is selected from C₁₋₄alkyl, C₂₋₄alkenyl, C₁₋₄alkyleneOH, C₂₋₆alkenyleneOH, C₁₋₄alkyleneC(O)H, C₂₋₄alkenyleneC(O)H, C₁₋₄alkyleneNR^bC(O)H, C₂₋₄alkenyleneNR^bC(O)H, C₁₋₄alkyleneC(O)NHR^b, C₂₋₄alkenyleneC(O)NHR^b, C₁₋₄alkyleneOC(O)H, C₂₋₄alkenyleneOC(O)H, C₁₋₄alkyleneC(O)OH, C₂₋₄alkenyleneC(O)H, C₁₋₄alkyleneOC(O)NHR^b, C₂₋₆alkenyleneOC(O)NHR^b, C₁₋₄alkyleneNR^bC(O)OH, C₂₋₄alkenyleneNR^bC(O)OH, C₁₋₄alkyleneOC(O)OH, C₂₋₄alkenyleneOC(O)OH, C₁₋₄alkyleneNR^bC(O)NHR^b and C₂₋₄alkenyleneNR^bC(O)NHR^b and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy.

[00177] In some embodiments, A is H and X is selected from O, C(O), NR^a, NR^aC(O), C(O)NR^a, OC(O), C(O)O, OC(O)O, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, A is H and X is selected from O, C(O), OC(O), C(O)O and OC(O)O. In some embodiments, A is H and X is selected from O, OC(O) and C(O)O. In some embodiments, A is H and X is O. In some embodiments, A is H and X is selected from OC(O) and C(O)O. In some embodiments, A is H and X is selected from NR^a, NR^aC(O), C(O)NR^a, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, A is H and X is selected from NR^aC(O), C(O)NR^a, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, A is H and X is selected from NR^aC(O), and C(O)NR^a. In some embodiments, A is H and X is selected from NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a.

[00178] In some embodiments, A is H, and L is a direct bond, and one of R³ and R⁴ is selected from X-H. Therefore, in some embodiments, and one of R³ and R⁴ is selected from OH, C(O)H, NHR^a, NHR^aC(O), C(O)NHR^a, OC(O)H, C(O)OH, OC(O)OH,

$\text{NR}^a\text{C}(\text{O})\text{OH}$, $\text{OC}(\text{O})\text{NHR}^a$ and $\text{NHR}^a\text{C}(\text{O})\text{NR}^a$, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00179] In some embodiments, when A is H, R^b is selected from H and $\text{C}_{1-4}\text{alkyl}$, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00180] In some embodiments, one of R^4 and R^5 is selected from A, O-A, $\text{C}(\text{O})\text{-A}$, $\text{C}(\text{O})\text{-O-A}$, $\text{C}_{1-4}\text{alkylene-A}$, $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$, $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$, $\text{O-C}_{1-4}\text{alkylene-A}$, $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$, and $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$ and the other of R^4 and R^5 is selected from H, halo, $\text{C}_{1-6}\text{alkyl}$ and $\text{C}_{1-6}\text{alkoxy}$, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00181] In some embodiments, one of R^4 and R^5 is selected from A, O-A, $\text{C}(\text{O})\text{-A}$, $\text{C}(\text{O})\text{-O-A}$, and $\text{C}(\text{O})\text{O-A}$ and the other of R^4 and R^5 is selected from H, halo, $\text{C}_{1-6}\text{alkyl}$ and $\text{C}_{1-6}\text{alkoxy}$, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R^4 and R^5 is A. In some embodiments, one of R^4 and R^5 is O-A. In some embodiments, one of R^4 and R^5 is $\text{C}(\text{O})\text{-A}$. In some embodiments, one of R^4 and R^5 is $\text{C}(\text{O})\text{O-A}$.

[00182] In some embodiments, one of R^4 and R^5 is selected from $\text{C}_{1-4}\text{alkylene-A}$, $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$, $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$, $\text{O-C}_{1-4}\text{alkylene-A}$, $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$, and $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$ and the other of R^4 and R^5 is selected from H, halo, $\text{C}_{1-6}\text{alkyl}$ and $\text{C}_{1-6}\text{alkoxy}$, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R^4 and R^5 is $\text{C}_{1-4}\text{alkylene-A}$. In some embodiments, one of R^4 and R^5 is $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$. In some embodiments, one of R^4 and R^5 is $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$. In some embodiments, one of R^4 and R^5 is $\text{O-C}_{1-4}\text{alkylene-A}$. In some embodiments, one of R^4 and R^5 is $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$. In some embodiments, one of R^4 and R^5 is $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$.

[00183] In some embodiments, one of R^4 and R^5 is selected from A, O-A, $\text{C}(\text{O})\text{-A}$, $\text{C}(\text{O})\text{O-A}$, $\text{C}_{1-4}\text{alkylene-A}$, $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$, $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$, $\text{O-C}_{1-4}\text{alkylene-A}$, $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$, and $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$ and the other of R^4 and R^5 is selected from H, F, Cl, $\text{C}_{1-4}\text{alkyl}$ and $\text{C}_{1-4}\text{alkoxy}$, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R^4 and R^5 is selected from A, O-A, $\text{C}(\text{O})\text{-A}$, $\text{C}(\text{O})\text{O-A}$, $\text{C}_{1-4}\text{alkylene-A}$, $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$, $\text{C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$, $\text{O-C}_{1-4}\text{alkylene-A}$, $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{-A}$, and $\text{O-C}_{1-4}\text{alkylene-C}(\text{O})\text{O-A}$ and the other of R^4 and R^5 is selected from H, F, Cl, $\text{C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{haloalkyl}$, $\text{C}_{1-4}\text{deuteroalkyl}$ and $\text{C}_{1-4}\text{alkoxy}$ wherein all available hydrogen atoms are

optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R^4 and R^5 is selected from A, O-A, C(O)-A, C(O)O-A, C_{1-2} alkylene-A, C_{1-2} alkylene-C(O)-A, C_{1-2} alkylene-C(O)O-A, O- C_{1-2} alkylene-A, O- C_{1-2} alkylene-C(O)-A, and O- C_{1-2} alkylene-C(O)O-A and the other of R^4 and R^5 is selected from D, F, Cl, CH_3 , $CH(CH_3)_2$, CF_3 , CF_2H , CD_3 , $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R^4 and R^5 is selected from A, O-A, C(O)-A, C(O)O-A, C_{1-2} alkylene-A, C_{1-2} alkylene-C(O)-A, C_{1-2} alkylene-C(O)O-A, O- C_{1-2} alkylene-A, O- C_{1-2} alkylene-C(O)-A, and O- C_{1-2} alkylene-C(O)O-A and the other of R^4 and R^5 is H or D, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R^4 and R^5 is selected from A, O-A, C(O)-A, C(O)O-A, CH_2 -A, CD_2 -A, CF_2 -A, CH_2 -C(O)-A, CF_2 -C(O)-A, CD_2 -C(O)-A, CH_2 -C(O)O-A, CD_2 -C(O)O-A, CF_2 -C(O)O-A, O- CH_2 A, O- CF_2 A, O- CD_2 A, - CH_2 -C(O)-A, O- CD_2 -C(O)-A, O- CF_2 -C(O)-A, O- CH_2 -C(O)O-A, O- CF_2 -C(O)O-A, O- CD_2 -C(O)O-A, and the other of R^4 and R^5 is H or D.

[00184] In some embodiments, R^4 is selected from A, O-A, C(O)-A, C(O)O-A, C_{1-2} alkylene-A, C_{1-2} alkylene-C(O)-A, C_{1-2} alkylene-C(O)O-A, O- C_{1-2} alkylene-A, O- C_{1-2} alkylene-C(O)-A, and O- C_{1-2} alkylene-C(O)O-A and R^5 is H or D, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, R^4 is selected from A, O-A, C(O)-A, C(O)O-A, CH_2 -A, CD_2 -A, CF_2 -A, CH_2 -C(O)-A, CF_2 -C(O)-A, CD_2 -C(O)-A, CH_2 -C(O)O-A, CD_2 -C(O)O-A, CF_2 -C(O)O-A, O- CH_2 A, O- CF_2 A, O- CD_2 A, O- CH_2 -C(O)-A, O- CD_2 -C(O)-A, O- CF_2 -C(O)-A, O- CH_2 -C(O)O-A, O- CF_2 -C(O)O-A, and O- CD_2 -C(O)O-A and R^5 is H or D. In some embodiments, R^5 is selected from A, O-A, C(O)-A, C(O)O-A, C_{1-2} alkylene-A, C_{1-2} alkylene-C(O)-A, C_{1-2} alkylene-C(O)O-A, O- C_{1-2} alkylene-A, O- C_{1-2} alkylene-C(O)-A, and O- C_{1-2} alkylene-C(O)O-A and R^4 is H or D, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, R^5 is selected from A, O-A, C(O)-A, C(O)O-A, CH_2 -A, CD_2 -A, CF_2 -A, CH_2 -C(O)-A, CF_2 -C(O)-A, CD_2 -C(O)-A, CH_2 -C(O)O-A, CD_2 -C(O)O-A, CF_2 -C(O)O-A, O- CH_2 A, O- CF_2 A, O- CD_2 A, O- CH_2 -C(O)-A, O- CD_2 -C(O)-A, O- CF_2 -C(O)-A, O- CH_2 -C(O)O-A, O- CF_2 -C(O)O-A, and O- CD_2 -C(O)O-A and R^4 is H or D.

[00185] In some embodiments, A is selected from C_{1-30} alkyl, C_{2-30} alkenyl, phenyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO_2 , N and NR^{64} and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO_2 , N and NR^{64} ,

wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, Cl, OH, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is selected from C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, Cl, OH, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00186] In some embodiments, A is selected from phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally replaced with one or two substituents independently selected from F, Cl, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl. In some embodiments, A is selected from phenyl, C₃₋₆cycloalkyl, 5- to 6-membered heterocycloalkyl comprising 1 to 2 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁴⁸ and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, Cl, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00187] In some embodiments, the C₃₋₆cycloalkyl in A is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. In some embodiments, the C₃₋₆cycloalkyl in A is cyclopropyl which is optionally substituted with one or two substituents independently selected from F, Cl, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00188] In some embodiments, the 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ in A is selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, azetidiny, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxthiolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, piperidinyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl oxide, tetrahydrothiopyranyl dioxide, dihydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl and dithianyl, each of which is optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl. In some embodiments, the 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ in A is selected from tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, dioxolanyl, , piperidinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl oxide, tetrahydrothiopyranyl dioxide, dihydropyranyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl, each of which is optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00189] In some embodiments, the 5- to 6-membered heteroaryl in A is selected from furyl, imidazolyl, isothiazolyl, thiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyrrolyl, thienofuryl, triazolyl and thienyl, each of which is optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl. In some embodiments, the 5- to 6-membered heteroaryl in A is selected from furyl, isothiazolyl, thiazolyl, pyridyl and pyrrolyl, each of which is optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00190] In some embodiments, the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl in A is optionally substituted with one or two substituents independently selected from F, Cl, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂, CF₃, CF₂H, CH₂CF₂H, CH₂CF₃, CH₂CFH₂, CH(CF₃)₂, CD₃, CH(CH₃)₂O, CH₃CH₂CH₂O, CH₃CH₂O, CH₃O, CF₃O, CHF₂O, CF₂HCH₂O, CF₃CH₂O, (CF₃)₂CHO, and CD₃O.

[00191] In some embodiments, A is selected from C₁₋₃₀alkyl and C₂₋₃₀alkenyl wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00192] In some embodiments, A is C₁₀₋₂₅alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is C₁₃₋₂₁alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00193] In some embodiments, A is C₁₀₋₂₅alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is C₁₃₋₂₁alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is C₁₀₋₂₅alkenyl and comprises 1, 2, 3, 4, 5 or 6 double bonds.

[00194] In some embodiments, the alkyl or alkene group of A is an alkyl or alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium. In some embodiments, A is an alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium. In some embodiments, the fatty acid is an omega-6 fatty acid (i.e. an unsaturated or polyunsaturated fatty acid wherein the double bond that is closest to the methyl end of the molecule is located at carbon numbered 6 starting from the end methyl group) or an omega-3 fatty acid (i.e. an unsaturated or polyunsaturated fatty acid wherein the double bond that is closest to the methyl end of the molecule is located at carbon numbered 3 starting from the end methyl group), wherein all available H atoms are optionally replaced with deuterium. In some embodiments, A is an alkyl group present in a fatty acid wherein all available H atoms are optionally replaced with deuterium. In some embodiments, the alkyl or alkene group of A is an alkyl or alkene group present in a fatty acid selected from the list of fatty acids in Table 1 wherein all available H atoms are optionally replaced with deuterium.

[00195] In some embodiments, the alkene group of A is an alkyl or alkenyl group present in linoleic acid, eicosadienoic acid or decosahexanoic acid.

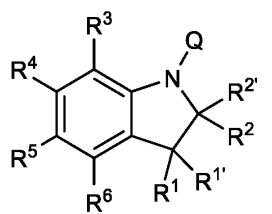
[00196] In some embodiments, when A is the alkyl or alkenyl group of a fatty acid wherein 1-10, 2-8, 2-6 or 2-4 H atoms are replaced with deuterium.

[00197] In some embodiments, A is (CH₂)₇CH=CH(CH₂)₇CH₃. In some embodiments, A is (CH₂)₇CH=CHCH₂CH=CH(CH₂)₄CH₃. In some embodiments, A is (CH₂)₈CH=CHCH₂CH=CH(CH₂)₄CH₃. In some embodiments, A is (CH₂)₇CH=CHCH₂CH=CHCH₂CH=CH(CH₂)₁CH₃. In some embodiments, A is

$(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$. In some embodiments, A is $(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$.

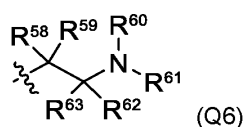
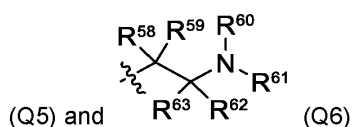
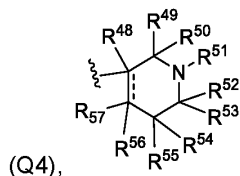
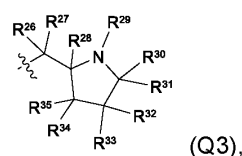
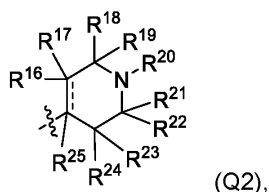
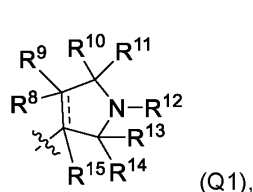
[00198] In some embodiments, R^{64} and R^{65} are independently selected from H, D, C_{1-4} alkyl, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl. In some embodiments, R^{64} and R^{65} are independently selected from H, D, CH_3 , CF_3 and CD_3 . In some embodiments, R^{64} and R^{65} are independently selected from CH_3 and CD_3 .

[00199] In some embodiments, the compound of Formula I is defined as follows:



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

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



--- is a single bond or a double bond provided that when --- in Q1 is a double bond then R^9 and R^{15} are not present, when --- in Q2 is a double bond then R^{17} and R^{25} are not present and when --- in Q5 is a double bond then R^{48} and R^{57} are not present;

R^1 , $\text{R}^{1'}$, R^2 , $\text{R}^{2'}$, R^3 and R^6 are independently selected from H, D and F;

one or both of R^4 and R^5 is selected from H, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy and C_{1-4} deuteroalkoxy, or

R^4 and R^5 are linked together to form $\text{O}-(\text{CH}_2)_{1-2}\text{O}$;

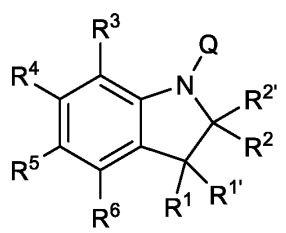
$R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{62}$ and R^{63} are independently selected from H and D;

$R^{12}, R^{20}, R^{29}, R^{39}$ and R^{51} are independently selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl, and

R^{60} and R^{61} are independently selected from H and C_{1-6} alkyl,

provided when Q is Q6 then the compound of Formula I comprises D.

[00200] In some embodiments, the compound of Formula I is defined as follows:



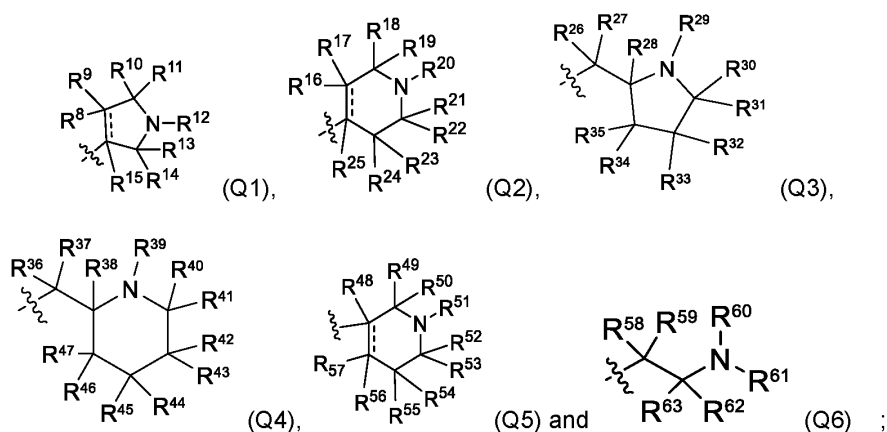
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

R^1 and $R^{1'}$ are independently selected from H, halo, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}alkyl)_2$;

R^2 and $R^{2'}$ are independently selected from H, halo, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}alkyl)_2$;

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



--- is a single bond or a double bond provided that when --- in Q1 is a double bond then R^9 and R^{15} are not present, when --- in Q2 is a double bond then R^{17} and R^{25} are not present, and when --- in Q5 is a double bond then R^{48} and R^{57} are not present;

one or both of R^4 and R^5 is independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy, or

R^4 and R^5 are linked together to form $O-(CH_2)_{1-2}O$, or

one of R^4 and R^5 is selected from X-L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy,

X is selected from a direct bond, O, $C(O)$, NR^a , $NR^aC(O)$, $C(O)NR^a$, $OC(O)$, $C(O)O$, $OC(O)O$, $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$;

L is selected from a direct bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{1-6} alkyleneO, C_{2-6} alkenyleneO, C_{1-6} alkyleneC(O), C_{2-6} alkenyleneC(O), C_{1-6} alkyleneNR^bC(O), C_{2-6} alkenyleneNR^bC(O), C_{1-6} alkyleneC(O)NR^b, C_{2-6} alkenyleneC(O)NR^b, C_{1-6} alkyleneOC(O), C_{2-6} alkenyleneOC(O), C_{1-6} alkyleneC(O)O, C_{2-6} alkenyleneC(O), C_{1-6} alkyleneOC(O)NR^b, C_{2-6} alkenyleneOC(O)NR^b, C_{1-6} alkyleneNR^bC(O)O, C_{2-6} alkenyleneNR^bC(O)O, C_{1-6} alkyleneOC(O)O, C_{2-6} alkenyleneOC(O)O, C_{1-6} alkyleneNR^bC(O)NR^b and C_{2-6} alkenyleneNR^bC(O)NR^b;

R^a is selected from H and C_{1-6} alkyl;

R^b is selected from H, C_{1-6} alkyl and A;

A is selected from H, C_{1-30} alkyl, C_{2-30} alkenyl, phenyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO_2 , N and NR^{64} and 5- to 6-membered heteroaryl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO_2 , N and NR^{64} , wherein the phenyl, C_{3-10} cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C_{1-4} alkyl and OC_{1-4} alkyl;

R^3 and R^6 are independently selected from H, halo, OH, C_{1-6} alkyl and C_{1-6} alkoxy;

$R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52},$

R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , R^{59} , R^{62} and R^{63} are independently selected from H, halo and C_{1-6} alkyl;

R^{12} , R^{20} , R^{29} , R^{39} and R^{51} are independently selected from H, C_{1-6} alkyl, $C(O)C_{1-6}$ alkyl and $C(O)-A'$;

R^{60} and R^{61} are independently selected from H and C_{1-6} alkyl; or

one of R^{60} and R^{61} is $C(O)-A'$ and the other is selected from H and C_{1-6} alkyl;

wherein A' is selected from Y, O-Y and O- C_{1-4} alkylene-O- $C(O)-Y$; and

Y is selected from C_{7-30} alkyl and C_{7-30} alkenyl; or

R^{60} and R^{61} , together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoieties independently selected from O, S, S(O), SO_2 , N, and NR^{65} and which is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-4} alkyl and OC_{1-4} alkyl;

R^{64} and R^{65} are independently selected from H and C_{1-6} alkyl; and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

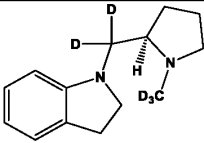
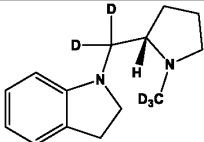
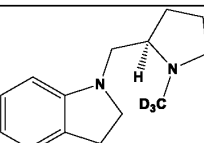
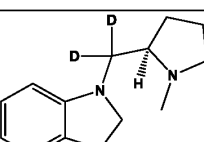
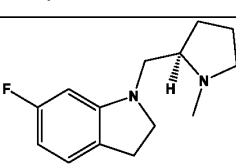
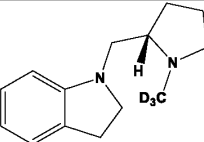
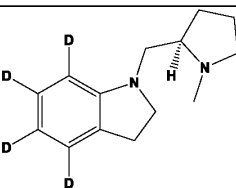
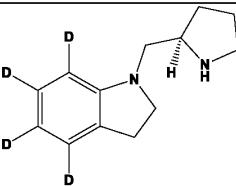
provided one of R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} is $C(O)-A'$; or

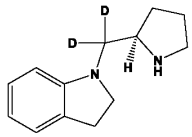
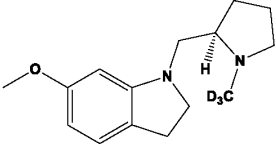
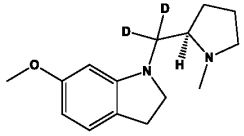
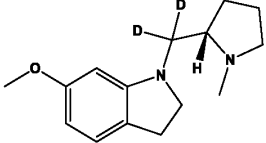
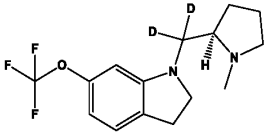
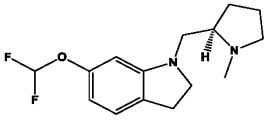
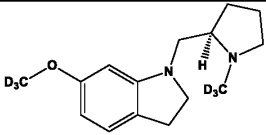
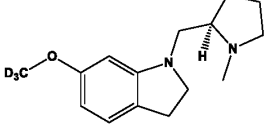
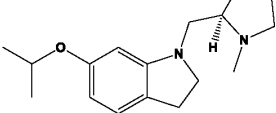
one of R^4 and R^5 is selected from X-L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy provided A is not H, C_{1-6} alkyl or C_{1-6} alkynyl when X and L are both direct bonds

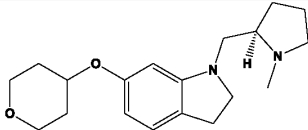
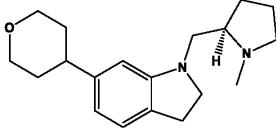
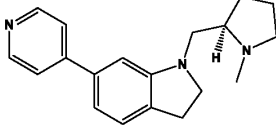
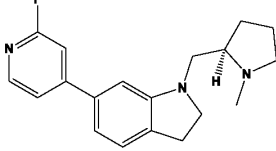
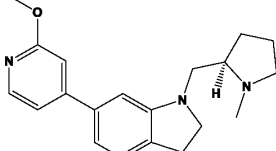
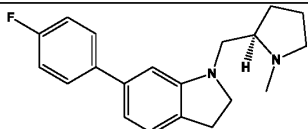
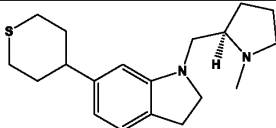
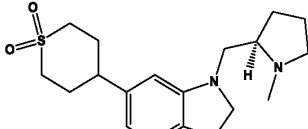
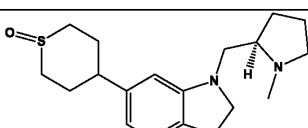
[00201] A person skilled in the art would appreciate that the carbon to which R^2 and $R^{2'}$ are bonded, when R^2 and $R^{2'}$ are different, is chiral. Therefore, the present application includes all stereoisomers at this carbon center and mixtures thereof.

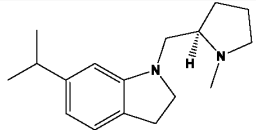
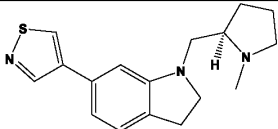
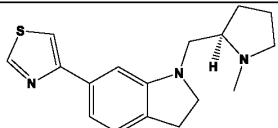
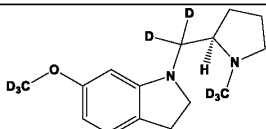
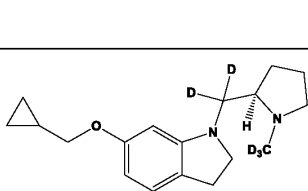
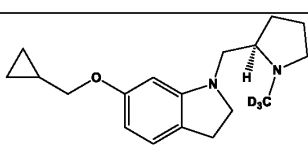
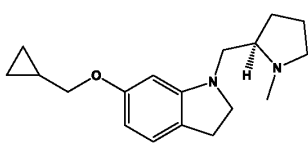
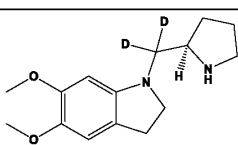
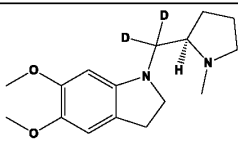
[00202] A person skilled in the art would appreciate that the carbon to which R^1 and $R^{1'}$ are bonded, when R^1 and $R^{1'}$ are different, is also chiral. Therefore, the present application includes all stereoisomers at this carbon center and mixtures thereof.

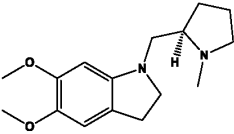
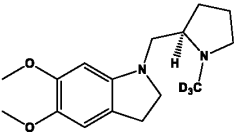
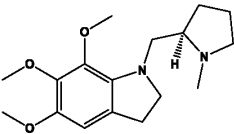
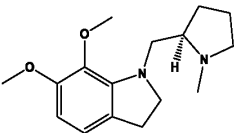
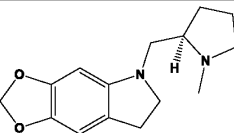
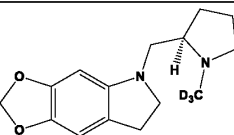
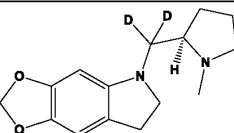
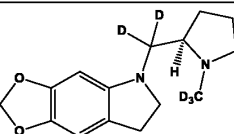
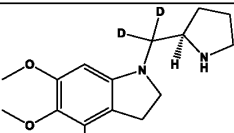
[00203] In some embodiments, the compounds of Formula I are selected from the compounds listed below, or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

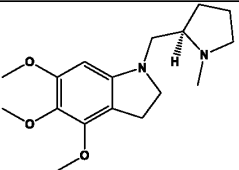
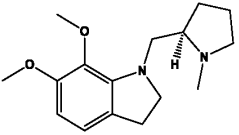
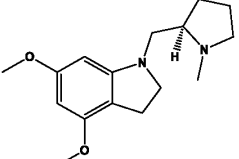
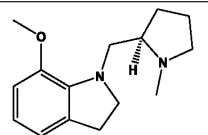
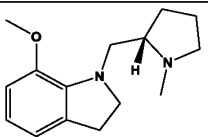
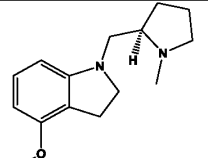
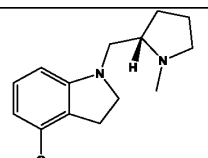
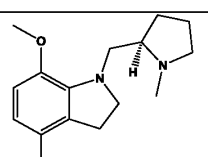
(R)-I-1	
(S)-I-1	
(R)-I-2	
(R)-I-3	
(R)-I-4	
(S)-I-5	
(R)-I-6	
(R)-I-7	

(R)-I-8	
(R)-I-9	
(R)-I-10	
(S)-I-10	
(R)-I-11	
(R)-I-12	
(R)-I-13	
(R)-I-14	
(R)-I-15	

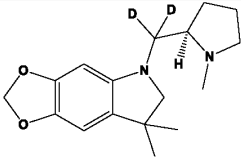
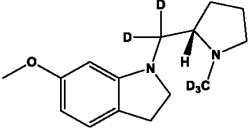
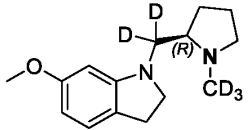
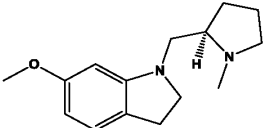
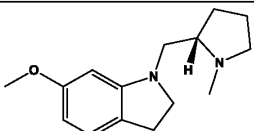
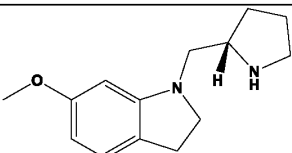
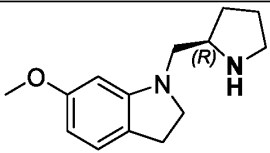
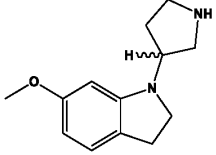
(R)-I-16	
(R)-I-17	
(R)-I-18	
(R)-I-19	
(R)-I-20	
(R)-I-21	
(R)-I-22	
(R)-I-23	
(R)-I-24	

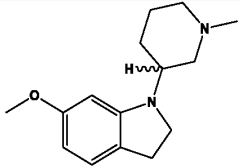
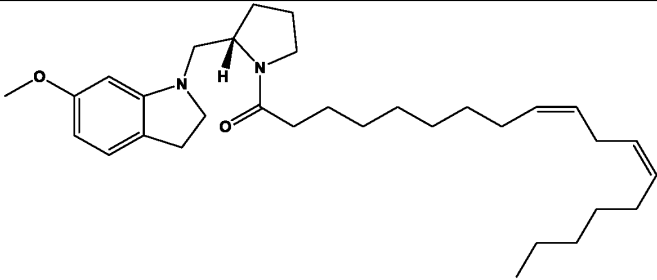
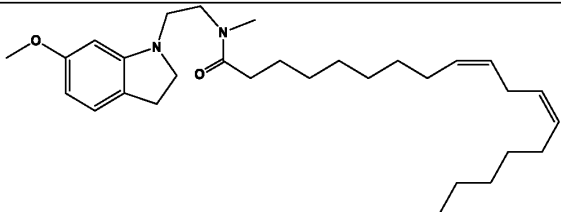
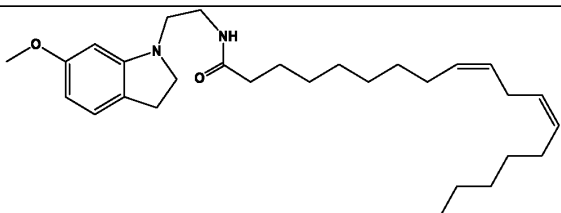
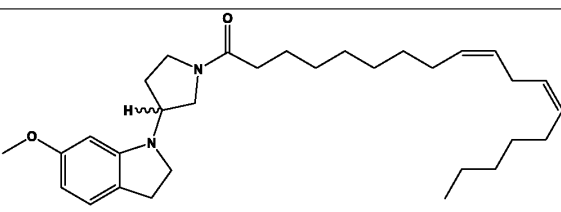
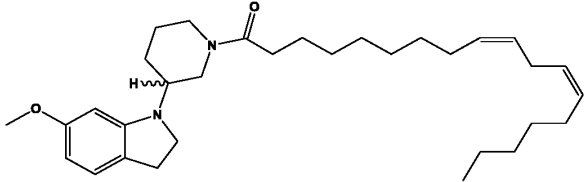
(R)-I-25	
(R)-I-26	
(R)-I-27	
(R)-I-28	
(R)-I-29	
(R)-I-30	
(R)-I-31	
(R)-I-32	
(R)-I-33	

(R)-I-34	
(R)-I-35	
(R)-I-36	
(R)-I-37	
(R)-I-38	
(R)-I-39	
(R)-I-40	
(R)-I-41	
(R)-I-42	

(R)-I-43	
(R)-I-44	
(R)-I-45	
(R)-I-46	
(S)-I-46	
(R)-I-47	
(S)-I-47	
(R)-I-48	

(R)-I-49	
(R)-I-50	
(R)-I-51	
(S)-I-51	
(R)-I-52	
(R)-I-53	
(R)-I-54	
(R)-I-55	

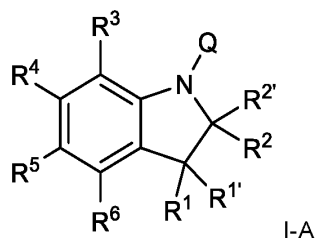
(R)-I-56	
(S)-I-57	
(R)-I-57	
(R)-I-58	
(S)-I-58	
(S)-I-59	
(R)-I-59	
I-60	

I-61	
(S)-I-62	
I-63	
I-64	
I-65	
I-66	

(S)-I-67	
(S)-I-68	
(S)-I-69	
I-70	
I-71	

III. Novel Compounds of the Application

[00204] Certain compound of Formula I are novel and therefore the present application includes these compounds and compositions comprising these compounds and uses thereof. Therefore, in some embodiments, the compounds of Formula I are compounds of Formula I-A. Accordingly, the present application includes compounds of Formula I-A:



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

wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 and Q are as defined above for Formula I, and

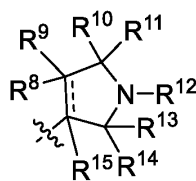
all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided when Q is Q_6 then the compound of Formula I-A comprises D,

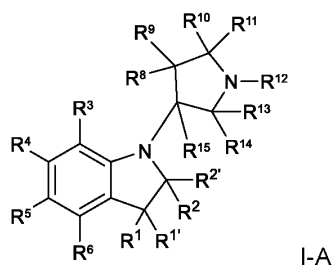
when Q is Q_3 or Q_4 , then R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^6 , R^{26} , R^{27} , R^{28} , R^{30} to R^{35} , R^{36} , R^{37} , R^{38} and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{29} or R^{39} is CH_3 ; and

when Q is Q_4 and R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^6 , R^{38} and R^{40} to R^{47} are all H, then R^{36} and R^{37} are not both D, when R^{39} is CD_3 .

[00205] In some embodiments, all available hydrogen atoms are optionally and independently replaced with a fluorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00206] In some embodiments, Q is Q_1 , R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^6 , R^{26} , R^{27} , R^{28} , R^{30} to R^{35} , R^{36} , R^{37} , R^{38} and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{29} or R^{39} is CH_3 ; and $==$ is a single bond and the compound of Formula I-A has the following structure:

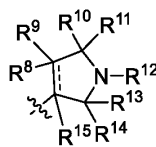


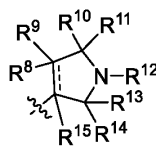
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

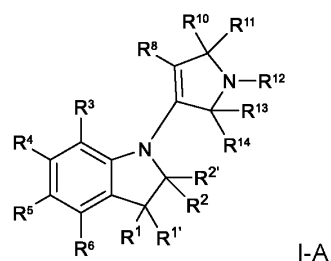
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} and R^{15} are as defined for Formula I-A, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00207] In some embodiments, Q is Q1, , and $\equiv$ is a double bond and the compound of Formula I-A has the following structure:



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

wherein:

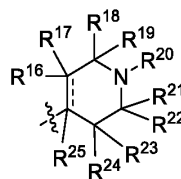
R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^8 , R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are as defined for Formula I-A, and

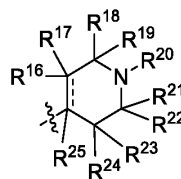
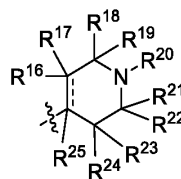
all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.

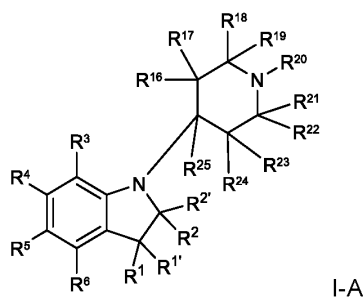
[00208] In some embodiments, when all available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is F, Cl or Br. In some

embodiments, when all available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is F or Br. In some embodiments, when all available hydrogen atoms are replaced with a halogen atom, the halogen atom is F or Cl. In some embodiments, when all available hydrogen atoms in a group are optionally replaced with a halogen atom, the halogen atom is F.

[00209] In some embodiments, when all available atoms are optionally replaced with alternate isotope thereof, all available hydrogen atoms in a group are optionally replaced with deuterium.



[00210] In some embodiments, Q is Q2, , and  is a single bond and the compound of Formula I-A has the following structure:

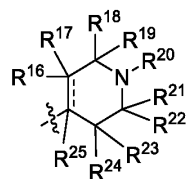


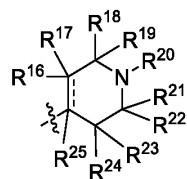
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

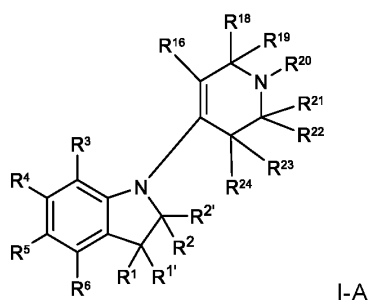
wherein:

R¹, R^{1'}, R², R^{2'}, R³, R⁴, R⁵, R⁶, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³, R²⁴ and R²⁵ are as defined for Formula I-A, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00211] In some embodiments, Q is Q2, , and $\equiv$ is a double bond and the compound of Formula I-A has the following structure:

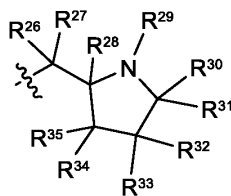


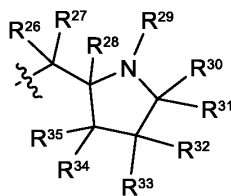
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

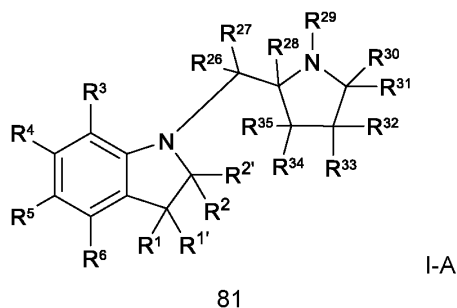
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{16} , R^{18} , R^{19} , R^{20} , R^{21} , R^{22} , R^{23} and R^{24} are as defined for Formula I-A, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00212] In some embodiments, Q is Q3, , and the compound of Formula I-A has the following structure:



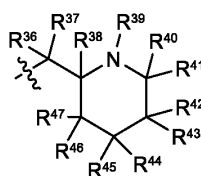
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

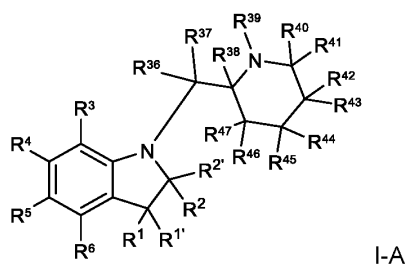
R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{26} , R^{27} , R^{28} , R^{29} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} and R^{35} are as defined for Formula I-A, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^6 , R^{26} , R^{27} , R^{28} , R^{30} to R^{35} , R^{36} , R^{37} , R^{38} and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{29} is CH_3 .



[00213] In some embodiments, Q is Q4, and the compound of Formula I-A has the following structure:



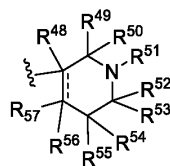
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

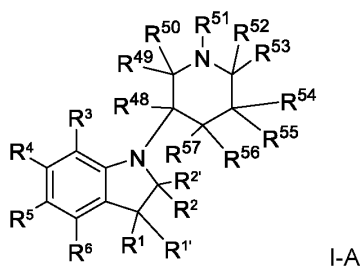
R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{36} , R^{37} , R^{38} , R^{39} , R^{40} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} and R^{47} are as defined for Formula I-A, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof, provided R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^6 , R^{36} , R^{37} , R^{38} and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{39} is CH_3 , and

when R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^6 , R^{38} and R^{40} to R^{47} are all H, then R^{36} and R^{37} are not both D, when R^{39} is CD_3 .



[00214] In some embodiments, Q is Q5, and $\equiv$ is a single bond and the compound of Formula I-A has the following structure:

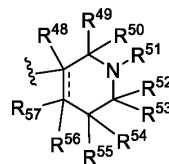


or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

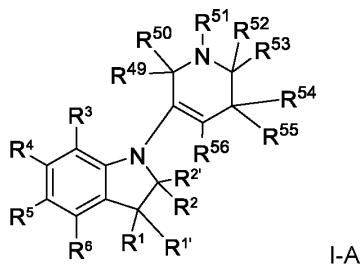
wherein:

$R^1, R^{1'}, R^2, R^{2'}, R^3, R^4, R^5, R^6, R^{48}, R^{49}, R^{50}, R^{51}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}$ and R^{57} are as defined for Formula I-A, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.



[00215] In some embodiments, Q is Q5, and $\equiv$ is a double bond and the compound of Formula I-A has the following structure:

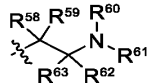


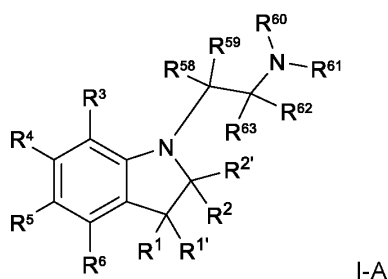
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{49} , R^{50} , R^{51} , R^{52} , R^{53} , R^{54} , R^{55} and R^{56} are as defined for Formula I-A, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.

[00216] In some embodiments, Q is Q6,  (Q6), and the compound of Formula I-A has the following structure:



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

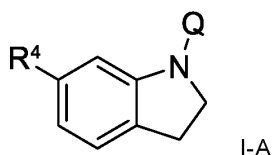
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 , R^6 , R^{58} , R^{59} , R^{60} , R^{61} , R^{62} and R^{63} are as defined for Formula I-A, and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided the compound of Formula I-A comprises D.

[00217] In some embodiments, R^1 , R^2 , $R^{2'}$, $R^{2''}$, R^3 , R^5 and R^6 are all H and the compound Formula I-A has the following structure:



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

wherein:

R^4 and Q are as defined for Formula I-A, and

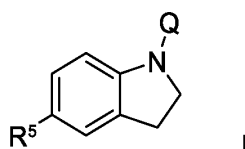
all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided when Q is Q6 then the compound of Formula I-A comprises D,

when Q is Q3 or Q4, then R^4 , R^{26} , R^{27} , R^{28} , R^{30} to R^{35} , R^{36} , R^{37} , R^{38} and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{29} or R^{39} is CH_3 , and

when Q is Q4 and R^4 , R^{38} and R^{40} to R^{47} are all H, then R^{36} and R^{37} are not both D, when R^{39} is CD_3 .

[00218] In some embodiments, R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 and R^6 are all H and the compound Formula I-A has the following structure:



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

wherein:

R^5 and Q are as defined for Formula I-A, and

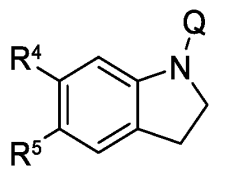
wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided when Q is Q6 then the compound of Formula I-A comprises D,

when Q is Q3 or Q4, R^{26} , then R^{27} , R^{28} , R^{30} to R^{35} , R^{36} , R^{37} , R^{38} and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{29} or R^{39} is CH_3 , and

when Q is Q4 and R^{38} and R^{40} to R^{47} are all H, then R^{36} and R^{37} are not both D, when R^{39} is CD_3 .

[00219] In some embodiments, R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 and R^6 are all H and the compound Formula I-A has the following structure:



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

wherein:

R^4 , R^5 and Q are as defined for Formula I, and

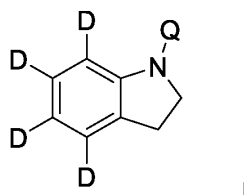
all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided when Q is Q6 then the compound of Formula I-A comprises D,

when Q is Q3 or Q4 then R^4 , R^{26} , R^{27} , R^{28} , R^{30} to R^{35} , R^{36} , R^{37} , R^{38} and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{29} or R^{39} is CH_3 , and

when Q is Q4 and R^4 , R^{38} and R^{40} to R^{47} are all H, then R^{36} and R^{37} are not both D, when R^{39} is CD_3 .

[00220] In some embodiments, R^1 , $R^{1'}$, R^2 and $R^{2'}$ are all H and R^3 , R^4 , R^5 and R^6 are all D and the compound of Formula I-A has the following structure:



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

wherein:

Q is as defined for Formula I, and

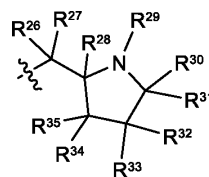
all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof.

[00221] In some embodiments, R^8 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} , R^{19} , R^{21} , R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} , R^{28} , R^{30} , R^{31} , R^{32} , R^{33} , R^{34} , R^{35} , R^{36} , R^{37} , R^{38} , R^{40} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{46} , R^{47} , R^{48} , R^{49} , R^{50} , R^{52} , R^{53} , R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , R^{59} , R^{62} and R^{63} are

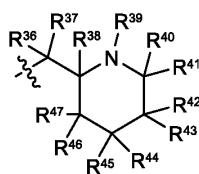
independently selected from H, D, F, Cl, C₁₋₆alkyl, C₁₋₆fluoroalkyl and C₁₋₆deuteroalkyl. In some embodiments, R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H, F, D, CH₃, CD₂H, CDH₂, CD₃, CF₃, CHF₂, CH₂CH₃, CH₂CH₂D, CH₂CD₂H and CD₂CD₃. In some embodiments, R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H and D.

[00222] In some embodiments, R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶ and R⁵⁷ are independently selected from H and D.

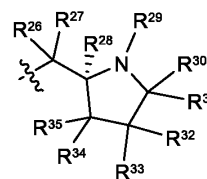
[00223] In some embodiments, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H and D. In some embodiments, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are H. In some embodiments, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are D. In some embodiments, R⁵⁸ and R⁵⁹ are H and R⁶² and R⁶³ are D. In some embodiments, R⁵⁸ and R⁵⁹ are D and R⁶² and R⁶³ are H.



[00224] In some embodiments, when Q is (Q3) or

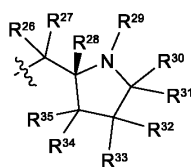


(Q4), the stereochemistry at the carbon to which R²⁸ or R³⁸ is bonded

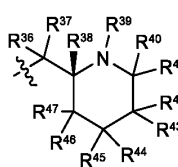


is either R or S. Therefore in some embodiments, Q3 is

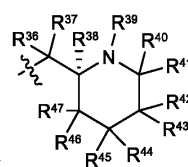
or



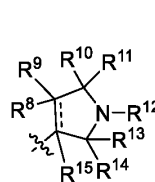
and Q4 is



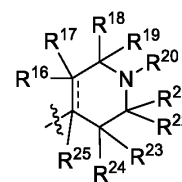
or



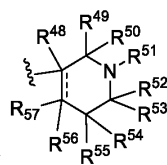
[00225] In some embodiments, the stereochemistry at the carbon to which R²⁸ or R³⁸ is bonded is R. In some embodiments, the stereochemistry at the carbon to which R²⁸ or R³⁸ is bonded is S.



(Q1),

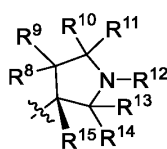


[00226] In some embodiments, when Q is

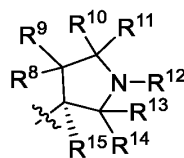


(Q2) or

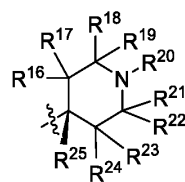
(Q5) and --- is a single bond, the stereochemistry at the carbon to which R¹⁵, R²⁵ or R⁴⁸ is bonded is either R or S. Therefore in some embodiments, Q1 is



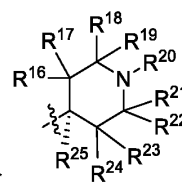
or



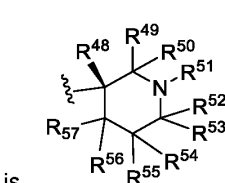
, Q2 is



or

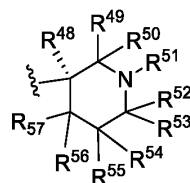


, and Q5



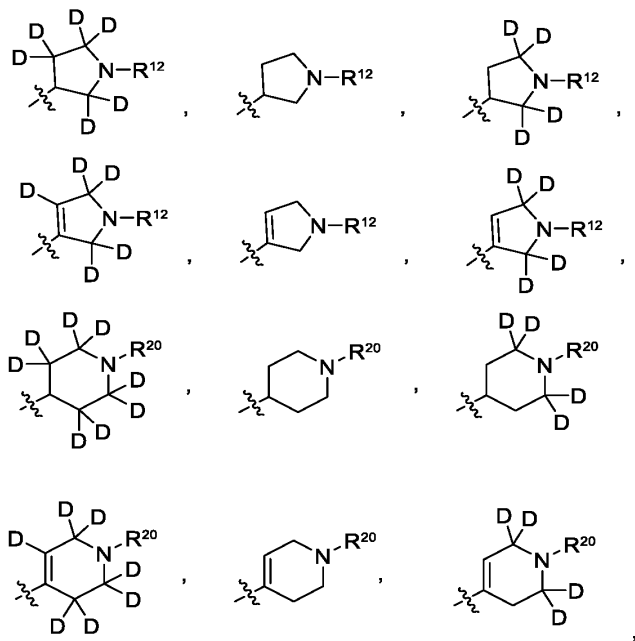
is .

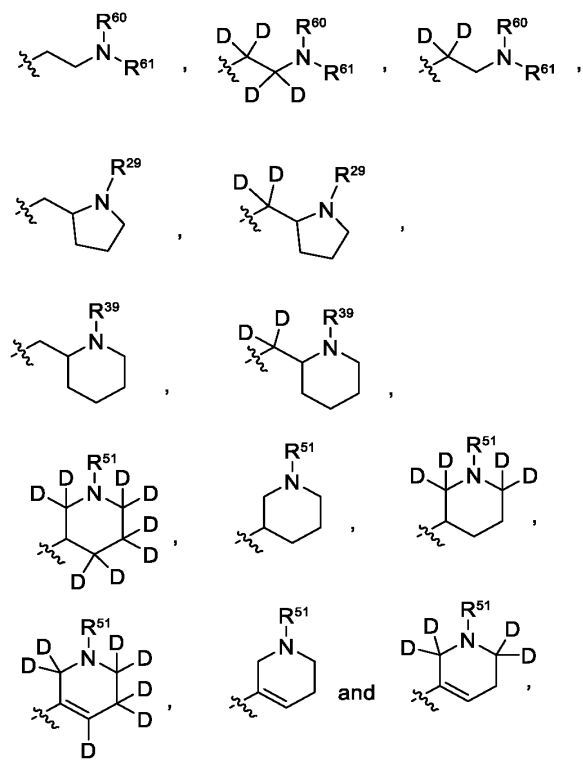
or



[00227] In some embodiments, the stereochemistry at the carbon to which R^{15} , R^{25} or R^{48} is bonded is R. In some embodiments, the stereochemistry at the carbon to which R^{15} , R^{25} or R^{48} is bonded is S.

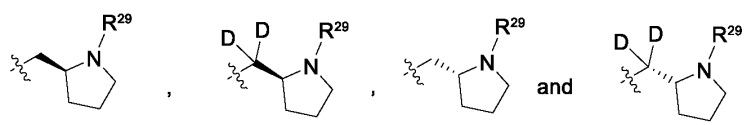
[00228] In some embodiments Q is selected from one of the following groups:





wherein R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from H, D, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl and $C(O)-A'$. In some embodiments, R^{12} , R^{20} , R^{29} and R^{39} are independently selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4} deuteroalkyl and $C(O)-A'$. In some embodiments, R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from H, CH_3 , CD_3 , CD_2H , CF_2H and CF_3 . In some embodiments, R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from H, CH_3 and CD_3 . In some embodiments, R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from CH_3 and CD_3 .

[00229] In some embodiments Q is selected from one of the following groups:



wherein R^{29} is selected from H, D, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl and $C(O)-A'$. In some embodiments, R^{29} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4} deuteroalkyl and $C(O)-A'$. In some embodiments, R^{29} is selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl. In some embodiments, R^{29} is selected from H, CH_3 , CD_3 , CD_2H , CF_2H and

CF₃. In some embodiments, R²⁹ is selected from H, CH₃ and CD₃. In some embodiments, R²⁹ is selected from CH₃ and CD₃.

[00230] In some embodiments, R⁶⁰ and R⁶¹, together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoieties independently selected from O, N and NR⁶⁵ and which is optionally substituted with one or more substituents independently selected from halo, OH, C₁₋₄alkyl and OC₁₋₄alkyl.

[00231] In some embodiments, R¹², R²⁰, R²⁹, R³⁹, R⁵¹, R⁶⁰ and R⁶¹ are independently selected from C(O)-A'.

[00232] In some embodiments, one of R⁶⁰ and R⁶¹ is C(O)-A' and the other is selected from H and C₁₋₆alkyl. In some embodiments, one of R⁶⁰ and R⁶¹ is C(O)-A' and the other is selected from H and C₁₋₄alkyl.

[00233] In some embodiments, A' is selected from Y, O-Y and O-C₁₋₂alkylene-O-C(O)-Y, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A' is selected from Y, O-Y and O-C₁alkylene-O-C(O)-Y, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00234] In some embodiments, Y is C₁₀₋₂₅alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, Y is C₁₃₋₂₁alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00235] In some embodiments, Y is C₁₀₋₂₅alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, Y is C₁₃₋₂₁alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, Y is C₁₀₋₂₅alkenyl and comprises 1, 2, 3, 4, 5 or 6 double bonds.

[00236] In some embodiments, the alkyl or alkene group of Y is an alkyl or alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium. In some embodiments, Y is an alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium. In some embodiments, the fatty acid is an omega-6 fatty acid (i.e. an unsaturated or polyunsaturated fatty acid wherein the double bond that is closest to the methyl end of the molecule is located at carbon numbered 6 starting from the end methyl group) or an omega-3 fatty acid (i.e. an unsaturated or

polyunsaturated fatty acid wherein the double bond that is closest to the methyl end of the molecule is located at carbon numbered 3 starting from the end methyl group), wherein all available H atoms are optionally replaced with deuterium. In some embodiments, Y is an alkyl group present in a fatty acid wherein all available H atoms are optionally replaced with deuterium. In some embodiments, the alkyl or alkene group of Y is an alkyl or alkene group present in a fatty acid selected from the list of fatty acids in Table 1 wherein all available H atoms are optionally replaced with deuterium.

[00237] In some embodiments, the alkene group of Y is an alkyl or alkenyl group present in linoleic acid, eicosadienoic acid or decosahexanoic acid.

[00238] In some embodiments, Y is the alkyl or alkenyl group of a fatty acid wherein 1-10, 2-8, 2-6 or 2-4 H atoms are replaced with deuterium.

[00239] In some embodiments, Y is $(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_8\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$. In some embodiments, Y is $(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$. Therefore, in some embodiments, Y is $(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$, $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$, $(\text{CH}_2)_8\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$, $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$, $(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$, or $(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$.

[00240] In some embodiments, A' is Y.

[00241] In some embodiments, A' is -O-Y.

[00242] In some embodiments, A' is -O-C₃alkylene-O-C(O)-Y.

[00243] In some embodiments, R¹ and R^{1'} are independently selected from H, OH, halo, NH₂, C₁₋₄alkyl, C₁₋₄alkoxy, NH(C₁₋₄alkyl) and N(C₁₋₄alkyl). In some embodiments, R¹ and R^{1'} are independently selected from H, D, Cl, F, OH, NH₂, C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄fluoroalkyl, C₁₋₄deuteroalkyl, NH(C₁₋₄alkyl), NH(C₁₋₄deuteroalkyl), NH(C₁₋₄fluoroalkyl), N(C₁₋₄alkyl)₂, N(C₁₋₄fluoroalkyl)₂, N(C₁₋₄deuteroalkyl)₂, N(C₁₋₄fluoroalkyl)(C₁₋₄alkyl), N(C₁₋₄fluoroalkyl)(C₁₋₄deuteroalkyl) and N(C₁₋₄deuteroalkyl)(C₁₋₄alkyl). In some embodiments, R¹ and R^{1'} are independently selected from H, D, Cl, F, OH, NH₂, C₁₋₂alkyl, C₁₋₂alkoxy, C₁₋₂fluoroalkyl and C₁₋₂deuteroalkyl, NH(C₁₋₂alkyl), NH(C₁₋₂deuteroalkyl), NH(C₁₋₂fluoroalkyl),

$N(C_{1-2}alkyl)_2$, $N(C_{1-2}fluoroalkyl)_2$, $N(C_{1-2}deuteroalkyl)_2$, $N(C_{1-2}fluoroalkyl)(C_{1-2}alkyl)$, $N(C_{1-2}fluoroalkyl)(C_{1-2}deuteroalkyl)$ and $N(C_{1-2}deuteroalkyl)(C_{1-2}alkyl)$. In some embodiments R^1 is selected from H, D, F, NH_2 , CH_3 , CF_2H , CD_2H , CH_3O , CF_3 , CD_3 , $NH(CH_3)$, $NH(CD_3)$, $NH(CF_3)$, $N(CH_3)_2$, $N(CF_3)_2$ and $N(CD_3)_2$. In some embodiments, R^1 and $R^{1'}$ are independently selected from H, D, F, NH_2 , CH_3 , CF_2H , CD_2H , CH_3O , CF_3 and CD_3 . In some embodiments R^1 and $R^{1'}$ are independently selected from H, D, F, OH, CH_3 , CF_2H , CD_2H , CH_3O , CF_3 and CD_3 . In some embodiments, R^1 and $R^{1'}$ are independently H, D or F. In some embodiments, R^1 and $R^{1'}$ are all H or are all D. In some embodiments, R^1 and $R^{1'}$ are both H.

[00244] In some embodiments, R^2 and $R^{2'}$ are independently selected from H, halo, NH_2 , $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $NH(C_{1-4}alkyl)$ and $N(C_{1-4}alkyl)$. In some embodiments, R^2 and $R^{2'}$ are independently selected from H, D, Cl, F, NH_2 , $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}fluoroalkyl$, $C_{1-4}deuteroalkyl$, $NH(C_{1-4}alkyl)$, $NH(C_{1-4}deuteroalkyl)$, $NH(C_{1-4}fluoroalkyl)$, $N(C_{1-4}alkyl)_2$, $N(C_{1-4}fluoroalkyl)_2$, $N(C_{1-4}deuteroalkyl)_2$, $N(C_{1-4}fluoroalkyl)(C_{1-4}alkyl)$, $N(C_{1-4}fluoroalkyl)(C_{1-4}deuteroalkyl)$ and $N(C_{1-4}deuteroalkyl)(C_{1-4}alkyl)$. In some embodiments, R^2 and $R^{2'}$ are independently selected from H, D, Cl, F, $C_{1-2}alkyl$, $C_{1-2}alkoxy$, $C_{1-2}fluoroalkyl$, $C_{1-2}deuteroalkyl$, $NH(C_{1-2}alkyl)$, $NH(C_{1-2}deuteroalkyl)$, $NH(C_{1-2}fluoroalkyl)$, $N(C_{1-2}alkyl)_2$, $N(C_{1-2}fluoroalkyl)_2$, $N(C_{1-2}deuteroalkyl)_2$, $N(C_{1-2}fluoroalkyl)(C_{1-2}alkyl)$, $N(C_{1-2}fluoroalkyl)(C_{1-2}deuteroalkyl)$ and $N(C_{1-2}deuteroalkyl)(C_{1-2}alkyl)$. In some embodiments, R^2 and $R^{2'}$ are independently selected from H, D, F, NH_2 , CH_3 , CF_2H , CD_2H , CH_3O , CF_3 , CD_3 , $NH(CH_3)$, $NH(CD_3)$, $NH(CF_3)$, $N(CH_3)_2$, $N(CF_3)_2$ and $N(CD_3)_2$. In some embodiments R^1 is selected from H, D, F, NH_2 , CH_3 , CF_2H , CD_2H , CH_3O , CF_3 and CD_3 . In some embodiments R^2 and $R^{2'}$ are independently selected from H, D, F, CH_3 , CF_2H , CD_2H , CH_3O , CF_3 and CD_3 . In some embodiments, R^2 and $R^{2'}$ are independently H, D or F. In some embodiments, R^2 and $R^{2'}$ are all H or are all D. In some embodiments, R^2 and $R^{2'}$ are all H.

[00245] In some embodiments, R^1 , $R^{1'}$, R^2 and $R^{2'}$ are independently H, D or F. In some embodiments, R^1 , $R^{1'}$, R^2 and $R^{2'}$ are all H or are all D. In some embodiments, R^1 , $R^{1'}$, R^2 and $R^{2'}$ are all H.

[00246] In some embodiments, R^3 and R^6 are independently selected from H, D, Cl, F, OH, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}fluoroalkoxy$, $C_{1-4}deuteroalkoxy$, $C_{1-4}fluoroalkyl$ and $C_{1-4}deuteroalkyl$. In some embodiments, R^3 and R^6 are independently selected from H, D, Cl, F, OH, $C_{1-4}alkyl$, $C_{1-4}alkoxy$, $C_{1-4}fluoroalkyl$ and $C_{1-4}deuteroalkyl$. In some embodiments, R^3 and R^6 are independently selected from H, D, Cl, F, OH, $C_{1-2}alkyl$, $C_{1-2}alkoxy$, $C_{1-2}fluoroalkoxy$, $C_{1-2}deuteroalkoxy$, $C_{1-2}fluoroalkyl$ and $C_{1-2}deuteroalkyl$. In some

embodiments, R^3 and R^6 are independently selected from H, D, Cl, F, OH, C_{1-2} alkyl, C_{1-2} alkoxy, C_{1-2} fluoroalkyl and C_{1-2} deuteroalkyl. In some embodiments, R^3 and R^6 are independently selected from H, D, F, OH, CH_3 , CH_3O , CF_2HO , CD_2HO , CF_3O , CD_3O , CF_2H , CD_2H , CF_3 and CD_3 . In some embodiments, R^3 and R^6 are independently selected from H, D, F, OH, CH_3 , CH_3O , CF_2H , CD_2H , CF_3 and CD_3 . In some embodiments, R^3 and R^6 are independently selected from H, D, F, OH, CH_3 , CH_3O , CF_2HO , CF_3O and CD_3O . In some embodiments, R^3 and R^6 are independently selected from H and D. In some embodiments, at least one of R^3 and R^6 is D. In some embodiments, each of R^3 and R^6 are D. In some embodiments, each of R^3 and R^6 are H.

[00247] In some embodiments, one or both of R^4 and R^5 is independently selected from H, D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy. In some embodiments both of R^4 and R^5 are independently selected from H, D, F, Cl, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy and C_{1-4} deuteroalkoxy. In some embodiments, one or both of R^4 and R^5 is independently selected from H, D, F, Cl, CH_3 , CH_2CH_3 , $CH_2CH_2CH_3$, $CH(CH_3)_2$, CF_3 , CF_2H , CH_2CF_2H , CH_2CF_3 , CH_2CFH_2 , $CH(CF_3)_2$, CD_3 , $CH(CH_3)_2O$, $CH_3CH_2CH_2O$, CH_3CH_2O , CH_3O , CF_3O , CHF_2O , CF_2HCH_2O , CF_3CH_2O , $(CF_3)_2CHO$, and CD_3O . In some embodiments, one or both of R^4 and R^5 is independently selected from H, D, F, Cl, CH_3 , $CH(CH_3)_2$, CF_3 , CF_2H , CD_3 , CH_3O , $CH(CH_3)_2O$, CF_3O , CHF_2O , and CD_3O .

[00248] In some embodiments both of R^4 and R^5 are independently selected from D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy. In some embodiments both of R^4 and R^5 are independently selected from H, D, F, Cl, CH_3 , $CH(CH_3)_2$, CF_3 , CF_2H , CD_3 , $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments both of R^4 and R^5 are independently selected from D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy. In some embodiments both of R^4 and R^5 are independently selected from H, D, F, Cl, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy and C_{1-4} deuteroalkoxy. In some embodiments both of R^4 and R^5 are independently selected from H, D, F, Cl, CH_3 , $CH(CH_3)_2$, CF_3 , CF_2H , CD_3 , $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments both of R^4 and R^5 are independently selected from D, F, Cl, CH_3 , $CH(CH_3)_2$, CF_3 , CF_2H , CD_3 , $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments both of R^4 and R^5 are independently selected from CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments both of R^4 and R^5 are CD_3O or both of R^4 and R^5 are CH_3O .

[00249] In some embodiments, R^4 is H or D and R^5 is selected from H, D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy. In some embodiments, R^4 is H or D and R^5 is selected from H, D, F, Cl, C_{1-4} alkyl, C_{1-4} fluoroalkyl, C_{1-4} deuteroalkyl, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy and C_{1-4} deuteroalkoxy. In some embodiments, R^4 is H or D and R^5 is selected from H, D, F, Cl, $CH(CH_3)_2$, CH_3 , CF_3 , CF_2H , CD_3 , $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, R^4 is H or D and R^5 is selected from D, F, Cl, $CH(CH_3)_2$, CH_3 , CF_3 , CF_2H , CD_3 , $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, R^4 is H or D and R^5 is selected from $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, R^4 is H and R^5 is selected from CH_3O and CD_3O .

[00250] In some embodiments, R^5 is H or D and R^4 is selected from H, D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy. In some embodiments, R^5 is H or D and R^4 is selected from D, F, Cl, CH_3 , $CH(CH_3)_2$, CF_3 , CF_2H , CD_3 , $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, R^5 is H or D and R^4 is selected from $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, R^5 is H and R^4 is selected from CH_3O and CD_3O .

[00251] In some embodiments, R^3 , R^4 , R^5 and R^6 are selected from D, F, Cl, CH_3 , $CH(CH_3)_2$, CF_3 , CF_2H , CD_3 , $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, R^3 , R^4 , R^5 and R^6 are all H or In some embodiments, R^3 , R^4 , R^5 and R^6 are all D. In some embodiments, R^3 , R^4 , R^5 and R^6 are selected from $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, two of R^3 , R^4 , R^5 and R^6 are selected from H or D and the remaining of R^3 , R^4 , R^5 and R^6 are selected from $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, two of R^3 , R^4 , R^5 and R^6 are selected from H or D and the remaining of R^3 , R^4 , R^5 and R^6 are selected from CH_3O and CD_3O . In some embodiments, one of R^3 , R^4 , R^5 and R^6 is selected from H or D and the remaining of R^3 , R^4 , R^5 and R^6 are selected from $CH(CH_3)_2O$, CH_3O , CF_3O , CHF_2O , and CD_3O . In some embodiments, one of R^3 , R^4 , R^5 and R^6 is selected from H or D and the remaining of R^3 , R^4 , R^5 and R^6 are selected from CH_3O and CD_3O .

[00252] In some embodiments, R^4 and R^5 are linked together to form $O-CH_2O$.

[00253] In some embodiments, one of R^4 and R^5 is selected from X-L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy.

[00254] In some embodiments, X is a direct bond and one of R^4 and R^5 is selected from L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy. In some embodiments, X is selected from O, C(O), NR^a , $NR^aC(O)$, $C(O)NR^a$, $OC(O)$, $C(O)O$,

OC(O)O, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, X is selected from O, C(O), OC(O), C(O)O and OC(O)O. In some embodiments, X is selected from O, OC(O) and C(O)O. In some embodiments, X is O. In some embodiments, X is selected from OC(O) and C(O)O. In some embodiments, X is selected from NR^a, NR^aC(O), C(O)NR^a, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, X is selected from NR^aC(O), C(O)NR^a, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, X is selected from NR^aC(O), and C(O)NR^a. In some embodiments, X is selected from NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a. In some embodiments, X is selected from O, OC(O), C(O)O, NR^aC(O), and C(O)NR^a.

[00255] In some embodiments, L is selected from a direct bond, C₁₋₄alkylene, C₂₋₄alkenylene, C₁₋₄alkyleneO, C₂₋₄alkenyleneO, C₁₋₄alkyleneC(O), C₂₋₄alkenyleneC(O), C₁₋₄alkyleneNR^bC(O), C₂₋₄alkenyleneNR^bC(O), C₁₋₄alkyleneC(O)NR^b, C₂₋₄alkenyleneC(O)NR^b, C₁₋₄alkyleneOC(O), C₂₋₄alkenyleneOC(O), C₁₋₄alkyleneC(O)O, C₂₋₄alkenyleneC(O)O, C₁₋₄alkyleneOC(O)NR^b, C₂₋₄alkenyleneOC(O)NR^b, C₁₋₄alkyleneNR^bC(O)O, C₂₋₄alkenyleneNR^bC(O)O, C₁₋₄alkyleneOC(O)O, C₂₋₄alkenyleneOC(O)O, C₁₋₄alkyleneNR^bC(O)NR^b and C₂₋₄alkenyleneNR^bC(O)NR^b. In some embodiments, L is selected from a direct bond, C₁₋₂alkylene, C₂₋₄alkenylene, C₁₋₂alkyleneO, C₂₋₄alkenyleneO, C₁₋₂alkyleneC(O), C₂₋₄alkenyleneC(O), C₁₋₂alkyleneNR^bC(O), C₂₋₄alkenyleneNR^bC(O), C₁₋₂alkyleneC(O)NR^b, C₂₋₄alkenyleneC(O)NR^b, C₁₋₂alkyleneOC(O), C₂₋₄alkenyleneOC(O), C₁₋₂alkyleneC(O)O, C₂₋₄alkenyleneC(O)O, C₁₋₂alkyleneOC(O)NR^b, C₂₋₄alkenyleneOC(O)NR^b, C₁₋₂alkyleneNR^bC(O)O, C₂₋₄alkenyleneNR^bC(O)O, C₁₋₂alkyleneOC(O)O, C₂₋₄alkenyleneOC(O)O, C₁₋₂alkyleneNR^bC(O)NR^b and C₂₋₄alkenyleneNR^bC(O)NR^b. In some embodiments, L is selected from a direct bond, C₁₋₂alkylene, C₁₋₂alkyleneO, C₁₋₂alkyleneC(O), C₁₋₂alkyleneNR^bC(O), C₁₋₂alkyleneC(O)NR^b, C₁₋₂alkyleneOC(O), C₁₋₂alkyleneC(O)O, C₁₋₂alkyleneOC(O)NR^b, C₁₋₂alkyleneNR^bC(O)O, C₁₋₂alkyleneOC(O)O, and C₁₋₂alkyleneNR^bC(O)NR^b. In some embodiments, L is selected from a direct bond, CH₂, CF₂, CD₂, CH₂-O, CF₂-O, CD₂-O, CH₂-C(O), CF₂-C(O), CD₂-C(O), CH₂-NR^bC(O), CD₂-NR^bC(O), CF₂-NR^bC(O), CH₂-C(O)NR^b, CF₂-C(O)NR^b, CD₂-C(O)NR^b, CH₂-OC(O), CD₂-OC(O), CF₂-OC(O), CH₂-C(O)O, CF₂-C(O)O, CD₂-C(O)O, CH₂-OC(O)NR^b, CD₂-OC(O)NR^b, CF₂-OC(O)NR^b, CH₂-NR^bC(O)O, CF₂-NR^bC(O)O, CD₂-NR^bC(O)O, CH₂-OC(O)O, CF₂-OC(O)O, CD₂-OC(O)O, CH₂-NR^bC(O)NR^b, CF₂-NR^bC(O)NR^b and CD₂-NR^bC(O)NR^b.

[00256] In some embodiments, X is a direct bond and L is a direct bond and one of R⁴ and R⁵ is selected from A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₄alkyl and C₁₋₄alkoxy.

[00257] In some embodiments, X is selected from O, OC(O), C(O)O, NR^aC(O), and C(O)NR^a and one of R⁴ and R⁵ is selected from O-C₁₋₂alkylene-A, O-C₁₋₂alkyleneO-A, O-C₁₋₂alkyleneC(O)-A, O-C₁₋₂alkyleneNR^bC(O)-A, O-C₁₋₂alkyleneC(O)NR^b-A, O-C₁₋₂alkyleneOC(O)-A, O-C₁₋₂alkyleneC(O)O-A, O-C₁₋₂alkyleneOC(O)NR^b-A, O-C₁₋₂alkyleneNR^bC(O)O-A, O-C₁₋₂alkyleneOC(O)O-A, O-C₁₋₂alkyleneNR^bC(O)NR^b-A, OC(O)-C₁₋₂alkylene-A, OC(O)-C₁₋₂alkyleneO-A, OC(O)-C₁₋₂alkyleneC(O)-A, OC(O)-C₁₋₂alkyleneNR^bC(O)-A, OC(O)-C₁₋₂alkyleneC(O)NR^b-A, OC(O)-C₁₋₂alkyleneOC(O)-A, OC(O)-C₁₋₂alkyleneC(O)O-A, OC(O)-C₁₋₂alkyleneOC(O)NR^b-A, OC(O)-C₁₋₂alkyleneNR^bC(O)O-A, OC(O)-C₁₋₂alkyleneOC(O)O-A, OC(O)-C₁₋₂alkyleneNR^bC(O)NR^b-A, C(O)O-C₁₋₂alkylene-A, C(O)O-C₁₋₂alkyleneO-A, C(O)O-C₁₋₂alkyleneC(O)-A, C(O)O-C₁₋₂alkyleneNR^bC(O)-A, C(O)O-C₁₋₂alkyleneC(O)NR^b-A, C(O)O-C₁₋₂alkyleneOC(O)-A, C(O)O-C₁₋₂alkyleneC(O)O-A, C(O)O-C₁₋₂alkyleneOC(O)NR^b-A, C(O)O-C₁₋₂alkyleneNR^bC(O)O-A, C(O)O-C₁₋₂alkyleneOC(O)O-A, C(O)O-C₁₋₂alkyleneNR^bC(O)NR^b-A, NR^aC(O)-C₁₋₂alkylene-A, NR^aC(O)-C₁₋₂alkyleneO-A, NR^aC(O)-C₁₋₂alkyleneC(O)-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)-A, NR^aC(O)-C₁₋₂alkyleneC(O)NR^b-A, NR^aC(O)-C₁₋₂alkyleneOC(O)-A, NR^aC(O)-C₁₋₂alkyleneC(O)O-A, NR^aC(O)-C₁₋₂alkyleneOC(O)NR^b-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)O-A, NR^aC(O)-C₁₋₂alkyleneOC(O)O-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)NR^b-A, C(O)NR^a-C₁₋₂alkylene-A, C(O)NR^a-C₁₋₂alkyleneO-A, C(O)NR^a-C₁₋₂alkyleneC(O)-A, C(O)NR^a-C₁₋₂alkyleneNR^bC(O)-A, C(O)NR^a-C₁₋₂alkyleneC(O)NR^b-A, C(O)NR^a-C₁₋₂alkyleneOC(O)-A, C(O)NR^a-C₁₋₂alkyleneC(O)O-A, C(O)NR^a-C₁₋₂alkyleneOC(O)NR^b-A, C(O)NR^a-C₁₋₂alkyleneNR^bC(O)O-A, C(O)NR^a-C₁₋₂alkyleneOC(O)O-A, and C(O)NR^a-C₁₋₂alkyleneNR^bC(O)NR^b-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₄alkyl and C₁₋₄alkoxy wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, X is selected from O, OC(O), C(O)O, NR^aC(O), and C(O)NR^a and one of R⁴ and R⁵ is selected from O-C₁₋₂alkylene-A, O-C₁₋₂alkyleneO-A, O-C₁₋₂alkyleneC(O)-A, O-C₁₋₂alkyleneNR^bC(O)-A, O-C₁₋₂alkyleneC(O)NR^b-A, O-C₁₋₂alkyleneOC(O)-A, O-C₁₋₂alkyleneC(O)O-A, O-C₁₋₂alkyleneOC(O)NR^b-A, O-C₁₋₂alkyleneNR^bC(O)O-A, O-C₁₋₂alkyleneOC(O)O-A, O-C₁₋₂alkyleneNR^bC(O)NR^b-A, OC(O)-C₁₋₂alkylene-A, OC(O)-C₁₋₂alkyleneO-A, OC(O)-C₁₋₂alkyleneC(O)-A, OC(O)-C₁₋₂alkyleneNR^bC(O)-A, OC(O)-C₁₋₂alkyleneC(O)NR^b-A, OC(O)-C₁₋₂alkyleneOC(O)-A, OC(O)-C₁₋₂alkyleneC(O)O-A, OC(O)-C₁₋₂alkyleneOC(O)NR^b-A, OC(O)-C₁₋₂alkyleneNR^bC(O)O-A, OC(O)-C₁₋₂alkyleneOC(O)O-A, OC(O)-C₁₋₂alkyleneNR^bC(O)NR^b-A, C(O)O-C₁₋₂alkylene-A, C(O)O-C₁₋₂alkyleneO-A, C(O)O-C₁₋₂alkyleneC(O)-A, C(O)O-C₁₋₂alkyleneNR^bC(O)-A, C(O)O-C₁₋₂alkyleneC(O)NR^b-A, C(O)O-C₁₋₂alkyleneOC(O)-A, C(O)O-C₁₋₂alkyleneC(O)O-A, C(O)O-C₁₋₂alkyleneOC(O)NR^b-A, C(O)O-C₁₋₂alkyleneNR^bC(O)O-A, C(O)O-C₁₋₂alkyleneOC(O)O-A, and C(O)O-C₁₋₂alkyleneNR^bC(O)NR^b-A.

$_2$ alkyleneOC(O)NR^b-A, C(O)O-C₁₋₂alkyleneNR^bC(O)O-A, C(O)O-C₁₋₂alkyleneOC(O)O-A, C(O)O-C₁₋₂alkyleneNR^bC(O)NR^b-A, NR^aC(O)-C₁₋₂alkylene-A, NR^aC(O)-C₁₋₂alkyleneO-A, NR^aC(O)-C₁₋₂alkyleneC(O)-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)-A, NR^aC(O)-C₁₋₂alkyleneC(O)NR^b-A, NR^aC(O)-C₁₋₂alkyleneOC(O)-A, NR^aC(O)-C₁₋₂alkyleneC(O)O-A, NR^aC(O)-C₁₋₂alkyleneOC(O)NR^b-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)O-A, NR^aC(O)-C₁₋₂alkyleneOC(O)O-A, NR^aC(O)-C₁₋₂alkyleneNR^bC(O)NR^b-A, C(O)NR^a-C₁₋₂alkylene-A, C(O)NR^a-C₁₋₂alkyleneO-A, C(O)NR^a-C₁₋₂alkyleneC(O)-A, C(O)NR^a-C₁₋₂alkyleneNR^bC(O)-A, C(O)NR^a-C₁₋₂alkyleneC(O)NR^b-A, C(O)NR^a-C₁₋₂alkyleneOC(O)-A, C(O)NR^a-C₁₋₂alkyleneC(O)O-A, C(O)NR^a-C₁₋₂alkyleneOC(O)NR^b-A, C(O)NR^a-C₁₋₂alkyleneNR^bC(O)O-A, C(O)NR^a-C₁₋₂alkyleneOC(O)O-A, and C(O)NR^a-C₁₋₂alkyleneNR^bC(O)NR^b-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₄alkyl and C₁₋₄alkoxy wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00258] In some embodiments, the other of R⁴ and R⁵ is selected from H, F, Cl, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄deuteroalkyl and C₁₋₄alkoxy wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, the other of R⁴ and R⁵ is selected from D, F, Cl, CH₃, CH(CH₃)₂, CF₃, CF₂H, CD₃, CH(CH₃)₂O, CH₃O, CF₃O, CHF₂O, and CD₃O wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium Atom. and the other of R⁴ and R⁵ is H or D.

[00259] In some embodiments, R⁴ is X-L-A and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy. In some embodiments, of R⁵ is X-L-A and R⁴ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy.

[00260] In some embodiments, R^a is selected from H and C₁₋₄alkyl.

[00261] In some embodiments, R^b is selected from H, C₁₋₄alkyl and A.

[00262] In some embodiments, A is H, and one of R⁴ and R⁵ is selected OH, C(O)H, NHR^a, NHR^aC(O), C(O)NHR^a, OC(O)H, C(O)OH, OC(O)OH, NR^aC(O)OH, OC(O)NHR^a, NHR^aC(O)NR^a, X-C₁₋₄alkylene, X-C₂₋₄alkenylene, X-C₁₋₄alkyleneOH, X-C₂₋₄alkenyleneOH, X-C₁₋₄alkyleneC(O)H, X-C₂₋₄alkenyleneC(O)H, X-C₁₋₄alkyleneNR^bC(O)H, X-C₂₋₄alkenyleneNR^bC(O)H, X-C₁₋₄alkyleneC(O)NHR^b, X-C₂₋₄alkenyleneC(O)NHR^b, X-C₁₋₄alkyleneOC(O)H, X-C₂₋₄alkenyleneOC(O)H, X-C₁₋₄alkyleneC(O)OH, C₂₋₄alkenyleneC(O)H, X-C₁₋₄alkyleneOC(O)NHR^b, X-C₂₋₄alkenyleneOC(O)NHR^b, X-C₁₋₄alkyleneNR^bC(O)OH, X-C₂₋₄alkenyleneNR^bC(O)OH, X-C₁₋₄alkyleneOC(O)OH, X-C₂₋₄alkenyleneOC(O)OH, X-C₁₋₄alkyleneNR^bC(O)NHR^b and X-C₂₋₄alkenyleneNR^bC(O)NHR^b

and the other of R^4 and R^5 is selected from H, halo, C_{1-4} alkyl and C_{1-4} alkoxy, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is H, and one of R^4 and R^5 is selected OH, $C(O)H$, NHR^a , $NHR^aC(O)$, $C(O)NHR^a$, $OC(O)H$, $C(O)OH$, $OC(O)OH$, $NR^aC(O)OH$, $OC(O)NHR^a$, $NHR^aC(O)NR^a$, $X-C_{1-2}$ alkylene, $X-C_{2-4}$ alkenylene, $X-C_{1-2}$ alkyleneOH, $X-C_{2-4}$ alkenyleneOH, $X-C_{1-2}$ alkyleneC(O)H, $X-C_{2-4}$ alkenyleneC(O)H, $X-C_{1-2}$ alkylene $NR^bC(O)H$, $X-C_{2-4}$ alkenylene $NR^bC(O)H$, $X-C_{1-2}$ alkyleneC(O) NHR^b , $X-C_{2-4}$ alkenyleneC(O) NHR^b , $X-C_{1-2}$ alkyleneOC(O)H, $X-C_{2-4}$ alkenyleneOC(O)H, $X-C_{1-2}$ alkyleneC(O)OH, C_{2-4} alkenyleneC(O)H, $X-C_{1-2}$ alkyleneOC(O) NHR^b , $X-C_{2-4}$ alkenyleneOC(O) NHR^b , $X-C_{1-2}$ alkylene $NR^bC(O)OH$, $X-C_{2-4}$ alkenylene $NR^bC(O)OH$, $X-C_{1-2}$ alkyleneOC(O)OH, $X-C_{2-4}$ alkenyleneOC(O)OH, $X-C_{1-2}$ alkylene $NR^bC(O)NHR^b$ and $X-C_{2-4}$ alkenylene $NR^bC(O)NHR^b$ and the other of R^4 and R^5 is selected from H, halo, C_{1-4} alkyl and C_{1-4} alkoxy, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00263] In some embodiments, A is H and X is a direct bond. Therefore, in some embodiments, and one of R^4 and R^5 is selected from C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkyleneOH, C_{2-6} alkenyleneOH, C_{1-4} alkyleneC(O)H, C_{2-4} alkenyleneC(O)H, C_{1-4} alkylene $NR^bC(O)H$, C_{2-4} alkenylene $NR^bC(O)H$, C_{1-4} alkyleneC(O) NHR^b , C_{2-4} alkenyleneC(O) NHR^b , C_{1-4} alkyleneOC(O)H, C_{2-4} alkenyleneOC(O)H, C_{1-4} alkyleneC(O)OH, C_{2-4} alkenyleneC(O)H, C_{1-4} alkyleneOC(O) NHR^b , C_{2-6} alkenyleneOC(O) NHR^b , C_{1-4} alkylene $NR^bC(O)OH$, C_{2-4} alkenylene $NR^bC(O)OH$, C_{1-4} alkyleneOC(O)OH, C_{2-4} alkenyleneOC(O)OH, C_{1-4} alkylene $NR^bC(O)NHR^b$ and C_{2-4} alkenylene $NR^bC(O)NHR^b$ and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy.

[00264] In some embodiments, A is H and X is selected from O, $C(O)$, NR^a , $NR^aC(O)$, $C(O)NR^a$, $OC(O)$, $C(O)O$, $OC(O)O$, $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$. In some embodiments, A is H and X is selected from O, $C(O)$, $OC(O)$, $C(O)O$ and $OC(O)O$. In some embodiments, A is H and X is selected from O, $OC(O)$ and $C(O)O$. In some embodiments, A is H and X is selected from $OC(O)$ and $C(O)O$. In some embodiments, A is H and X is selected from NR^a , $NR^aC(O)$, $C(O)NR^a$, $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$. In some embodiments, A is H and X is selected from $NR^aC(O)$, $C(O)NR^a$, $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$. In some embodiments, A is H and X is selected from $NR^aC(O)$, and $C(O)NR^a$. In some embodiments, A is H and X is selected from $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$.

[00265] In some embodiments, A is H, and L is a direct bond, and one of R³ and R⁴ is selected from X-H. Therefore, in some embodiments, and one of R³ and R⁴ is selected from OH, C(O)H, NHR^a, NHR^aC(O), C(O)NHR^a, OC(O)H, C(O)OH, OC(O)OH, NR^aC(O)OH, OC(O)NHR^a and NHR^aC(O)NR^a, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00266] In some embodiments, when A is H, R^b is selected from H and C₁₋₄alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00267] In some embodiments, one of R⁴ and R⁵ is selected from A, O-A, C(O)-A, C(O)-A, C(O)O-A, C₁₋₄alkylene-A, C₁₋₄alkylene-C(O)-A, C₁₋₄alkylene-C(O)O-A, O-C₁₋₄alkylene-A, O-C₁₋₄alkylene-C(O)-A, and O-C₁₋₄alkylene-C(O)O-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00268] In some embodiments, one of R⁴ and R⁵ is selected from A, O-A, C(O)-A, C(O)-A, and C(O)O-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R⁴ and R⁵ is A. In some embodiments, one of R⁴ and R⁵ is O-A. In some embodiments, one of R⁴ and R⁵ is C(O)-A. In some embodiments, one of R⁴ and R⁵ is C(O)O-A.

[00269] In some embodiments, one of R⁴ and R⁵ is selected from C₁₋₄alkylene-A, C₁₋₄alkylene-C(O)-A, C₁₋₄alkylene-C(O)O-A, O-C₁₋₄alkylene-A, O-C₁₋₄alkylene-C(O)-A, and O-C₁₋₄alkylene-C(O)O-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R⁴ and R⁵ is C₁₋₄alkylene-A. In some embodiments, one of R⁴ and R⁵ is C₁₋₄alkylene-C(O)-A. In some embodiments, one of R⁴ and R⁵ is C₁₋₄alkylene-C(O)O-A. In some embodiments, one of R⁴ and R⁵ is O-C₁₋₄alkylene-A. In some embodiments, one of R⁴ and R⁵ is O-C₁₋₄alkylene-C(O)-A. In some embodiments, one of R⁴ and R⁵ is O-C₁₋₄alkylene-C(O)O-A.

[00270] In some embodiments, one of R⁴ and R⁵ is selected from A, O-A, C(O)-A, C(O)O-A, C(O)-A, C(O)O-A, C₁₋₄alkylene-A, C₁₋₄alkylene-C(O)-A, C₁₋₄alkylene-C(O)O-A, O-C₁₋₄alkylene-A, O-C₁₋₄alkylene-C(O)-A, and O-C₁₋₄alkylene-C(O)O-A and the other of R⁴ and R⁵ is selected from H, F, Cl, C₁₋₄alkyl and C₁₋₄alkoxy, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R⁴ and R⁵ is selected from A, O-A, C(O)-A, C(O)O-A, C(O)-

A, C(O)O-A, C₁₋₄alkylene-A, C₁₋₄alkylene-C(O)-A, C₁₋₄alkylene-C(O)O-A, O-C₁₋₄alkylene-A, O-C₁₋₄alkylene-C(O)-A, and O-C₁₋₄alkylene-C(O)O-A and the other of R⁴ and R⁵ is selected from H, F, Cl, C₁₋₄alkyl, C₁₋₄haloalkyl, C₁₋₄deuteroalkyl and C₁₋₄alkoxy wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R⁴ and R⁵ is selected from A, O-A, C(O)-A, C(O)O-A, C(O)-A, C(O)O-A, C₁₋₂alkylene-A, C₁₋₂alkylene-C(O)-A, C₁₋₂alkylene-C(O)O-A, O-C₁₋₂alkylene-A, O-C₁₋₂alkylene-C(O)-A, and O-C₁₋₂alkylene-C(O)O-A and the other of R⁴ and R⁵ is selected from D, F, Cl, CH₃, CH(CH₃)₂, CF₃, CF₂H, CD₃, CH(CH₃)₂O, CH₃O, CF₃O, CHF₂O, and CD₃O wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R⁴ and R⁵ is selected from A, O-A, C(O)-A, C(O)O-A, C₁₋₂alkylene-A, C₁₋₂alkylene-C(O)-A, C₁₋₂alkylene-C(O)O-A, O-C₁₋₂alkylene-A, O-C₁₋₂alkylene-C(O)-A, and O-C₁₋₂alkylene-C(O)O-A and the other of R⁴ and R⁵ is H or D, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, one of R⁴ and R⁵ is selected from A, O-A, C(O)-A, C(O)O-A, CH₂-A, CD₂-A, CF₂-A, CH₂-C(O)-A, CF₂-C(O)-A, CD₂-C(O)-A, CH₂-C(O)O-A, CD₂-C(O)O-A, CF₂-C(O)O-A, O-CH₂A, O-CF₂A, O-CD₂A, -CH₂-C(O)-A, O-CD₂-C(O)-A, O-CF₂-C(O)-A, O-CH₂-C(O)O-A, O-CF₂-C(O)O-A, O-CD₂-C(O)O-A, and the other of R⁴ and R⁵ is H or D.

[00271] In some embodiments, R⁴ is selected from A, O-A, C(O)-A, C(O)O-A, C₁₋₂alkylene-A, C₁₋₂alkylene-C(O)-A, C₁₋₂alkylene-C(O)O-A, O-C₁₋₂alkylene-A, O-C₁₋₂alkylene-C(O)-A, and O-C₁₋₂alkylene-C(O)O-A and R⁵ is H or D, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, R⁴ is selected from A, O-A, C(O)-A, C(O)O-A, CH₂-A, CD₂-A, CF₂-A, CH₂-C(O)-A, CF₂-C(O)-A, CD₂-C(O)-A, CH₂-C(O)O-A, CD₂-C(O)O-A, CF₂-C(O)O-A, O-CH₂A, O-CF₂A, O-CD₂A, O-CH₂-C(O)-A, O-CD₂-C(O)-A, O-CF₂-C(O)-A, O-CH₂-C(O)O-A, O-CF₂-C(O)O-A, and O-CD₂-C(O)O-A and R⁵ is H or D. In some embodiments, R⁵ is selected from A, O-A, C(O)-A, C(O)O-A, C₁₋₂alkylene-A, C₁₋₂alkylene-C(O)-A, C₁₋₂alkylene-C(O)O-A, O-C₁₋₂alkylene-A, O-C₁₋₂alkylene-C(O)-A, and O-C₁₋₂alkylene-C(O)O-A and R⁴ is H or D, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, R⁵ is selected from A, O-A, C(O)-A, C(O)O-A, CH₂-A, CD₂-A, CF₂-A, CH₂-C(O)-A, CF₂-C(O)-A, CD₂-C(O)-A, CH₂-C(O)O-A, CD₂-C(O)O-A, CF₂-C(O)O-A, O-CH₂A, O-CF₂A, O-CD₂A, O-CH₂-C(O)-A, O-CD₂-C(O)-A, O-CF₂-C(O)-A, O-CH₂-C(O)O-A, O-CF₂-C(O)O-A, and O-CD₂-C(O)O-A and R⁴ is H or D.

[00272] In some embodiments, A is selected from C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, Cl, OH, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is selected from C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, Cl, OH, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00273] In some embodiments, A is selected from phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl. In some embodiments, A is selected from phenyl, C₃₋₆cycloalkyl, 5- to 6-membered heterocycloalkyl comprising 1 to 2 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00274] In some embodiments, the C₃₋₆cycloalkyl in A is selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. In some embodiments, the C₃₋₆cycloalkyl in A is cyclopropyl which is optionally substituted with one or two substituents independently

selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00275] In some embodiments, the 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ in A is selected from aziridinyl, oxiranyl, thiiranyl, oxaxiridinyl, dioxiranyl, azetidiny, oxetanyl, theitanyl, diazetidinyl, dioxetanyl, dithietanyl, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, isoxthiolidinyl, thiazolidinyl, isothiazolidinyl, dioxolanyl, dithiolanyl, piperidinyl, triazolyl, furazanyl, oxadiazolyl, thiadiazolyl, dioxazolyl, dithiazolyl, tetrazolyl, oxatetrazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl oxide, tetrahydrothiopyranyl dioxide, dihydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, dioxanyl and dithianyl, each of which is optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl. In some embodiments, the 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ in A is selected from tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, dioxolanyl, piperidinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, tetrahydropyranyl, tetrahydrothiopyranyl, dihydropyranyl, tetrahydrothiopyranyl oxide, tetrahydrothiopyranyl dioxide, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl, each of which is optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00276] In some embodiments, the 5- to 6-membered heteroaryl in A is selected from furyl, imidazolyl, isothiazolyl, thiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyrrolyl, thienofuryl, triazolyl and thienyl, each of which is optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl. In some embodiments, the 5- to 6-membered heteroaryl in A is selected from furyl, isothiazolyl, thiazolyl, pyridyl and pyrrolyl, each of which is optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

[00277] In some embodiments, the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl in A is optionally substituted with one or two substituents independently selected from F, Cl, CH₃, CH₂CH₃, CH₂CH₂CH₃, CH(CH₃)₂,

CF₃, CF₂H, CH₂CF₂H, CH₂CF₃, CH₂CFH₂, CH(CF₃)₂, CD₃, CH(CH₃)₂O, CH₃CH₂CH₂O, CH₃CH₂O, CH₃O, CF₃O, CHF₂O, CF₂HCH₂O, CF₃CH₂O, (CF₃)₂CHO, and CD₃O.

[00278] In some embodiments, A is selected from C₁₋₃₀alkyl and C₂₋₃₀alkenyl wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00279] In some embodiments, A is C₁₀₋₂₅alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is C₁₃₋₂₁alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

[00280] In some embodiments, A is C₁₀₋₂₅alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is C₁₃₋₂₁alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom. In some embodiments, A is C₁₀₋₂₅alkenyl and comprises 1, 2, 3, 4, 5 or 6 double bonds.

[00281] In some embodiments, the alkyl or alkene group of A is an alkyl or alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium. In some embodiments, A is an alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium. In some embodiments, the fatty acid is an omega-6 fatty acid (i.e. an unsaturated or polyunsaturated fatty acid wherein the double bond that is closest to the methyl end of the molecule is located at carbon numbered 6 starting from the end methyl group) or an omega-3 fatty acid (i.e. an unsaturated or polyunsaturated fatty acid wherein the double bond that is closest to the methyl end of the molecule is located at carbon numbered 3 starting from the end methyl group), wherein all available H atoms are optionally replaced with deuterium. In some embodiments, A is an alkyl group present in a fatty acid wherein all available H atoms are optionally replaced with deuterium. In some embodiments, the alkyl or alkene group of A is an alkyl or alkene group present in a fatty acid selected from the list of fatty acids in Table 1 wherein all available H atoms are optionally replaced with deuterium.

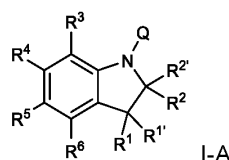
[00282] In some embodiments, the alkene group of A is an alkyl or alkenyl group present in linoleic acid, eicosadienoic acid or decosahexanoic acid.

[00283] In some embodiments, when A is the alkyl or alkenyl group of a fatty acid wherein 1-10, 2-8, 2-6 or 2-4 H atoms are replaced with deuterium.

[00284] In some embodiments, A is $(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$. In some embodiments, A is $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$. In some embodiments, A is $(\text{CH}_2)_8\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$. In some embodiments, A is $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$. In some embodiments, A is $(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$. In some embodiments, A is $(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$.

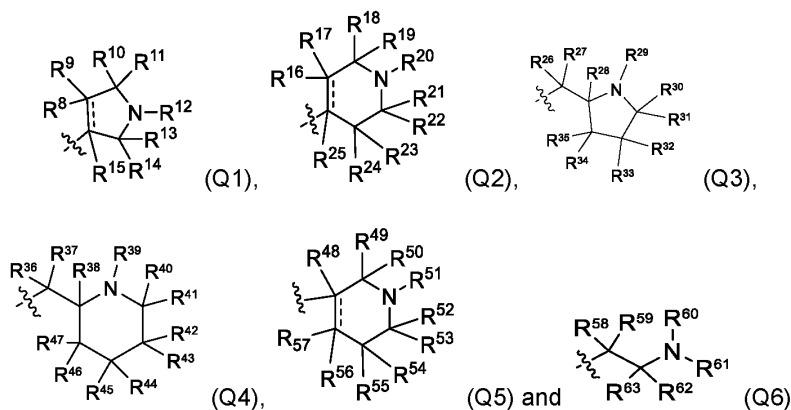
[00285] In some embodiments, R^{64} and R^{65} are independently selected from H, D, C_{1-4} alkyl, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl. In some embodiments, R^{64} and R^{65} are independently selected from H, D, CH_3 , CF_3 and CD_3 . In some embodiments, R^{64} and R^{65} are independently selected from CH_3 and CD_3 .

[00286] In some embodiments, the compound of Formula I-A is defined as follows:



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

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



== is a single bond or a double bond provided that when == in Q1 is a double bond then R^9 and R^{15} are not present, when == in Q2 is a double bond then R^{17} and R^{25} are not present and when == in Q5 is a double bond then R^{48} and R^{57} are not present;

R^1 , $\text{R}^{1'}$, R^2 , $\text{R}^{2'}$, R^3 and R^6 are independently selected from H, D and F;

one or both of R^4 and R^5 is selected from H, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy and C_{1-4} deuteroalkoxy, or

R^4 and R^5 are linked together to form $O-(CH_2)_{1-2}O$;

$R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{62}$ and R^{63} are independently selected from H and D;
 $R^{12}, R^{20}, R^{29}, R^{39}$ and R^{51} are independently selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl, and

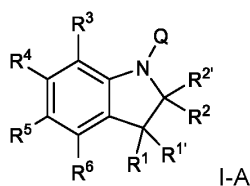
R^{60} and R^{61} are independently selected from H and C_{1-6} alkyl;

provided when Q is Q6 then the compound of Formula I comprises D;

when Q is Q3 or Q4, then $R^1, R^{1'}, R^2, R^{2'}, R^3, R^4, R^6, R^{26}, R^{27}, R^{28}, R^{30}$ to $R^{35}, R^{36}, R^{37}, R^{38}$ and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{29} or R^{39} is CH_3 and

when Q is Q4 and $R^1, R^{1'}, R^2, R^{2'}, R^3, R^4, R^6, R^{38}$ and R^{40} to R^{47} are all H, then R^{36} and R^{37} are not both D, when R^{39} is CD_3 .

[00287] In some embodiments, the compound of Formula I-A is defined as follows:



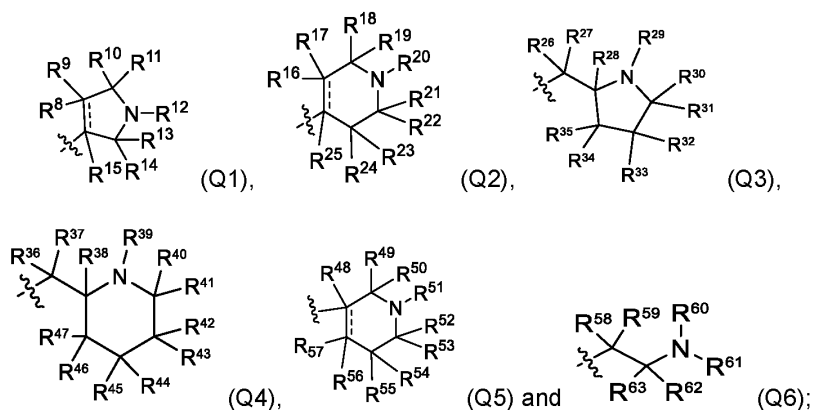
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

R^1 and $R^{1'}$ are independently selected from H, halo, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl) $_2$;

R^2 and $R^{2'}$ are independently selected from H, halo, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl) $_2$;

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



$\equiv$ is a single bond or a double bond provided that when $\equiv$ in Q1 is a double bond then R^9 and R^{15} are not present, when $\equiv$ in Q2 is a double bond then R^{17} and R^{25} are not present, and when $\equiv$ in Q5 is a double bond then R^{48} and R^{57} are not present;

one or both of R^4 and R^5 is independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy, or

R^4 and R^5 are linked together to form $O-(CH_2)_{1-2}O$, or

one of R^4 and R^5 is selected from X-L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy,

X is selected from a direct bond, O, $C(O)$, NR^a , $NR^aC(O)$, $C(O)NR^a$, $OC(O)$, $C(O)O$, $OC(O)O$, $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$;

L is selected from a direct bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{1-6} alkyleneO, C_{2-6} alkenyleneO, C_{1-6} alkyleneC(O), C_{2-6} alkenyleneC(O), C_{1-6} alkylene $NR^bC(O)$, C_{2-6} alkenylene $NR^bC(O)$, C_{1-6} alkyleneC(O) NR^b , C_{2-6} alkenyleneC(O) NR^b , C_{1-6} alkyleneOC(O), C_{2-6} alkenyleneOC(O), C_{1-6} alkyleneC(O)O, C_{2-6} alkenyleneC(O)O, C_{1-6} alkyleneOC(O) NR^b , C_{2-6} alkenyleneOC(O) NR^b , C_{1-6} alkylene $NR^bC(O)O$, C_{2-6} alkenylene $NR^bC(O)O$, C_{1-6} alkyleneOC(O)O, C_{2-6} alkenyleneOC(O)O, C_{1-6} alkylene $NR^bC(O)NR^b$ and C_{2-6} alkenylene $NR^bC(O)NR^b$;

R^a is selected from H and C_{1-6} alkyl;

R^b is selected from H, C_{1-6} alkyl and A;

A is selected from C_{1-30} alkyl, C_{2-30} alkenyl, phenyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 4 heteromoeities independently selected from O, S, S(O),

SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C₁₋₄alkyl and OC₁₋₄alkyl;

R³ and R⁶ are independently selected from H, halo, OH, C₁₋₆alkyl and C₁₋₆alkoxy;

R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H, halo and C₁₋₆alkyl;

R¹², R²⁰, R²⁹, R³⁹ and R⁵¹ are independently selected from H, C₁₋₆alkyl, C(O)C₁₋₆alkyl and C(O)-A';

R⁶⁰ and R⁶¹ are independently selected from H and C₁₋₆alkyl; or

one of R⁶⁰ and R⁶¹ is C(O)-A' and the other is selected from H and C₁₋₆alkyl;

wherein A' is selected from Y, O-Y and O-C₁₋₄alkylene-O-C(O)-Y; and

Y is selected from C₇₋₃₀alkyl and C₇₋₃₀alkenyl; or

R⁶⁰ and R⁶¹, together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoeities independently selected from O, S, S(O), SO₂, N, and NR⁶⁵ and which is optionally substituted with one or more substituents independently selected from halo, OH, C₁₋₄alkyl and OC₁₋₄alkyl;

R⁶⁴ and R⁶⁵ are independently selected from H and C₁₋₆alkyl; and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

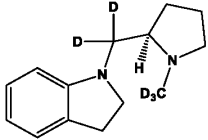
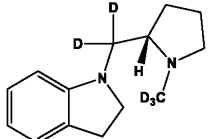
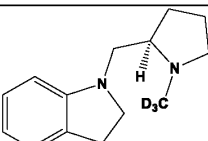
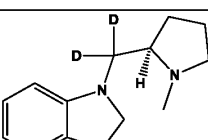
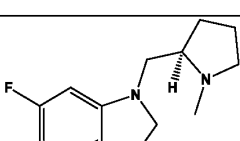
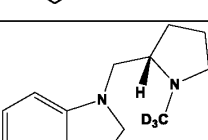
provided one of R¹², R²⁰, R²⁹, R³⁹, R⁵¹, R⁶⁰ and R⁶¹ is C(O)-A'; or

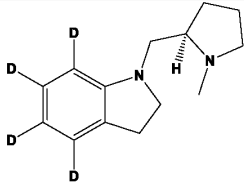
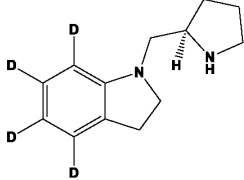
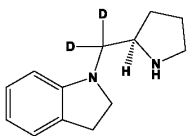
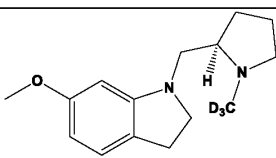
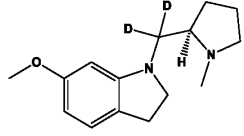
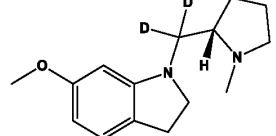
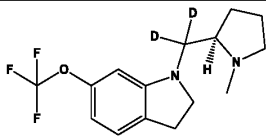
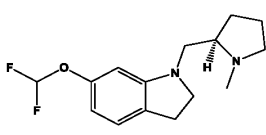
one of R⁴ and R⁵ is selected from X-L-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy provided A is not H, C₁₋₆alkyl or C₁₋₆alkynyl when X and L are both direct bonds.

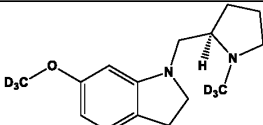
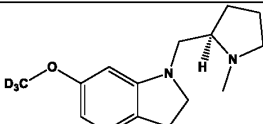
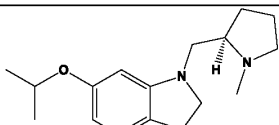
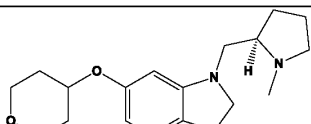
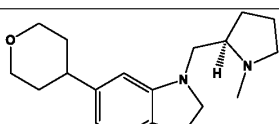
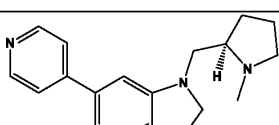
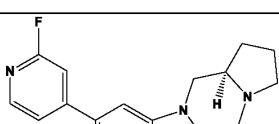
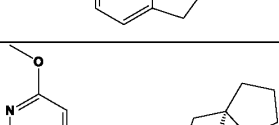
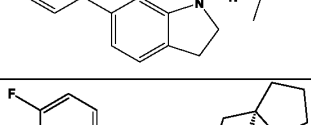
[00288] A person skilled in the art would appreciate that the carbon to which R^2 and $R^{2'}$ are bonded, when R^2 and $R^{2'}$ are different, is chiral. Therefore, the present application includes all stereoisomers at this carbon center and mixtures thereof.

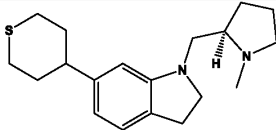
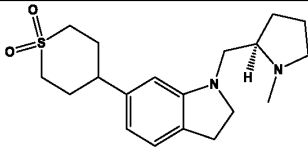
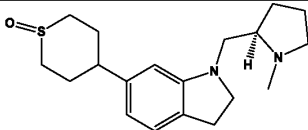
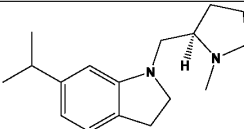
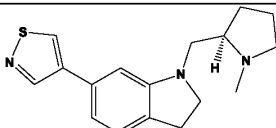
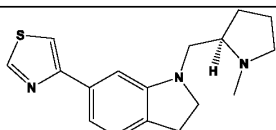
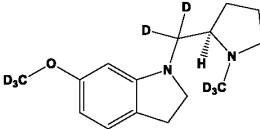
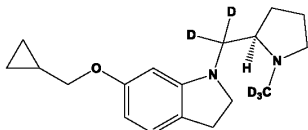
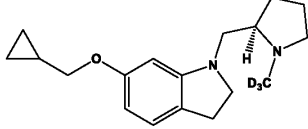
[00289] A person skilled in the art would appreciate that the carbon to which R^1 and $R^{1'}$ are bonded, when R^1 and $R^{1'}$ are different, is also chiral. Therefore, the present application includes all stereoisomers at this carbon center and mixtures thereof.

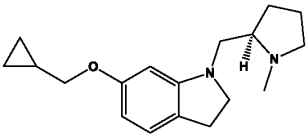
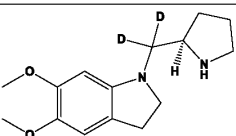
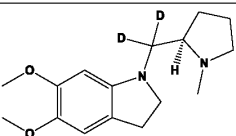
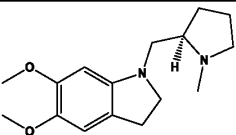
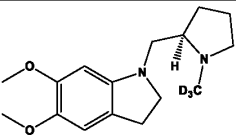
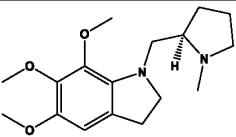
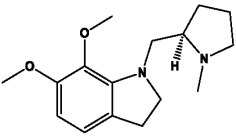
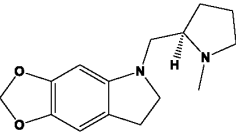
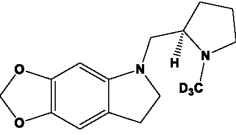
[00290] In some embodiments, the compounds of Formula I-A are selected from the compounds listed below, or a pharmaceutically acceptable salt, solvate and/or prodrug thereof:

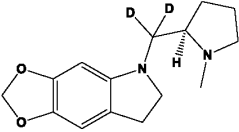
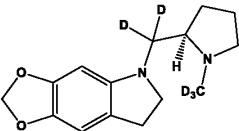
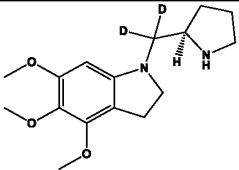
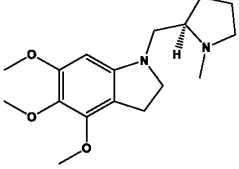
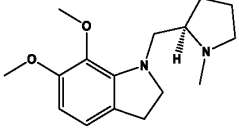
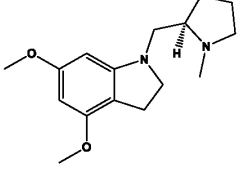
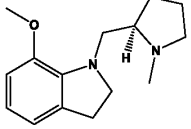
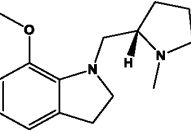
(R)-I-1	
(S)-I-1	
(R)-I-2	
(R)-I-3	
(R)-I-4	
(S)-I-5	

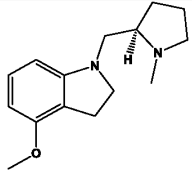
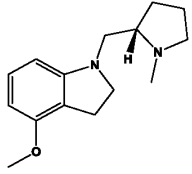
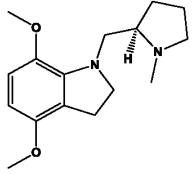
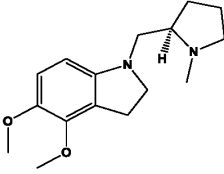
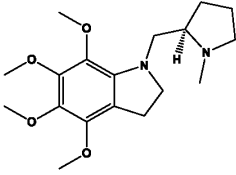
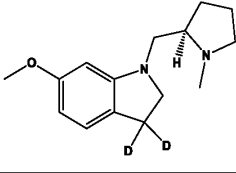
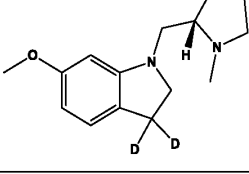
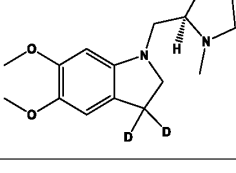
(R)-I-6	
(R)-I-7	
(R)-I-8	
(R)-I-9	
(R)-I-10	
(S)-I-10	
(R)-I-11	
(R)-I-12	

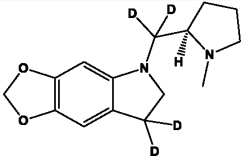
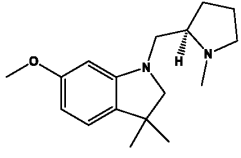
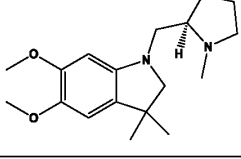
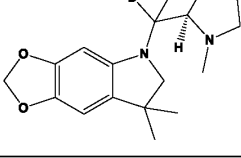
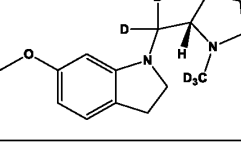
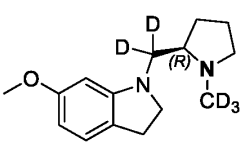
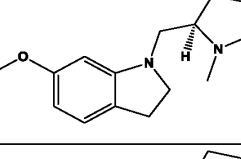
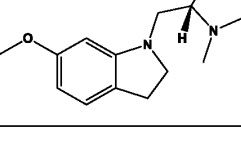
(R)-I-13	
(R)-I-14	
(R)-I-15	
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(R)-I-17	
(R)-I-18	
(R)-I-19	
(R)-I-20	
(R)-I-21	

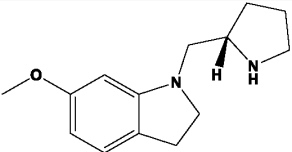
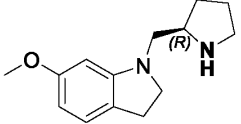
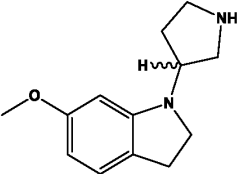
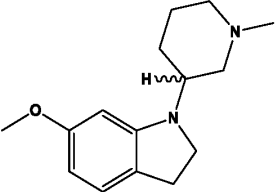
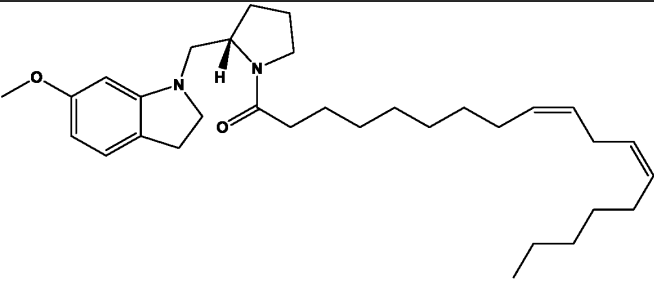
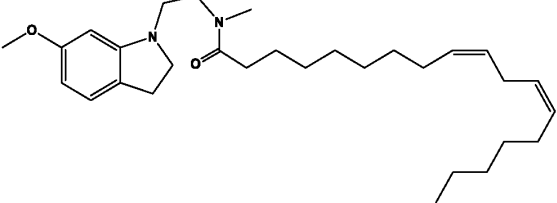
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(R)-I-23	
(R)-I-24	
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(R)-I-26	
(R)-I-27	
(R)-I-28	
(R)-I-29	
(R)-I-30	

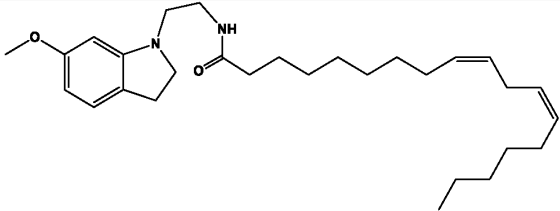
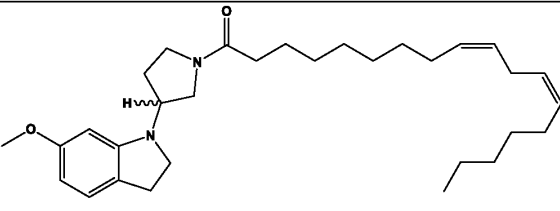
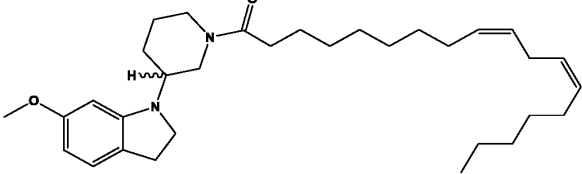
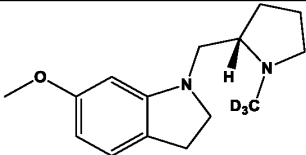
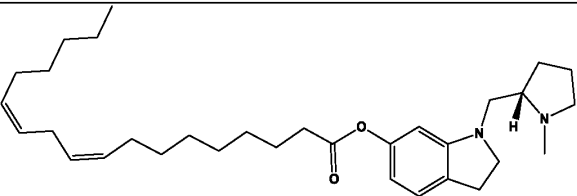
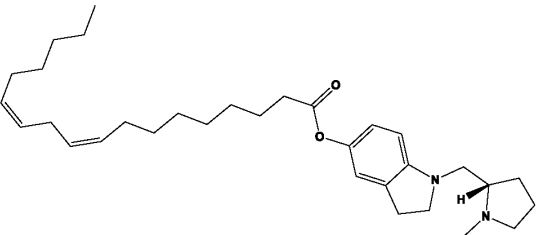
(R)-I-31	
(R)-I-32	
(R)-I-33	
(R)-I-34	
(R)-I-35	
(R)-I-36	
(R)-I-37	
(R)-I-38	
(R)-I-39	

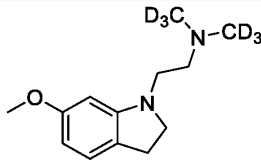
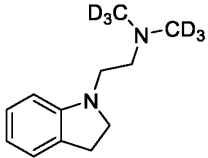
(R)-I-40	
(R)-I-41	
(R)-I-42	
(R)-I-43	
(R)-I-44	
(R)-I-45	
(R)-I-46	
(S)-I-46	

(R)-I-47	
(S)-I-47	
(R)-I-48	
(R)-I-49	
(R)-I-50	
(R)-I-51	
(S)-I-51	
(R)-I-52	

(R)-I-53	
(R)-I-54	
(R)-I-55	
(R)-I-56	
(S)-I-57	
(R)-I-57	
(R)-I-58	
(S)-I-58	

(S)-I-59	
(R)-I-59	
I-60	
I-61	
(S)-I-62	
I-63	

I-64	
I-65	
I-66	
(S)-I-67	
(S)-I-68	
(S)-I-69	

I-70	 , and
I-71	 .

[00291] 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, trifluoroacetic 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).

[00292] 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 application for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

[00293] 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, Abutyl 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.

[00294] All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the application and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the application. In addition, when a compound of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 application.

[00295] Solvates of compounds of Formula I or I-A or a pharmaceutically salt and/or prodrug thereof 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.

[00296] Prodrugs of the compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 (C₁-C₂₄) esters, acyloxymethyl esters, carbamates and amino acid esters.

[00297] It is understood and appreciated that in some embodiments, compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 application. 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 application.

[00298] In some embodiments, the compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 application.

[00299] The compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 application.

[00300] The compounds of the present application may further be radiolabeled and accordingly all radiolabeled versions of the compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof are included within the scope of the present application. Therefore, the compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof also include those in which one or more radioactive atoms are incorporated within their structure.

IV. Compositions

[00301] The compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof are suitably formulated in a conventional manner into compositions using one or more carriers. Accordingly, the present application also includes a composition comprising one or more compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof and a carrier. The compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof are suitably formulated into pharmaceutical compositions for administration to subjects in a biologically compatible form

suitable for administration in vivo. Accordingly, the present application further includes a pharmaceutical composition comprising one or more compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof and a pharmaceutically acceptable carrier. In embodiments of the application the pharmaceutical compositions are used in the treatment of any of the diseases, disorders or conditions described herein.

[00302] The compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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.

[00303] 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.

[00304] In some embodiments, a compound of Formula I or I-A or a pharmaceutically acceptable salt, solvate and/or prodrug thereof 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 and used in the form of ingestible tablets, buccal tablets, troches, capsules, caplets, pellets, granules, lozenges, chewing gum, powders, syrups, elixirs, wafers, aqueous solutions and 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); or wetting agents (e.g., sodium lauryl sulphate), or solvents (e.g. medium chain triglycerides, ethanol, 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.

[00305] 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid). Useful diluents include lactose and high molecular weight polyethylene glycols.

[00306] It is also possible to freeze-dry the compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof and use the lyophilizates obtained, for example, for the preparation of products for injection.

[00307] In some embodiments, a compound of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof is administered parenterally. For example, solutions of a compound of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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.

[00308] In some embodiments, a compound of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 multi-dose 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof are suitably in a sterile powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[00309] 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof and a suitable powder base such as lactose or starch. The aerosol dosage forms can also take the form of a pump-atomizer.

[00310] Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein a compound of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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.

[00311] Suppository forms of the compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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.

[00312] In some embodiments a compound of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

[00313] The compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof are particularly amenable to administration with the aid of nano-carrier systems, such as liposomes, micelles, nanoparticles, nano-emulsions, lipidic nano-systems and the like (see for example, Bhat, M. et al., Chem. and Phys. of Lipids, 2021, 236, 105053). Accordingly the present application includes a composition comprising one or more compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof and one or more components of a nano-carrier system.

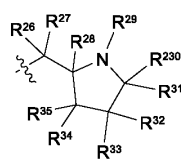
[00314] A compound of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof including pharmaceutically acceptable salts, solvates and/or prodrugs thereof is suitably used on their own but will generally be administered in the form of a pharmaceutical composition in which the one or more compounds of Formula I or I-A or a pharmaceutically salt, solvate and/or prodrug thereof (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.

[00315] In some embodiments, the compounds of Formula I or I-A including pharmaceutically acceptable salts, solvates and/or prodrugs thereof are used are administered in a composition comprising an additional therapeutic agent. Therefore the present application also includes a pharmaceutical composition comprising one or more compounds of Formula I or I-A, 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.

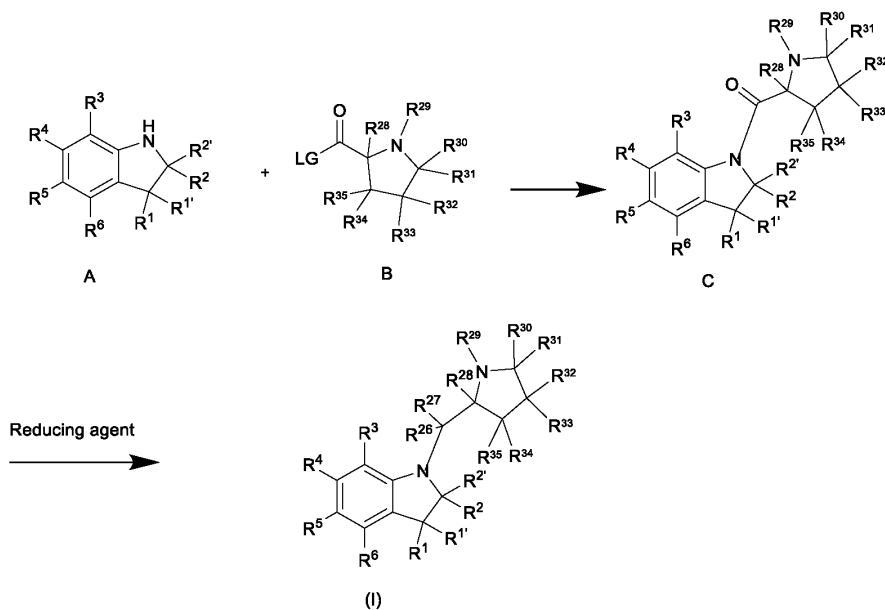
[00316] In the above, the term "a compound" also includes embodiments wherein one or more compounds are referenced.

V. Preparation of Compounds

[00317] Compounds of Formula I or a pharmaceutically salt, solvate and/or prodrug thereof including compounds of Formula I-A or a pharmaceutically salt, solvate and/or prodrug thereof 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof is within the purview of the person of skill in the art. Some starting materials for preparing compounds of Formula I or a pharmaceutically salt, solvate and/or prodrug thereof 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 application, all variables are as defined in Formula I, unless otherwise stated.



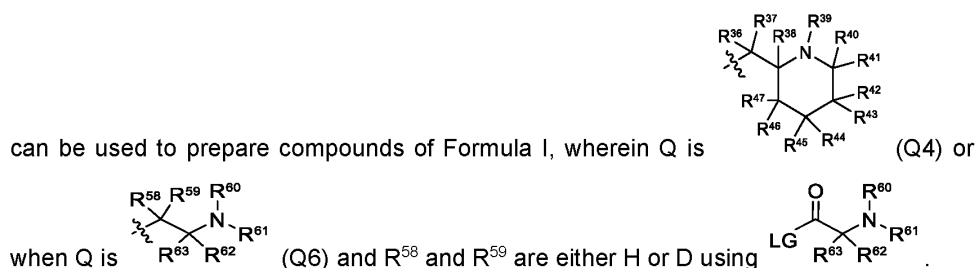
[00318] In some embodiments, when Q is (Q3) and R^{26} and R^{27} are either H or D, the compounds of Formula I are prepared as shown in Scheme 1:

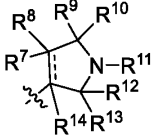


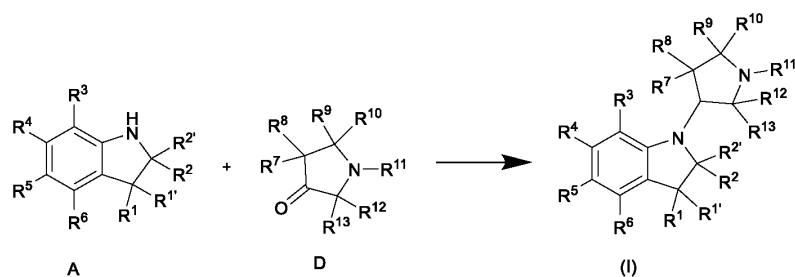
Scheme 1

[00319] Therefore, in some embodiments, compounds of Formula A, wherein R¹, R^{1'}, R², R^{2'}, R³, R⁴, R⁵ and R⁶ are as defined in Formula I, are reacted under basic conditions using, for example, pyridine with compounds of Formula B, wherein R²⁸ and R³⁰-R³⁵ are as defined in Formula I, R²⁹ is as defined in Formula I or is a suitable protecting group and LG is a suitable leaving group, such as chloro or OH, to provide compounds of Formula C. Reduction of keto group in the compounds of Formula C, for example using Al-based reducing agents such as lithium borohydride, lithium aluminum hydride or lithium aluminum deuteride, provides the compounds of Formula (I), wherein R³³ and R³⁴ are either H or D. If R²⁹ is a protecting group, it is removed in a separate step or, wherein the protecting group is removed in the presence of Al-based reducing agents is removed during the reduction of the compounds of Formula C.

[00320] A person skilled in the art would appreciate that a similar reaction sequence



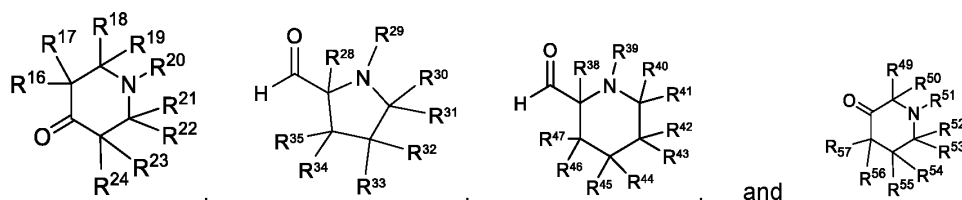
[00321] In some embodiments, when Q is  (Q1) and --- is a single bond and R^{14} is either H or D, the compounds of Formula I are prepared as shown in Scheme 2:



Scheme 2

[00322] Therefore, in some embodiments, the compounds of Formula A, wherein R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 and R^6 are as defined in Formula I, are reacted with keto compounds of Formula D, wherein R^7 , R^{10} , R^{12} , R^{13} are as defined in Formula I, R^{11} is as defined in Formula I or is a suitable protecting group in the presence of a suitable reducing agent such as sodium triacetoxyborohydride (STAB) to provide the compounds of Formula (I), wherein R^{14} is either H or D. If R^{11} is a protecting group, it is removed in a separate step.

[00323] A person skilled in the art would appreciate that a similar reaction sequence can be used to prepare compounds of Formula I, wherein Q is (Q2) and --- is a single bond, (Q3), (Q4) and (Q5) and --- is a single bond using the following keto compounds

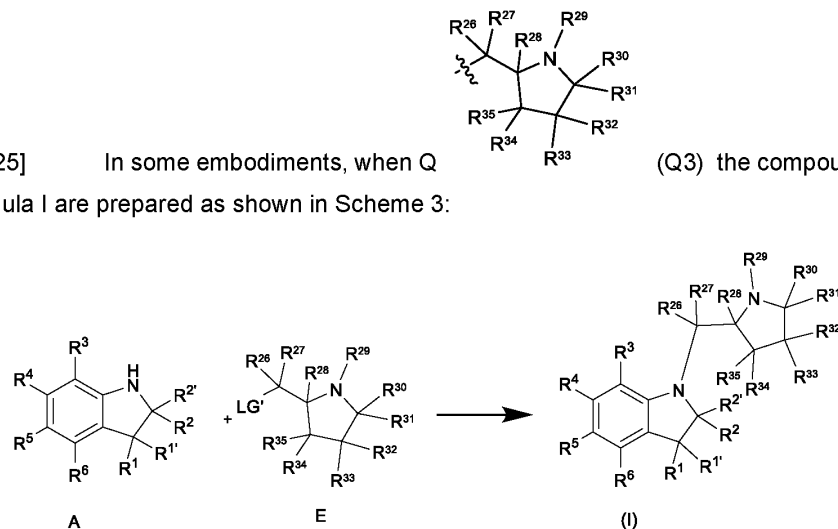


respectively.

[00324] In some embodiments, when Q is (Q1) and --- is a single bond and R^{14} is either H or D, Q is (Q2) and --- is a single bond and R^{25} is either H or D, Q is (Q3), Q is (Q4) or Q is (Q5) and --- is a single bond the compounds of Formula I are prepared as shown using methods known in the art, for example, the methods described

in WO2013122107, US20080234237, US20070099913 and/or Annedi S. C et al., European Journal of Medicinal Chemistry, 55, 94-107, 2012.

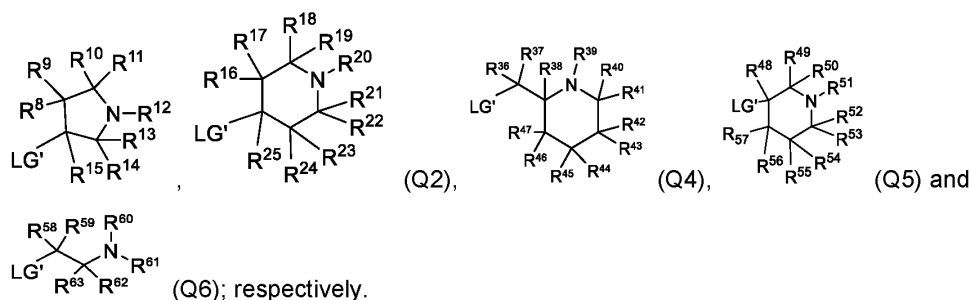
[00325] In some embodiments, when Q (Q3) the compounds of Formula I are prepared as shown in Scheme 3:



Scheme 3

[00326] Therefore, in some embodiments, the compounds of Formula A, wherein R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , R^4 , R^5 and R^6 are as defined in Formula I, are reacted with compounds of Formula E, wherein R^{26} , R^{27} , R^{28} , R^{30} - R^{36} are as defined in Formula I, R^{29} is as defined in Formula I or is a suitable protecting group and LG is a suitable leaving group, such as chloro, bromo, iodo, mesylate or tosylate, in the presence of a suitable base such as N,N-diisopropylethylamine (DIPEA) to provide compounds of Formula I. If R^{29} is a protecting group, it is removed in a separate step.

[00327] A person skilled in the art would appreciate that a similar reaction sequence can be used to prepare compounds of Formula I, wherein Q is Q1 and --- is a single bond, Q2 and --- is a single bond, Q4, Q5 and --- is a single bond and Q6 using



[00328] In some embodiments, wherein Q is Q1 and --- is a single bond, Q2 and --- is a single bond, Q3, Q4, Q5 and --- is a single bond and Q6 the compounds of Formula I are prepared as shown using methods known in the art, for example, the methods described in WO2008153207, Takahashi et al. Chem. Pharm. Bull. (2010) 58(8) 1057—1065 (2010), and/or Mino et al. The Journal of Organic Chemistry (2005), 70, 5, 1937-1940.

[00329] A person skilled in the art would appreciate that specific enantiomers or diastereomers of the compounds of the application are available by using corresponding single enantiomers or diastereomers of the corresponding starting materials.

[00330] 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).

[00331] 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).

[00332] 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.

[00333] The products of the processes of the application 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.

[00334] Generally, the reactions described above are performed in a suitable inert organic solvent and at temperatures and for times that will optimize the yield of the desired compounds. Examples of suitable inert organic solvents include, but are not limited to, 2-propanol, dimethylformamide (DMF), 1,4-dioxane, methylene chloride, chloroform, tetrahydrofuran (THF), toluene, and the like.

[00335] The formation of a desired compound salt is achieved using standard techniques. For example, the neutral compound is treated with an acid or base in a suitable solvent and the formed salt is isolated by filtration, extraction or any other suitable method.

[00336] The formation of solvates of the compounds of the application 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.

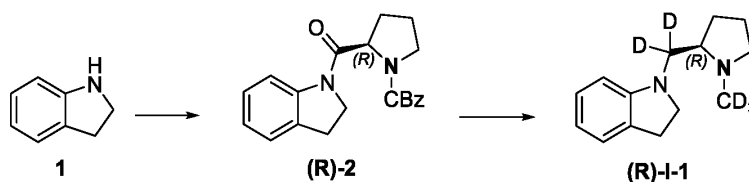
[00337] Prodrugs of the compounds of the present application may be, for example, conventional esters formed with available hydroxy, thiol, amino or carboxyl groups. For example, available hydroxy or amino groups may be acylated using an activated acid in the presence of a base, and optionally, in inert solvent (e.g. an acid chloride in pyridine).

[00338] One skilled in the art will recognize that where a reaction step of the present application 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

A. Synthesis of Exemplary Compounds of the Application

Example 1: (R)-1-((1-(Methyl-d₃)pyrrolidin-2-yl)methyl-d₂)indoline ((R)-I-1)

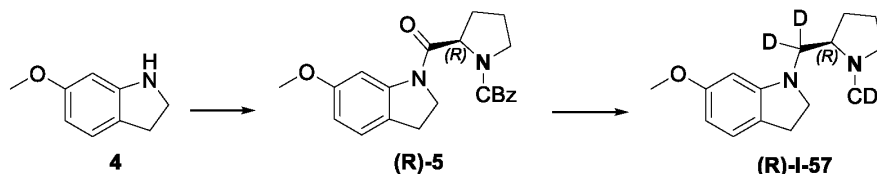


[00339] Synthesis of (R)-2-(2-(indoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2 λ 2-ethan-1-one ((R)-2): A solution of ((benzyloxy)carbonyl)-D-proline (5.0 g, 20.05 mmol) in dry THF (60 mL) was treated with thionyl chloride (2.92 mL, 40.11 mmol) at room temperature and the resulting solution was refluxed for additional 2 h. The reaction was brought to room temperature and solvent was evaporated to obtain the crude acid chloride as pale-yellow oil.

[00340] A solution of above crude acid chloride in CH₂Cl₂ (30 mL) was treated with a solution of indoline (2.25 mL, 20.05 mmol) in CH₂Cl₂ (20 mL), followed by pyridine (3.24 mL, 40.11 mmol) at 0 °C. The reaction was brought to room temperature and stirred overnight (16 h). The reaction was diluted with CH₂Cl₂ (100 mL), washed with water (100 mL), 1 N HCl solution (50 mL), brine (50 mL) and dried (Na₂SO₄). Solvent was evaporated and crude was purified by flash column chromatography (EtOAc: CH₂Cl₂, 1:9) on silica gel to obtain the title compound (R)-2 (7.0 g, quantitative) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 8.10, 8.06 (2d, 1H, J = 3.0, 6.0 Hz), 7.38-7.23 (m, 6H), 7.19-6.99 (m, 2H), 5.11-4.89 (m, 2H), 4.64-4.60 (m, 1H), 4.25-3.95 (m, 2H), 3.51-3.45 (m, 2H), 3.20-2.94 (m, 2H), 2.31-2.27 (m, 1H), 1.99-1.85 (m, 3H); ESI-MS (*m/z*, %): 373 (M+Na), 351 (MH⁺), 277 (100).

[00341] Synthesis of (R)-1-((1-(methyl-*d*₃)pyrrolidin-2-yl)methyl-*d*₂)indoline ((R)-I-1): A solution of (R)-2-(2-(indoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2 λ 2-ethan-1-one (1.96 g, 5.89 mmol) in dry THF (50 mL) was treated with LiAlD₄ (1.24 g, 29.48 mmol) at 0 °C over a period of 10 min. and refluxed for overnight (16 h). The reaction was brought to room temperature, then cooled to 0 °C, treated with water (1.24 mL), 2 N NaOH solution (1.24 mL) and water (1.24 mL). The reaction was brought to room temperature and stirred for additional 30 min. Solid was filtered off and washed with THF (3 x 25 mL). Solvent was evaporated and crude was purified by column chromatography (2 M NH₃ in MeOH: CH₂Cl₂, 5:95) on silica gel to obtain the title compound (R)-I-1 (0.31 g, 24.2%) as pale-yellow oil. ¹H NMR (DMSO-*d*₆): δ 7.02-6.95 (m, 2H), 6.54 (t, 1H, J = 6.0 Hz), 6.46 (d, 1H, J = 6.0 Hz), 3.43-3.31 (m, 2H), 2.99-2.95 (m, 1H), 2.88 (t, 2H, J = 6.0 Hz), 2.38 (d, 2H, J = 6.0 Hz), 2.15-2.12 (m, 1H), 1.95-1.90 (m, 1H), 1.69-1.52 (m, 3H); ESI-MS (*m/z*, %): 222 (MH⁺, 100).

Example 2: (R)-6-Methoxy-1-((1-(methyl-*d*₃)pyrrolidin-2-yl)methyl-*d*₂)indoline ((R)-I-57)



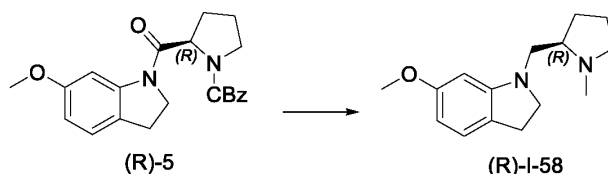
[00342] Synthesis of (R)-2-(2-(6-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2λ²-ethan-1-one ((R)-5): A solution of ((benzyloxy)carbonyl)-D-proline (6.0 g, 24.07 mmol) in dry THF (70 mL) was treated with thionyl chloride (3.51 mL, 48.14 mmol) at room temperature and the resulting solution was refluxed for additional 2 h. The reaction was brought to room temperature and solvent was evaporated to obtain the crude acid chloride as pale-yellow oil.

[00343] A solution of above crude acid chloride in CH₂Cl₂ (50 mL) was treated with a solution of 6-methoxyindoline (3.6 g, 24.07 mmol) in CH₂Cl₂ (30 mL), followed by pyridine (3.89 mL, 48.14 mmol) at 0 °C. The reaction was brought to room temperature and stirred overnight (16 h). The reaction was diluted with CH₂Cl₂ (100 mL), washed with water (2 x 100 mL), 1 N HCl solution (100 mL), brine (50 mL) and dried (Na₂SO₄). Solvent was evaporated and crude was purified by flash column chromatography (EtOAc: CH₂Cl₂, 1:9) on silica gel to obtain the title compound (R)-5 (8.9 g, 97%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 7.77, 7.74 (2d, 1H, J = 3.0 Hz), 7.38-7.36 (m, 2H), 7.33-7.04 (m, 4H), 6.61-6.57 (m, 1H), 5.12-4.89 (m, 2H), 4.63-4.59 (m, 1H), 4.24-3.97 (m, 2H), 3.72, 3.71 (2s, 3H), 3.51-3.32 (m, 2H), 3.11-2.86 (m, 2H), 2.30-2.30 (m, 1H), 1.97-1.85 (m, 3H); ESI-MS (*m/z*, %): 403 (M+Na), 381 (MH⁺).

[00344] Synthesis of (R)-6-methoxy-1-((1-(methyl-*d*₃)pyrrolidin-2-yl)methyl-*d*₂)indoline ((R)-I-57): A suspension of LiAlD₄ (0.83 g, 19.71 mmol) in dry THF (40 mL) was treated with AlCl₃ (3.15 g, 23.65 mmol) at 0 °C. The reaction was treated with (R)-2-(2-(6-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2λ²-ethan-1-one (1.5 g, 3.94 mmol) in dry THF (20 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was cooled to 0 °C, quenched with water (1.0 mL), 2 N NaOH solution (1 mL) and water (1 mL). The reaction was brought to room temperature and stirred for additional 30 min. The reaction was diluted with THF (50 mL), filtered through a pad of Na₂SO₄, followed by a pad of silica gel. Solvent was evaporated and crude was purified by column chromatography (2 M NH₃ in MeOH: CH₂Cl₂, 5:95) on silica gel to obtain the title compound (R)-I-57 (0.92 g, 93%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 6.89 (d, 1H, J = 3.0 Hz), 6.21 (brs, 1H), 6.13 (dd, 1H,

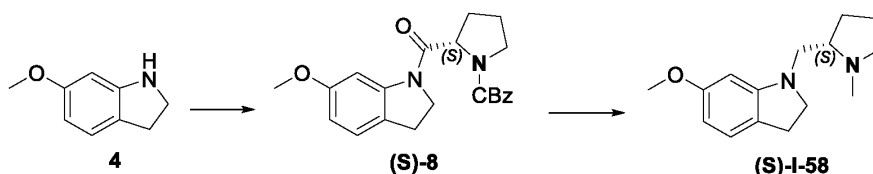
3.0, 4.5 Hz), 3.68 (s, 3H), 3.49-3.46 (m, 1H), 3.31-3.16 (m, 4H), 2.84-2.78 (m, 2H), 2.12-2.07 (m, 1H), 1.90-1.80 (m, 2H), 1.68-1.60 (m, 1H); ESI-MS (m/z, %): 252 (MH⁺, 100).

Example 3: (R)-6-Methoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((R)-I-58)



[00345] Synthesis of (R)-6-methoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((R)-I-58): A suspension of LiAlH₄ (0.74 g, 19.71 mmol) in dry THF (40 mL) was treated with AlCl₃ (3.15 g, 23.65 mmol) at 0 °C. The reaction was treated with (R)-2-(2-(6-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2λ²-ethan-1-one (1.5 g, 3.94 mmol) in dry THF (20 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was cooled to 0 °C, quenched with water (1.0 mL), 2 N NaOH solution (1 mL) and water (1 mL). The reaction was brought to room temperature and stirred for additional 30 min. The reaction was diluted with THF (50 mL), filtered through a pad of Na₂SO₄, followed by a pad of silica gel. Solvent was evaporated and crude was purified by column chromatography (2 M NH₃ in MeOH: CH₂Cl₂, 5:95) on silica gel to obtain the title compound (R)-I-58 (0.8 g, 82.5%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 6.87 (d, 1H, J = 6.0 Hz), 6.10-6.08 (m, 2H), 3.67 (s, 3H), 3.44-3.39 (m, 1H), 3.35-3.33 (m, 1H), 3.31-3.29 (m, 1H), 3.20-3.15 (m, 1H), 2.96-2.91 (m, 1H), 2.82-2.77 (m, 2H), 2.60-2.52 (m, 1H), 2.40 (s, 3H), 2.30-2.25 (m, 1H), 2.00-1.92 (m, 1H), 1.72-1.67 (m, 2H), 1.59-1.52 (m, 1H); ESI-MS (m/z, %): 247 (MH⁺, 100).

Example 4: (S)-6-Methoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((S)-I-58)



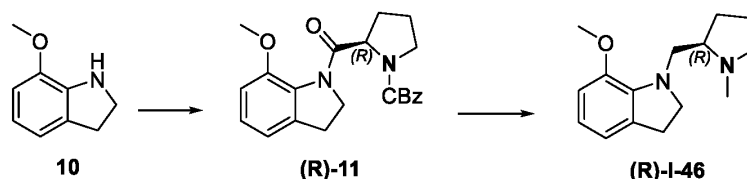
[00346] Synthesis of (S)-2-(2-(6-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2λ²-ethan-1-one ((S)-8): A solution of ((benzyloxy)carbonyl)-L-proline (2.2 g, 8.82

mmol) in dry THF (30 mL) was treated with thionyl chloride (1.29 mL, 17.65 mmol) at room temperature and the resulting solution was refluxed for additional 2 h. The reaction was brought to room temperature and solvent was evaporated to obtain the crude acid chloride as pale-yellow oil.

[00347] A solution of above crude acid chloride in CH₂Cl₂ (20 mL) was treated with a solution of 6-methoxyindoline (1.32 g, 8.82 mmol) in CH₂Cl₂ (10 mL), followed by pyridine (1.43 mL, 17.65 mmol) at 0 °C. The reaction was brought to room temperature and stirred overnight (16 h). The reaction was diluted with CH₂Cl₂ (100 mL), washed with water (100 mL), 1 N HCl solution (50 mL), brine (50 mL) and dried (Na₂SO₄). Solvent was evaporated and crude was purified by flash column chromatography (EtOAc: CH₂Cl₂, 1:9) on silica gel to obtain the title compound (S)-8 (3.1 g, 96.8%) as a pale-yellow glue. ¹H NMR (DMSO-*d*₆): δ 7.78, 7.75 (2d, 1H, J = 3.0 Hz), 7.39-7.33 (m, 2H), 7.19-7.05 (m, 4H), 6.63-6.58 (m, 1H), 5.13-4.90 (m, 2H), 4.65-4.60 (m, 1H), 4.25-3.98 (m, 2H), 3.73, 3.72 (2s, 3H), 3.53-3.45 (m, 2H), 3.13-2.87 (m, 2H), 2.31-2.29 (m, 1H), 2.00-1.86 (m, 3H); ESI-MS (m/z, %): 403 (M+Na), 381 (MH⁺, 100).

[00348] Synthesis of (S)-6-methoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((S)-I-58): A suspension of LiAlH₄ (1.34 g, 35.48 mmol) in dry THF (60 mL) was treated with AlCl₃ (5.67 g, 42.58 mmol) at 0 °C. The reaction was treated with (S)-2-(2-(6-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2λ²-ethan-1-one (2.7 g, 7.09 mmol) in dry THF (30 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was cooled to 0 °C, quenched with water (1.34 mL), 2 N NaOH solution (1.34 mL) and water (1.34 mL). The reaction was brought to room temperature and stirred for additional 30 min. The reaction was diluted with THF (50 mL), filtered through a pad of Na₂SO₄, followed by a pad of silica gel. Solvent was evaporated and crude was purified by column chromatography (2 M NH₃ in MeOH: CH₂Cl₂, 5:95) on silica gel to obtain the title compound (S)-I-58 (1.14 g, 65.5%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 6.90 (d, 1H, J = 3.0 Hz), 6.27 (brs, 1H), 6.15 (dd, 1H, J = 3.0 Hz), 3.68 (s, 3H), 3.50-3.25 (m, 5H), 3.11-3.09 (m, 1H), 2.87-2.79 (m, 2H), 2.77-2.65 (m, 1H), 2.50 (s, 3H, merged with DMSO peak), 2.15-2.10 (m, 1H), 1.90-1.85 (m, 2H), 1.71-1.63 (m, 1H); ESI-MS (m/z, %): 247 (MH⁺, 100).

Example 5: (R)-7-Methoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((R)-I-46)



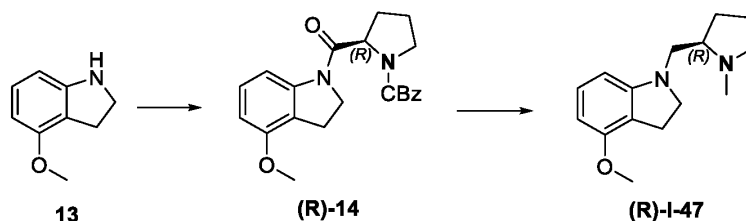
[00349] Synthesis of (R)-2-(2-(7-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2λ²-ethan-1-one ((R)-11): A solution of ((benzyloxy)carbonyl)-D-proline (1.67 g, 6.70 mmol) in dry THF (20 mL) was treated with thionyl chloride (0.97 mL, 13.40 mmol) at room temperature and the resulting solution was refluxed for additional 2 h. The reaction was brought to room temperature and solvent was evaporated to obtain the crude acid chloride as pale-yellow oil.

[00350] A solution of above crude acid chloride in CH₂Cl₂ (20 mL) was treated with a solution of 7-methoxyindoline (1.0 g, 6.70 mmol) in CH₂Cl₂ (10 mL), followed by pyridine (1.0 mL, 13.40 mmol) at 0 °C. The reaction was brought to room temperature and stirred overnight (16 h). The reaction was diluted with CH₂Cl₂ (100 mL), washed with water (100 mL), 1 N HCl solution (50 mL), brine (50 mL) and dried (Na₂SO₄). Solvent was evaporated and crude was purified by flash column chromatography (EtOAc: CH₂Cl₂, 1:9) on silica gel to obtain the title compound (R)-11 (2.1 g, 84%) as purple glue. ¹H NMR (DMSO-*d*₆): δ 7.37-7.30 (m, 4H), 7.26-7.22 (m, 2H), 7.11-6.86 (m, 2H), 5.02-4.85 (m, 2H), 4.64-4.50 (m, 1H), 4.30-4.20 (m, 1H), 3.81, 3.77 (2s, 3H), 3.50-3.31 (m, 3H), 3.05-2.70 (m, 1H), 2.65-2.55 (m, 1H), 2.23-2.21 (m, 1H), 2.04-1.81 (m, 3H); ESI-MS (*m/z*, %): 403 (M+Na, 100), 381 (MH⁺).

[00351] Synthesis of (R)-7-methoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((R)-I-46): A suspension of LiAlH₄ (0.8 g, 21.02 mmol) in dry THF (50 mL) was treated with AlCl₃ (3.36 g, 25.23 mmol) at 0 °C. The reaction was treated with (R)-2-(2-(7-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2λ²-ethan-1-one (1.6 g, 4.20 mmol) in dry THF (20 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was cooled to 0 °C, quenched with water (0.8 mL), 2 N NaOH solution (0.8 mL) and water (0.8 mL). The reaction was brought to room temperature and stirred for additional 30 min. The reaction was diluted with THF (50 mL), filtered through a pad of Na₂SO₄, followed by a pad of silica gel. Solvent was evaporated and crude was purified by column chromatography (2 M NH₃ in MeOH: CH₂Cl₂, 5:95) on silica gel to obtain the title compound (R)-I-46 (0.77 g, 74.7%) as colourless oil. ¹H NMR (DMSO-*d*₆): δ 6.71-6.66 (m, 2H), 6.57 (t, 1H, *J* = 3.0 Hz), 3.71 (s, 3H), 3.51 (dd, 1H, *J* = 3.0, 6.0 Hz), 3.37-3.28 (m, 2H), 3.14 (dd, 1H, *J* = 3.0 Hz), 2.97-2.93 (m, 1H), 2.86

(t, 2H, $J = 3.0$ Hz), 2.37-2.34 (m, 1H), 2.30 (s, 3H), 2.12-2.08 (m, 1H), 1.92-1.88 (m, 1H), 1.67-1.61 (m, 3H); ESI-MS (m/z , %): 247 (MH^+ , 100).

Example 6: (R)-4-Methoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((R)-I-47)



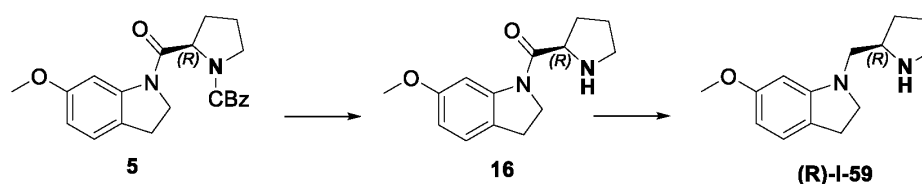
[00352] Synthesis of (R)-2-(2-(4-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2,2-ethan-1-one ((R)-14): A solution of ((benzyloxy)carbonyl)-D-proline (1.67 g, 6.70 mmol) in dry THF (20 mL) was treated with thionyl chloride (0.97 mL, 13.40 mmol) at room temperature and the resulting solution was refluxed for additional 2 h. The reaction was brought to room temperature and solvent was evaporated to obtain the crude acid chloride as pale-yellow oil.

[00353] A solution of above crude acid chloride in CH_2Cl_2 (20 mL) was treated with a solution of 4-methoxyindoline (1.0 g, 6.70 mmol) in CH_2Cl_2 (10 mL), followed by pyridine (1.0 mL, 13.40 mmol) at 0 °C. The reaction was brought to room temperature and stirred overnight (16 h). The reaction was diluted with CH_2Cl_2 (100 mL), washed with water (100 mL), 1 N HCl solution (50 mL), brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated and crude was purified by flash column chromatography (EtOAc: CH_2Cl_2 , 1:9) on silica gel to obtain the title compound (R)-14 (2.4 g, 94%) as light purple solid. 1H NMR ($DMSO-d_6$): δ 7.74, 7.69 (2d, 1H, $J = 6.0$ Hz), 7.39-7.32 (m, 2H), 7.20-7.13 (m, 3H), 7.08-7.04 (m, 1H), 6.71 (t, 1H, $J = 6.0$ Hz), 5.12-4.90 (m, 2H), 4.63-4.58 (m, 1H), 4.27-3.97 (m, 2H), 3.81, 3.80 (2s, 3H), 3.53-3.45 (m, 2H), 3.09-2.82 (m, 2H), 2.31-2.27 (m, 1H), 2.00-1.85 (m, 3H); ESI-MS (m/z , %): 403 ($M+Na$, 100), 381 (MH^+).

[00354] Synthesis of (R)-4-methoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((R)-I-47): A suspension of $LiAlH_4$ (1.0 g, 26.28 mmol) in dry THF (50 mL) was treated with $AlCl_3$ (4.2 g, 31.54 mmol) at 0 °C. The reaction was treated with (R)-2-(2-(4-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2,2-ethan-1-one (2.0 g, 5.25 mmol) in dry THF (30 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was cooled to 0 °C, quenched with water (1.0 mL), 2 N NaOH solution (1.0 mL) and water (1.0 mL). The reaction was brought

to room temperature and stirred for additional 30 min. The reaction was diluted with THF (50 mL), filtered through a pad of Na₂SO₄, followed by a pad of silica gel. Solvent was evaporated and crude was purified by column chromatography (2 M NH₃ in MeOH: CH₂Cl₂, 5:95) on silica gel to obtain the title compound (R)-I-47 (0.98 g, 76%) as an off-white solid. ¹H NMR (DMSO-*d*₆): δ 7.00 (t, 1H, J = 6.0 Hz), 6.34-6.32 (m, 2H), 3.73 (s, 3H), 3.59-3.12 (m, 6H), 2.87-2.73 (m, 3H), 2.50 (s, 3H, merged with DMSO peak), 2.20-2.10 (m, 1H), 1.95-1.85 (m, 2H), 1.72-1.64 (m, 1H); ESI-MS (m/z, %): 247 (MH⁺, 100).

Example 7: (R)-6-Methoxy-1-(pyrrolidin-2-ylmethyl)Indoline((R)-I-59)

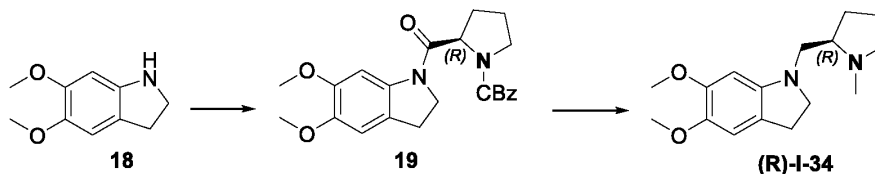


[00355] **Synthesis of (R)-6-methoxy-1-prolylindoline (16):** A solution of (R)-2-(2-(6-methoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2-oxoethan-1-one (1.5 g, 3.94 mmol) in dry methanol (50 mL) was treated with 10% Palladium on carbon (1.5 g, dry basis) and hydrogenated under hydrogen atm (40 PSI) for overnight (18 h). The reaction was filtered through a pad of celite, and washed with methanol (2 x 25 mL). Combined methanol layer was evaporated and crude was purified by flash column chromatography (2 M NH₃ in MeOH: CH₂Cl₂, 5:95) on silica gel to obtain the title compound 16 (0.78 g, 80.4%) as a pale-yellow glue. ¹H NMR (DMSO-*d*₆): 7.75 (d, 1H, J = 3.0 Hz), 7.13 (d, 1H, J = 6.0 Hz), 6.58 (dd, 1H, J = 3.0, 6.0 Hz), 4.30-4.23 (m, 1H), 4.13-4.04 (m, 1H), 3.87-3.84 (m, 1H), 3.72 (s, 3H), 3.18 (s, 1H), 3.09-2.97 (m, 3H), 2.74-2.68 (m, 1H), 2.10-2.01 (m, 1H), 1.79-1.61 (m, 3H); ESI-MS (m/z, %): 247 (MH⁺, 100).

[00356] **Synthesis of (R)-6-methoxy-1-(pyrrolidin-2-ylmethyl)indoline (R)-I-59:** A suspension of LiAlH₄ (0.55 g, 14.61 mmol) in dry THF (20 mL) was treated with AlCl₃ (2.33 g, 17.53 mmol) at 0 °C. The reaction was treated with (R)-6-methoxy-1-prolylindoline (0.72 g, 2.92 mmol) in dry THF (20 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was cooled to 0 °C, quenched with water (0.6 mL), 2 N NaOH solution (0.6 mL) and water (0.6 mL). The reaction was brought to room temperature and stirred for additional 30 min. The reaction was diluted with THF (50 mL), filtered through a pad of Na₂SO₄, followed by a pad of silica gel. Solvent was evaporated and crude was purified by column chromatography (2 M NH₃ in MeOH: CH₂Cl₂, 5:95) on silica gel to obtain the title compound (R)-I-59 (0.6 g,

89.5%) as a pale-yellow glue. ^1H NMR ($\text{DMSO}-d_6$): 6.87 (d, 1H, $J = 6.0$ Hz), 6.09-6.05 (m, 2H), 3.67 (s, 3H), 3.42-3.36 (m, 2H), 3.24-3.21 (m, 1H), 2.98-2.90 (m, 2H), 2.88-2.71 (m, 4H), 1.83-1.61 (m, 3H), 1.36-1.30 (m, 1H); ESI-MS (m/z , %): 233 (MH^+ , 100).

Example 8: (R)-5,6-dimethoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((R)-I-34)

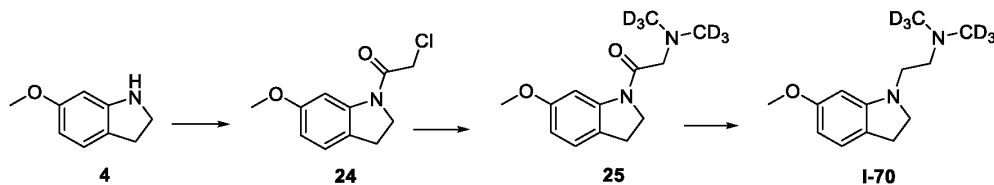


[00357] Synthesis of (R)-2-(2-(5,6-dimethoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2H-ethan-1-one (19): A solution of ((benzyloxy)carbonyl)-D-proline (1.39 g, 5.57 mmol) in dry THF (20 mL) was treated with thionyl chloride (0.4 mL, 11.16 mmol) at room temperature and the resulting solution was refluxed for additional 2 h. The reaction was brought to room temperature and solvent was evaporated to obtain the crude acid chloride as pale-yellow oil.

[00358] A solution of above crude acid chloride in CH_2Cl_2 (10 mL) was treated with a solution of 5,6-dimethoxyindoline (1.0 g, 5.57 mmol) in CH_2Cl_2 (20 mL), followed by pyridine (0.9 mL, 11.15 mmol) at 0°C . The reaction was brought to room temperature and stirred overnight (16 h). The reaction was worked-up and purified as described for compound 8 to obtain the title compound 19 (2.05 g, 89.5%) as tan solid. ESI-MS (m/z , %): 433 ($\text{M}+\text{Na}$), 411 (MH^+ , 100).

[00359] Synthesis of (R)-5,6-dimethoxy-1-((1-methylpyrrolidin-2-yl)methyl)indoline ((R)-I-34): A suspension of LiAlH_4 (0.76 g, 20.22 mmol) in dry THF (50 mL) was treated with AlCl_3 (3.2 g, 24.26 mmol) at 0°C . The reaction was treated with (R)-2-(2-(5,6-dimethoxyindoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2H-ethan-1-one (1.66 g, 4.04 mmol) in dry THF (20 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was worked-up and purified as described for compound 6 to obtain the title compound (R)-I-34 (0.7 g, 63%) as a pale-yellow oil. ^1H NMR ($\text{DMSO}-d_6$): δ 6.75 (s, 1H), 6.27 (s, 1H), 3.71 (s, 3H), 3.63 (s, 3H), 3.31-3.24 (m, 2H), 3.07 (dd, 1H, $J = 3.0, 9.0$ Hz), 3.00-2.95 (m, 1H), 2.87 (dd, 1H, $J = 3.0, 9.0$ Hz), 2.78 (t, 2H, $J = 6.0$ Hz), 2.38-2.34 (m, 4H), 2.15-2.13 (m, 1H), 1.96-1.91 (m, 1H), 1.70-1.55 (m, 3H); ESI-MS (m/z , %): 277 (MH^+ , 100).

Example 9: 2-(6-Methoxyindolin-1-yl)-N,N-bis(methyl-d3)ethan-1-amine (I-70)

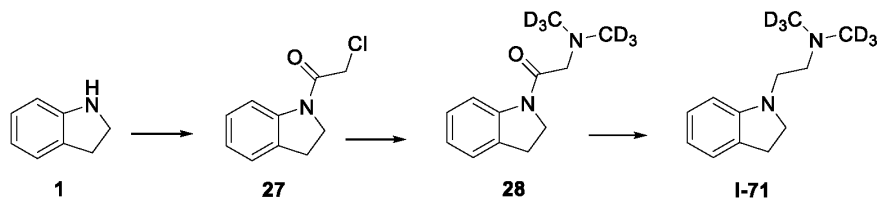


[00360] Synthesis of 2-chloro-1-(6-methoxyindolin-1-yl)ethan-1-one (24): A solution of 6-methoxyindoline (2.0 g, 13.40 mmol) and pyridine (2.38 mL, 29.49 mmol) in dry CH_2Cl_2 (30 mL) was treated with 2-chloroacetyl chloride (2.13 mL, 26.81 mmol) over a period of 10 min. at 0 °C. The reaction was brought to room temperature and stirred overnight (16 h). The reaction was worked-up and purified as described for compound 21 to obtain the title compound 24 (3.0 g, quantitative) as an off-white solid.

[00361] Synthesis of 2-(bis(methyl- d_3)amino)-1-(6-methoxyindolin-1-yl)ethan-1-one (25): A solution of 2-chloro-1-(6-methoxyindolin-1-yl)ethan-1-one (2.0 g, 8.86 mmol), K_2CO_3 (3.67 g, 26.58 mmol), bis(methyl- d_3)amine hydrochloride (1.16 mL, 13.29 mmol) and DMF (0.3 mL) in dry ACN (50 mL) was stirred at 50 °C in a sealed tube for overnight (16 h). The reaction was cooled to room temperature, worked-up and purified as described for compound 22 to obtain the title compound 25 (1.7 g, 80%) as light brown oil. ^1H NMR ($\text{DMSO}-d_6$): δ 7.73 (d, 1H, J = 3.0 Hz), 7.12 (d, 1H, J = 6.0 Hz), 6.57 (dd, 1H, J = 3.0, 6.0 Hz), 4.16 (t, 2H, J = 6.0 Hz), 3.72 (s, 3H), 3.20 (s, 2H), 3.05 (t, 2H, J = 6.0 Hz); ESI-MS (m/z , %): 241 (MH^+ , 100).

[00362] Synthesis of 2-(6-methoxyindolin-1-yl)- N,N -bis(methyl- d_3)ethan-1-amine (I-70): A suspension of LiAlH_4 (0.98 g, 26.01 mmol) in dry THF (50 mL) was treated with AlCl_3 (4.2 g, 31.21 mmol) at 0 °C. The reaction was treated with 1-(6-methoxyindolin-1-yl)-2-(dimethylamino)ethan-1-one (1.78 g, 7.43 mmol) in dry THF (20 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was worked-up and purified as described for compound 6 to obtain the title compound I-70 (1.15 g, 68.8%) as pale-yellow oil. ^1H NMR ($\text{DMSO}-d_6$): δ 6.88-6.86 (m, 1H), 6.10-6.07 (m, 2H), 3.67 (s, 3H), 3.36 (t, 2H, J = 6.0 Hz), 3.12 (t, 2H, J = 6.0 Hz), 2.78 (t, 2H, J = 6.0 Hz), 2.42 (t, 2H, J = 6.0 Hz); ESI-MS (m/z , %): 227 (MH^+ , 100).

Example 10: 2-(Indolin-1-yl)- N,N -bis(methyl- d_3)ethan-1-amine (I-71)

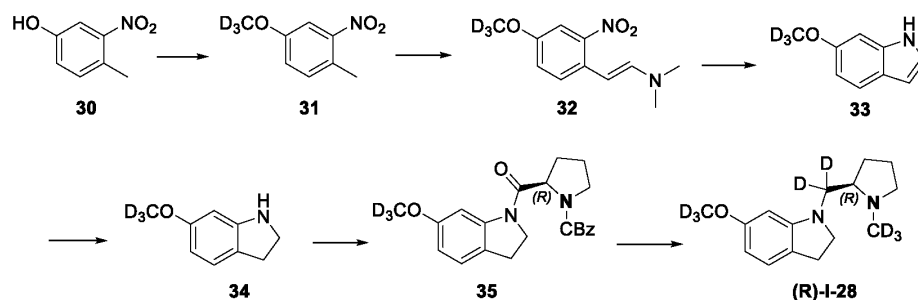


[00363] Synthesis of 2-chloro-1-(indolin-1-yl)ethan-1-one (27): A solution of indoline (1.0 g, 8.39 mmol) and pyridine (1.49 mL, 18.46 mmol) in dry CH_2Cl_2 (20 mL) was treated with 2-chloroacetyl chloride (1.33 mL, 16.78 mmol) over a period of 10 min. at 0 °C. The reaction was brought to room temperature and stirred overnight (16 h). The reaction was worked-up and purified as described for compound 21 to obtain the title compound 27 (1.6 g, 97.5%) as an off-white solid.

[00364] Synthesis of 2-(bis(methyl- d_3)amino)-1-(indolin-1-yl)ethan-1-one (28): A solution of 2-chloro-1-(indolin-1-yl)ethan-1-one (2.0 g, 10.22 mmol), K_2CO_3 (4.23 g, 30.66 mmol), bis(methyl- d_3)amine hydrochloride (1.34 mL, 15.33 mmol) and DMF (0.3 mL) in dry ACN (50 mL) was stirred at 50 °C in a sealed tube for overnight (16 h). The reaction was cooled to room temperature, worked-up and purified as described for compound 22 to obtain the title compound 28 (1.8 g, 83.7%) as pale-yellow oil. ^1H NMR ($\text{DMSO}-d_6$): δ 8.07 (d, 1H, $J = 6.0$ Hz), 7.24 (d, 1H, $J = 6.0$ Hz), 7.15 (t, 1H, $J = 6.0$ Hz), 7.02-6.98 (m, 1H), 4.16 (t, 2H, $J = 6.0$ Hz), 3.21 (s, 2H), 3.13 (t, 2H, $J = 6.0$ Hz); ESI-MS (m/z , %): 211 (MH^+ , 100).

[00365] Synthesis of 2-(indolin-1-yl)-N,N-bis(methyl- d_3)ethan-1-amine (I-71): A suspension of LiAlH_4 (1.098 g, 28.92 mmol) in dry THF (50 mL) was treated with AlCl_3 (4.62 g, 34.71 mmol) at 0 °C. The reaction was treated with 2-(bis(methyl- d_3)amino)-1-(indolin-1-yl)ethan-1-one (1.738 g, 8.26 mmol) in dry THF (20 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was worked-up and purified as described for compound 6 to obtain the title compound I-71 (0.96 g, 59.2%) as light brown oil. ^1H NMR ($\text{DMSO}-d_6$): δ 7.02-6.95 (m, 2H), 6.56-6.47 (m, 2H), 3.34 (t, 2H, $J = 6.0$ Hz), 3.12 (t, 2H, $J = 6.0$ Hz), 2.86 (t, 2H, $J = 60$ Hz), 2.43 (t, 2H, $J = 6.0$ Hz); ESI-MS (m/z , %): 197 (MH^+ , 100).

Example 11: (R)-6-(Methoxy- d_3)-1-((1-(methyl- d_3)pyrrolidin-2-yl)methyl- d_2)indoline ((R)-I-28)



[00366] Synthesis of 4-(methoxy- d_3)-1-methyl-2-nitrobenzene (31): A solution of 4-methyl-3-nitrophenol (25.3 g, 165.25 mmol) in dry DMF (200 mL) was treated with KOH (10.2 g, 181.77 mmol), t Bu₄NBr (0.53 g, 1.65 mmol) and CD₃I (10.8 mL, 173.51 mmol) at room temperature. The reaction was stirred at 60 °C in a sealed tube for 24 h. The reaction was brought to room temperature, diluted with water (1 L) and product was extracted into diethyl ether (2 x 300 mL). Combined diethyl ether layer was washed with water (2 x 100 mL), brine (100 mL) and dried (Na₂SO₄). Solvent was evaporated to obtain the crude title compound 31 (28.0 g) as a brown liquid.

[00367] Synthesis of 2-(4-(methoxy- d_3)-2-nitrophenyl)-N,N-dimethylethen-1-amine (32): A solution of 4-(methoxy- d_3)-1-methyl-2-nitrobenzene (28.0 g, 164.53 mmol) in DMF (150 mL) was treated with DMF.DMA (65.6 mL, 493.59 mmol) at room temperature and the resulting solution was stirred at 130 °C for overnight (16 h). The temperature of reaction was reduced to 90 °C and solvent was distilled off to obtain crude title compound 32, which was used in the next step without any further purification.

[00368] Synthesis of 6-(methoxy- d_3)-1H-indole (33): A solution of above crude 2-(4-(methoxy- d_3)-2-nitrophenyl)-N,N-dimethylethen-1-amine in toluene (150 mL) was treated with palladium on carbon (2.1 g, 10% dry basis) and hydrogenated using Paar apparatus. The reaction was filtered through a pad celite and washed with ethyl acetate (3 x 50 mL). Combined organic layer was evaporated and crude was purified by flash column chromatography (EtOAc: hexane, 1:4) on silica gel to obtain the title compound (4.52 g, 18.2% over three steps). ¹H NMR (CDCl₃): δ 8.03 (brs, 1H), 7.55 (d, 1H, J = 6.0 Hz), 7.12 (dd, 1H, J = 3.0 Hz), 6.90 (d, 1H, J = 3.0 Hz), 6.84 (dd, 1H, J = 3.0, 6.0 Hz), 6.53-6.51 (m, 1H).

[00369] Synthesis of 6-(methoxy- d_3)indoline (34): A solution of 6-(methoxy- d_3)-1H-indole (1.5 g, 9.98 mmol) in acetic acid (30 mL) was treated with sodium cyanoborohydride (1.88 g, 29.96 mmol) portion-wise at 0 °C. The reaction was brought to room temperature and stirred for additional 1 h. The reaction was quenched with 4 N NaOH solution at 0 °C

and product was extracted into ethyl acetate (2 x 50 mL). Combined ethyl acetate layer was washed with brine (25 mL) and dried (Na₂SO₄). Solvent was evaporated and crude was purified by column chromatography (EtOAc: Hexanes, 1:4) on silica gel to obtain the title compound 34 (1.27 g, 83.5%) as brown liquid. ¹H NMR (CDCl₃): δ 7.03-7.00 (m, 1H), 6.29-6.26 (m, 2H), 3.59 (t, 2H, J = 6.0 Hz), 2.98 (t, 2H, J = 6.0 Hz).

[00370] Synthesis of (R)-2-(2-(6-(methoxy-*d*₃)indoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2¹²-ethan-1-one (35): A solution of ((benzyloxy)carbonyl)-D-proline (2.08 g, 8.34 mmol) in dry THF (30 mL) was treated with thionyl chloride (1.21 mL, 16.69 mmol) at room temperature and the resulting solution was refluxed for additional 2 h. The reaction was brought to room temperature and solvent was evaporated to obtain the crude acid chloride as pale-yellow oil.

[00371] A solution of above crude acid chloride in CH₂Cl₂ (10 mL) was treated with a solution of 6-(methoxy-*d*₃)indoline (1.27 g, 8.34 mmol) in CH₂Cl₂ (30 mL), followed by pyridine (1.35 mL, 16.69 mmol) at 0 °C. The reaction was brought to room temperature and stirred overnight (16 h). The reaction was worked-up and purified as described for compound 8 to obtain the title compound 35 (3.1 g, 96.8%) as light brown oil. ESI-MS (m/z, %): 406 (M+Na), 384 (MH⁺).

[00372] Synthesis of (R)-6-(methoxy-*d*₃)-1-((1-(methyl-*d*₃)pyrrolidin-2-yl)methyl-*d*₂)indoline ((R)-I-28): A suspension of LiAlD₄ (1.42 g, 33.90 mmol) in dry THF (50 mL) was treated with AlCl₃ (5.4 g, 40.68 mmol) at 0 °C. The reaction was treated with (R)-2-(2-(6-(methoxy-*d*₃)indoline-1-carbonyl)pyrrolidin-1-yl)-1-phenyl-2¹²-ethan-1-one (2.6 g, 6.78 mmol) in dry THF (30 mL) over a period of 5 min. after stirring for 15 min. The reaction was brought to room temperature and stirred for additional 4 h. The reaction was worked-up and purified as described for compound 6 to obtain the title compound (R)-I-28 (1.26 g, 73%) as a pale-yellow oil. ¹H NMR (DMSO-*d*₆): δ 6.88-6.85 (m, 1H), 6.09-6.03 (m, 2H), 3.44-3.31 (m, 2H), 2.99-2.94 (m, 1H), 2.82-2.78 (m, 2H), 2.36 (t, 1H, J = 6.0 Hz), 2.16-2.09 (m, 1H), 1.94-1.87 (m, 1H), 1.70-1.50 (m, 3H); ESI-MS (m/z, %): 255 (MH⁺, 100).

B. Biological Testing

Example 12: FLIPR assay: human 5-HT_{2A}

Objective:

[00373] Assessment of the effect of exemplary compounds of Formula I targeting on human 5-HT_{2A} (h5-HT_{2A}) receptor under agonist mode.

Materials and Instrumentation

1.1 Cell line

Cell line Name	Target	Host cell
HTR2A&Gr15-HEK293	5HT2A	Flp-In-293

1.2 Compound Preparation and Assay Controls

Reagent and Materials:

Reagents	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

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

Item	Supplier	Cat#
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

2 Experimental Methods

2.1 Cell culture

[00374] 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

[00375] 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.

[00376] 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.

[00377] 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.

[00378] 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.

[00379] 5. The cell suspension was transferred into a 15 mL centrifuge tube, and then centrifuged at 1,200 rpm for 5 minutes.

[00380] 6. The supernatant was removed. The cell pellet was resuspended with 2 mL cell culture medium.

[00381] 7. The cell density was counted using cell counter. Only cells with >85% viability were used for the assay.

[00382] 8. Cells were diluted to 6.67×10^5 /mL with cell culture medium.

[00383] 9. 30 µL/well cell suspensions added into a 384-well cell plate (The cell density was 20,000 cells/well).

[00384] 10. The cell plate was incubated overnight at 37°C, 5% (v/v) CO₂.

2.3 Cell handling

[00385] 1. On the day of experiments, culture medium was removed from the cell plate.

[00386] 2. 10 µL of assay buffer (20 mM HEPES, in 1× HBSS, pH 7.4) was added to each well of the cell plate.

[00387] 3. 2×dye solution was prepared following the manual of the FLIPR® Calcium 6 Assay Kit:

[00388] i. The dye was diluted with assay buffer.

[00389] ii. Probenecid was added to the final concentration of 5 mM.

[00390] iii. Vortexed vigorously for 1–2 minutes.

[00391] 4. 10 µL of 2× dye solution was added to each well of the cell plate

[00392] 5. The cell plate was placed on plate shaker, followed by shaking at 600 rpm for 2 minutes.

[00393] 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

[00394] 1. Serotonin HCl was prepared to the concentration of 10 mM with DMSO.

[00395] 2. The test compounds were prepared to the concentration of 10 mM with DMSO.

[00396] 3. The compounds were added to a 384-well compound source plate.

[00397] 4. 3-folds serial dilutions were performed with DMSO.

[00398] 5. 90 nL/well of serial diluted compounds was transferred from source plate to a 384-well compound plate by using an Echo.

[00399] 6. 30 µL/well of assay buffer (20mM HEPES in 1× HBSS, pH 7.4) was added to the compound plate.

[00400] 7. The plate was mixed on-plate shaker for 2 minutes.

2.5 FLIPR assay

[00401] 1. After the cells were incubated with dye solution, the cell plate, compound plate containing 3×compounds and FLIPR tips were placed into FLIPR.

[00402] 2. 10 µL of 3×compounds transferred from the compound plate to the cell plate by FLIPR.

[00403] 3. The plate was read for 160 sec with 1 sec interval and the data of agonist mode was obtained.

3 2.6 Data Analysis

[00404] 1. The normalized fluorescence reading (RFU) was calculated as shown below, wherein Fmax and Fmin stand for maximum and minimum of calcium signal during defined time window:

$$\text{RFU} = \text{Fmax} - \text{Fmin}$$

[00405] 2. EC_{50} by fitting RFU against log of compound concentrations with Hill equation was calculated using XLfit.

3.0 Experimental Methods and Procedures:

The following procedure can also be followed:

[00406] 1. Cells are cultured in cell culture medium (DMEM containing 10% FBS, 1× penicillin-streptomycin 300 µg/ml G418 and 100 µg/ml hygromycin B) at 37°C, 5% (v/v) CO₂.

[00407] 2. One day before the assays, the cells are detached using TrypLE™ Express and cells are counted using cell counter. Only cells with >85% viability are used for the assay.

[00408] 3. 20000 cells/well are seeded in 30 µl/well culture medium to a 384-well cell plate and cells are incubated overnight at 37°C, 5% (v/v) CO₂.

[00409] 4. On the assay day, 2×dye solution is prepared following the manual of the FLIPR® Calcium 6 Assay Kit: i. The dye is diluted with assay buffer (20mM HEPES in 1× HBSS, PH7.4); ii. Probenecid is added to the final concentration of 5 mM; iii. Vortex vigorously for 1–2 minutes.

[00410] 5. Medium is removed from cell plate by flicking the cell plate on towel papers.

[00411] 6. 10 µl of assay buffer and 10 µl of 2×dye solution is added to each well of the cell plate.

[00412] 7. The cell plate is placed on plate shaker, the plate is agitated at 600rpm for 2 minutes. The plate is incubated at 37°C for 2 hours followed by additional 15-minute incubation at 25°C.

[00413] 8. 3×compound in assay buffer is prepared: a. Reference compounds are diluted to required concentration with DMSO. The compounds are added to a 384-well compound plate; b. Serial dilutions are performed; c. 10mM test compounds are added to the compound plate, and 3-fold serial dilutions are performed. d. Transfer 60 nl/well of compounds from source plate to a 384-well compound plate (Corning, 3657) by using an Echo; e. Add 20µl/well assay buffer to the compound plate; f. Mix the plate on plate shaker for 2 mins;

[00414] 9. The cell plate, compound plate and tips are put into FLIPR, 10µl of 3× compound is transferred to the cell plate per well with FLIPR.

Data Analysis

[00415] i. The normalized fluorescence reading (RFU) is calculated as shown below, where Fmax and Fmin stand for maximum and minimum of calcium signal during defined time window: $RFU = F_{max} - F_{min}$

[00416] ii. Calculate the percentage activation using following equation:

$$\%Activation = \frac{(RFU_{compound} - RFU_{low\ control})}{(RFU_{top\ concentration\ of\ reference\ agonist} - RFU_{low\ control})} \times 100\%$$

[00417] iii. Calculate EC_{50} by fitting %activation against log of compound concentrations with Hill equation using XLfit.

Results & Discussion

[00418] Exemplary compounds of Formula I were evaluated functionally using FLIPR assay for their effect on h5-HT2A receptor under agonist mode. The results of potential competition binding properties of the exemplary compounds of the application targeting the human 5-hydroxytryptamine receptor 2A (5-HT2A) are summarized in Table 2. The results of exemplary compounds of the application are presented as IC_{50} is provided in Table 2.

Table 2: Effect of exemplary compounds of Formula I using FLIPR functional assay on human 5-HT2A receptor

Compound ID#	h5-HT2A, EC_{50} [nM]	$RFU@10\ \mu M^{(1)}$
Psilocybin	ND ⁽²⁾	257
Psilocin	72.5	308
(R)-I-1	3551	386
(R)-I-57	422	749
(R)-I-58	322	796
(S)-I-58	ND	203
(R)-I-46	1137	487
(R)-I-47	ND	174
(R)-I-59	1211	801
(R)-I-34	ND	268
I-70	ND	303
I-71	ND	280
(R)-I-28	1,093	3744

- (1) Curve fitting with activation (%) @ 10mM with RFU
- (2) ND: not detected

[00419] Exemplary compounds of Formula I were evaluated using radioligand binding assay on human 5-HT_{2A} receptor. EC₅₀ (nM) concentrations are illustrated in Table 2. This assay confirms that compounds of the application are effective ligands of the target human 5-HT_{2A} receptors.

Example 13: Human 5-HT_{2A}: Radioligand binding assay:

Objective

[00420] Exemplary compounds of Formula I were evaluated functionally using FLIPR assay for their effect on h5-HT_{2A} receptor under agonist mode. 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}).

Human 5-HT_{2A}: Radioligand binding assay:

1 Materials and Instrumentals

1.1 Regents

Items	Vendor	Cat#
Ketanserin Hydrochloride, [Ethylene- ³ H]-	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

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

Item	Supplier	Cat#
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 Experiment Procedure

[00421] i. The assay buffer was prepared following the table below.

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	

[00422] ii. 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.

[00423] iii. UniFilter-96 GF/B plate was pretreated:

[00424] a. 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.

[00425] b. After incubation, the plates were washed 3 times with ice-cold wash buffer (50 mM Tris, pH7.4).

[00426] iv. The assay plate was prepared:

[00427] a. 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.

[00428] b. 8 concentrations of reference or test compounds were prepared and 110 µl/well was added to 96 round deep well plates.

[00429] c. [3H]-ketanserin was diluted with assay buffer to 5 nM (5X final concentration) and 110 µl/well was added to 96 round deep well plates.

- [00430] v. The plate was centrifuged at 1000 rpm for 30 secs and then agitated at 600 rpm, R.T. for 5 min.
- [00431] vi. The plates were sealed and the plate incubated at 27°C for 90 min.
- [00432] vii. 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).
- [00433] viii. The plates were dried at 37°C for 45 min.
- [00434] ix. The filter plates were sealed and 40 µl/well of scintillation cocktail was added.
- [00435] x. The plate was read by using a Microbeta² microplate counter.

3 Data Analysis

- [00436] 1. For reference and test compounds, the results were expressed as % Inhibition, using the normalization equation: $N = 100 - 100 \times (U - C2) / (C1 - C2)$, where U is the unknown value, C1 is the average of high controls, and C2 is the average of low controls.
- [00437] 2. The IC₅₀ was determined by fitting percentage of inhibition as a function of compound concentrations with Hill equation using XLfit.

Results and Discussion

[00438] The results of potential competition binding properties of the exemplary compounds the application targeting the human 5-hydroxytryptamine receptor 2A (5-HT_{2A}) are summarized in Table 3. The results of exemplary compounds of the application are presented as IC₅₀ provided in Table 3.

Table 3: 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]
Psilocybin	4248
Psilocin	187.2
(R)-I-1	4528
(R)-I-57	7955
(R)-I-58	6525
(S)-I-58	>30000
(R)-I-46	2460
(R)-I-47	>30000

(R)-I-59	15253
(R)-I-34	>30000
I-70	25794
I-71	14972
(R)-I-28	8483

II. Results & Discussion

[00439] Exemplary compounds of Formula I were evaluated using radioligand binding assay on human 5-HT_{2A} receptor. IC₅₀ (nM) concentrations are illustrated in Table 3. This assay confirms that compounds of the application are effective ligands of the target human 5-HT_{2A} receptors.

Example 14: Human 5-HT_{1A}: Functional FLIPR assay

1 Objective

[00440] The potential excitatory effects of compounds targeting on 5-hydroxytryptamine receptor 1A (5-HT_{1A}) under agonist mode was assessed.

2 Materials and Instrumentation

2.1 Cell line

Cell line Name	Target	Host cell
HTR1A&Gα15-CHO	5HT1A	Flp-in CHO

2.2 Materials

Reagents	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

2.3 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

3 Experimental Methods

3.1 Cell culture

[00441] HTR1A&Gα15-CHO 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

[00442] 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.

[00443] 2. The cell culture medium was removed from flask. Washed cells with DPBS.

[00444] 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.

[00445] 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.

[00446] 5. The cell suspension was transferred into a 15 mL centrifuge tube, and then centrifuged at 1,200 rpm for 5 minutes.

[00447] 6. The supernatant was removed. The cell pellet were resuspended with 2 mL cell culture medium.

[00448] 7. The cell density were counted using cell counter. Only cells with >85% viability were used for the assay.

[00449] 8. Cells were diluted to 4×10^5 /mL with cell culture medium.

[00450] 9. 30 µL/well cell suspensions were added into a 384-well cell plate (The cell density was 12,000 cells/well).

[00451] 10. The cell plate was incubated overnight at 37°C, 5% (v/v) CO₂.

3.3 Cell handling

[00452] 1. On the day of experiments, culture medium was removed from the cell plate.

[00453] 2. 10 μ L of assay buffer (20 mM HEPES, in 1 $\times$ HBSS, pH 7.4) was added to each well of the cell plate.

[00454] 3. 2 $\times$ dye solution was prepared following the manufacture's instruction of the FLIPR® Calcium 6 assay kit:

[00455] i. The dye was diluted with assay buffer.

[00456] ii. probenecid was added to the final concentration of 5 mM.

[00457] iii. Vortexed vigorously for 1–2 minutes, adjust pH to 7.4.

[00458] 4. 10 μ L of 2 $\times$ dye solution was added to each well of the cell plate.

[00459] 5. The cell plate was placed on plate shaker, followed by shaking at 600 rpm for 2 minutes.

[00460] 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 $\times$ compounds.

[00461] 1. Serotonin was prepared to the concentration of 10 mM with DMSO, 3-folds serial dilutions were performed with DMSO.

[00462] 2. Prepare the test compound to the concentration of 10 mM with DMSO, preform 3-folds serial dilutions with DMSO.

[00463] 3. The compounds were added to a 384-well compound source plate.

[00464] 4. 90 nL/well of serial diluted compounds were transferred from source plate to a 384-well compound plate by using an Echo.

[00465] 5. 30 μ L/well of assay buffer was added to the compound plate.

[00466] 6. The plate was mixed on-plate shaker for 2 minutes.

3.5 FLIPR assay

[00467] 1. After the cells incubate with dye solution, the cell plate, compound plate containing 3 $\times$ compounds and FLIPR tips were placed into FLIPR.

[00468] 2. 10 μ L of 3 $\times$ compounds were transferred from the compound plate to the cell plate by FLIPR.

[00469] 3. The plate was read for 160 sec with 1 sec interval to obtain the data of agonist mode.

4 Data Analysis

[00470] 1. The normalized fluorescence reading (RFU) was calculated as shown below, wherein Fmax and Fmin stand for maximum and minimum of calcium signal during defined time window:

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

[00471] 2. EC₅₀ was calculated by fitting RFU against log of compound concentrations with Hill equation using XLfit.

Results & Discussion

[00472] The results of potential competition binding properties of the exemplary compounds of the application targeting the human 5-hydroxytryptamine receptor 1A (5-HT1A) are summarized in Table 4. The results of exemplary compounds of the application are presented as EC₅₀ provided in Table 4.

Table 4: Effect of exemplary compounds of Formula I using FLIPR functional assay on human 5-HT1A receptor

Compound ID#	h5-HT1A, EC ₅₀ [nM]	RFU@10 μ M ⁽¹⁾
Psilocybin	ND ⁽²⁾	143
Psilocin	ND	140
(R)-I-1	ND	84
(R)-I-57	1264	2081
(R)-I-58	2042	2444
(R)-I-46	ND	373
(R)-I-47	ND	70
(R)-I-59	ND	521
(R)-I-34	ND	155
I-70	ND	161
I-71	ND	145
(R)-I-28	2339	1981

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

(2) Not detected

[00473] Exemplary compounds of Formula I were evaluated using functional FLIPR assay on human 5-HT1A receptor. EC₅₀ (nM) concentrations are illustrated in Table 4.

This assay confirms that compounds of the application have moderate functional activity at the target human 5-HT1A receptors.

Example 15: Human 5-HT1A: Radioligand binding assay:

1 Objective

[00474] The objective of this study was to evaluate the binding properties of test compounds on 5-hydroxytryptamine receptor 1A (5-HT1A).

2 Materials and Instrumentation

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

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

Item	Supplier	Cat#
96 Round Deep Well Plate	Axygen	P-DW-11-C
Echo	LABCYTE	550

3 Experimental Methods

[00475] 1. The assay buffer was prepared following the table below.

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	

[00476] 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.

[00477] 3. UniFilter-96 GF/B plate was pretreated:

[00478] i. 50 µl/well of 0.5% (v/v) PEI was added to UniFilter-96 GF/B plates. The plates were sealed and incubated at 4°C for 3 hrs.

[00479] ii. After incubation, the plates were washed 3 times with ice-cold wash buffer (50 mM Tris, pH7.4).

[00480] 4. Assay plate was prepared:

[00481] 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.

[00482] ii. 8 concentrations of reference or test compounds were prepared and 50 µl/well was added to 96 round deep well plates.

[00483] iii. [3H]-8-Hydroxy-DPAT was diluted with assay buffer to 2 nM (4X final concentration) and 50 µl/well was added to 96 round well plates.

[00484] 5. The plate was centrifuged at 1000 rpm for 30 secs and then agitated at 600 rpm, R.T. for 5 min.

[00485] 6. The plates were sealed and the plate was incubated at 27°C for 90 min.

[00486] 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).

- [00487] 8. The plates were dried at 37°C for 45 min.
- [00488] 9. The filter plates were sealed and 40 µl/well of scintillation cocktail was added.
- [00489] 10. The plate was read by using a Microbeta² microplate counter.

4 Data Analysis

- [00490] 1. For reference and test compounds, the results were expressed as % Inhibition, using the normalization equation: $N = 100 - 100 \times (U - C2) / (C1 - C2)$, where U is the unknown value, C1 is the average of high controls, and C2 is the average of low controls.
- [00491] 2. The IC₅₀ was determined by fitting percentage of inhibition as a binding of compound concentrations with Hill equation using XLfit.

Results

[00492] The results of potential competition binding properties of the exemplary compounds of the application targeting the human 5-hydroxytryptamine receptor (5-HT1A) are summarized in Table 5. The results of exemplary compounds of the application are presented as IC₅₀ provided in Table 5.

Table 5: Effect of exemplary compounds of Formula I using Radioligand binding assay on human 5-HT1A receptor

Compound ID#	h5-HT1A, IC ₅₀ [nM]
Psilocybin	4785
Psilocin	195.7
(R)-I-1	444.13
(R)-I-57	10.00
(R)-I-58	13.00
(R)-I-46	211.41
(R)-I-47	15320.57
(R)-I-59	85
(R)-I-34	7750.56
I-70	193.00
I-71	1623.00
(R)-I-28	5.04

Discussion

[00493] Exemplary compounds of Formula I were evaluated using radioligand binding assay on human 5-HT_{1A} receptor. IC₅₀ (nM) concentrations are illustrated in Table 5. This assay confirms that compounds of the application are effective ligands of the target human 5-HT_{1A} receptors.

Example 16: Human, Rat and Mouse Liver Microsomes Stability

Objective

[00494] The objective of this study is 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 are 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 are determined as well.

Protocol

[00495] A master solution in the "Incubation Plate" containing phosphate buffer, ultra-pure H₂O, MgCl₂ solution and liver microsomes is made according to Table 6. The mixture is pre-warmed at 37°C water bath for 5 minutes.

Table 6: Preparation of master solution

Reagent	Stock Concentration	Volume	Final Concentration
Phosphate buffer	200 mM	200 µL	100 mM
Ultra-pure H ₂ O	-	106 µL	-
MgCl ₂ solution	50 mM	40 µL	5 mM
Microsomes	20 mg/mL	10 µL	0.5 mg/mL

[00496] 40 µL of 10 mM NADPH solution is added to each well. The final concentration of NADPH is 1 mM. The negative control samples are prepared by replacing NADPH with 40 µL of ultra-pure H₂O. Samples are prepared in duplicate. Negative controls are prepared in singlet.

[00497] The reaction is started with the addition of 4 µL of 200 µM exemplary test compounds of the application or control compounds to each master solution to get the final concentration of 2 µM. This study is performed in duplicate.

[00498] Aliquots of 50 µL are taken from the reaction solution at 0, 15, 30, 45 and 60 minutes. The reaction solutions are stopped by the addition of 4 volumes of cold

methanol with IS (100 nM alprazolam, 200 nM imipramine, 200 nM labetalol and 2 μ M ketoprofen). Samples are centrifuged at 3,220 g for 40 minutes. Aliquot of 90 μ L of the supernatant is mixed with 90 μ L of ultra-pure H₂O and then is used for LC-MS/MS analysis.

[00499] LC/MS analysis is 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 is performed using a Triple QuadTM 5500 instrument.

[00500] All calculations are carried out using Microsoft Excel. Peak area ratios of test compound to internal standard (listed in the below table) are determined from extracted ion chromatograms.

[00501] All calculations are carried out using Microsoft Excel. Peak areas are determined from extracted ion chromatograms. The slope value, k, is determined by linear regression of the natural logarithm of the remaining percentage of the parent drug vs. incubation time curve.

[00502] The in vitro half-life (in vitro t_{1/2}) is determined from the slope value:

$$\text{in vitro } t_{1/2} = - \{0.693 / k\}$$

[00503] Conversion of the in vitro t_{1/2} (min) into the in vitro intrinsic clearance (in vitro CL_{int}, in μ L/min/mg proteins) is done using the following equation (mean of duplicate determinations):

$$\text{in vitro } CL_{int} = \left\{ \frac{0.693}{\{t_{1/2}\}} \right\} * \left\{ \frac{\text{volume of incubation } (\mu\text{L})}{\text{amount of proteins } (\text{mg})} \right\}$$

[00504] For the exemplary compounds of the application or control compound that show an initial fast disappearance followed by a slow disappearance, only the time points that are within the initial rate are included in the calculation.

Results & Discussion

[00505] 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 application are evaluated for their stability in human, rat and mouse liver microsomes.

Example 17: Human, Rat, Mouse and Dog: Plasma stability

[00506] 1. Preparation of Stock Solutions

[00507] The stock solution of test compound was prepared in DMSO and diluted at the final concentration of 200 μ M. 1 mM lovastatin and propantheline working solution was pre-pared 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.

[00508] 2. Procedures for Plasma Stability

[00509] a. 2.5 μ L of 200 μ M or 1 mM test compound or control compound solution was spiked to 497.5 μ L plasma to reach a final concentration of 1 μ M or 5 μ M. The final concentration of organic solvents was 0.5 %. The assay was performed in duplicated.

[00510] b. The reaction samples were incubated at 37°C at approximately 60 rpm in a water bath.

[00511] c. Aliquots of 50 μ L 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 labetalol and 2 μ M ketoprofen).

[00512] d. All samples were vortexed for 2 minutes, followed by centrifugation at 3,220 g for 30 minutes to precipitate proteins. 100 μ L 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.

[00513] 3. Sample Analysis

[00514] Samples were analyzed by LC-MS/MS.

- LC system: Shimadzu
- MS analysis: Triple QuadTM 6500+ from AB Inc (Canada) with an ESI interface
- Column temperature: 40 °C
- Column: Xselect® Hss T3 2.5 μ (2.1×30 mm) coupled with preguard column

- 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

[00515] 4. Data Analysis

[00516] 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.

Table 7. Stability Results of Exemplary Compounds in Plasma of Different Species

Compound ID#	Species	T _{1/2} (min)	Remaining Percentage (%)		
			0 min	30 min	60 min
Propantheline	Human	11.37	100.00	28.96	2.58
(R)-I-57		>255.85	100.00	108.18	112.69
(R)-I-58		>255.85	100.00	108.03	98.49
(R)-I-46		>255.85	100.00	104.22	93.02
(R)-I-28		>255.85	100.00	95.13	94.23
Lovastatin	Rat	N.A.	100.00	0.61	0.33
(R)-I-57		>255.85	100.00	92.47	89.72
(R)-I-58		>255.85	100.00	111.06	109.59
(R)-I-46		>255.85	100.00	91.33	86.67
(R)-I-28		>255.85	100.00	97.86	94.67
Propantheline	Mouse	37.14	100.00	61.61	32.64
(R)-I-57		>255.85	100.00	104.82	100.28
(R)-I-58		>255.85	100.00	97.41	105.08
(R)-I-46		>255.85	100.00	103.39	92.36
(R)-I-28		>255.85	100.00	99.16	93.28

Note:

1. If the percentage remaining at 60 min was greater than 85%, then T_{1/2} was reported as >255.85 min.
2. 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.

Example 18: Psychedelic-like Effect of exemplary compounds of Formula I

[00517] The effect of different doses of exemplary compounds of Formula I are evaluated on head-twitch response (HTR) and other behavioural responses as behavior-based models of psychedelic activity.

Protocols

Mouse head twitch

[00518] Male, C57BL/6J mice (body weight range 20-30g) are dosed with the appropriate dose of test article, and following a 1-minute pre-treatment time, placed in individual observation chambers. Animals are visually assessed for the incidence head twitches continuously over a 1hr period. Head twitches are defined as a rapid jerk of the head which is not elicited by an external tactile stimulus (Corne and Pickering, *Psychopharmacologia*, 1967, 11(1): 65-78). Each head twitch is individually counted by a trained observer, and the data expressed as the mean $\pm$ SEM of 6-10 mice per group. Mice are used in a single experiment only.

Rat behavioural test

[00519] Male, Sprague-Dawley rats (body weight range 250-400g) are dosed with the appropriate dose of test article and following a 1-minute pre-treatment time, placed in locomotor activity boxes (dimensions 17" W x 17" L x 12" H) and continuously monitored for a 1 hr period with data collected into 10 minute time bins. Animals are visually assessed for overt behavioural signs, including behaviours characteristic of 5-HT_{2A} receptor activation (wet dog shakes, back muscle contractions), 5-HT_{2A} receptor activation (yawning, penile grooming) and 5-HT_{1A} behaviours (forepaw treading, hindlimb abduction) (Halberzetti et al, *Behav Brain Res.* 256: 328-345, 2013). Additional behavioural and somatic signs characteristic of 5-HT syndrome (e.g. tremor, salivation, flat body posture, core body temperature change) are also measured. Simultaneously, the spontaneous activity of the rats is measured using an automated tracking system (Med Associates, VT, USA). Activity data collected included total distance traveled, rearing counts and ambulatory episodes. All data are expressed as the mean $\pm$ SEM of 6-10 rats per group.

Drug discrimination in the rat

[00520] Male Sprague-Dawley rats are initially food restricted by presentation of 18-20g food at day end (single housing). After 7 days acclimatisation to the food restriction procedure, they are trained daily to lever press for food (45mg Bioserve pellet) in standard 2-lever operant conditioning chambers controlled by Med-PC software over a period of 1 week (Med. Associates Ins., St. Albans, VT). The rats are trained to lever press for food to

an FR10 value (i.e., 10 lever presses for a single food reward). Once stable food responding is acquired to both response levers, discrimination training began. Over a period of 20-50 training sessions, the rats are trained to associate one lever to a psilocybin training dose of 1 mg/kg SC, and the second lever to a neutral stimulus (saline, SC) (Winter et al, Pharmacol Biochem Behav. 87(4): 472-480, 2007). Training sessions lasted 30-min or until the delivery of 50 pellets and continue until the animals attain appropriate stimulus control (defined as six consecutive sessions where animals makes no more than 16 lever presses before the delivery of the first reward, and at least 95% total responses on the appropriate lever). The rats continue to receive daily food ration in their home cage at day end.

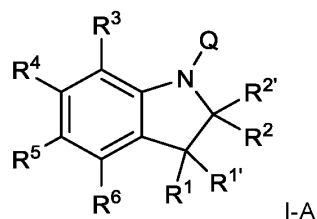
[00521] Once trained, tests of substitution are conducted. On test days, both levers are designated active, i.e., every 10th response on either lever results in delivery of a food pellet. Test sessions continue until 50 pellets have been obtained or 30 min has elapsed. During these sessions response rate is also measured.

[00522] While the present application 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.

[00523] 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.

CLAIMS:

1. A compound of Formula I-A:

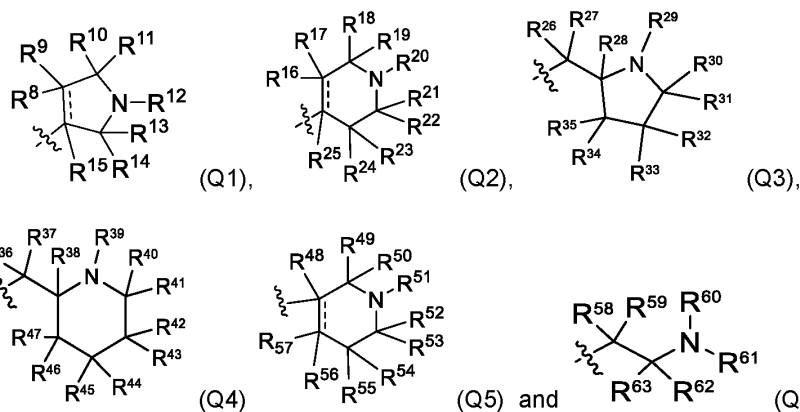


or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,
wherein:

R^1 and $R^{1'}$ are independently selected from H, halo, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxy, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}alkyl)_2$;

R^2 and $R^{2'}$ are independently selected from H, halo, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxy, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}alkyl)_2$;

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



$\equiv$ is a single bond or a double bond provided that when $\equiv$ in Q1 is a double bond then R^9 and R^{15} are not present, when $\equiv$ in Q2 is a double bond then R^{17} and R^{25} are not present, and when $\equiv$ in Q5 is a double bond then R^{48} and R^{57} are not present;

one or both of R^4 and R^5 is independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy,
or

R^4 and R^5 are linked together to form $O-(CH_2)_{1-2}O$, or

one of R^4 and R^5 is selected from X-L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy,

X is selected from a direct bond, O, C(O), NR^a, NR^aC(O), C(O)NR^a, OC(O), C(O)O, OC(O)O, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a;

L is selected from a direct bond, C₁₋₆alkylene, C₂₋₆alkenylene, C₁₋₆alkyleneO, C₂₋₆alkenyleneO, C₁₋₆alkyleneC(O), C₂₋₆alkenyleneC(O), C₁₋₆alkyleneNR^bC(O), C₂₋₆alkenyleneNR^bC(O), C₁₋₆alkyleneC(O)NR^b, C₂₋₆alkenyleneC(O)NR^b, C₁₋₆alkyleneOC(O), C₂₋₆alkenyleneOC(O), C₁₋₆alkyleneC(O)O, C₂₋₆alkenyleneC(O)O, C₁₋₆alkyleneOC(O)NR^b, C₂₋₆alkenyleneOC(O)NR^b, C₁₋₆alkyleneNR^bC(O)O, C₂₋₆alkenyleneNR^bC(O)O, C₁₋₆alkyleneOC(O)O, C₂₋₆alkenyleneOC(O)O, C₁₋₆alkyleneNR^bC(O)NR^b and C₂₋₆alkenyleneNR^bC(O)NR^b;

R^a is selected from H and C₁₋₆alkyl;

R^b is selected from H, C₁₋₆alkyl and A;

A is selected from H, C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C₁₋₄alkyl and OC₁₋₄alkyl;

R³ and R⁶ are independently selected from H, halo, OH, C₁₋₆alkyl and C₁₋₆alkoxy;

R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H, halo and C₁₋₆alkyl;

R¹², R²⁰, R²⁹, R³⁹ and R⁵¹ are independently selected from H, C₁₋₆alkyl, C(O)C₁₋₆alkyl and C(O)-A';

R⁶⁰ and R⁶¹ are independently selected from H and C₁₋₆alkyl; or

one of R⁶⁰ and R⁶¹ is C(O)-A' and the other is selected from H and C₁₋₆alkyl;

wherein A' is selected from Y, O-Y and O-C₁₋₄alkylene-O-C(O)-Y; and

Y is selected from C₇₋₃₀alkyl and C₇₋₃₀alkenyl; or

R⁶⁰ and R⁶¹, together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoeities independently selected from O, S, S(O), SO₂, N, and NR⁶⁵ and which is optionally

substituted with one or more substituents independently selected from halo, OH, C₁₋₄alkyl and OC₁₋₄alkyl;

R⁶⁴ and R⁶⁵ are independently selected from H and C₁₋₆alkyl; and
all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

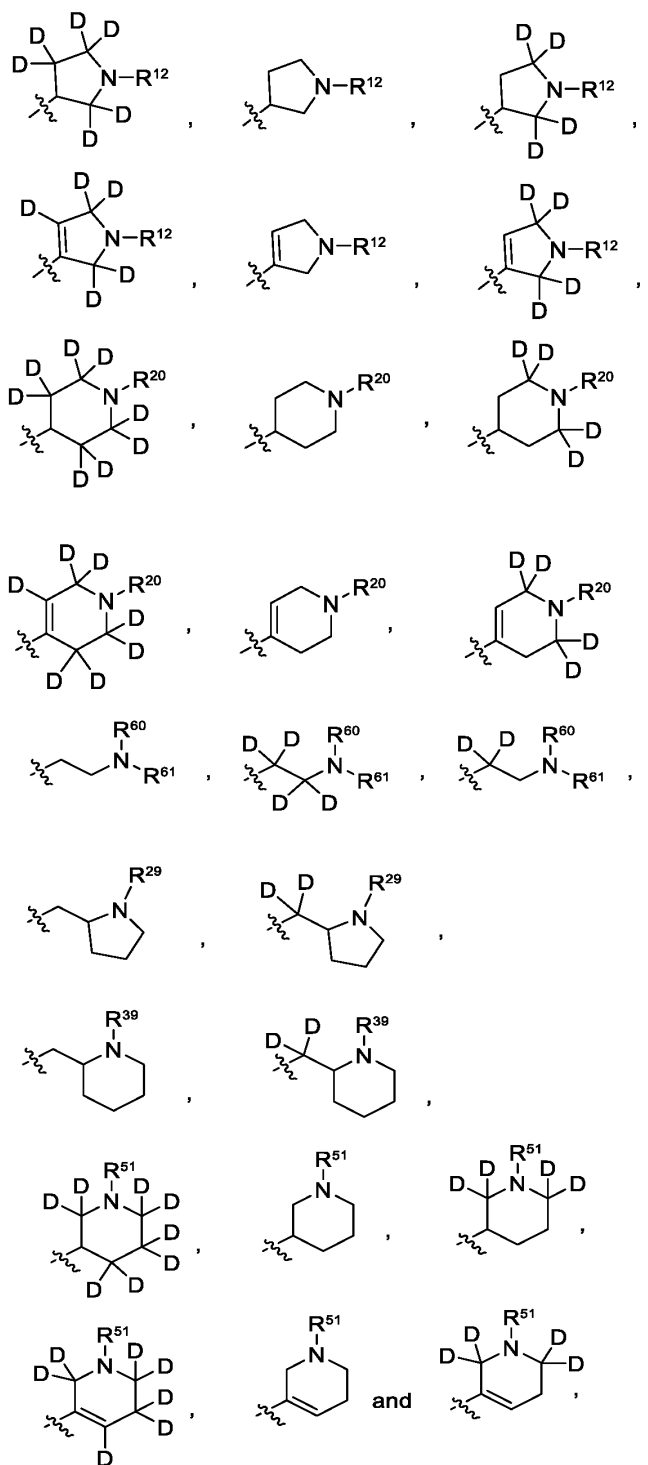
provided when Q is Q6 then the compound of Formula I comprises D,

when Q is Q3 or Q4, R¹, R^{1'}, R², R^{2'}, R³, R⁴, R⁶, R²⁶, R²⁷, R²⁸, R³⁰ to R³⁵, R³⁶, R³⁷, R³⁸ and R⁴⁰ to R⁴⁷ are not all H, when R⁵ is H or OCH₃, and R²⁹ or R³⁹ is CH₃; and

when Q is Q4 and R¹, R^{1'}, R², R^{2'}, R³, R⁴, R⁶, R³⁸ and R⁴⁰ to R⁴⁷ are all H, then R³⁶ and R³⁷ are not both D, when R³⁹ is CD₃.

2. The compound of claim 1, wherein R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H and D.

3. The compound of claim 1, wherein Q is selected from one of the following groups:

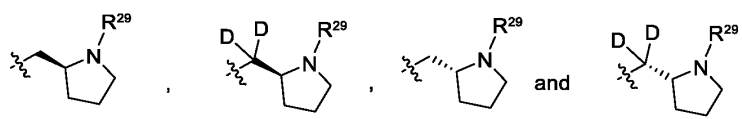


wherein R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from H, D, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl and $C(O)-A'$.

4. The compound of claim 3, wherein R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl.

5. The compound of claim 3, wherein R^{60} and R^{61} , together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoieties independently selected from O, N and NR^{65} and which is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-4} alkyl and OC_{1-4} alkyl.

6. The compound of claim 3, wherein Q is selected from one of the following groups:



wherein R^{29} is selected from H, D, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl and $C(O)-A'$.

7. The compound of claim 6, wherein R^{29} is selected from H, CH_3 , CD_3 , CF_2H and CF_3 .

8. The compound of claim 1 or claim 3, wherein R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} are independently selected from $C(O)-A'$.

9. The compound of claim 1 or claim 3, wherein one of R^{60} and R^{61} is $C(O)-A'$ and the other is selected from H and C_{1-6} alkyl.

10. The compound of claim 8 or claim 9, wherein A' is selected from Y, O-Y and O- C_1 alkylene-O- $C(O)-Y$, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

11. The compound of claim 10, wherein Y is C_{10-25} alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

12. The compound of claim 10, wherein Y is C_{10-25} alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

13. The compound of claim 12, wherein Y is an alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium.

14. The compound of claim 11, wherein Y is an alkyl group present in a fatty acid wherein all available H atoms are optionally replaced with deuterium.

15. The compound of claim 10, wherein Y is an alkyl or alkenyl group present in linoleic acid, eicosadienoic acid or decosahexanoic acid.

16. The compound of claim 10, wherein Y is the alkyl or alkenyl group of a fatty acid wherein 1-10, 2-8, 2-6 or 2-4 H atoms are replaced with deuterium.

17. The compound of claim 10, wherein Y is $(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$, $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$, $(\text{CH}_2)_8\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$, $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$, $(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$, or $(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$.

18. The compound of any one of claims 1 to 17, wherein R^1 and $\text{R}^{1'}$ are independently selected from H, D and CH_3 .

19. The compound of any one of claims 1 to 18, wherein R^2 and $\text{R}^{2'}$ are independently H, D or F.

20. The compound of any one of claims 1 to 19, wherein R^3 and R^6 are independently selected from H, D, Cl, F, OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy, C_{1-4} deuteroalkoxy, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl.

21. The compound of claim 20, wherein R^3 and R^6 are independently selected from H, D, F, OH, CH_3 , CH_3O , CF_2HO , CD_2HO , CF_3O , CD_3O , CF_2H , CD_2H , CF_3 and CD_3 .

22. The compound of claim 21, wherein R^3 and R^6 are independently selected from H and D.

23. The compound of any one of claims 1 to 22, wherein one or both of R^4 and R^5 is independently selected from H, D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy.

24. The compound of any one of claims 1 to 22, wherein both of R^4 and R^5 are independently selected from H, D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy.

25. The compound of any one of claims 1 to 22, wherein R^4 is H or D and R^5 is selected from H, D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy.

26. The compound of any one of claims 1 to 22, wherein R^5 is H or D and R^4 is selected from H, D, F, Cl, C_{1-6} alkyl, C_{1-6} fluoroalkyl, C_{1-6} deuteroalkyl, C_{1-6} alkoxy, C_{1-6} fluoroalkoxy and C_{1-6} deuteroalkoxy.

27. The compound of any one of claims 1 to 22, wherein R^4 and R^5 are linked together to form $O-CH_2O$.

28. The compound of any one of claims 1 to 22, wherein one of R^4 and R^5 is selected from X-L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy.

29. The compound of claim 28, wherein X is a direct bond and one of R^4 and R^5 is selected from L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy.

30. The compound of claim 28, wherein X is selected from O, $C(O)$, NR^a , $NR^aC(O)$, $C(O)NR^a$, $OC(O)$, $C(O)O$, $OC(O)O$, $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$.

31. The compound of claim 28, wherein X is selected from O, NR^a , $NR^aC(O)$, $C(O)NR^a$, $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$.

32. The compound of any one of claims 28 to 31, wherein L is selected from a direct bond, C_{1-4} alkylene, C_{2-4} alkenylene, C_{1-4} alkyleneO, C_{2-4} alkenyleneO, C_{1-4} alkylene $C(O)$, C_{2-4} alkenylene $C(O)$, C_{1-4} alkylene $NR^bC(O)$, C_{2-4} alkenylene $NR^bC(O)$, C_{1-4} alkylene $C(O)NR^b$, C_{2-4} alkenylene $C(O)NR^b$, C_{1-4} alkylene $OC(O)$, C_{2-4} alkenylene $OC(O)$, C_{1-4} alkylene $C(O)O$, C_{2-4} alkenylene $C(O)O$, C_{1-4} alkylene $OC(O)NR^b$, C_{2-4} alkenylene $OC(O)NR^b$, C_{1-4} alkylene $NR^bC(O)O$, C_{2-4} alkenylene $NR^bC(O)O$, C_{1-4} alkylene $OC(O)O$, C_{2-4} alkenylene $OC(O)O$, C_{1-4} alkylene $NR^bC(O)NR^b$ and C_{2-4} alkenylene $NR^bC(O)NR^b$.

33. The compound of any one of claims 28 to 32, wherein the other of R^4 and R^5 is selected from H, F, Cl, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} deuteroalkyl and C_{1-4} alkoxy.

34. The compound of any one of claims 28 to 33, wherein A is H.

35. The compound of any one of claims 28 to 33, wherein A is selected from C_{1-30} alkyl, C_{2-30} alkenyl, phenyl, C_{3-6} cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 3 heteromoeities independently selected from O, S, $S(O)$, SO_2 , N and NR^{63} and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, $S(O)$, SO_2 , N and NR^{53} , wherein the phenyl, C_{3-10} cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, Cl, OH, C_{1-4} alkyl, C_{1-4} deuteroalkyl, C_{1-4}

4fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

36. The compound of claim 35, wherein A is selected from phenyl, C₃₋₆cycloalkyl, 5- to 6-membered heterocycloalkyl comprising 1 to 2 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 3 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁴⁸, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or two substituents independently selected from F, C, C₁₋₄alkyl, C₁₋₄deuteroalkyl, C₁₋₄fluoroalkyl, OC₁₋₄alkyl, OC₁₋₄deuteroalkyl and OC₁₋₄fluoroalkyl.

37. The compound of claim 36, wherein R⁶⁴ is selected from H, D, C₁₋₄alkyl, C₁₋₄fluoroalkyl and C₁₋₄deuteroalkyl.

38. The compound of claim 35, wherein A is selected from C₁₋₃₀alkyl and C₂₋₃₀alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

39. The compound of claim 38, wherein A is C₁₀₋₂₅alkyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom

40. The compound of claim 38, wherein A is C₁₀₋₂₅alkenyl, wherein all available hydrogen atoms are optionally and independently replaced with a fluorine atom or deuterium atom.

41. The compound of claim 40, wherein A is an alkenyl group present in a fatty acid, wherein all available H atoms are optionally replaced with deuterium.

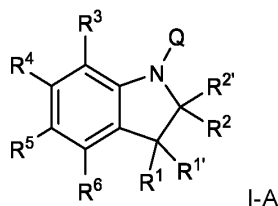
42. The compound of claim 38, wherein A is an alkyl group present in a fatty acid wherein all available H atoms are optionally replaced with deuterium.

43. The compound of claim 38, wherein A is an alkyl or alkenyl group present in linoleic acid, eicosadienoic acid or decosahexanoic acid.

44. The compound of claim 38, wherein A is the alkyl or alkenyl group of a fatty acid wherein 1-10, 2-8, 2-6 or 2-4 H atoms are replaced with deuterium.

45. The compound of claim 38, wherein A is $(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{CH}_3$,
 $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$, $(\text{CH}_2)_8\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_4\text{CH}_3$,
 $(\text{CH}_2)_7\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$,
 $(\text{CH}_2)_3\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$, or
 $(\text{CH}_2)_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_1\text{CH}_3$.

46. The compound of claim 1, wherein the compound of Formula I-A is defined as follows:

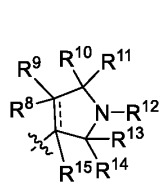


or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

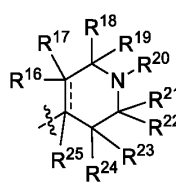
wherein:

R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 and R^6 are independently selected from H, D and F;

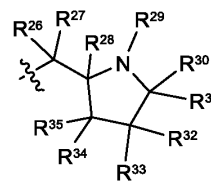
Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



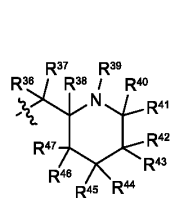
(Q1),



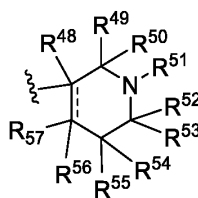
(Q2),



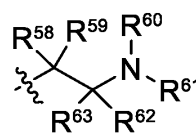
(Q3),



(Q4),



(Q5) and



(Q6);

$\equiv$ is a single bond or a double bond provided that when $\equiv$ in Q1 is a double bond then R^9 and R^{15} are not present, when $\equiv$ in Q2 is a double bond then R^{17} and R^{25} are not present and when $\equiv$ in Q5 is a double bond then R^{48} and R^{57} are not present;

one or both of R^4 and R^5 is selected from H, C_{1-4} alkoxy, C_{1-4} fluoroalkoxy and C_{1-4} deuteroalkoxy, or

R^4 and R^5 are linked together to form $\text{O}-(\text{CH}_2)_{1-2}\text{O}$;

$R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{62}$ and R^{63} are independently selected from H and D;

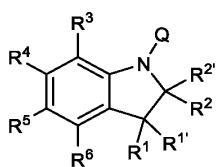
$R^{12}, R^{20}, R^{29}, R^{39}$ and R^{51} are independently selected from H, C_{1-4} alkyl, C_{1-4} fluoroalkyl and C_{1-4} deuteroalkyl, and

R^{60} and R^{61} are independently selected from H and C_{1-6} alkyl,

provided when Q is Q6 then the compound of Formula I comprises D,

when Q is Q3 or Q4, $R^1, R^{1'}, R^2, R^{2'}, R^3, R^4, R^6, R^{26}, R^{27}, R^{28}, R^{30}$ to $R^{35}, R^{36}, R^{37}, R^{38}$ and R^{40} to R^{47} are not all H, when R^5 is H or OCH_3 , and R^{29} or R^{39} is CH_3 .

47. The compound of claim 1, wherein the compound of Formula I-A is defined as follows:



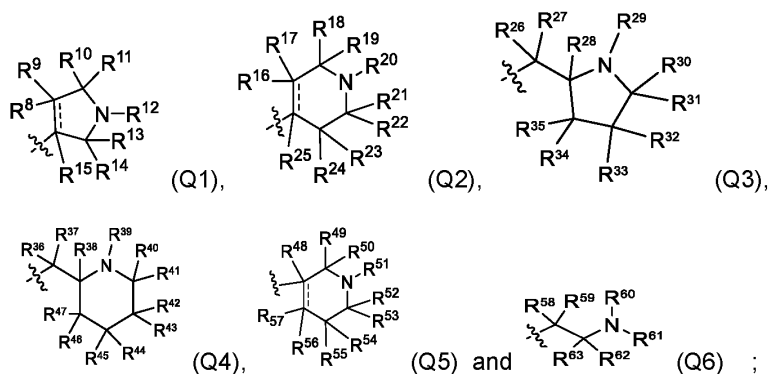
or a pharmaceutically acceptable salt, solvate and/or prodrug thereof,

wherein:

R^1 and $R^{1'}$ are independently selected from H, halo, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl) $_2$;

R^2 and $R^{2'}$ are independently selected from H, halo, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl) $_2$;

Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



$\equiv$ is a single bond or a double bond provided that when $\equiv$ in Q1 is a double bond then R⁹ and R¹⁵ are not present, when $\equiv$ in Q2 is a double bond then R¹⁷ and R²⁵ are not present, and when $\equiv$ in Q5 is a double bond then R⁴⁸ and R⁵⁷ are not present;

one or both of R⁴ and R⁵ is independently selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy, or

R⁴ and R⁵ are linked together to form O-(CH₂)₁₋₂O, or

one of R⁴ and R⁵ is selected from X-L-A and the other of R⁴ and R⁵ is selected from H, halo, C₁₋₆alkyl and C₁₋₆alkoxy,

X is selected from a direct bond, O, C(O), NR^a, NR^aC(O), C(O)NR^a, OC(O), C(O)O, OC(O)O, NR^aC(O)O, OC(O)NR^a and NR^aC(O)NR^a;

L is selected from a direct bond, C₁₋₆alkylene, C₂₋₆alkenylene, C₁₋₆alkyleneO, C₂₋₆alkenyleneO, C₁₋₆alkyleneC(O), C₂₋₆alkenyleneC(O), C₁₋₆alkyleneNR^bC(O), C₂₋₆alkenyleneNR^bC(O), C₁₋₆alkyleneC(O)NR^b, C₂₋₆alkenyleneC(O)NR^b, C₁₋₆alkyleneOC(O), C₂₋₆alkenyleneOC(O), C₁₋₆alkyleneC(O)O, C₂₋₆alkenyleneC(O)O, C₁₋₆alkyleneOC(O)NR^b, C₂₋₆alkenyleneOC(O)NR^b, C₁₋₆alkyleneNR^bC(O)O, C₂₋₆alkenyleneNR^bC(O)O, C₁₋₆alkyleneOC(O)O, C₂₋₆alkenyleneOC(O)O, C₁₋₆alkyleneNR^bC(O)NR^b and C₂₋₆alkenyleneNR^bC(O)NR^b;

R^a is selected from H and C₁₋₆alkyl;

R^b is selected from H, C₁₋₆alkyl and A;

A is selected from H, C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C₁₋₄alkyl and OC₁₋₄alkyl;

R³ and R⁶ are independently selected from H, halo, OH, C₁₋₆alkyl and C₁₋₆alkoxy;

R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H, halo and C₁₋₆alkyl;

R^{12} , R^{20} , R^{29} , R^{39} and R^{51} are independently selected from H, C_{1-6} alkyl, $C(O)C_{1-6}$ alkyl and $C(O)-A'$;

R^{60} and R^{61} are independently selected from H and C_{1-6} alkyl; or

one of R^{60} and R^{61} is $C(O)-A'$ and the other is selected from H and C_{1-6} alkyl;

wherein A' is selected from Y, O-Y and O- C_{1-4} alkylene-O- $C(O)-Y$; and

Y is selected from C_{7-30} alkyl and C_{7-30} alkenyl; or

R^{60} and R^{61} , together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoiety independently selected from O, S, S(O), SO_2 , N, and NR^{65} and which is optionally substituted with one or more substituents independently selected from halo, OH, C_{1-4} alkyl and OC_{1-4} alkyl;

R^{64} and R^{65} are independently selected from H and C_{1-6} alkyl; and

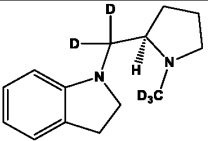
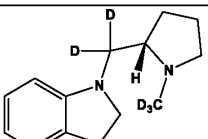
all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

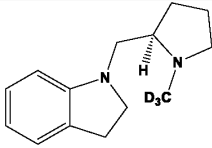
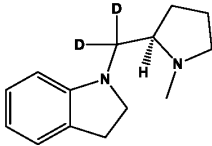
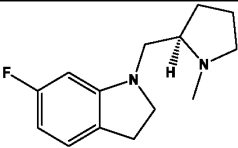
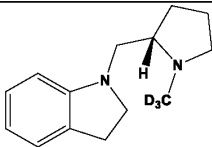
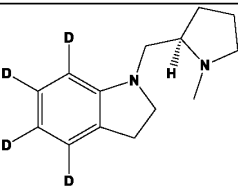
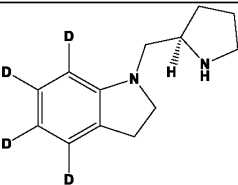
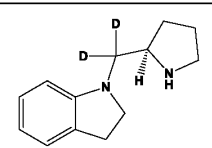
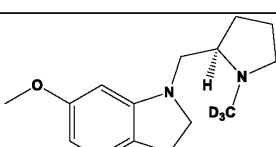
provided one of R^{12} , R^{20} , R^{29} , R^{39} , R^{51} , R^{60} and R^{61} is $C(O)-A'$; or one of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy provided A is not H, C_{1-6} alkyl or C_{1-6} alkenyl when X and L are both direct bonds.

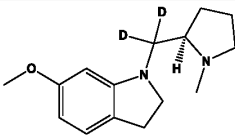
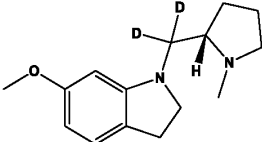
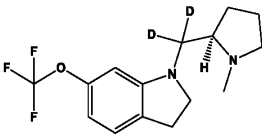
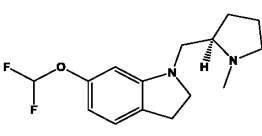
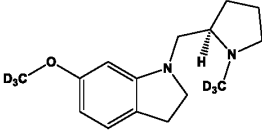
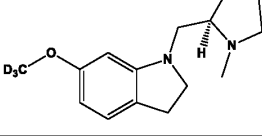
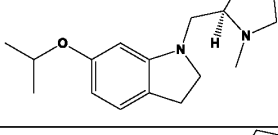
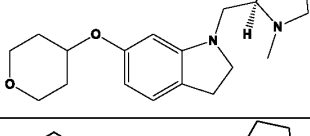
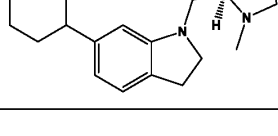
48. The compound of any one of claims 1 to 47, wherein R^2 and $R^{2'}$ are different and the carbon to which R^2 and $R^{2'}$ are bonded, is chiral.

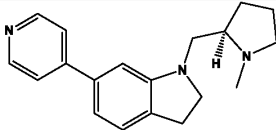
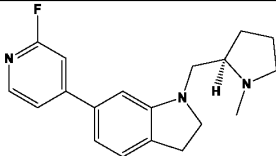
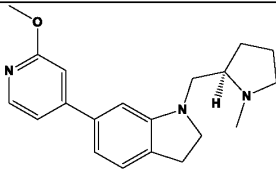
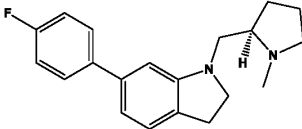
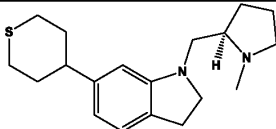
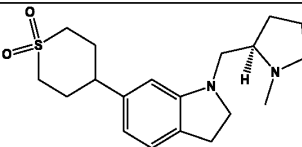
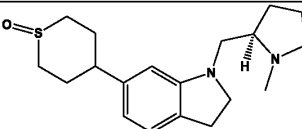
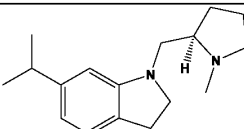
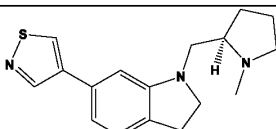
49. The compound of any one of claims 1 to 48, wherein R^1 and $R^{1'}$ are different and the carbon to which R^1 and $R^{1'}$ are bonded is chiral.

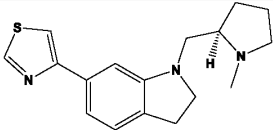
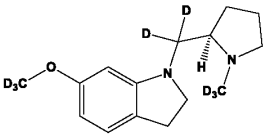
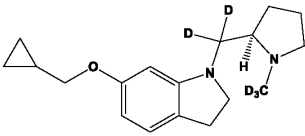
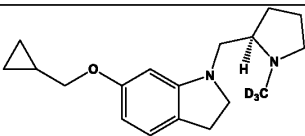
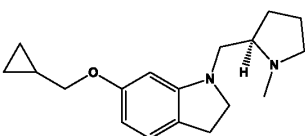
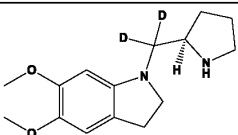
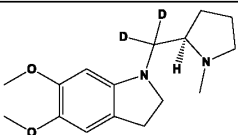
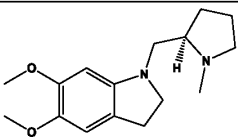
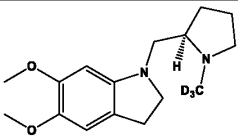
50. The compound of claim 1 selected from:

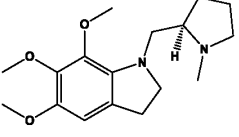
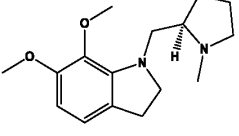
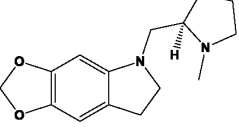
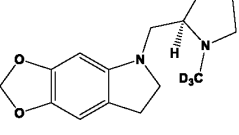
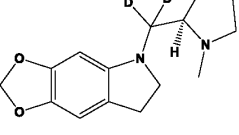
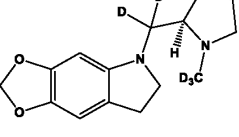
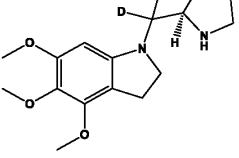
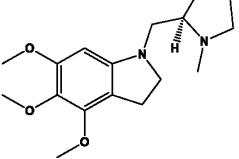
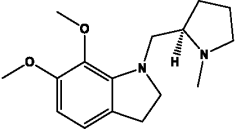
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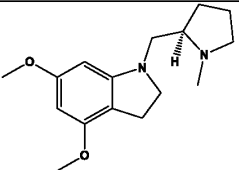
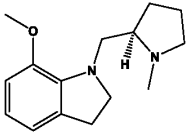
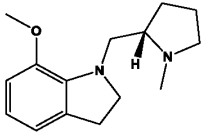
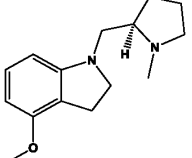
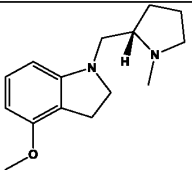
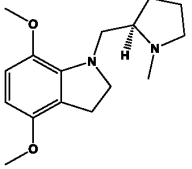
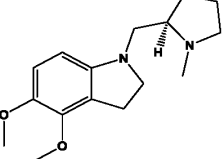
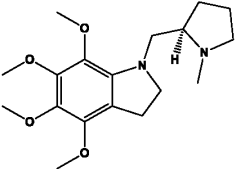
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(R)-I-7	
(R)-I-8	
(R)-I-9	

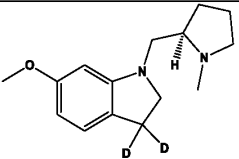
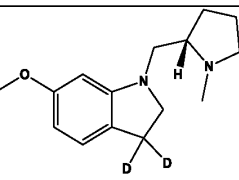
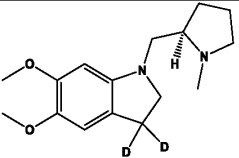
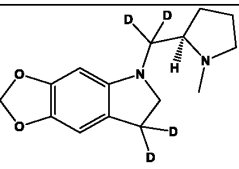
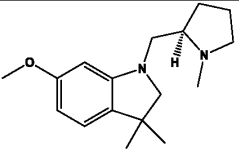
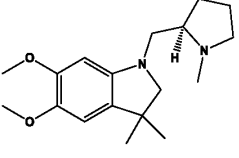
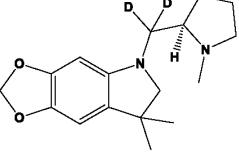
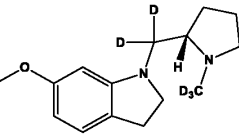
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(R)-I-16	
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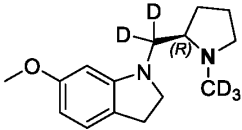
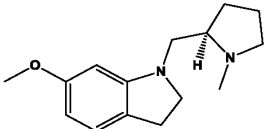
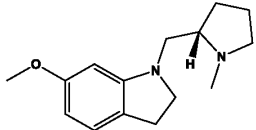
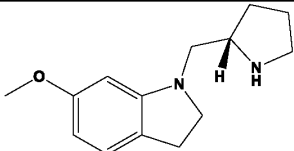
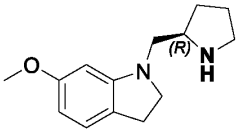
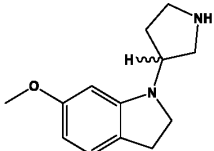
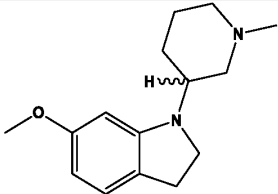
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(R)-I-26	

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(R)-I-35	

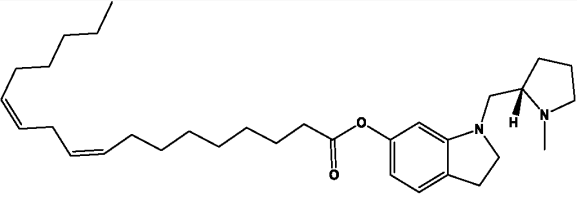
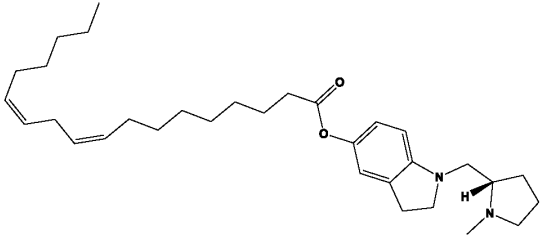
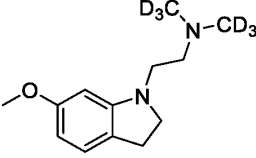
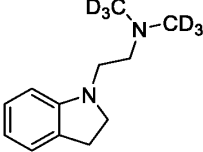
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(R)-I-41	
(R)-I-42	
(R)-I-43	
(R)-I-44	

(R)-I-45	
(R)-I-46	
(S)-I-46	
(R)-I-47	
(S)-I-47	
(R)-I-48	
(R)-I-49	
(R)-I-50	

(R)-I-51	
(S)-I-51	
(R)-I-52	
(R)-I-53	
(R)-I-54	
(R)-I-55	
(R)-I-56	
(S)-I-57	

(R)-I-57	
(R)-I-58	
(S)-I-58	
(S)-I-59	
(R)-I-59	
I-60	
I-61	

(S)-I-62	
I-63	
I-64	
I-65	
I-66	
(S)-I-67	

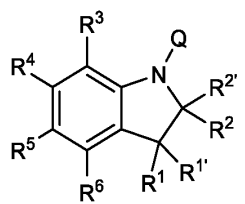
(S)-I-68	
(S)-I-69	
I-70	 , and
I-71	

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

51. A composition comprising one or more compounds of any one of claims 1 to 50 and a carrier.

52. A pharmaceutical composition comprising one or more compounds of any one of claims 1 to 50 and pharmaceutically acceptable carrier.

53. 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 Formula I or a pharmaceutically acceptable salt, solvate and/or prodrug thereof to a subject in need thereof,

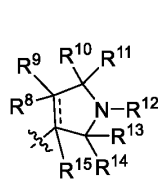


wherein:

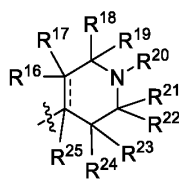
R^1 and $R^{1'}$ are independently selected from H, halo, OH, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl) $_2$;

R^2 and $R^{2'}$ are independently selected from H, halo, NH_2 , C_{1-6} alkyl, C_{1-6} alkoxyl, $NH(C_{1-6}$ alkyl) and $N(C_{1-6}$ alkyl) $_2$;

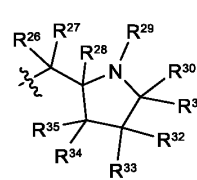
Q is selected from Q1, Q2, Q3, Q4, Q5 and Q6:



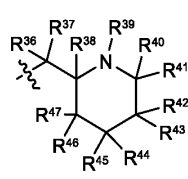
(Q1),



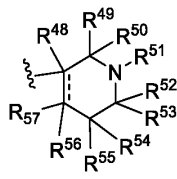
(Q2),



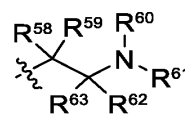
(Q3),



(Q4),



(Q5) and



(Q6) ;

$\equiv$ is a single bond or a double bond provided that when $\equiv$ in Q1 is a double bond then R^9 and R^{15} are not present, when $\equiv$ in Q2 is a double bond then R^{17} and R^{25} are not present, and when $\equiv$ in Q5 is a double bond then R^{48} and R^{57} are not present;

one or both of R^4 and R^5 is independently selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy, or

R^4 and R^5 are linked together to form $O-(CH_2)_{1-2}O$, or

one of R^4 and R^5 is selected from X-L-A and the other of R^4 and R^5 is selected from H, halo, C_{1-6} alkyl and C_{1-6} alkoxy,

X is selected from a direct bond, O, $C(O)$, NR^a , $NR^aC(O)$, $C(O)NR^a$, $OC(O)$, $C(O)O$, $OC(O)O$, $NR^aC(O)O$, $OC(O)NR^a$ and $NR^aC(O)NR^a$;

L is selected from a direct bond, C₁₋₆alkylene, C₂₋₆alkenylene, C₁₋₆alkyleneO, C₂₋₆alkenyleneO, C₁₋₆alkyleneC(O), C₂₋₆alkenyleneC(O), C₁₋₆alkyleneNR^bC(O), C₂₋₆alkenyleneNR^bC(O), C₁₋₆alkyleneC(O)NR^b, C₂₋₆alkenyleneC(O)NR^b, C₁₋₆alkyleneOC(O), C₂₋₆alkenyleneOC(O), C₁₋₆alkyleneC(O)O, C₂₋₆alkenyleneC(O)O, C₁₋₆alkyleneOC(O)NR^b, C₂₋₆alkenyleneOC(O)NR^b, C₁₋₆alkyleneNR^bC(O)O, C₂₋₆alkenyleneNR^bC(O)O, C₁₋₆alkyleneOC(O)O, C₂₋₆alkenyleneOC(O)O, C₁₋₆alkyleneNR^bC(O)NR^b and C₂₋₆alkenyleneNR^bC(O)NR^b;

R^a is selected from H and C₁₋₆alkyl;

R^b is selected from H, C₁₋₆alkyl and A;

A is selected from H, C₁₋₃₀alkyl, C₂₋₃₀alkenyl, phenyl, C₃₋₆cycloalkyl, 3- to 6-membered heterocycloalkyl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴ and 5- to 6-membered heteroaryl comprising 1 to 4 heteromoeities independently selected from O, S, S(O), SO₂, N and NR⁶⁴, wherein the phenyl, C₃₋₁₀cycloalkyl, 3- to 6-membered heterocycloalkyl and 5- to 6-membered heteroaryl are optionally substituted with one or more substituents independently selected from halo, C₁₋₄alkyl and OC₁₋₄alkyl;

R³ and R⁶ are independently selected from H, halo, OH, C₁₋₆alkyl and C₁₋₆alkoxy;

R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³, R²⁴, R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁴, R³⁵, R³⁶, R³⁷, R³⁸, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁶, R⁴⁷, R⁴⁸, R⁴⁹, R⁵⁰, R⁵², R⁵³, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶² and R⁶³ are independently selected from H, halo and C₁₋₆alkyl;

R¹², R²⁰, R²⁹, R³⁹ and R⁵¹ are independently selected from H, C₁₋₆alkyl, C(O)C₁₋₆alkyl and C(O)-A';

R⁶⁰ and R⁶¹ are independently selected from H and C₁₋₆alkyl; or

one of R⁶⁰ and R⁶¹ is C(O)-A' and the other is selected from H and C₁₋₆alkyl;

wherein A' is selected from Y, O-Y and O-C₁₋₄alkylene-O-C(O)-Y; and

Y is selected from C₇₋₃₀alkyl and C₇₋₃₀alkenyl; or

R⁶⁰ and R⁶¹, together with the N atom to which they are bound, form a 3- to 6-membered heterocyclic ring which optionally comprises one or two additional heteromoeities independently selected from O, S, S(O), SO₂, N, and NR⁶⁵ and which is optionally

substituted with one or more substituents independently selected from halo, OH, C₁₋₄alkyl and OC₁₋₄alkyl;

R⁶⁴ and R⁶⁵ are independently selected from H and C₁₋₆alkyl; and

all available hydrogen atoms are optionally and independently replaced with a fluorine atom or chlorine atom and all available atoms are optionally replaced with alternate isotope thereof,

provided when Q is Q6 then the compound of Formula I comprises D.

54. A method of treating a mental illness comprising administering a therapeutically effective amount of one or more compounds of Formula I as defined in claim 53 to a subject in need thereof.

55. The method of claim 54, wherein the mental illness is selected from hallucinations and delusions and a combination thereof.

56. The method of claim 54, wherein the mental illness is selected anxiety disorders; depression; mood disorders; psychotic disorders; impulse control and addiction disorders; drug addiction; obsessive-compulsive disorder (OCD); post-traumatic stress disorder (PTSD); stress response syndromes; dissociative disorders; depersonalization disorder; factitious disorders; sexual and gender disorders; and somatic symptom disorders and combinations thereof.

57. A method of treating psychosis or psychotic symptoms comprising administering a therapeutically effective amount of one or more compounds of Formula I as defined in claim 53 to a subject in need thereof.

58. 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 Formula I as defined in claim 53 to a subject in need thereof.

59. The method of claim 58, wherein 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; 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"), trichotillomania, dermatillomania, nail biting; migraine; fibromyalgia; and peripheral neuropathy of any etiology, and combinations thereof.

60. A method of treating a behavioral problem comprising administering a therapeutically effective amount of one or more compounds of Formula I as defined in claim 53 to a non-human subject in need thereof.

61. The method of claim 60, wherein the non-human subject is a canine or feline suffering from neurological diseases, behavioral problems, trainability problems and/or a combination thereof.

62. The method of claim 61, wherein and the neurological diseases, behavioral problems, trainability problems include, but are not limited to, anxiety, fear and stress, sleep disturbances, cognitive dysfunction, aggression, and/or a combination thereof.

63. 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 Formula I as defined in claim 53 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.

64. The method of any one of claims 53 to 63, wherein $R^8, R^9, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35}, R^{36}, R^{37}, R^{38}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46}, R^{47}, R^{48}, R^{49}, R^{50}, R^{52}, R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{62}$ and R^{63} are as defined in claim 2.

65. The method of any one of claims 53 to 63, wherein $R^{12}, R^{20}, R^{29}, R^{39}, R^{51}, R^{60}$ and R^{61} are as defined in any one of claims 4, 5 and 8.

66. The method of any one of claims 53 to 64, wherein Q is as defined in claim 3 or claim 6.

67. The method of any one of claims 53 to 66, wherein A' is as defined in claim 10.

68. The method of any one of claims 53 to 66, wherein Y is as defined in any one of claims 11 to 17.

69. The method of any one of claims 53 to 68, wherein R^1 and $R^{1'}$ are as defined in claim 18.

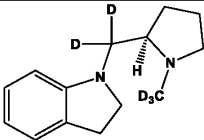
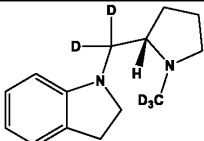
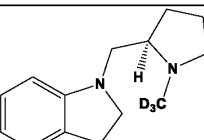
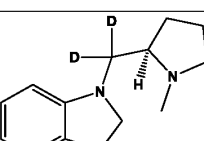
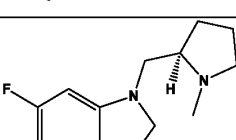
70. The method of any one of claims 53 to 69, wherein R^2 and $R^{2'}$ are as defined in claim 19.

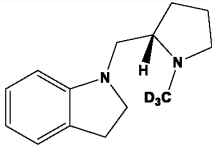
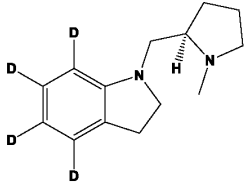
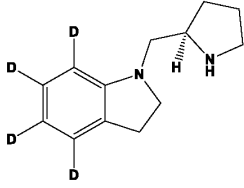
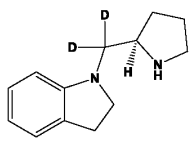
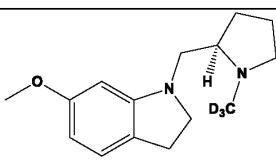
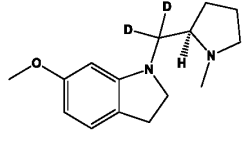
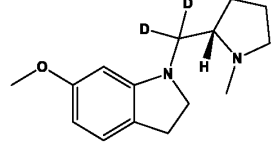
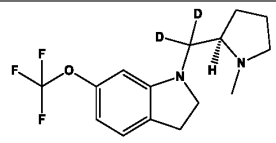
71. The method of any one of claims 53 to 70, wherein R^3 and R^6 are as defined in any one of claims 20 to 22.

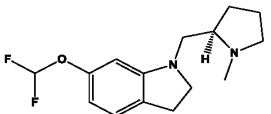
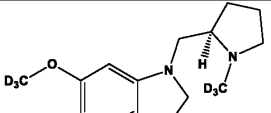
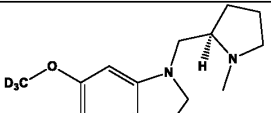
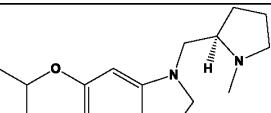
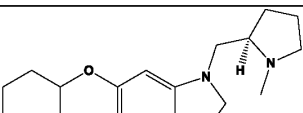
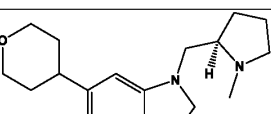
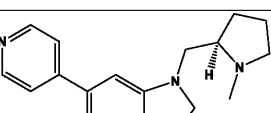
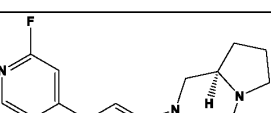
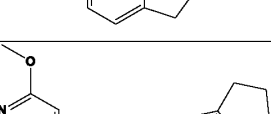
72. The method of any one of claims 53 to 71, wherein R^4 and R^5 are as defined in any one of claims 23 to 28.

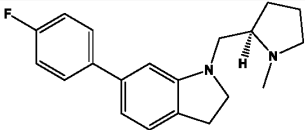
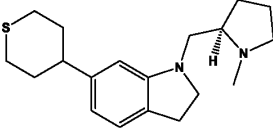
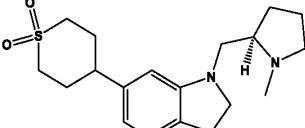
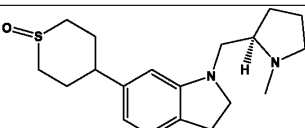
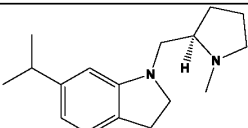
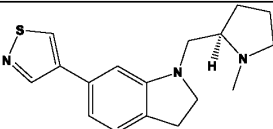
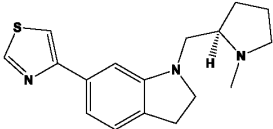
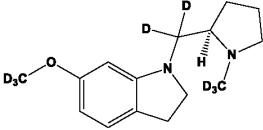
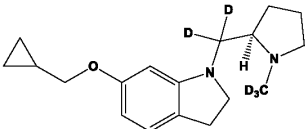
73. The method of any one of claims 53 to 72, wherein A is as defined in any one of claims 34, 35, 36, 38 to 45.

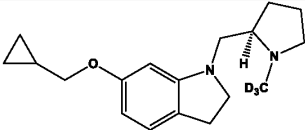
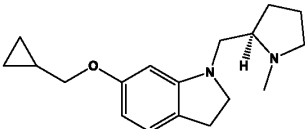
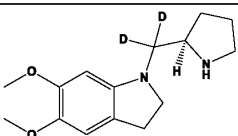
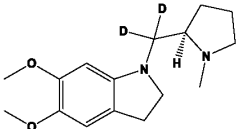
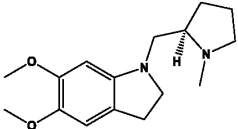
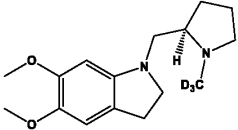
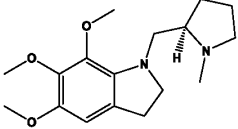
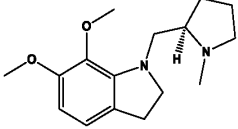
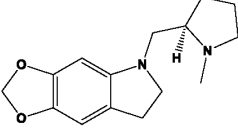
74. The method of claim 53, wherein compound of Formula I is selected from:

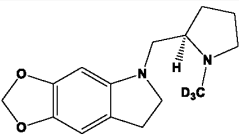
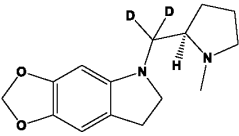
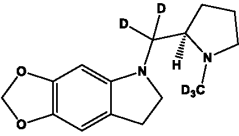
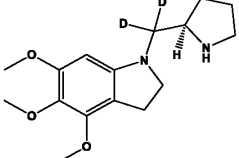
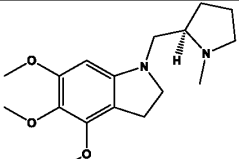
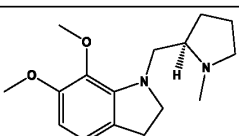
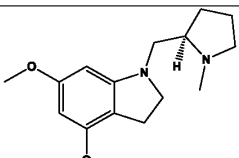
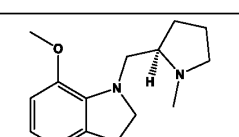
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(S)-I-1	
(R)-I-2	
(R)-I-3	
(R)-I-4	

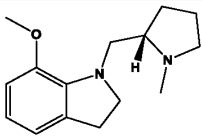
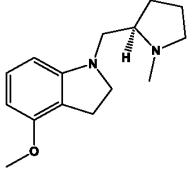
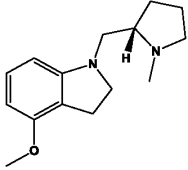
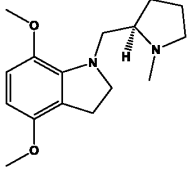
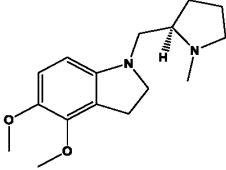
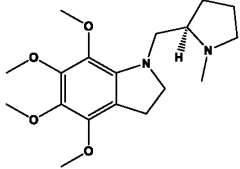
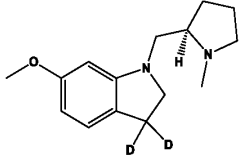
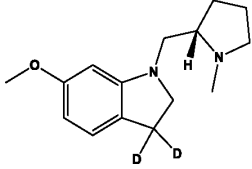
(S)-I-5	
(R)-I-6	
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(R)-I-8	
(R)-I-9	
(R)-I-10	
(S)-I-10	
(R)-I-11	

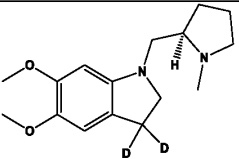
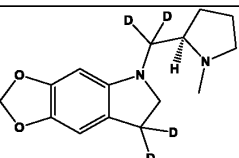
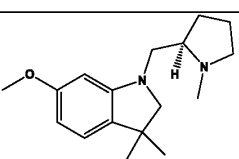
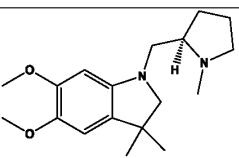
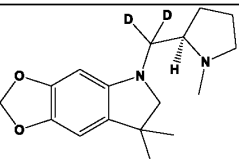
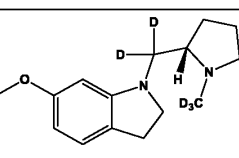
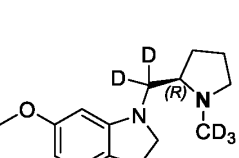
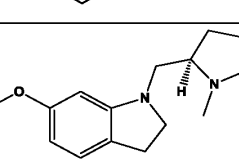
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(R)-I-14	
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(R)-I-18	
(R)-I-19	
(R)-I-20	

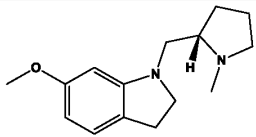
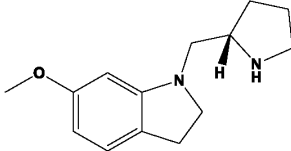
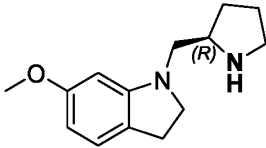
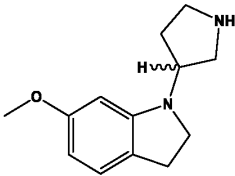
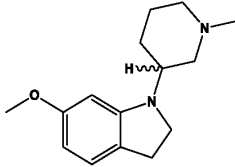
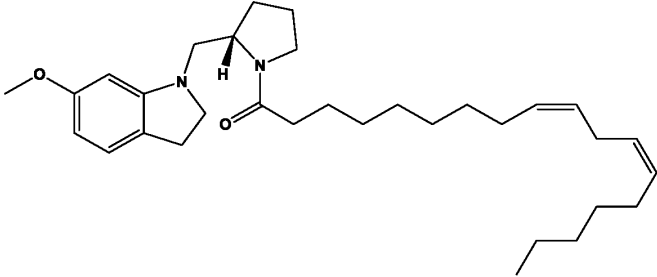
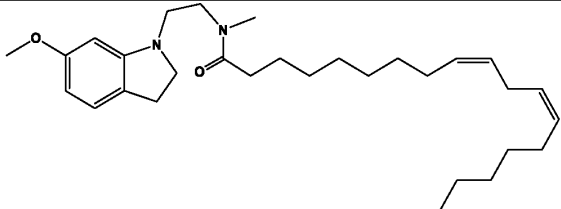
(R)-I-21	
(R)-I-22	
(R)-I-23	
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(R)-I-27	
(R)-I-28	
(R)-I-29	

(R)-I-30	
(R)-I-31	
(R)-I-32	
(R)-I-33	
(R)-I-34	
(R)-I-35	
(R)-I-36	
(R)-I-37	
(R)-I-38	

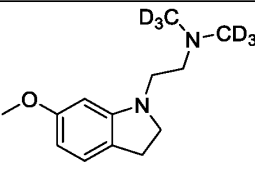
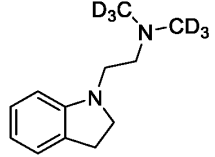
(R)-I-39	
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(R)-I-41	
(R)-I-42	
(R)-I-43	
(R)-I-44	
(R)-I-45	
(R)-I-46	

(S)-I-46	
(R)-I-47	
(S)-I-47	
(R)-I-48	
(R)-I-49	
(R)-I-50	
(R)-I-51	
(S)-I-51	

(R)-I-52	
(R)-I-53	
(R)-I-54	
(R)-I-55	
(R)-I-56	
(S)-I-57	
(R)-I-57	
(R)-I-58	

(S)-I-58	
(S)-I-59	
(R)-I-59	
I-60	
I-61	
(S)-I-62	
I-63	

I-64	
I-65	
I-66	
(S)-I-67	
(S)-I-68	
(S)-I-69	

I-70	 and
I-71	

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

75. A pharmaceutical composition comprising a compound of any one of claims 1 to 50 and an additional therapeutic agent.

76. The composition of claim 75, wherein the additional therapeutic agent is a psychoactive drug.