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(54) Title: ANALOGUES OF MDMA FOR MODULATING SERT, DAT, AND / OR NET ACTIVITY

(57) Abstract: Analogues of 3,4-methylenedioxymethamphetamine (MDMA), processes for their preparation, medicaments and medical methods of treatment comprising said MDMA analogues, and medical uses of said MDMA analogues. The MDMA analogues are capable of modulating SERT, DAT, and / or NET activity.

ANALOGUES OF MDMA FOR MODULATING SERT, DAT, AND / OR NET ACTIVITY

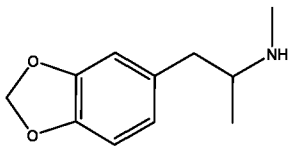
TECHNICAL FIELD

[0001] The disclosure herein relates to compounds which are analogues of 3,4-methylenedioxymethamphetamine (MDMA), processes for their preparation, medicaments and medical methods of treatment comprising said MDMA analogues, and medical uses of said MDMA analogues.

BACKGROUND ART

[0002] The following discussion of the background art is intended to facilitate an understanding of the present invention only. The discussion is not an acknowledgement or admission that any of the material referred to is or was part of the common general knowledge as at the priority date of the application.

[0003] The active constituent of the illegal drug ecstasy, 3,4-methylenedioxymethamphetamine (MDMA), is a psychotropic substance whose entactogenic effects are principally mediated by the serotonergic system. MDMA has been found to possess therapeutic effects against a range of medical conditions by a number of research studies in recent years.



MDMA

[0004] The United States Food and Drug Administration (FDA) has approved limited research on MDMA-assisted psychotherapy for post-traumatic stress disorder (PTSD), and phase III clinical trials indicate that MDMA has clinical benefit in facilitating psychotherapeutic efficacy for PTSD.

[0005] In humans, MDMA increases the amount of serotonin in the synaptic clefts of serotonergic neurons by inhibiting its uptake into neurons and by directly releasing it from the neurons. The released serotonin binds to various serotonin receptors and activates them in excess, which is the primary mechanism through which MDMA causes intoxication. MDMA also induces significant norepinephrine and dopamine release.

[0006] Extracellular MDMA binds to presynaptic serotonin reuptake transporter (SERT), norepinephrine reuptake transporter (NET) and dopamine reuptake transporter (DAT), as a reuptake inhibitor, so that these transporters uptake less of their corresponding monoamine

neurotransmitters, inducing higher concentrations and/or residence times of serotonin, norepinephrine and dopamine in the synaptic cleft.

[0007] Burkitt's lymphoma (BL) is an aggressive lymphoma that attacks the B-lymphocytes. B-cell lines have been shown to possess a functioning serotonin reuptake transporter (SERT). MDMA binds strongly to SERT, and shows potential as a target for chemotherapy in BL patients, exhibiting an antiproliferative and pro-apoptotic response in BL cell line L3055.

[0008] Transport of endogenous serotonin by SERT terminates the action of the serotonin and recycles it in a sodium-dependent manner. SERT acts to remove serotonin from the synaptic cleft back into the synaptic boutons. Thus, it terminates the effects of serotonin and simultaneously enables its reuse by the presynaptic neuron. SERT is the target of many antidepressant medications of the Selective Serotonin Reuptake Inhibitor (SSRI) and tricyclic antidepressant classes.

[0009] Abnormal serotonin reuptake rates have been implicated in sudden infant death syndrome, aggressive behaviour in Alzheimer disease patients, post-traumatic stress disorder and depression-susceptibility in people experiencing emotional trauma. Numerous studies have shown that changes in SERT metabolism appear to be associated with many different phenomena, including alcoholism, clinical depression, obsessive-compulsive disorder (OCD), romantic love, hypertension and generalized social phobia. SERT is also present in platelets, and serotonin functions as a vasoconstrictive substance, and as a signalling molecule to induce platelet aggregation.

[0010] Compounds such as MDMA analogues, possessing the ability to modulate SERT activity, therefore represent an area of great potential in the treatment of a vast number of medical conditions, including but not limited to medical conditions associated with the Central Nervous System (CNS).

[0011] Parkinson's disease (PD) is a neurodegenerative disorder for which the symptoms are commonly treated with levodopa, resulting, after long-term therapy, in adverse side-effects including levodopa-induced dyskinesia (LID), thereby negating the benefits of the therapy. MDMA has been shown to have, in primate models, limited anti-parkinsonian activity, anti-LID activity, and extends therapeutic duration of levodopa.

[0012] The dopamine active transporter (DAT) is a membrane-spanning protein that pumps the neurotransmitter dopamine out of the synaptic cleft back into cytosol. Dopamine reuptake via DAT provides the primary mechanism through which dopamine is cleared from synapses. Aside from MDMA, other amphetamines (including amphetamine itself) bind strongly to DAT.

[0013] Amphetamine enters the presynaptic neuron directly through the neuronal membrane or through DAT, competing for reuptake with dopamine. Once inside the presynaptic neuron, amphetamine triggers a cascade of effects including the firing rate of the postsynaptic neuron, inducing protein kinase signaling resulting in DAT phosphorylation (causing DAT to operate in reverse and/or withdraw into the presynaptic neuron, ceasing transport altogether), and entry into the synaptic vesicles inducing an efflux of dopamine into the cytosol. The dopaminergic mechanisms of the drug are believed to underlie the pleasurable feelings elicited by it.

[0014] DAT is implicated in a number of dopamine-related disorders, including attention deficit hyperactivity disorder, bipolar disorder, clinical depression, alcoholism, and substance use disorder. Dopamine underlies several aspects of cognition, including reward, and DAT facilitates regulation of that signal. The rate at which DAT removes dopamine from the synapse can have a profound effect on the amount of dopamine in the cell, as evidenced by severe cognitive deficits, motor abnormalities, and hyperactivity in knockout mice without dopamine transporters, showing striking similarities to the symptoms of ADHD.

[0015] Specific alleles and mutations of the DAT gene have been associated with non-smoking behaviour and ease of quitting, a statistically significant affinity for antisocial peers in male adolescents, dopamine transporter deficiency syndrome, and an autosomal recessive movement disorder characterized by progressively worsening dystonia and parkinsonism. Clinical depression is correlated with increased activity of DAT.

[0016] Compounds of the amphetamine family such as MDMA and analogues thereof, possessing the ability to modulate DAT activity, therefore represent an area of great potential in the treatment of a vast number of medical conditions, including but not limited to medical conditions associated with the Central Nervous System (CNS).

[0017] The norepinephrine transporter (NET) is a monoamine transporter responsible for the sodium-chloride dependent reuptake of extracellular norepinephrine. NET can also reuptake extracellular dopamine. The reuptake of these two neurotransmitters regulates concentrations in the synaptic cleft. NET, along with the other monoamine transporters (DAT and SERT), are the targets of many antidepressants and recreational drugs.

[0018] Overexpression of NET is associated with individuals diagnosed with ADHD. Mutations in NET have been implicated in ADHD, psychiatric disorders, postural tachycardia, orthostatic intolerance, postural orthostatic tachycardia syndrome and panic disorder. Norepinephrine has an important role in controlling mood, arousal, memory, learning, and pain perception. Dysregulation of the removal of norepinephrine by NET is associated with many neuropsychiatric diseases, including schizophrenia, affective disorder, and autonomic disorders.

In addition, many antidepressants and recreational drugs compete for the binding of NET with norepinephrine.

[0019] Inhibition of NET has potential therapeutic applications in the treatment of a broad range of medical conditions, including but not limited to attention deficit hyperactivity disorder (ADHD), substance abuse, neurodegenerative disorders (e.g., Alzheimer's disease (AD) and Parkinson's disease (PD)), and clinical depression. NET inhibitors such as reboxetine have been shown to reduce the stimulant effects of MDMA in humans, demonstrating the crucial role NET plays in the cardiovascular and stimulant-like effects of MDMA.

[0020] Compounds such as MDMA analogues, possessing the ability to modulate NET activity, therefore represent an area of great potential in the treatment of a vast number of medical conditions, including but not limited to medical conditions associated with the Central Nervous System (CNS).

[0021] Monoamine oxidases (MAOs) are a family of enzymes found bound to the outer membrane of mitochondria in most cell types of the body, that catalyse the oxidative deamination of monoamines, employing oxygen to remove their amine group. MAOs are important in the breakdown of exogenously ingested monoamines, and also serve to inactivate monoamine neurotransmitters (including serotonin, dopamine and norepinephrine). Due to their action on monoamine neurotransmitters, MAOs are implicated in a number of psychiatric and neurological diseases, some of which can be treated via inhibition of MAOs. Monoamine oxidase subtype A (MAO-A) is found in neurons and astroglia of the central nervous system (CNS), as well as outside the CNS in the liver, pulmonary vascular endothelium, gastrointestinal tract, and placenta.

[0022] Mutations in the MAO gene have been correlated with Brunner syndrome, antisocial conduct disorders, adolescent conduct disorder, sympathetic arousal and rage, predisposition to novelty seeking. Due to the vital role that MAOs play in the inactivation of neurotransmitters, MAO dysfunction (too much or too little MAO activity) is associated with a broad range of psychiatric and neurological disorders. For example, unusually high or low levels of MAOs in the body have been correlated with schizophrenia, depression, attention deficit disorder, substance abuse, migraines, and irregular sexual maturation. Unusually high levels of catecholamines (including epinephrine, norepinephrine, and dopamine) may lead to a hypertensive crisis, and abnormally high levels of serotonin may lead to serotonin syndrome. Meanwhile, inhibition of MAOs often provides useful antidepressant and anti-anxiety therapeutic effects, and can be used in the treatment of a broad range of medical conditions, including but not limited to Alzheimer's disease, Parkinson's disease, psychomotor retardation, weight gain, interpersonal sensitivity, and resistant depression.

[0023] Compounds such as MDMA analogues, possessing the ability to modulate MAO activity, therefore represent an area of great potential in the treatment of a vast number of medical conditions, including but not limited to medical conditions associated with the Central Nervous System (CNS).

[0024] 5-HT receptors, or serotonin receptors, are a group of G protein-coupled receptor and ligand-gated ion channels found in both the central and peripheral nervous systems. They mediate excitatory and inhibitory neurotransmission and are activated by their natural endogenous ligand the neurotransmitter serotonin. 5-HT receptors modulate the release of many neurotransmitters, including glutamate, GABA, dopamine, epinephrine, norepinephrine, and acetylcholine, as well as many hormones, including oxytocin, prolactin, vasopressin, cortisol, corticotropin, and substance P, among others. 5-HT receptors influence many biological and neurological processes including aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep, and thermoregulation.

[0025] 5-HT receptors are the target of a variety of pharmaceutical and recreational drugs, including many antidepressants, antipsychotics, anorectics, antiemetics, gastroprokinetic agents, antimigraine agents, hallucinogens, and entactogens such as MDMA.

[0026] MDMA binds as an agonist to 5-HT1A, 5-HT2A, 5-HT2B and 5-HT2C serotonin receptors. Modulation of these receptor subtypes is implicated in a broad range of functions, behaviours and their associated medical conditions, including;

5-HT1A;

addiction, aggression, anxiety, appetite, autoreceptor signaling, blood pressure, cardiovascular function, emesis, heart rate, impulsivity, memory, mood, nausea, nociception, penile erection, pupil dilation, respiration, sexual behaviour, sleep, sociability, thermoregulation, and vasoconstriction;

5-HT2A;

addiction (potentially modulating), anxiety, appetite, cognition, imagination, learning, memory, mood, perception, sexual behaviour, sleep, thermoregulation, and vasoconstriction;

5-HT2B;

anxiety, appetite, cardiovascular function, gastrointestinal motility, sleep, and vasoconstriction;

5-HT2C;

addiction (potentially modulating), anxiety, appetite, gastrointestinal motility, heteroreceptor signaling for norepinephrine and dopamine, locomotion, mood, penile erection, sexual behaviour, sleep, thermoregulation, and vasoconstriction.

[0027] Activation of 5-HT2B receptors, in particular, has also been strongly implicated in drug-induced valvular heart disease, with the result that this receptor subtype is generally considered to be an anti-target. Correspondingly, antagonists of 5-HT2B receptors such as aripiprazole and clozapine (among others) have found clinical use in antipsychotic therapies. More recent research suggests that 5-HT2B antagonists may be useful in the treatment of chronic heart disease, in the attenuation of fibrogenesis to improve liver function in diseases in which fibrosis is pre-established and progressive.

[0028] Compounds such as MDMA analogues, possessing the ability to modulate 5-HT receptor activity, therefore represent an area of great potential in the treatment of a vast number of medical conditions, including but not limited to medical conditions associated with the Central Nervous System (CNS).

[0029] Although, as discussed above, MDMA shows great potential and has been found to possess therapeutic effects against a range of medical conditions by a number of research studies in recent years, including clinical benefit in PTSD therapy, significant problems exist with implementing MDMA as a prescribed treatment. Not least of these problems is the abuse potential arising from the extrapyramidal and euphoric effects potentially induced by the drug. Although controversial, long-term use of high-dose MDMA has also been associated with neurotoxicity. Long-term use of MDMA can lead to memory problems, paranoia and difficulty sleeping. Even short-term use can produce adverse effects including grinding of the teeth, blurred vision, sweating and a rapid heartbeat. Furthermore, deaths have been reported due to increased body temperature, dehydration and hyponatremia (low blood sodium concentration). Following use, subjects often feel depressed and tired.

[0030] There is a need to provide alternative compounds possessing similar structural and biological properties to MDMA, that avoid one or more of the problems associated with producing extrapyramidal and euphoric effects, or leading to abuse or addiction, neurotoxicity or other adverse effects such as memory problems, paranoia, difficulty sleeping, grinding of the teeth, blurred vision, sweating, rapid heartbeat, depression, tiredness or death.

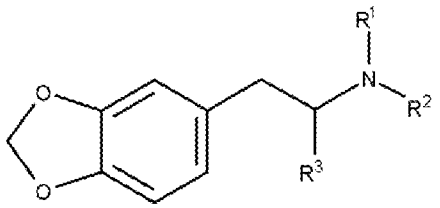
[0031] There is a need to provide new compounds having the ability to modulate the activity of one or more of SERT, DAT, NET, MAOs and/or 5-HT receptors, preferably, but not necessarily (depending on the condition to be treated) whilst avoiding agonist activity against 5-HT2B receptors.

[0032] It is against this background that the present invention has been developed.

SUMMARY OF THE INVENTION

[0033] The present disclosure provides novel MDMA analogue compounds, processes for their synthesis, medicaments and medical uses comprising them and methods of medical treatment involving their administration to a subject in need thereof.

[0034] In one embodiment, the present disclosure provides a compound of Formula I;



Formula I

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula I may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c,

-C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

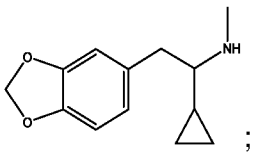
R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, -OR^a, -SR^a, -NR^bR^c, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a,

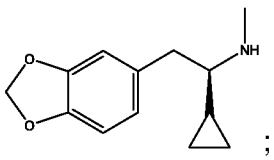
-C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

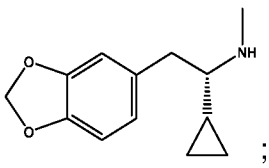
or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

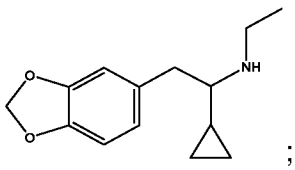
R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl;

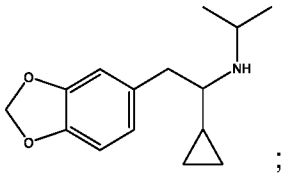
wherein the compound of Formula I is not a compound selected from the group comprising;

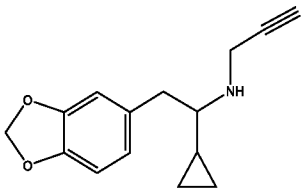

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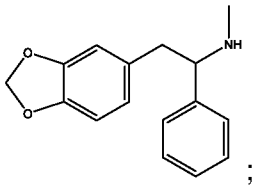

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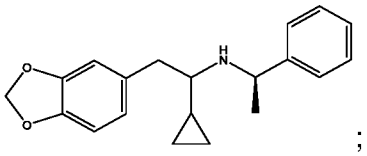

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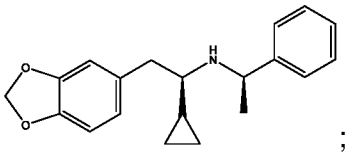

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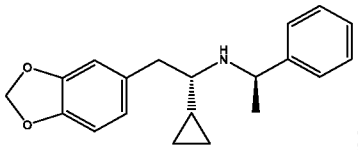

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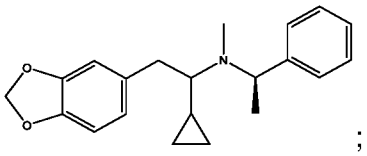
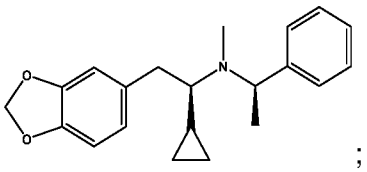
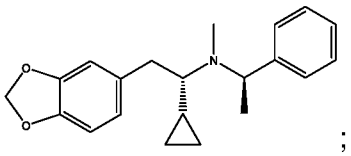
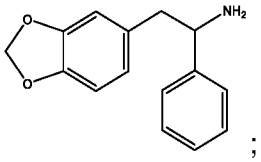
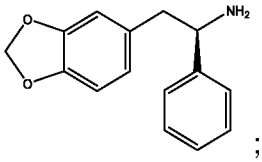
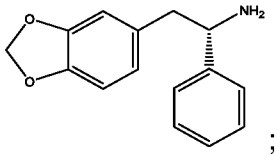
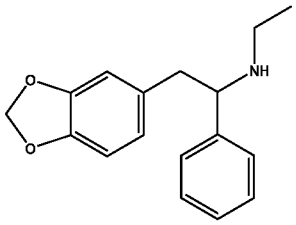
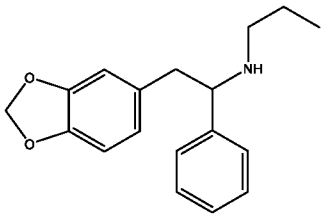
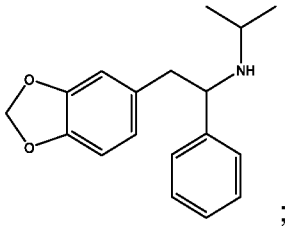
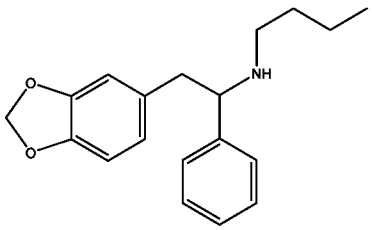
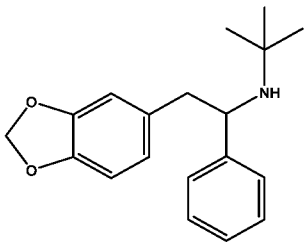
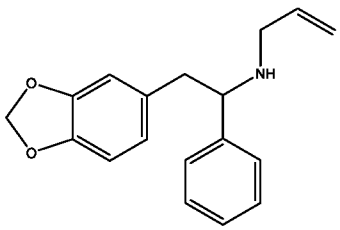
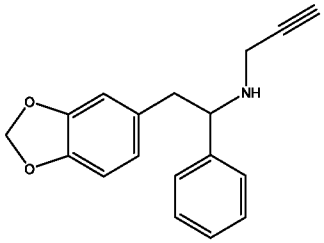
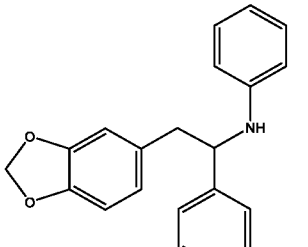
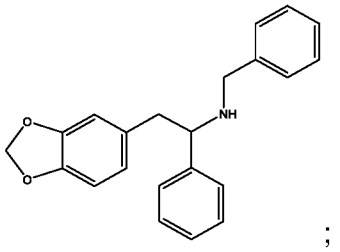
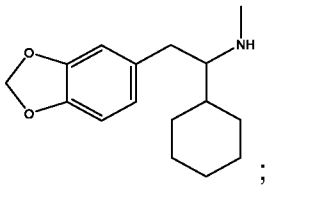
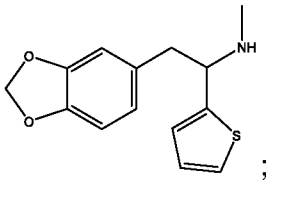
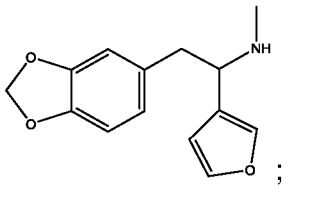
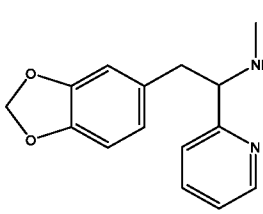
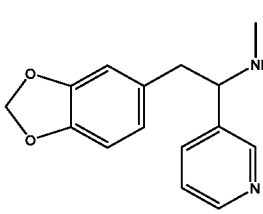
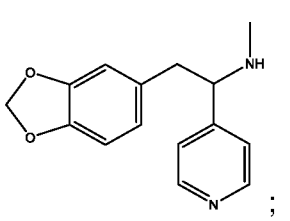

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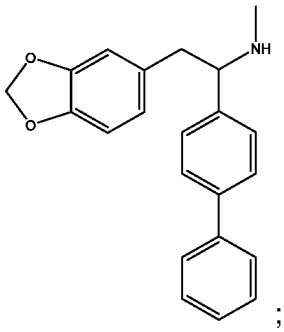
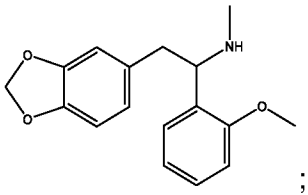
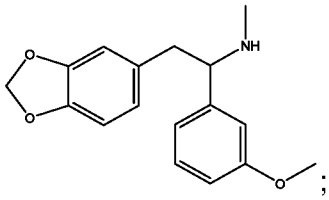
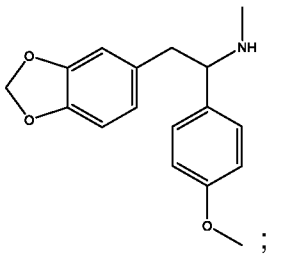
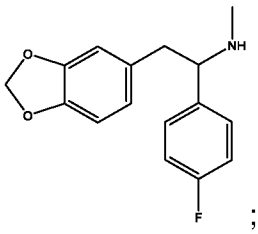
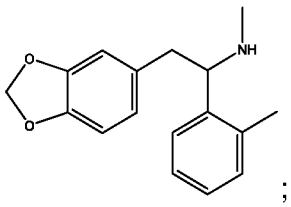
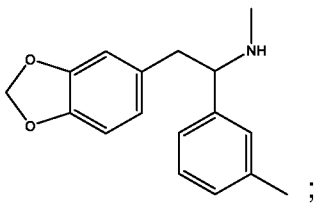
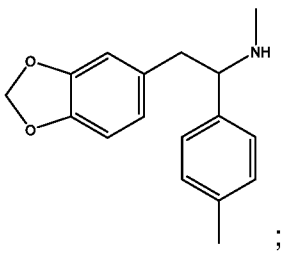
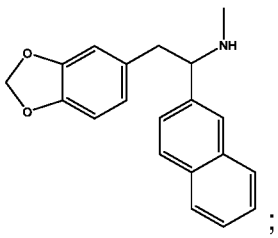

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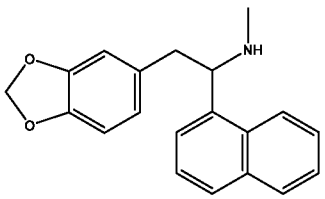
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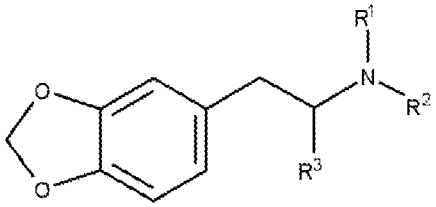

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and


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and, wherein the compound of Formula I is not a compound published before the earliest priority date of the present disclosure, or wherein the compound of Formula I is not a compound hitherto not ascertained by the present inventors as being published before the earliest priority date of the present disclosure.

[0035] In one embodiment, the present disclosure provides for the use of a compound of Formula II;



Formula II

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula II may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, $-OR^a$, $-SR^a$, $-NR^bR^c$, methyl, ethyl, $-C_{3-9}$alkyl, $-C_{1-9}$haloalkyl, $-C_{2-9}$alkenyl, $-C_{2-9}$haloalkenyl, $-C_{2-9}$alkynyl, $-C_{2-9}$haloalkynyl, $-C_{3-9}$cycloalkyl, $-C_{6-12}$bicycloalkyl, $-C_{6-12}$spirocycloalkyl, $-C_{3-9}$cyclohaloalkyl, $-C_{6-12}$bicyclohaloalkyl, $-C_{6-12}$spirocyclohaloalkyl, $-C_{3-9}$cycloalkenyl, $-C_{6-12}$bicycloalkenyl, $-C_{6-12}$spirocycloalkenyl, $-C_{3-9}$cyclohaloalkenyl, $-C_{6-12}$bicyclohaloalkenyl, $-C_{6-12}$spirocyclohaloalkenyl, $-C_{8-12}$cycloalkynyl, $-C_{9-14}$bicycloalkynyl, $-C_{9-14}$spirocycloalkynyl, $-C_{8-12}$cyclohaloalkynyl, $-C_{9-14}$bicycloalkynyl, $-C_{9-14}$spirocycloalkynyl, aryl, heteroaryl, $-C_{1-5}$alkyl-aryl, $-C_{2-5}$alkenyl-aryl, $-C_{2-5}$alkynyl-aryl, $-C_{1-5}$alkyl-heteroaryl, $-C_{2-5}$alkenyl-heteroaryl, $-C_{2-5}$alkynyl-heteroaryl, $-C_{1-5}$haloalkyl-aryl, $-C_{2-5}$haloalkenyl-aryl, $-C_{2-5}$haloalkynyl-aryl, $-C_{1-5}$haloalkyl-heteroaryl, $-C_{2-5}$haloalkenyl-heteroaryl, $-C_{2-5}$haloalkynyl-heteroaryl, $-C(=O)R^a$, $-C_{1-8}$alkyl-$C(=O)R^a$, $-C_{2-8}$alkenyl-$C(=O)R^a$, $-C_{2-8}$alkynyl-$C(=O)R^a$, $-C_{1-8}$haloalkyl-$C(=O)R^a$, $-C_{2-8}$haloalkenyl-$C(=O)R^a$, $-C_{2-8}$haloalkynyl-$C(=O)R^a$, $-CO_2R^a$, $-C_{1-8}$alkyl-CO_2R^a, $-C_{2-8}$alkenyl-CO_2R^a, $-C_{2-8}$alkynyl-CO_2R^a, $-C_{1-8}$haloalkyl-CO_2R^a, $-C_{2-8}$haloalkenyl-CO_2R^a, $-C_{2-8}$haloalkynyl-CO_2R^a, $-SO_2R^a$, $-C_{1-8}$alkyl-SO_2R^a, $-C_{2-8}$alkenyl-SO_2R^a, $-C_{2-8}$alkynyl-SO_2R^a, $-C_{1-8}$haloalkyl-SO_2R^a, $-C_{2-8}$haloalkenyl-SO_2R^a, $-C_{2-8}$haloalkynyl-SO_2R^a, $-C(=O)NR^bR^c$, $-C_{1-8}$alkyl-$C(=O)NR^bR^c$, $-C_{2-8}$alkynyl-$C(=O)NR^bR^c$, $-C_{2-8}$alkenyl-$C(=O)NR^bR^c$, $-C_{1-8}$haloalkyl-$C(=O)NR^bR^c$, $-C_{2-8}$haloalkynyl-$C(=O)NR^bR^c$, $-C_{2-8}$haloalkenyl-$C(=O)NR^bR^c$, -CN, $-C_{1-8}$alkyl-CN, $-C_{2-8}$alkenyl-CN, $-C_{2-8}$alkynyl-CN, $-C_{1-8}$haloalkyl-CN, $-C_{2-8}$haloalkenyl-CN, $-C_{2-8}$haloalkynyl-CN, $-CH_2$-O-R^a, $-C_{2-9}$alkyl-O-R^a, $-C_{2-9}$alkenyl-O-R^a, $-C_{2-9}$alkenyl-O-R^a, $-C_{2-9}$haloalkyl-O-R^a, $-C_{2-9}$haloalkenyl-O-R^a, $-C_{2-9}$haloalkenyl-O-R^a, $-CH_2$-S-R^a, $-C_{2-9}$alkyl-S-R^a, $-C_{2-9}$alkenyl-S-R^a, $-C_{2-9}$alkenyl-S-R^a, $-C_{2-9}$haloalkyl-S-R^a, $-C_{2-9}$haloalkenyl-S-R^a, and $-C_{2-9}$haloalkenyl-S-R^a;

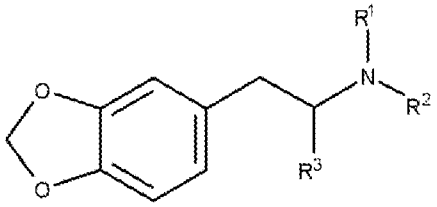
or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, $-C_{3-9}$alkyl, $-C_{1-9}$haloalkyl, $-C_{2-9}$alkenyl, $-C_{2-9}$haloalkenyl, $-C_{2-9}$alkynyl, $-C_{2-9}$haloalkynyl, $-C_{3-9}$cycloalkyl, aryl, heteroaryl, $-C_{1-5}$alkyl-aryl, $-C_{1-5}$haloalkyl-aryl, $-C_{2-5}$alkenyl-aryl, $-C_{2-5}$haloalkenyl-aryl, $-C_{2-5}$alkynyl-aryl, $-C_{2-5}$haloalkynyl-aryl,

-C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl;

for the manufacture of a medicament for the treatment or prevention of a disease, disorder, injury or trauma.

[0036] In one embodiment, the present disclosure provides a method of treating or preventing a disease, disorder, injury or trauma, comprising the administration of an effective amount of a compound of Formula II to a subject in need thereof;



Formula II

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula II may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -$C(=O)R^a$, -C_{1-8}alkyl-$C(=O)R^a$, -C_{2-8}alkenyl-$C(=O)R^a$, -C_{2-8}alkynyl-$C(=O)R^a$, -C_{1-8}haloalkyl-$C(=O)R^a$, -C_{2-8}haloalkenyl-$C(=O)R^a$, -C_{2-8}haloalkynyl-$C(=O)R^a$, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -$C(=O)NR^bR^c$, -C_{1-8}alkyl-$C(=O)NR^bR^c$, -C_{2-8}alkynyl-$C(=O)NR^bR^c$, -C_{2-8}alkenyl-$C(=O)NR^bR^c$, -C_{1-8}haloalkyl-$C(=O)NR^bR^c$, -C_{2-8}haloalkynyl-$C(=O)NR^bR^c$,

-C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

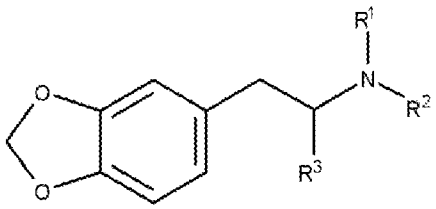
R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, -OR^a, -SR^a, -NR^bR^c, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a,

-C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl.

[0037] In one embodiment, the present disclosure provides a process for the preparation of a compound according to Formula II';



Formula II'

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula II' may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl,

-C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

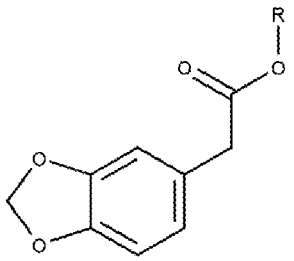
R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, -OR^a, -SR^a, -NR^bR^c, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl,

-C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl;

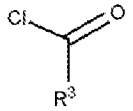
wherein the process comprises reacting a compound according to Formula III;



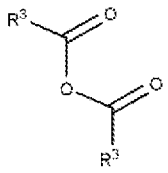
Formula III

wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl;

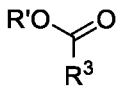
with a compound according to Formula IVa, or Formula IVb, or Formula IVc;



Formula IVa;



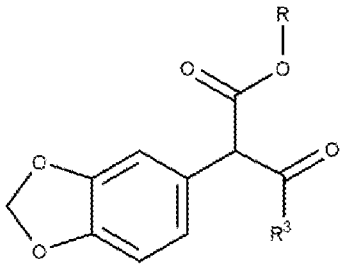
Formula IVb;



Formula IVc;

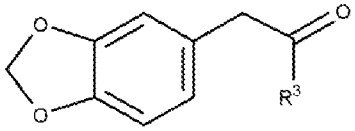
wherein R^3 is as defined for the compound of Formula II', and wherein, for the compound of Formula IVb, each R^3 may be the same or different, and wherein R' is selected from the group consisting of; methyl, ethyl, -C_{3-9}alkyl, aryl and haloaryl;

under a first set of reaction conditions, to produce a compound of Formula V;



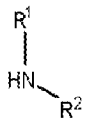
Formula V

followed by subjecting the compound of Formula V to a second set of reaction conditions to produce a ketone intermediate of Formula VI;



Formula VI

and subsequent reductive amination of the compound of Formula VI with a compound of Formula VII;



Formula VII

wherein R^1 and R^2 are as defined for the compound of Formula II';

under a third set of reaction conditions, to produce the compound of Formula II'.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] Further features of the present invention are more fully described in the following description of several non-limiting embodiments thereof. This description is included solely for the purposes of exemplifying the present invention. It should not be understood as a restriction on the broad summary, disclosure or description of the invention as set out above. The description will be made with reference to the accompanying drawings in which:

DEFINITIONS

[0039] Throughout this specification, unless the context requires otherwise, the word "comprise" or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

[0040] As used herein, the term “stereoisomer”, and grammatical variations thereof such as “stereoisomers”, “stereoisomerism”, “stereoisomeric”, *et cetera*, refers to spatial isomerism in the molecular entity to which it is contextually applied. More specifically, the term is to be understood to include molecules having the same molecular formula and sequence of bonded atoms (constitution) but differing in the three-dimensional orientations of their atoms in space. Thus stereoisomers are to be understood as including optical isomers or enantiomers, diastereoisomers, cis-trans or E-Z isomers, conformers, anomers, atropisomers, configurational stereoisomers and epimers of the molecular entity to which the term is applied. By definition, molecules that are stereoisomers of each other represent the same structural isomer, and the same constitutional isomer.

[0041] All chiral, diastereomeric, racemic mixtures, non-racemic mixtures and geometric isomeric forms of a structure are intended, unless specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention.

[0042] As used herein, the term “isotopologue”, and grammatical variations thereof such as “isotopologue”, *et cetera*, is to be understood to mean molecules that differ only in their isotopic composition. That is to say, the term refers to molecules having the same chemical formula and bonding arrangement of atoms, but at least one atom has a different number of neutrons than the parent.

[0043] As used herein, the term “prodrug”, and grammatical variations thereof such as “prodrugs”, *et cetera*, is to be understood to mean a compound that, after administration, is *in*

vivo hydrolyzed or metabolized (i.e., converted within the body) into a pharmacologically active drug. Thus, "prodrug" refers to a compound that is metabolized, for example, hydrolyzed or oxidized, in the host to form a compound of the Formula (I) or Formula (II). Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs may include, for example, compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. The skilled addressee will be aware that compounds containing, for example, hydroxyl, carboxylic acid or amine substituents may be derivatized as esters or amides and that such derivatives will be susceptible to *in vivo* hydrolysis and/or metabolism to yield the parent, underivatized compound. Such derivatives are to be understood as falling within the scope of the term "prodrugs". Prodrugs can be readily prepared from the compounds of Formula (I) or Formula (II) using methods known in the art. See, for example, Notari, R. E., "Theory and Practice of Prodrug Kinetics," Methods in Enzymology, 112:309 323 (1985); Bodor, N., "Novel Approaches in Prodrug Design," Drugs of the Future, 6(3): 165 182 (1981); and Bundgaard, H., "Design of Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities," in Design of Prodrugs (H. Bundgaard, ed.), Elsevier, N.Y. (1985); Burger's Medicinal Chemistry and Drug Chemistry, Fifth Ed., Vol. 1, pp. 172- 178, 949-982 (1995).

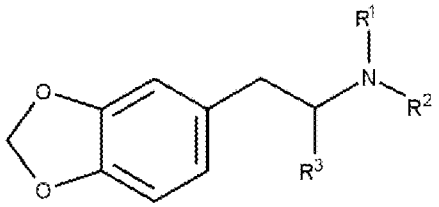
[0044] As used herein, the term "pharmaceutically acceptable", will be understood to mean a material that is not biologically or otherwise undesirable, i.e., the material can be administered to an individual along with the compounds or compositions of this invention, without causing substantial deleterious biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. The material would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the subject, as would be well known to one of skill in the art.

[0045] Compounds of the Invention may exist in free or salt form, e.g., as acid addition salts. In this specification unless otherwise indicated language such as "Compounds of the Invention" is to be understood as embracing the compounds in any form, for example free or acid addition salt form, or where the compounds contain acidic substituents, in base addition salt form. The Compounds of the Invention are intended for use as pharmaceuticals or vetinary medicines, therefore pharmaceutically acceptable salts are preferred. Salts which are unsuitable for pharmaceutical uses may be useful, for example, for the isolation or purification of free Compounds of the Invention or their salts or pharmaceutically acceptable salts, are therefore also included. "Pharmaceutically acceptable salts" include, without limitation, sodium,

magnesium, calcium, lithium, potassium, chloride, bromide, iodide, hydrochloride, hydrobromide, sulfate, acetate, tartrate, malate, mesylate and tosylate salts, for example.

[0046] As used herein, the term “alkyl”, by itself or as part of another substituent, will be understood to mean unless otherwise stated, a straight or branched chain hydrocarbon, and where designated, having the number of carbon atoms designated (i.e., “-C_{1-10}alkyl” means an alkyl having between one to ten carbon atoms). By way of illustration, but without limitation, the term "-C_{1-8}alkyl" refers to a straight chain or branched hydrocarbon moiety having from 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. "-C_{1-6}alkyl" refers to a straight chain or branched hydrocarbon moiety having from 1, 2, 3, 4, 5, or 6 carbon atoms. "-C_{1-4}alkyl" refers to a straight chain or branched hydrocarbon moiety having from 1, 2, 3, or 4 carbon atoms, including methyl, ethyl, n-propyl, n-propyl, n-butyl, iso-butyl, sec-butyl, and tert-butyl. The term “-C_{1-9}haloalkyl” refers to a straight chain or branched hydrocarbon moiety having from 1, 2, 3, 4, 5, 6, 7, 8 or 9 carbon atoms, wherein one or more of said carbon atoms are substituted with one or more halogen atoms selected from F, Cl, Br or I.

[0047] As used herein, the term “parent molecular structure”, “parent molecule”, and grammatical variations thereof, when used in the context of defining variable substituents of Markush Formulae, will be understood to refer to the core structure or non-variable portion of the Markush Formula to which it is being applied. For example, Formula I as defined herein has the variables R^1, R^2 and R^3 attached to the parent molecular structure:



Formula I

[0048] As used herein, the term "alkenyl" employed alone or in combination with other terms means, unless otherwise stated, a straight chain or branched hydrocarbon group containing at least one double bond, and where designated, having the number of carbon atoms designated. For example, from two to ten carbon atoms (i.e., -C_{2-10}alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" or “2-10”, refers to each integer in the given range; e.g., "2 to 10 carbon atoms" means that the -C_{2-10}alkenyl group can consist of 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The alkenyl group is attached to the parent molecular structure by a single bond, for example, ethenyl (i.e., vinyl), propen-1-yl (i.e., allyl), buten-1-yl, penten-1-yl, penta-1,4-dienyl, and the like. The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of -C_{2-4}alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), 2-methylprop-2-enyl (C_4),

butadienyl (C_4) and the like. Examples of -C_{2-6}alkenyl groups include the aforementioned -C_{2-4}alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), 2,3-dimethyl-2-butenyl (C_6) and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8) and the like. Further examples include vinyl, propenyl (or allyl), crotyl, isopentenyl, butadienyl, 1,3-pentadienyl, 1,4-pentadienyl, and the higher homologs and isomers. An example of a functional group representing an alkene is -CH_2-CH=CH_2. The term "-C_{2-9}haloalkenyl" refers to a straight chain or branched hydrocarbon moiety containing at least one double bond, having 2, 3, 4, 5, 6, 7, 8 or 9 carbon atoms, wherein one or more of said carbon atoms are substituted with one or more halogen atoms selected from F, Cl, Br or I.

[0049] As used herein, the term "alkynyl" employed alone or in combination with other terms will be understood to mean, unless otherwise stated, a straight chain or branched chain hydrocarbon group containing at least one triple bond, having the number of carbon atoms specified (i.e., -C_{2-10}alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range; e.g., "-C_{2-10}alkynyl" means that the alkynyl group can consist of 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. In certain embodiments, an alkynyl comprises two to nine carbon atoms. The alkynyl is attached to the parent molecular structure by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, 3-methyl-4-pentenyl, hexynyl, and the like. Non-limiting examples include ethynyl and propynyl, and the higher homologs and isomers. The term "propargylic" and grammatical variations such as "propargyl" refers to a group exemplified by -CH_2-C≡CH. The term "-C_{2-9}haloalkynyl" refers to a straight chain or branched hydrocarbon moiety containing at least one triple bond, having from 2, 3, 4, 5, 6, 7, 8 or 9 carbon atoms, wherein one or more of said carbon atoms are substituted with one or more halogen atoms selected from F, Cl, Br or I.

[0050] As used herein, the term "halo", employed alone or in combination with other terms will be understood to mean, unless otherwise stated, one or more halogen atom substituents independently selected from the group consisting of fluorine (F), chlorine (Cl), bromine (Br) and iodine (I). The term "halo" is understood to be used interchangeably with the term "halogen".

[0051] As used herein, the term "cyclo" employed in combination with other terms will be understood to mean, unless otherwise stated, a cyclic moiety.

[0052] As used herein, the term "aromatic" refers to a carbocycle or heterocycle with one or more polyunsaturated rings and having aromatic character, for example, under classical circumstances, having (4n+2) delocalized π (pi) electrons, where n is an integer. This skilled addressee will be aware that there are exceptions to the general (4n+2) delocalized π (pi) electron rule that still possess aromatic character and that will therefore also fall within the definition of "aromatic".

[0053] As used herein, the term "aryl" employed alone or in combination with other terms means, unless otherwise stated, a carbocyclic aromatic system containing one or more rings (typically one, two or three rings) wherein such rings may be fused, such as naphthalene. In a multi-ring group, only one ring is required to be aromatic, so groups such as indanyl are encompassed by the aryl definition, provided the aromatic ring of such groups is attached directly to the parent molecule. The ring or ring system can have 6 to 14 ring atoms (e.g., C_{6-14}aromatic or C_{6-14}aryl). Whenever it appears herein, a numerical range such as "6 to 14 aryl" refers to each integer in the given range; e.g., "C_{6-14}aryl" means that the aryl group can consist of 6, 7, 8, 9, 10, 11, 12, 13, or 14 ring atoms. Non-limiting examples of aryl groups include phenyl, phenalenyl, naphthalenyl, tetrahydronaphthyl, phenanthrenyl, anthracenyl, fluorenyl, indolyl, indanyl, and the like.

[0054] As used herein, the term “hetero” employed in combination with other terms will be understood to mean, unless otherwise stated, replacement of one or more carbon atoms in the other term to which it is applied, with a heteroatom independently selected in each instance from the group consisting of oxygen (O), nitrogen (N), sulfur (S), selenium (Se), silicon (Si) or phosphorus (P).

[0055] The term "heteroaryl" as used herein includes 5-, 6- and 7-membered monocyclic or poly cyclic (e.g., bicyclic or tricyclic) aromatic ring systems having ring carbon atoms and 1, 2, 3, or 4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, phosphorous and sulfur. For example, a heteroaryl can have one or two 5-, 6- or 7-membered rings and 1 to 4 heteroatoms selected from N, O, and S. Heteroaryl bicyclic ring systems can include 1, 2, 3, or 4 heteroatoms in one or both rings. Exemplary heteroaryls include, but are not limited to, pyrrole, furan, thiophene, imidazole, oxazole, oxadiazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine, azepine, oxepine, oxazine, triazine, pyrimidine, indole, and benzoimidazole, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics."

[0056] As used herein, the term "cycloalkyl" employed alone or in combination with other terms will be understood to mean, unless otherwise stated, a cycloalkyl moiety. Where a number of carbon atoms is specified, the cycloalkyl moiety will contain the specified number of carbon atoms. Where a range in the number of carbon atoms is specified, the cycloalkyl moiety will contain a number of carbon atoms selected from integer within the specified range. For example, “-C_{3-9}cycloalkyl” will be understood to mean a saturated carbocyclic ring moiety comprising 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and will therefore be understood to include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl moieties. “-C_{6-12}bicycloalkyl” will be understood to mean a saturated carbocyclic ring system comprising

two fused carbocyclic rings and having 6, 7, 8, 9, 10, 11 or 12 carbon atoms. "-C_{6-12}spirocycloalkyl" will be understood to mean a saturated carbocyclic ring system comprising two carbocyclic rings wherein only one carbon atom is common to both rings, and having 6, 7, 8, 9, 10, 11 or 12 carbon atoms. "-C_{3-9}cyclohaloalkyl" will be understood to mean a saturated carbocyclic ring moiety comprising 3, 4, 5, 6, 7, 8 or 9 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I. "-C_{6-12}bicyclohaloalkyl" will be understood to mean a saturated carbocyclic ring system comprising two fused carbocyclic rings and having 6, 7, 8, 9, 10, 11 or 12 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I. "-C_{6-12}spirocyclohaloalkyl" will be understood to mean a saturated carbocyclic ring system comprising two carbocyclic rings wherein only one carbon atom is common to both rings, and having 6, 7, 8, 9, 10, 11 or 12 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0057] As used herein, the term "cycloalkenyl" employed alone or in combination with other terms will be understood to mean, unless otherwise stated, a cycloalkyl moiety containing one or more double bonds. Where a number of carbon atoms is specified, the cycloalkenyl moiety will contain the specified number of carbon atoms. Where a range in the number of carbon atoms is specified, the cycloalkenyl moiety will contain a number of carbon atoms selected from integer within the specified range. For example, "-C_{3-9}cycloalkenyl" will be understood to mean a carbocyclic ring moiety having at least one double bond, and comprising 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and will therefore be understood to include cyclopropenyl, cyclobutenyl, cyclobutadienyl, cyclopentenyl, cyclopentadienyl cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, cyclooctenyl, cyclooctadienyl, cyclooctatrienyl, cyclooctatetraenyl, cyclononenyl, cyclononadienyl, cyclononatrienyl, and cyclononatetraenyl moieties. "-C_{6-12}bicycloalkenyl" will be understood to mean a carbocyclic ring system having at least one double bond, comprising two fused carbocyclic rings and having 6, 7, 8, 9, 10, 11 or 12 carbon atoms. "-C_{6-12}spirocycloalkenyl" will be understood to mean a carbocyclic ring system comprising two carbocyclic rings and at least one double bond, wherein only one carbon atom is common to both rings, and having 6, 7, 8, 9, 10, 11 or 12 carbon atoms. "-C_{3-9}cyclohaloalkenyl" will be understood to mean a carbocyclic ring moiety having at least one double bond, comprising 3, 4, 5, 6, 7, 8 or 9 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I. "-C_{6-12}bicyclohaloalkenyl" will be understood to mean a carbocyclic ring system having at least one double bond, comprising two fused carbocyclic rings and having 6, 7, 8, 9, 10, 11 or 12 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo

groups independently selected in each instance from F, Cl, Br and I. "-C_{6-12}spirocyclohaloalkenyl" will be understood to mean a carbocyclic ring system having at least one double bond, comprising two carbocyclic rings wherein only one carbon atom is common to both rings, and having 6, 7, 8, 9, 10, 11 or 12 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0058] As used herein, the term "cycloalkynyl" employed alone or in combination with other terms will be understood to mean, unless otherwise stated, a cycloalkyl moiety containing one or more triple bonds. Where a number of carbon atoms is specified, the cycloalkynyl moiety will contain the specified number of carbon atoms. Where a range in the number of carbon atoms is specified, the cycloalkynyl moiety will contain a number of carbon atoms selected from integer within the specified range. For example, "-C_{8-12}cycloalkynyl" will be understood to mean a carbocyclic ring moiety having at least one triple bond, and comprising 8, 9, 10, 11, or 12 carbon atoms, and will therefore be understood to include cyclooctynyl, cyclooctadiynyl, cyclononynyl, cyclononadiynyl, cyclononatriynyl, cyclodecynyl, cyclodecadiynyl, cyclodecatriynyl, cycloundecynyl, cycloundecadiynyl, cycloundecatriynyl, cyclododecynyl, cyclododecadiynyl, cyclododecatriynyl, and cyclododecatetraynyl, moieties. "-C_{9-14}bicycloalkynyl" will be understood to mean a carbocyclic ring system having at least one triple bond, comprising two fused carbocyclic rings and having 9, 10, 11, 12, 13 or 14 carbon atoms. "-C_{9-14}spirocycloalkynyl" will be understood to mean a carbocyclic ring system comprising two carbocyclic rings and at least one triple bond, wherein only one carbon atom is common to both rings, and having 9, 10, 11, 12, 13 or 14 carbon atoms. "-C_{8-12}cyclohaloalkenyl" will be understood to mean a carbocyclic ring moiety having at least one triple bond, comprising 8, 9, 10, 11 or 12 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I. "-C_{9-14}bicyclohaloalkenyl" will be understood to mean a carbocyclic ring system having at least one triple bond, comprising two fused carbocyclic rings and having 9, 10, 11, 12, 13 or 14 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I. "-C_{9-14}spirocyclohaloalkenyl" will be understood to mean a carbocyclic ring system having at least one triple bond, comprising two carbocyclic rings wherein only one carbon atom is common to both rings, and having 9, 10, 11, 12, 13 or 14 carbon atoms wherein one or more of the carbon atoms is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0059] The term "-C_{1-5}alkyl-aryl" will be understood to mean a substituent comprising an aryl (aromatic) group connected to the parent molecule via a branched chain or straight chain fully saturated linker wherein said linker comprises 1, 2, 3, 4 or 5 carbon atoms.

[0060] The term "-C_{2-5}alkenyl-aryl" will be understood to mean a substituent comprising an aryl (aromatic) group connected to the parent molecule via a branched chain or straight chain linker wherein said linker has at least one double bond, and comprises 2, 3, 4 or 5 carbon atoms.

[0061] The term "-C_{2-5}alkynyl-aryl" will be understood to mean a substituent comprising an aryl (aromatic) group connected to the parent molecule via a branched chain or straight chain linker wherein said linker has at least one triple bond, and comprises 2, 3, 4 or 5 carbon atoms.

[0062] The term "-C_{1-5}alkyl-heteroaryl" will be understood to mean a substituent comprising an heteroaryl (heteroaromatic) group connected to the parent molecule via a branched chain or straight chain fully saturated linker wherein said linker comprises 1, 2, 3, 4 or 5 carbon atoms.

[0063] The term "-C_{2-5}alkenyl-heteroaryl" will be understood to mean a substituent comprising an heteroaryl (heteroaromatic) group connected to the parent molecule via a branched chain or straight chain linker wherein said linker has at least one double bond, and comprises 2, 3, 4 or 5 carbon atoms.

[0064] The term "-C_{2-5}alkynyl-heteroaryl" will be understood to mean a substituent comprising an heteroaryl (heteroaromatic) group connected to the parent molecule via a branched chain or straight chain linker wherein said linker has at least one triple bond, and comprises 2, 3, 4 or 5 carbon atoms.

[0065] The term "-C_{1-5}haloalkyl-aryl" will be understood to mean a substituent comprising an aryl (aromatic) group connected to the parent molecule via a branched chain or straight chain fully saturated linker wherein said linker comprises 1, 2, 3, 4 or 5 carbon atoms, wherein one or more of the carbon atoms of the linker is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0066] The term "-C_{2-5}haloalkenyl-aryl" will be understood to mean a substituent comprising an aryl (aromatic) group connected to the parent molecule via a branched chain or straight chain linker wherein said linker has at least one double bond, and comprises 2, 3, 4 or 5 carbon atoms, wherein one or more of the carbon atoms of the linker is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0067] The term "-C_{2-5}haloalkynyl-aryl" will be understood to mean a substituent comprising an aryl (aromatic) group connected to the parent molecule via a branched chain or straight chain linker wherein said linker has at least one triple bond, and comprises 2, 3, 4 or 5 carbon atoms, wherein one or more of the carbon atoms of the linker is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0068] The term "-C_{1-5}haloalkyl-heteroaryl" will be understood to mean a substituent comprising an heteroaryl (heteroaromatic) group connected to the parent molecule via a branched chain or straight chain fully saturated linker wherein said linker comprises 1, 2, 3, 4 or 5 carbon atoms, wherein one or more of the carbon atoms of the linker is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0069] The term "-C_{2-5}haloalkenyl-heteroaryl" will be understood to mean a substituent comprising an heteroaryl (heteroaromatic) group connected to the parent molecule via a branched chain or straight chain linker wherein said linker has at least one double bond, and comprises 2, 3, 4 or 5 carbon atoms, wherein one or more of the carbon atoms of the linker is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0070] The term "-C_{2-5}haloalkynyl-heteroaryl" will be understood to mean a substituent comprising an heteroaryl (heteroaromatic) group connected to the parent molecule via a branched chain or straight chain linker wherein said linker has at least one triple bond, and comprises 2, 3, 4 or 5 carbon atoms, wherein one or more of the carbon atoms of the linker is substituted with one or more halo groups independently selected in each instance from F, Cl, Br and I.

[0071] It will be understood that the description of compounds herein is limited by principles of chemical bonding and valency known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding with regard to valencies, and to give compounds which are not inherently unstable.

[0072] The words "treatment" and "treating" are to be understood accordingly as embracing prophylaxis and treatment or amelioration of symptoms of diseases, disorders, medical conditions or ailments as well as treatment of the cause of the diseases, disorders, medical conditions or ailments.

[0073] The term "subject" in the context of methods of treatment may include a human or non-human subject.

[0074] As used herein, the term "an effective amount" refers to an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications, or dosages. Determination of an effective amount for a given administration is well within the ordinary skill in the pharmaceutical arts.

[0075] As used herein, the term "diluent" refers to a pharmacologically inert substance that is nevertheless suitable for human consumption, which serves as an excipient in the dosage form. A diluent serves to dilute the active pharmaceutical ingredient in the dosage form, such that tablets of a typical size can be prepared incorporating a wide range of actual doses of the active pharmaceutical ingredient. A diluent need not be included if the content per dosage form of one or both pharmaceutical ingredients is desired to be maximized for a particular dosage unit size. A diluent can comprise a microcrystalline cellulose, for example, AVICEL. Lactose and isomalt are other common diluents. AVICEL, a form of microcrystalline cellulose, is a commercially available product that is formed of acid-treated cellulose, which treatment tends to dissolve more amorphous regions of the cellulose and to leave more crystalline regions of the cellulose. Microcrystalline cellulose can be a diluent in the inventive dosage form.

[0076] Other diluents well-known to those skilled in the art include monobasic calcium phosphate, dibasic calcium phosphate and tribasic calcium phosphate. Almost completely water-insoluble, calcium phosphates are particularly well-known pharmacologically inert diluents or fillers that are compatible with a wide range of active pharmaceutical ingredients. By the term "calcium phosphate" is meant herein calcium phosphate in any of its forms, including, for example, monobasic calcium phosphate ($Ca(H_2PO_4)_2$), dibasic calcium phosphate ($CaHPO_4$), and tricalcium phosphate ($Ca_2(PO_4)S$), including any orthophosphates, pyrophosphates, or superphosphates, or other polymeric phosphates wherein the counterion includes calcium.

[0077] As used herein, the term "excipient" refers to an ingredient of the dosage form that is not medicinally active, but serves to dilute the active pharmaceutical ingredient, assist in dispersion of the tablet in the patient's stomach, bind the tablet together, and serve other functions like stabilizing the active pharmaceutical ingredient against decomposition.

[0078] As used herein, the term “pharmaceutically acceptable carrier,” and grammatical variations thereof, refers to adjuvants, binders, etc. known to the person skilled in the art that are suitable for administration to an individual (e.g., a mammal or non-mammal). The pharmaceutically acceptable carrier(s) and any additional components, as described herein, should be compatible for use in the intended route of administration (e.g., oral, parenteral) for a particular dosage form. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug Administration (FDA).

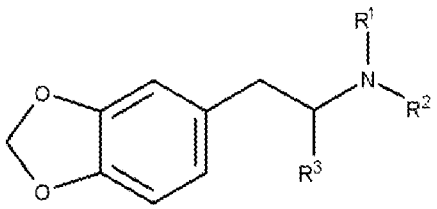
[0079] Other definitions for selected terms used herein may be found within the detailed description of the invention and apply throughout. Unless otherwise defined, all other scientific

and technical terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which the invention belongs.

DETAILED DESCRIPTION

[0080] The present invention seeks to address the need to provide alternative analogues of MDMA that possess the same methylenedioxy-phenylethylamine backbone as MDMA, but that vary the substituents on the nitrogen and/or at the α-position of the ethylamine, and thereby provide compounds possessing similar structural and biological properties to MDMA and other phenethylamine or tryptamine drugs and neurotransmitter compounds, including their significant therapeutic potential in the treatment of a vast number of medical conditions, whilst avoiding, circumventing, overcoming or obviating one or more of the problems associated with prescribing MDMA and other phenethylamine or tryptamine based compounds as a therapeutic treatment.

[0081] In a first aspect, the present disclosure provides compounds according to Formula I;



Formula I

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula I may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a,

-C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

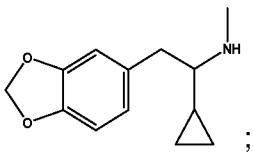
R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, -OR^a, -SR^a, -NR^bR^c, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl,

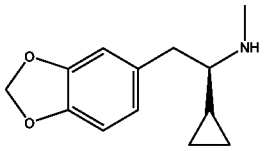
-C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

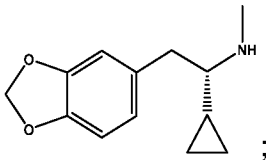
or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

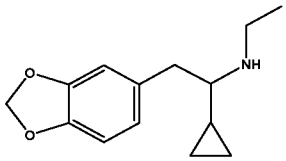
R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl;

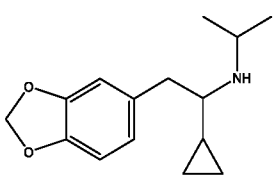
wherein the compound of Formula I is not a compound selected from the group comprising;

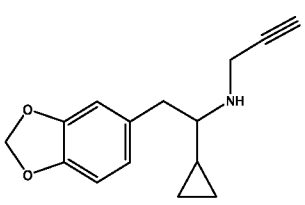

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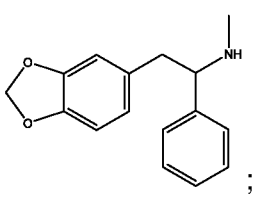

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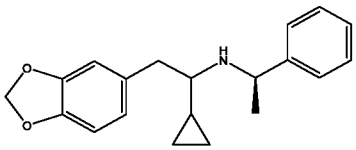
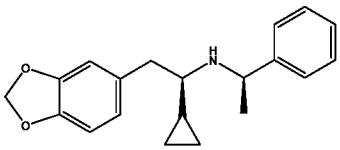
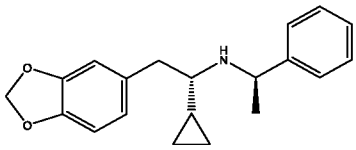
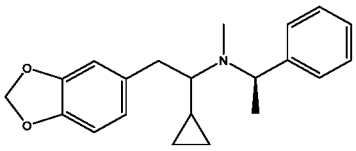
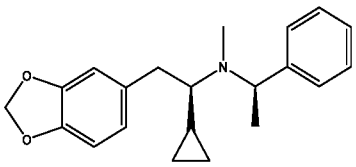
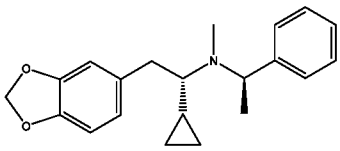
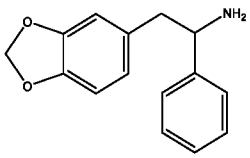
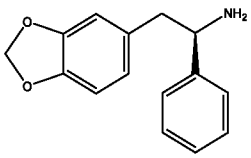
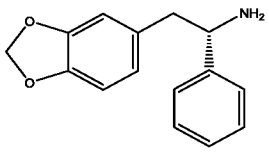
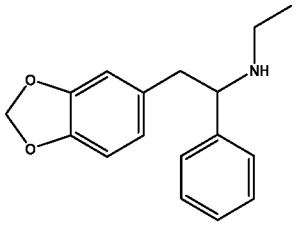
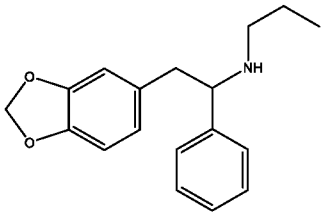
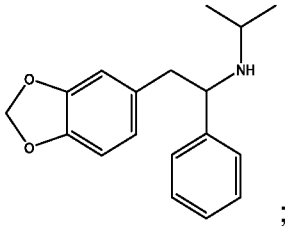
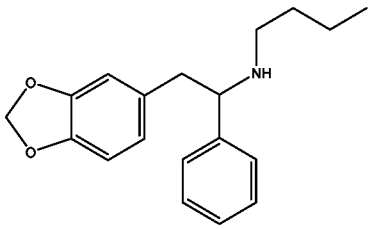
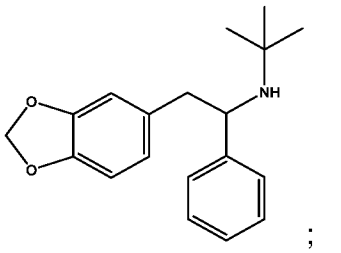
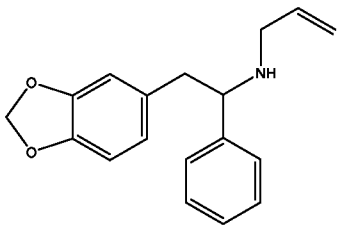
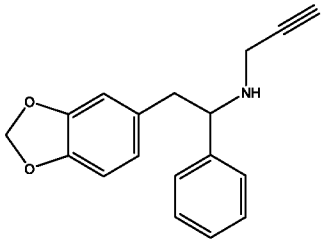
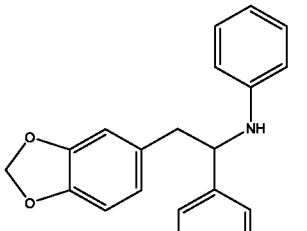
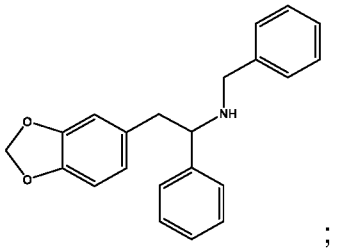
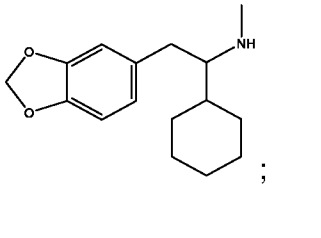
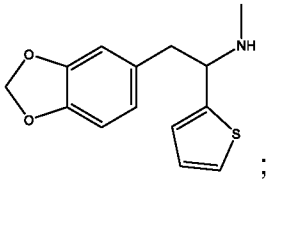
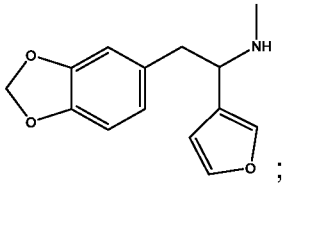

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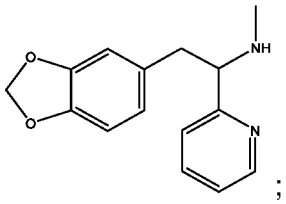
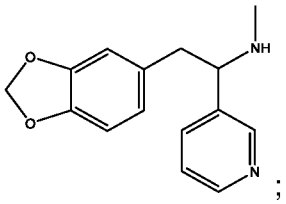
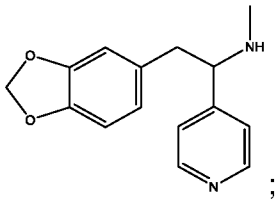
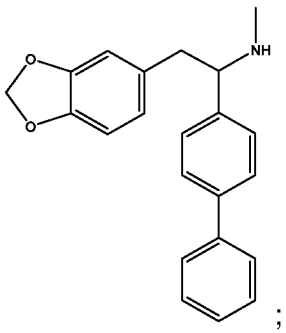
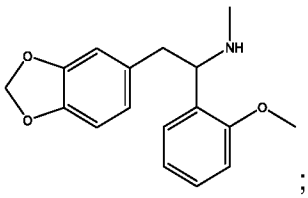
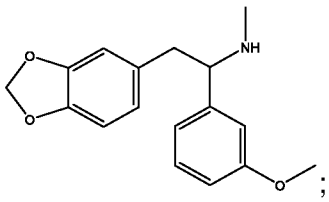
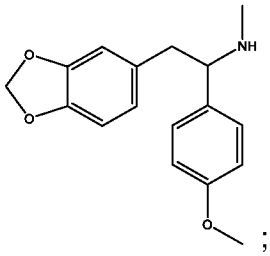
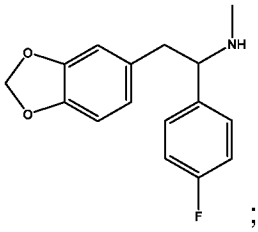
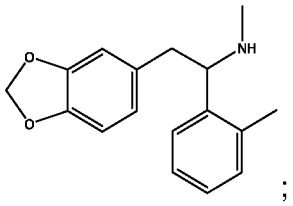
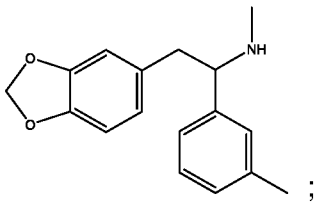
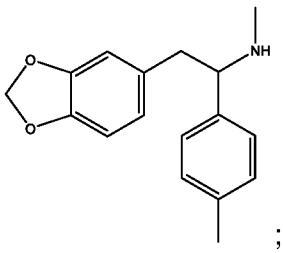
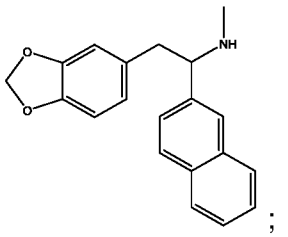
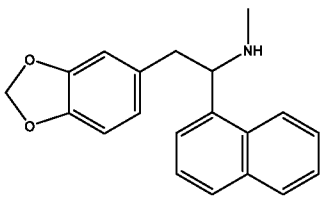

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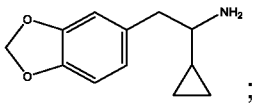
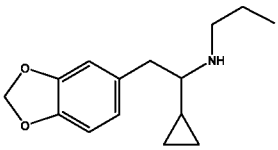
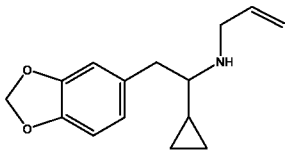
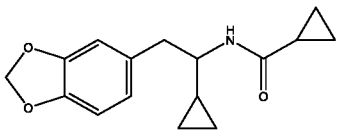
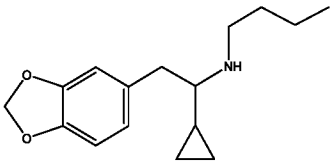
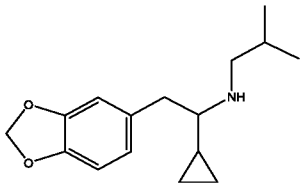
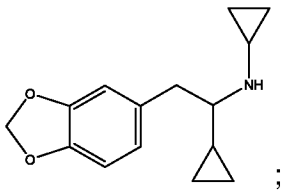
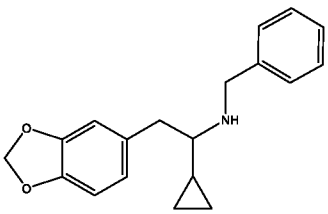
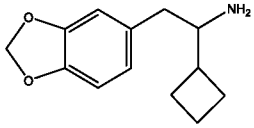
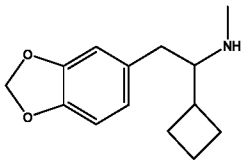
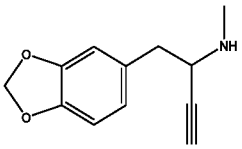
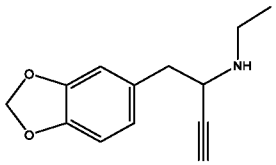
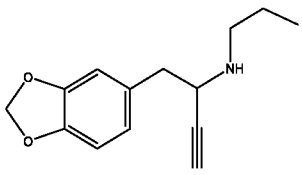
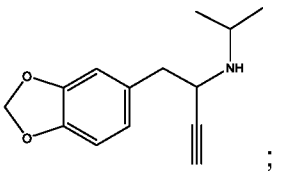
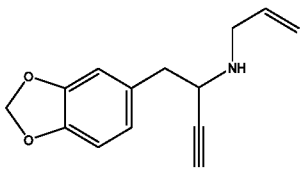
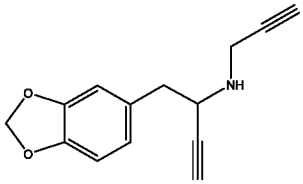
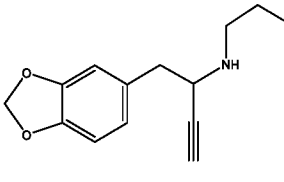
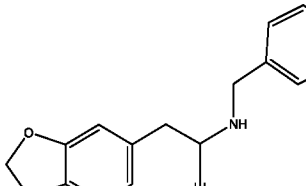
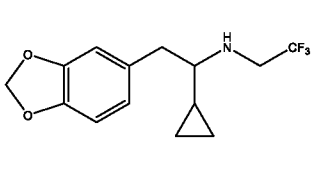
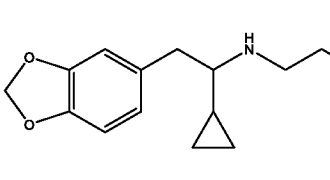
and, wherein the compound of Formula I is not a compound published before the earliest priority date of the present disclosure, or wherein the compound of Formula I is not a compound hitherto not ascertained by the present inventors as being published before the earliest priority date of the present disclosure.

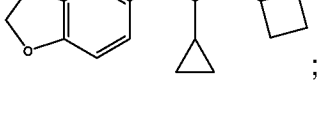
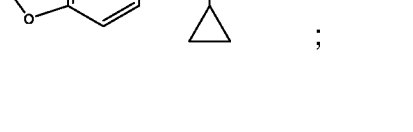
[0082] In a preferred aspect, the compound of Formula I is a compound wherein R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, propyl, isopropyl, allyl, cyclopropylmethyl, propargyl, butyl, isobutyl, *t*-butyl, cyclobutyl, -C_{1-9}haloalkyl, -C_{2-9}alkyl-O-R^a, -C_{3-9}heterocycloalkyl, cyclopropyl, phenyl, benzyl, and 1-phenylethyl; or wherein R^1 and R^2 together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring.

[0083] In a particularly preferred aspect, the compound of Formula I is a compound wherein R^1 is H or methyl, and R^2 is selected from the group consisting of; methyl, ethyl, propyl, isopropyl, allyl, cyclopropylmethyl, propargyl, butyl, isobutyl, *t*-butyl, $-CH_2CF_3$, $-C_3$alkyl-OH, oxanyl, cyclopropyl, cyclobutyl, phenyl, benzyl, and 1-phenylethyl; or wherein R^1 and R^2 together form a pyrrolidinyl or morpholinyl ring.

[0084] In a further particularly preferred aspect, the compound of Formula I is a compound wherein R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, fluorocyclopropyl, 1-fluorocyclopropan-1-yl, cyclobutyl, fluorocyclobutyl, difluorocyclobutyl, 3,3-difluorocyclobutan-1-yl, methylcyclobutyl, dimethylcyclobutyl, 3,3-dimethylcyclobutan-1-yl, cyclopentyl, vinyl, allyl, acetylenyl, cyclohexyl, propargyl, cyanomethyl, thiophen-2-yl, thiophen-3-yl, furan-2-yl, furan-3-yl, triazol-1-yl, triazol-4-yl, triazol-5-yl, oxan-4-yl, oxan-3-yl, oxan-2-yl, pyridine-2-yl, pyridine-3-yl, pyridine-4-yl, phenyl, 1,1'-biphenyl, 1,2'-biphenyl, 1,3'-biphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, o-tolyl, m-tolyl, p-tolyl, naphthalen-1-yl, naphthalen-2-yl, cyclopent-1-en-1-yl, cyclopent-1-en-3-yl, cyclopent-1-en-4-yl, cyclopenta-1,3-dien-2-yl, cyclopenta-1,3-dien-1-yl, cyclopenta-1,3-dien-5-yl, cyclohex-1-en-1-yl, cyclohex-1-en-3-yl, cyclohex-1-en-5-yl, cyclohexa-1,3-dien-1-yl, cyclohexa-1,3-dien-2-yl, cyclohexa-1,3-dien-5-yl, cyclohexa-1,4-dien-1-yl, cyclohexa-1,4-dien-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothiophene-2-yl, tetrahydrothiophene-3-yl, oxazolidin-5-yl, oxazolidin-4-yl, oxazolidin-2-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, 1,3-dioxolan-2-yl, 1,3-dioxolan-4-yl, bicyclo[1.1.0]butan-1-yl, tricyclo[1.1.0.$0^{2,4}$]butan-1-yl, bicyclo[1.1.0]butan-2-yl, spiro[2.2]pentan-1-yl, bicyclo[2.1.0]pentan-1-yl, bicyclo[2.1.0]pentan-5-yl, bicyclo[2.1.0]pentan-1-yl, bicyclo[2.1.0]pentan-2-yl, bicyclo[1.1.1]pentan-2-yl, bicyclo[1.1.1]pentan-1-yl, spiro[2.3]hexan-4-yl, spiro[2.3]hexan-5-yl, oxetan-2-yl, thietane-2-yl, oxetan-3-yl, thietane-3-yl, 2-oxabicyclo[2.1.0]pentan-1-yl, 2-thiabicyclo[2.1.0]pentan-1-yl, 2-oxabicyclo[2.1.0]pentan-5-yl, 2-thiabicyclo[2.1.0]pentan-5-yl, 2-oxabicyclo[2.1.0]pentan-4-yl, 2-thiabicyclo[2.1.0]pentan-4-yl, 2-oxabicyclo[2.1.0]pentan-3-yl, 2-thiabicyclo[2.1.0]pentan-3-yl, 2-oxabicyclo[2.1.0]pentan-4-yl, 2-thiabicyclo[2.1.0]pentan-4-yl, oxabicyclo[2.1.0]pentan-5-yl, 2-thiabicyclo[2.1.0]pentan-5-yl, 2-oxabicyclo[2.1.0]pentan-1-yl, 2-thiabicyclo[2.1.0]pentan-1-yl, 2-oxabicyclo[1.1.1]pentan-4-yl, 2-oxabicyclo[1.1.1]pentan-1-yl, 5-oxaspiro[2.3]hexan-4-yl, 4-oxaspiro[2.3]hexan-5-yl, 2-thiabicyclo[1.1.1]pentan-4-yl, 2-thiabicyclo[1.1.1]pentan-1-yl, 5-thiaspiro[2.3]hexan-4-yl, 4-thiaspiro[2.3]hexan-5-yl, 4-oxaspiro[2.3]hexan-6-yl, and 4-thiaspiro[2.3]hexan-6-yl.

[0085] In a further particularly preferred aspect, the compound of Formula I is a compound selected from the group consisting of;

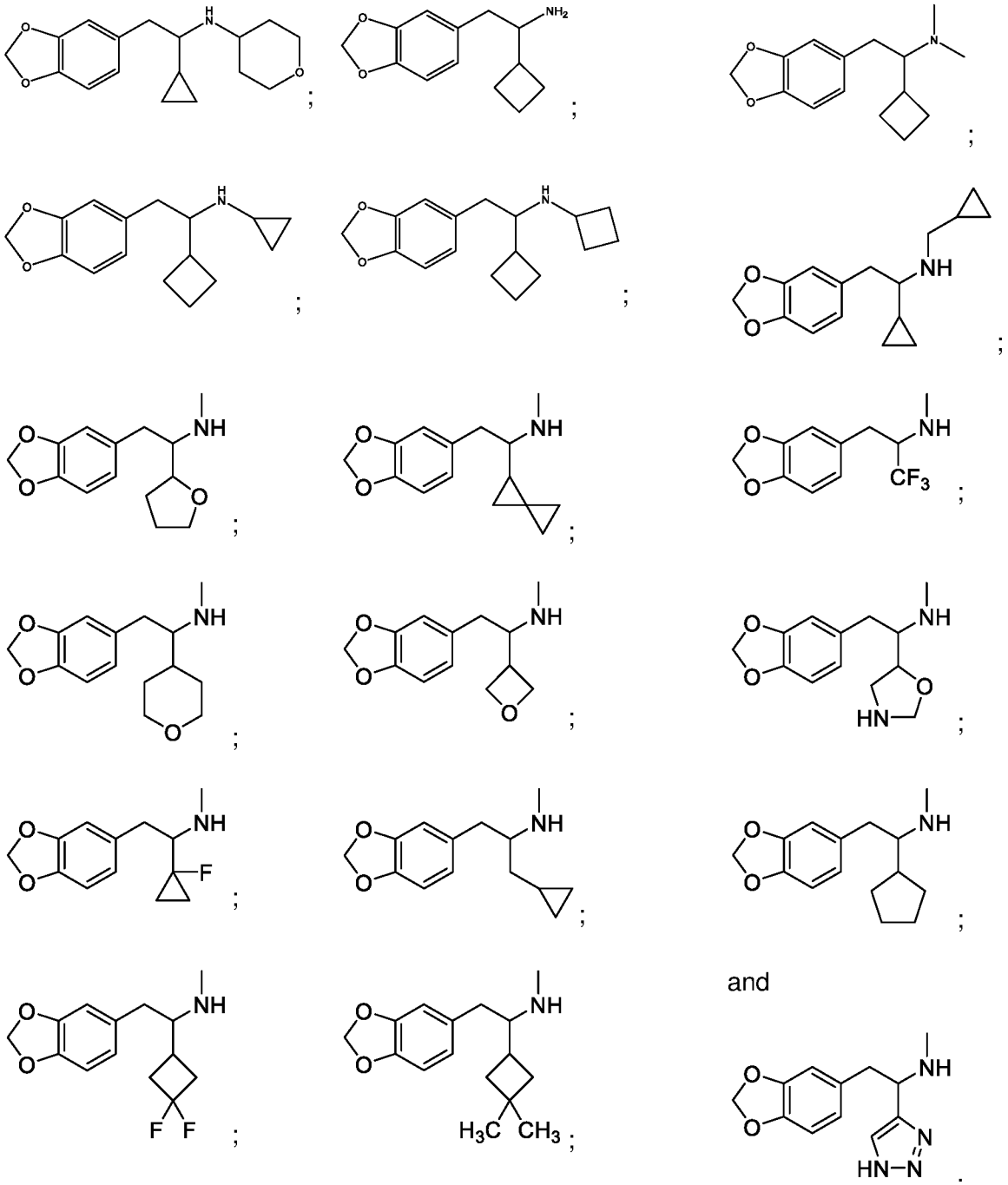

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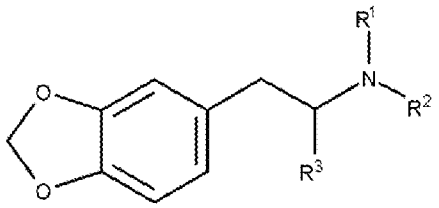


and

[0086] In a second aspect, the present disclosure provides a compound in accordance with the first aspect, for use, as a medicament, and/or a composition comprising a compound in accordance with the first aspect, and one or more pharmaceutically acceptable carrier(s) and/or diluent(s) and/or excipient(s).

[0087] In a third aspect, the present disclosure provides the use of a compound of Formula II, for the manufacture of a medicament for the treatment or prevention of a disease, disorder, injury or trauma; and/or a compound of Formula II for use, in the treatment or prevention of a disease, disorder, injury or trauma; and/or a method of treating or preventing a disease,

disorder, injury or trauma, comprising the administration of an effective amount of a compound of Formula II to a subject in need thereof; wherein the compound of Formula II is defined as;



Formula II

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula II may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, -OR^a, -SR^a, -NR^bR^c, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -$C(=O)R^a$, -C_{1-8}alkyl-$C(=O)R^a$, -C_{2-8}alkenyl-$C(=O)R^a$, -C_{2-8}alkynyl-$C(=O)R^a$, -C_{1-8}haloalkyl-$C(=O)R^a$, -C_{2-8}haloalkenyl-$C(=O)R^a$, -C_{2-8}haloalkynyl-$C(=O)R^a$, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -$C(=O)NR^bR^c$, -C_{1-8}alkyl-$C(=O)NR^bR^c$, -C_{2-8}alkynyl-$C(=O)NR^bR^c$, -C_{2-8}alkenyl-$C(=O)NR^bR^c$, -C_{1-8}haloalkyl-$C(=O)NR^bR^c$, -C_{2-8}haloalkynyl-$C(=O)NR^bR^c$, -C_{2-8}haloalkenyl-$C(=O)NR^bR^c$, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl.

[0088] In some aspects, the disease, disorder, injury or trauma may be treated or prevented via the modulation of;

(i) Serotonin Transporter (SERT) activity; and/or
(ii) Dopamine Transporter (DAT) activity; and/or
(iii) Norepinephrine Transporter (NET) activity; and/or
(iv) Monoamine Oxidase A (MAO-A) activity; and/or
(v) Serotonin Receptor (5-HT2B) activity.

[0089] In some aspects, the disease, disorder, injury or trauma is a disease, disorder, injury or trauma associated with the central nervous system.

[0090] In some aspects, the disease, disorder, injury or trauma is a disease, disorder, injury or trauma associated with the central nervous system is selected from the group consisting of; dementia in Alzheimer disease (including early onset, late onset, atypical, mixed, or unspecified), vascular dementia (including arteriosclerotic, acute onset, multi-infarct, subcortical, mixed cortical or unspecified), dementia in Pick disease, dementia in Creutzfeldt-Jakob disease, dementia in Huntington disease, dementia in Parkinson disease, dementia in human immunodeficiency virus [HIV] disease, dementia in cerebral lipidosis, dementia in epilepsy, dementia in hepatolenticular degeneration, dementia in hypercalcaemia, dementia in hypothyroidism, dementia in intoxications, dementia in Lewy Body disease, dementia in Multiple Sclerosis, dementia in neurosyphilis, dementia in niacin deficiency, dementia in polyarteritis nodosa, dementia in systemic lupus erythematosus, dementia in trypanosomiasis, dementia in uraemia, dementia in vitamin b_{12} deficiency, unspecified dementia (including dementia not otherwise specified, psychosis not otherwise specified, senile, delirium, depressed, paranoid, or acute confusional state), organic amnesic syndrome, Korsakov psychosis, Korsakov syndrome, delirium, brain syndrome, confusional state, infective psychosis, organic reaction, psycho-organic syndrome, organic hallucinosis, organic catatonic disorder, organic delusional [schizophrenia-like] disorder, organic mood [affective] disorders, organic anxiety disorder, organic dissociative disorder, organic emotionally labile [asthenic] disorder, mild cognitive

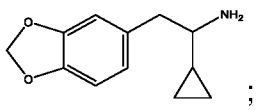
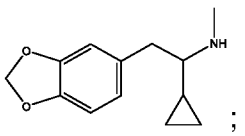
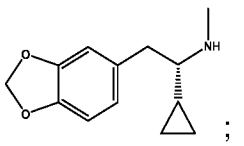
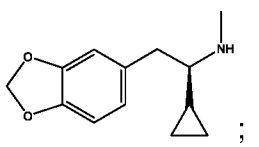
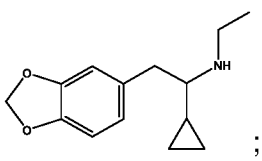
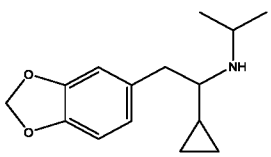
disorder, epileptic psychosis, brain syndrome not otherwise specified, mental disorder not otherwise specified, organic personality disorder, pseudopsychopathic personality disorder, pseudoretarded personality disorder, frontal lobe syndrome, limbic epilepsy personality syndrome, lobotomy syndrome, postleucotomy syndrome, postencephalitic syndrome, postconcussional syndrome, postcontusional syndrome (encephalopathy), post-traumatic brain syndrome, nonpsychotic, right hemispheric organic affective disorder, organic psychosyndrome, mental and behavioural disorders due to use of alcohol, mental and behavioural disorders due to use of opioids, mental and behavioural disorders due to use of cannabinoids, mental and behavioural disorders due to use of sedatives or hypnotics, mental and behavioural disorders due to use of cocaine, mental and behavioural disorders due to use of stimulants including caffeine, mental and behavioural disorders due to use of hallucinogens, mental and behavioural disorders due to use of tobacco, mental and behavioural disorders due to use of volatile solvents, mental and behavioural disorders due to use of other psychoactive substances (including any combination of psychoactive substances), schizophrenia, paranoid schizophrenia, paraphrenic schizophrenia, hebephrenic schizophrenia, hebephrenia, disorganized schizophrenia, catatonic schizophrenia, catatonic stupor, schizophrenic catalepsy, schizophrenic catatonia, schizophrenic flexibilitas cerea, undifferentiated schizophrenia, atypical schizophrenia, post-schizophrenic depression, residual schizophrenia, chronic undifferentiated schizophrenia, schizophrenic Restzustand, simple schizophrenia, cenesthopathic schizophrenia, schizophreniform disorder, schizophreniform psychosis, schizophrenia not otherwise specified, schizotypal disorder, latent schizophrenic reaction, borderline schizophrenia, latent schizophrenia, prepsychotic schizophrenia, prodromal schizophrenia, pseudoneurotic schizophrenia, pseudopsychopathic schizophrenia, schizotypal personality disorder, persistent delusional disorder, delusional disorder, paranoia, paranoid psychosis, paranoid state, paraphrenia (late), Sensitiver Beziehungswahn, delusional dysmorphophobia, involutional paranoid state, paranoia querulans, acute and transient psychotic disorder, acute polymorphic psychotic disorder without symptoms of schizophrenia, acute polymorphic psychotic disorder with symptoms of schizophrenia, Bouffée délirante, cycloid psychosis, acute schizophrenia-like psychotic disorder, acute (undifferentiated) schizophrenia, brief schizophreniform disorder, brief schizophreniform psychosis, oneirophrenia, schizophrenic reaction, paranoid reaction, psychogenic paranoid psychosis, acute transient psychotic disorders, induced delusional disorder, Folie à deux, induced paranoid disorder, induced psychotic disorder, schizoaffective disorder (including manic, depressive, mixed and unspecified), nonorganic psychotic disorder, chronic hallucinatory psychosis, manic episode disorder, bipolar disorder, single manic episode disorder, hypomania, mania without psychotic symptoms, mania with psychotic symptoms, mania with mood-congruent psychotic symptoms, mania with mood-incongruent psychotic symptoms, manic stupor, mania not otherwise specified, bipolar affective disorder, manic depression, manic-depressive illness, manic-

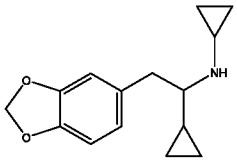
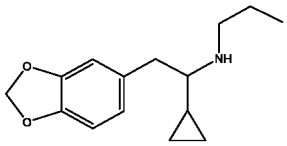
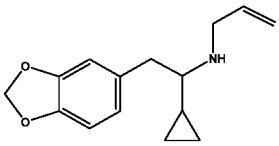
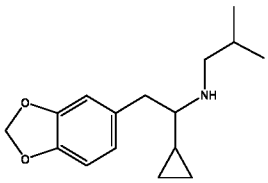
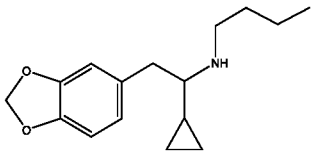
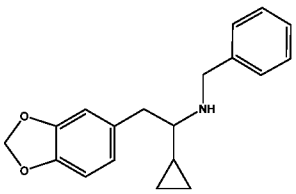
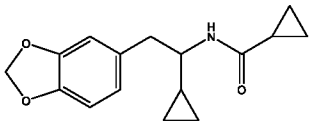
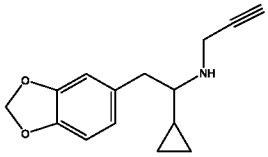
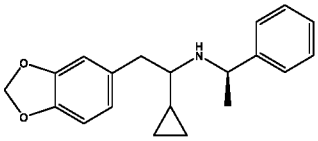
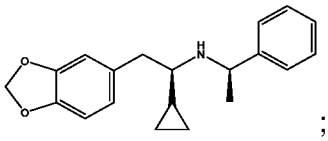
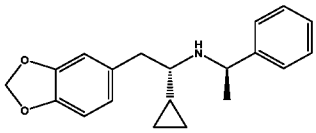
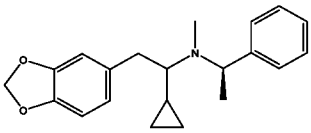
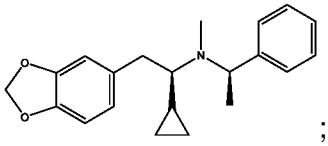
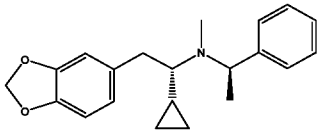
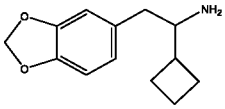
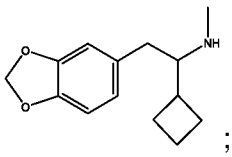
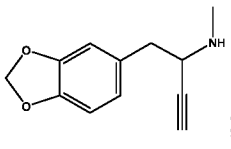
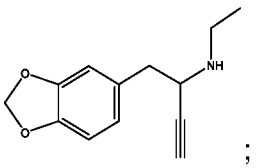
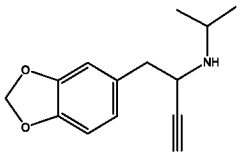
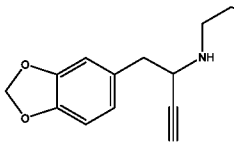
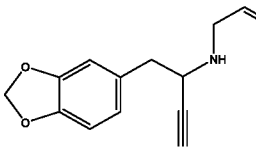
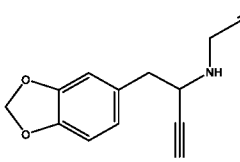
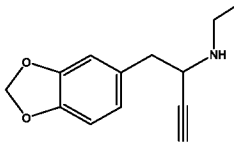
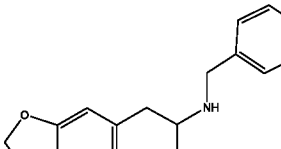
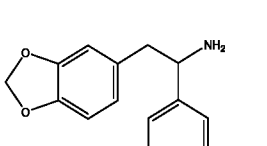
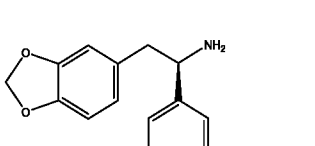
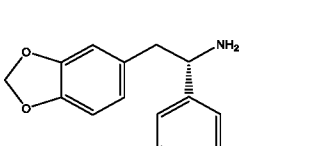
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disorder, nonorganic insomnia, nonorganic hypersomnia, nonorganic disorder of the sleep-wake schedule, psychogenic inversion of circadian rhythm, psychogenic inversion of nyctohemeral rhythm, psychogenic inversion of sleep rhythm, sleepwalking [somnambulism], sleep terrors [night terrors], nightmares, dream anxiety disorder, emotional sleep disorder not otherwise specified, sexual dysfunction not caused by organic disorder or disease, lack or loss of sexual desire, frigidity, hypoactive sexual desire disorder, sexual aversion, lack of sexual enjoyment, sexual anhedonia, failure of genital response, female sexual arousal disorder, male erectile disorder, psychogenic impotence, orgasmic dysfunction, inhibited orgasm, psychogenic anorgasmy, premature ejaculation, psychogenic vaginismus, nonorganic dyspareunia, psychogenic dyspareunia, nymphomania, satyriasis, sexual dysfunction not otherwise specified, postnatal depression, postpartum depression, puerperal psychosis, puerperal mental disorder, psychological and behavioural factors associated with physical disorders or diseases (including but not limited to asthma, dermatitis, gastric ulcer, irritable bowel syndrome, ulcerative colitis, and urticaria), abuse of non-dependence-producing substances (including but not limited to antacids, herbal remedies, folk remedies, steroids, hormones, vitamins, and laxatives), psychogenic physiological dysfunction not otherwise specified, paranoid personality disorder, expansive paranoid personality disorder, fanatic paranoid personality disorder, querulant paranoid personality disorder, sensitive paranoid personality disorder, schizoid personality disorder, dissocial personality disorder, amoral personality disorder, antisocial personality disorder, asocial personality disorder, psychopathic personality disorder, sociopathic personality disorder, emotionally unstable personality disorder, aggressive personality disorder, borderline personality disorder, explosive personality disorder, histrionic personality disorder, hysterical personality disorder, psychoinfantile personality disorder, anankastic personality disorder, compulsive personality disorder, obsessional personality disorder, obsessive-compulsive personality disorder, anxious [avoidant] personality disorder, dependent personality disorder, asthenic personality disorder, inadequate personality disorder, passive personality disorder, self-defeating personality disorder, eccentric personality disorder, haltlose type personality disorder, immature personality disorder, narcissistic personality disorder, passive-aggressive personality disorder, psychoneurotic personality disorder, character neurosis not otherwise specified, pathological personality not otherwise specified, mixed personality disorders, personality and behavioural disorder due to brain disease, personality and behavioural disorder due to brain damage, personality and behavioural disorder due to brain dysfunction, enduring personality change after catastrophic experience (including but not limited to concentration camp experiences, disasters, prolonged captivity with an imminent possibility of being killed, prolonged exposure to life-threatening situations such as being a victim of terrorism, or prolonged torture), enduring personality change after psychiatric illness, chronic pain personality syndrome, enduring personality change unspecified, habit disorder, impulse disorder, pathological gambling, compulsive gambling, pathological fire-setting [pyromania], pathological

stealing [kleptomania], trichotillomania, intermittent explosive disorder, gender identity disorder, transsexualism, dual-role transvestism, gender-role disorder, sexual preference disorder, fetishism, fetishistic transvestism, exhibitionism, voyeurism, paedophilia, sadomasochism, frotteurism, necrophilia, sexual deviation not otherwise specified, sexual maturation disorder, egodystonic sexual orientation, sexual relationship disorder, psychosexual development disorder, elaboration of physical symptoms for psychological reasons, compensation neurosis, intentional production or feigning of symptoms or disabilities, either physical or psychological [factitious disorder], hospital hopper syndrome, Münchhausen syndrome, peregrinating patient, character disorder not otherwise specified, relationship disorder not otherwise specified, hyperkinetic disorder, disturbance of activity and attention, attention deficit disorder with hyperactivity, attention deficit hyperactivity disorder, attention deficit syndrome with hyperactivity, hyperkinetic conduct disorder, hyperkinetic syndrome not otherwise specified, conduct disorder, unsocialized conduct disorder, socialized conduct disorder, oppositional defiant disorder, depressive conduct disorder, separation anxiety disorder, sibling rivalry disorder, overanxious disorder, childhood emotional disorder not otherwise specified, elective mutism, selective mutism, reactive attachment disorder, disinhibited attachment disorder, affectionless psychopathy, institutional syndrome, childhood disorder of social functioning, tic disorder, transient tic disorder, chronic motor tic disorder, chronic vocal tic disorder, combined vocal and multiple motor tic disorder [de la Tourette], Tourette's syndrome, nonorganic enuresis, functional enuresis, psychogenic enuresis, urinary incontinence of nonorganic origin, nonorganic encopresis, functional encopresis, incontinence of faeces of nonorganic origin, psychogenic encopresis, feeding disorder of infancy and childhood, rumination disorder of infancy, stereotyped movement disorder, stuttering [stammering], cluttering, attention deficit disorder without hyperactivity, excessive masturbation, nail-biting, nose-picking, thumb-sucking, and mental disorders not otherwise specified.

[0091] In a preferred aspect, the compound of Formula II is selected from the group consisting of;


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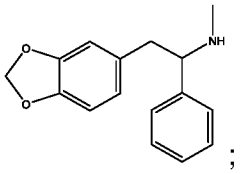
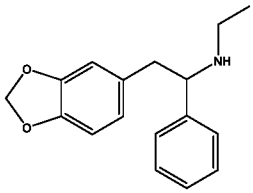
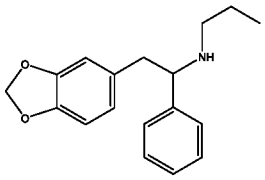
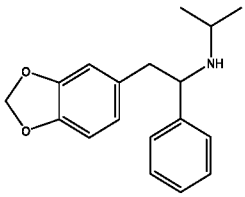
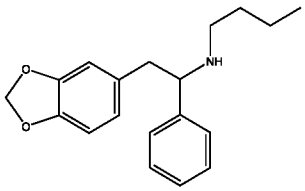
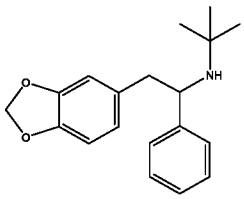
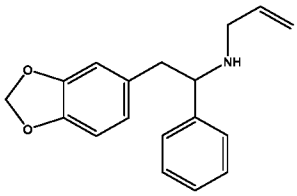
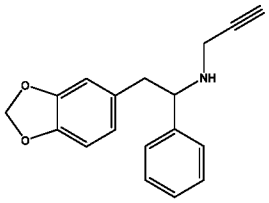
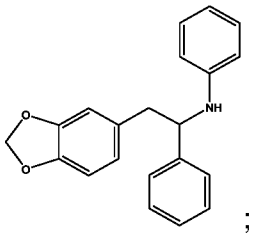
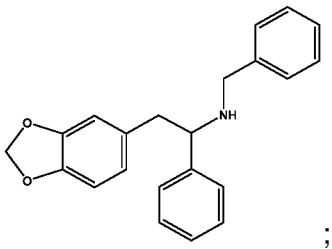
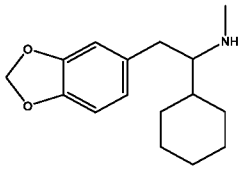
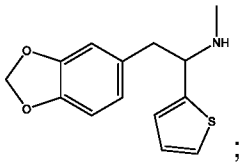
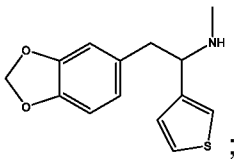
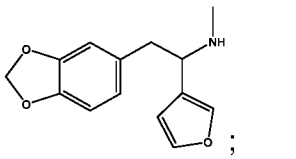
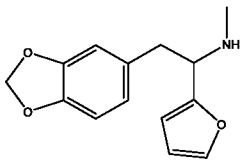
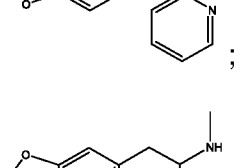
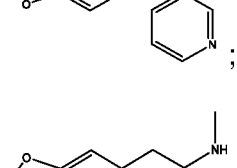
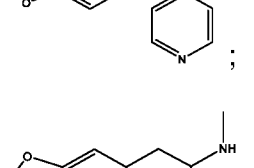
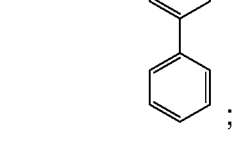
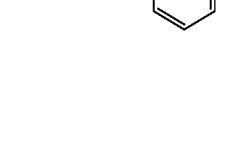
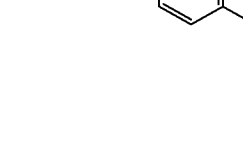
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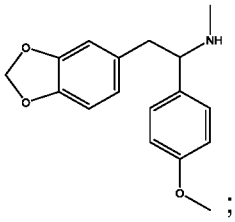
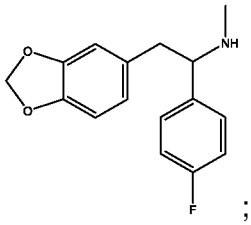
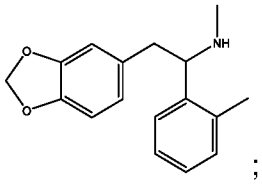
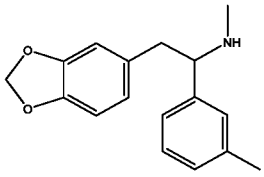
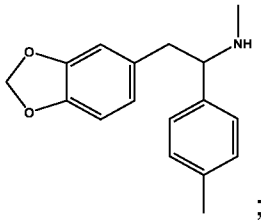
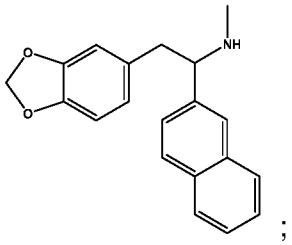
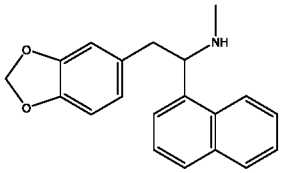
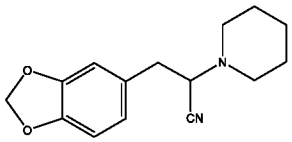
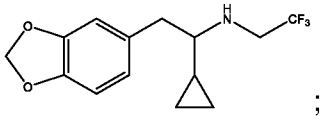
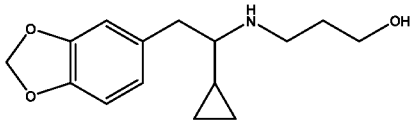
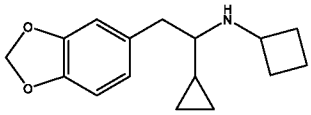
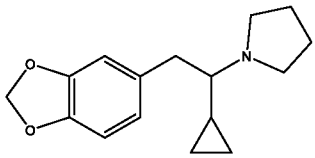
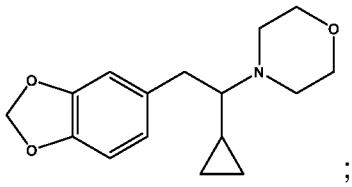
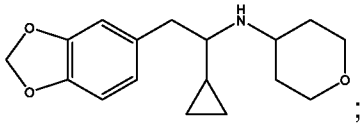
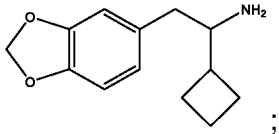
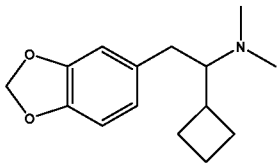
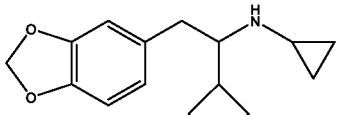
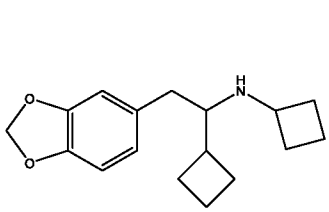
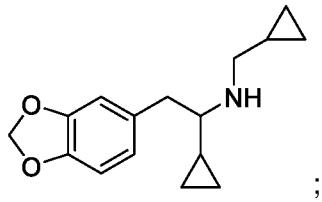
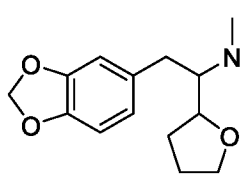
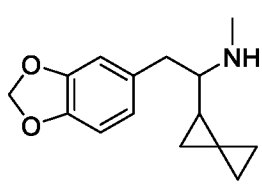
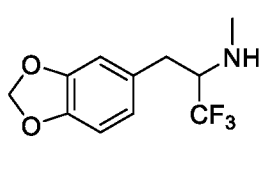
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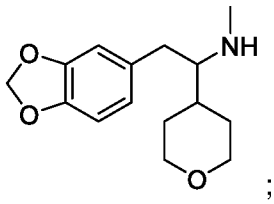
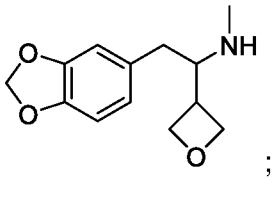
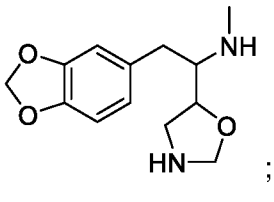
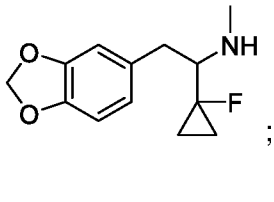
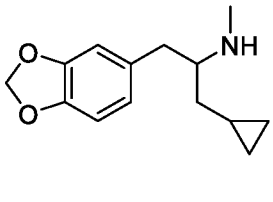
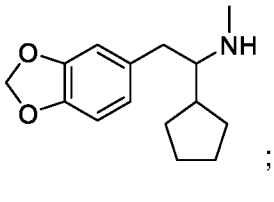
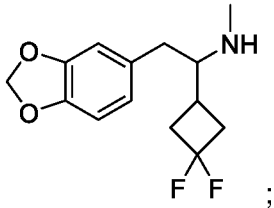
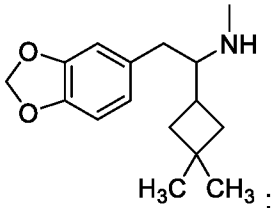
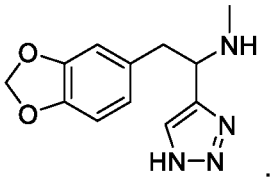

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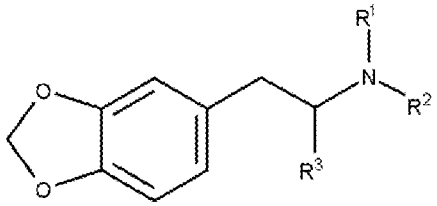
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[0092] In a fourth aspect, the present disclosure provides a process for the preparation of a compound according to Formula II';



Formula II'

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula II' may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl,

-C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

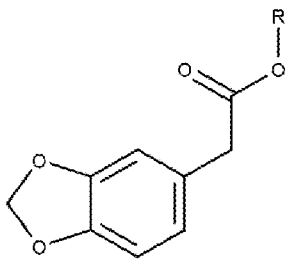
R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, -OR^a, -SR^a, -NR^bR^c, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicycloalkynyl,

-C_{9-14}spirocycloalkynyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl;

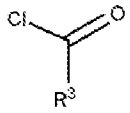
wherein the process comprises reacting a compound according to Formula III;



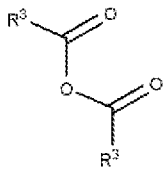
Formula III

wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl;

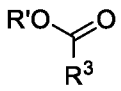
with a compound according to Formula IVa, or Formula IVb, or Formula IVc;



Formula IVa;



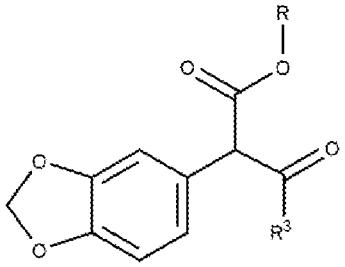
Formula IVb;



Formula IVc;

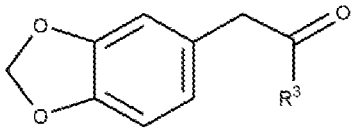
wherein R^3 is as defined for the compound of Formula II', and wherein, for the compound of Formula IVb, each R^3 may be the same or different, and wherein R' is selected from the group consisting of; methyl, ethyl, -C_{3-9}alkyl, aryl and haloaryl;

under a first set of reaction conditions, to produce a compound of Formula V;



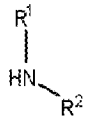
Formula V

followed by subjecting the compound of Formula V to a second set of reaction conditions to produce a ketone intermediate of Formula VI;



Formula VI

and subsequent reductive amination of the compound of Formula VI with a compound of Formula VII;



Formula VII

wherein R^1 and R^2 are as defined for the compound of Formula II';

under a third set of reaction conditions, to produce the compound of Formula II'.

[0093] In some aspects, the first set of reaction conditions comprises reacting 1 equivalent of a compound of Formula III with an excess of a compound of Formula IVa or Formula IVb or Formula IVc, in an organic solvent, in the presence of an excess of a base.

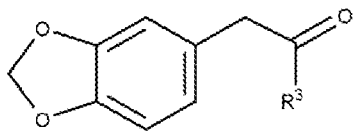
[0094] In some aspects, the organic solvent in the first set of reaction conditions is a polar aprotic solvent, preferably tetrahydrofuran (THF), and the base in the first set of reaction conditions is a strong base, for example sodium hexamethyldisilazide (NaHMDS) or potassium hexamethyldisilazide (KHMDS), most preferably a lithium base, for example lithium hexamethyldisilazide (LiHMDS).

[0095] In some aspects, the second set of reaction conditions comprises heating a solution of the compound of Formula V in a mixture of DMSO and water, in the presence of a source of chloride ions, preferably KCl or LiCl or NaCl, most preferably NaCl. The person skilled in the art will be aware that alternative Krapcho decarboxylation conditions to those preferred conditions described above will be equally applicable and effective in the second set of reaction conditions.

[0096] In some aspects, the third set of reaction conditions comprises reductive amination of the compound of Formula VI with a compound of Formula VII, preferably in the presence of acetic acid and sodium cyanoborohydride in a mixture of anhydrous THF and anhydrous methanol. The person skilled in the art will be aware that alternative reductive amination conditions to those preferred conditions described above will be equally applicable and effective in the third set of reaction conditions. For example, acetic acid and sodium cyanoborohydride in in ethanol alone (or in combination with anhydrous THF) would be equally effective in the third set of reaction conditions.

[0097] In a fifth aspect, the present disclosure provides a compound of Formula II', when made via the process of the fourth aspect.

[0098] In a sixth aspect, the present disclosure provides a compound according to Formula VI;



Formula VI

wherein R^3 is as defined for the compound of Formula II', when the compound of Formula VI is made via the process of the fourth aspect.

EXAMPLES

[0099] Synthesis

General procedure for obtaining hydrochloride salts of free base compounds of the invention

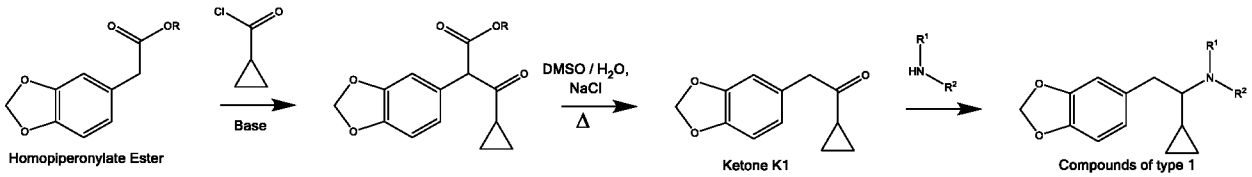
[00100] The free base is dissolved in MeOH (1 mL) and 32% HCl (2 eq.) is added dropwise. The solution is evaporated to dryness under a stream of N_2 and the residue is recrystallised using a suitable solvent (for example, 2-propanol or 2-propanol/Et_2O, or toluene, or toluene/cyclohexane) to give the desired hydrochloride.

General procedure A for reductive aminations with methylamine

[00101] An 8.0 M solution of methylamine in EtOH (10.0 equiv) and AcOH (10.0 equiv) are added successively to a cold (0°C), stirred mixture of specified ketone (1.0 equiv) and 3A sieves (1 mg/mg ketone) in 2:1 THF/MeOH (6.0 mL/mmol ketone). Sodium cyanoborohydride (1.10 equiv) is added and the reaction vessel is flushed with N_2, sealed and stirred at 50 °C until TLC analysis indicates complete consumption of the starting ketone. The reaction mixture is cooled to room temperature, quenched with 1 M HCl (approx. pH 1) and vacuum filtered through a pad of Celite, washing through with water and MeOH. The filtrate is concentrated under reduced pressure and the residue is diluted with 0.1 M HCl and washed with Et_2O. The aqueous phase is basified with 1 M NaOH (approx. pH 12) and extracted with CH_2Cl_2. The extract is washed with brine, dried and evaporated, to afford the desired free base. The free base thus obtained may be purified by chromatographic techniques where required.

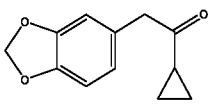
Compounds of type 1

[00102] Compounds of type 1 may be synthesised via the following general procedure 1;



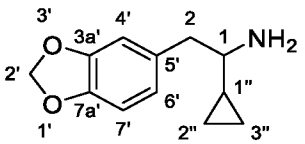
wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 1 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethanone ("Ketone K1")



[00103] A solution of 1.0 M LiHMDS in THF (375 mL, 0.38 mol) and cyclopropanecarbonyl chloride (20 mL, 0.22 mol) were added sequentially to a stirred solution of methyl homopiperonylate[1] (35 g, 0.18 mol) in THF (250 mL) at –78 °C. The solution was warmed to room temperature and allowed to stand for 30 min. The reaction mixture was then cooled to 0 °C and quenched with 1 M HCl (400 mL), then diluted with water (600 mL) and extracted with Et_2O (3 x 300 mL). The extract was washed with water (2 x 300 mL) and brine (300 mL), dried and evaporated to give a brown oil, which was partially purified by rapid silica filtration (1:4, EtOAc/hexanes). The resulting yellow oil was immediately dissolved in 2:1 DMSO/H_2O (300 mL) and treated with NaCl (40 g, 0.69 mol) and the mixture was stirred at 140 °C for 24 h. The reaction mixture was diluted with water (1 L) and extracted with Et_2O (3 x 300 mL). The extract was washed with water (2 x 300 mL) and brine (300 mL), dried and evaporated. The residual oil was subjected to flash chromatography. Elution with 1:20 EtOAc/hexanes furnished the ketone K1 as a colourless oil (30 g, 82 %). Characterisation data were in good agreement with the previously published synthesis of ketone K1.[4]

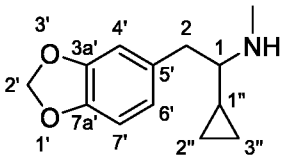
2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethanamine (UWA-033, MNG6012, "Compound 1A")



[00104] Following an adapted literature procedure,[3] to freshly activated 3Å sieves (ca 300 mg) was added a solution of the ketone K1 (1.03 g, 5.05 mmol) in anhydrous MeOH (20 mL), ammonium acetate (2.75 g, 35.7 mmol) and sodium cyanoborohydride (438 mg, 6.97 mmol). The mixture was stirred at rt under N_2 for 3 d. The reaction was quenched, and the product extracted and chromatographed by elution with 2:3 EtOAc/hexanes followed by 1:20:79 NEt_3 /MeOH/EtOAc to afford the desired product as a yellow oil (700 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (d, J = 8.0 Hz, 1H, H7'), 6.64 (d, J = 2.0 Hz, 1H, H4'), 6.60 (dd, J = 8.0, 2.0 Hz, 1H, H6'), 5.85 (s, 2H, H2'), 2.79 (dd, J = 13.5, 4.5 Hz, 1H, H2a), 2.50 (dd, J = 13.5, 8.5 Hz, 1H, H2b), 2.50 (dd, J = 13.5, 8.5 Hz, 1H, H2b), 2.11 (ddd [app dt], J = 8.5, 8.5, 4.5, 1H, H1), 1.59 (br s, NH_2 +H_2O), 0.76–0.68 (m, 1H), 0.46–0.38 (m, 2H), 0.17–0.04 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3 and 145.7 (C3a' and C7a'), 133.0 (C5'), 122.0 (C6'), 109.4 and 107.9 (C4' and C7'), 100.6 (C2'), 58.2 (C1), 43.5 (C2), 18.0 (C1"), 2.92 and 2.89 (C2" and C3"). HRMS–EI (m/z): M^+ calcd for $C_{12}H_{15}NO_2$, 205.1103; found, 205.1111.

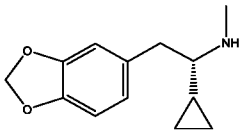
[00105] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as a colourless amorphous powder (mp 138–141 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (s, 1H), 6.73 (s, 2H), 5.93–5.91 (m [app AB system], 2H, H2"), 3.21 (dd, J = 14.0, 5.5 Hz, 1H, H2a), 3.04 (dd, J = 14.0, 8.0 Hz, 1H, H2b), 2.68–2.58 (m, 1H), 1.13–1.03 (m, 1H), 0.68–0.51 (m, 3H), 0.10–0.02 (m, 1H). Anal. Calcd for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79. Found: C, 59.33; H, 6.78; N, 5.67.

2-(1,3-Benzodioxol-5-yl)-1-cyclopropyl-N-methylethanamine (UWA-101, "Compound 1B")



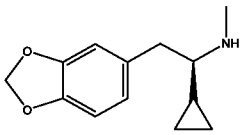
[00106] Compound 1B is a known compound previously synthesised.[4] Following the general procedure 1, reaction of the ketone K1 (378 mg, 1.85 mmol) with 8.03 M methylamine in MeOH (2.28 mL, 18.3 mmol) and elution with EtOAc afforded the product as a pale yellow oil (331 mg, 82%). The ^{1}H NMR and ^{13}C NMR spectra were identical to those reported.[4] The free base was dissolved in methanolic hydrogen chloride and evaporated to dryness under a stream of N_2. The crude hydrochloride and was recrystallised from 2-propanol as a colourless amorphous powder: mp 157–159 °C (lit. mp 156–158 °C). The ^{1}H NMR spectrum was identical to that reported.[4]

(S)-2-(1,3-Benzodioxol-5-yl)-1-cyclopropyl-N-methylethanamine ("Compound 1BS")



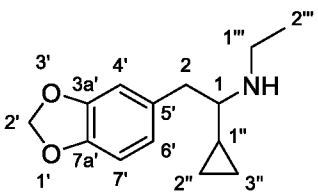
[00107] Compound 1BS is a known compound previously synthesized, and was obtained following the procedure in the literature.[2 – page 119]

(R)-2-(1,3-Benzodioxol-5-yl)-1-cyclopropyl-N-methylethanamine ("Compound 1BR")



[00108] Compound 1BR is a known compound previously synthesized, and was obtained following the procedure in the literature.[2 – page 118]

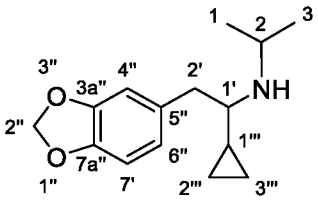
2-(1,3-Benzodioxol-5-yl)-1-cyclopropyl-N-ethylethanamine (MNG5164, "Compound 1C")



[00109] Compound 1C is a known compound previously synthesized.[2 – page 86] Following the general procedure 1, reaction of the ketone K1 (208 mg, 1.02 mmol) with 2.0 M ethylamine in MeOH (5.00 mL, 10.0 mmol) and elution with EtOAc afforded the product as a pale yellow oil (101 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (d, J = 8.0 Hz, 1H, H7'), 6.69 (d, J = 1.5 Hz, 1H, H4'), 6.65 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.94–5.91 (m, 2H, H2'), 2.87–2.79 (m, 2H, H2a+H1a'''), 2.68 (dd, J = 14.0, 7.5 Hz, 1H, H2b), 2.56 (dq, J = 11.5, 7.0 Hz, 1H, H1b'''), 1.89 (ddd, J = 9.0, 8.0, 5.0 Hz, 1H, H1), 1.46 (br s, 1H, NH+H_2O), 1.05 (t, J = 7.0 Hz, 3H, H2'''), 0.73–0.64 (m, 1H), 0.58–0.51 (m, 1H), 0.45–0.38 (m, 1H), 0.25–0.19 (m [app sextet], 1H), 0.02–0.05 (m [app sextet], 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 145.8 (C3a' and C7a'), 133.2 (C5'), 122.2 (C6'), 109.6 and 108.0 (C4' and C7'), 100.7 (C2'), 65.0 (C1), 42.1 and 41.7 (C2 and C1'''), 16.0 and 15.5 (C1'' and C2'''), 4.9 and 2.0 (C2'' and C3''). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{19}NO_2$, 234.1494; found, 234.1486.

[00110] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol/Et_2O as colourless rods (mp 154–156 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.8–9.5 (2×br s, 2H, NH_2), 6.78–6.72 (m, 3H, H4', H6', H7'), 5.98–5.93 (m [app d], 2H, H2'), 3.53 (dd, J = 13.5, 4.0 Hz, 1H, H1a), 3.36–3.25 (m, 1H, H1a''), 3.18–3.07 (m, 2H, H1b+H1b''), 2.54–2.45 (m, 1H, H2), 1.54 (t, J = 7.5 Hz, 3H, H2''), 1.17–1.07 (m, 1H), 0.72–0.64 (m, 1H), 0.53–0.45 (m, 2H), -0.15–-0.23 (m, 1H). Anal. Calcd for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19. Found: C, 62.54; H, 7.87; N, 5.17.

N-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]propan-2-amine (UWA-004, KDL03-158, "Compound 1D")

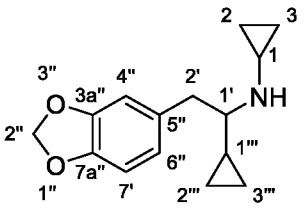


[00111] Compound 1D is a known compound previously synthesized.[2 – page 87] Following the general procedure 1, the ketone K1 (204 mg, 1.00 mmol) was reacted with isopropylamine (852 µL, 9.92 mmol). After 24 h, TLC analysis showed some starting material remained and the reaction was supplemented with further sodium cyanoborohydride (63 mg, 1.00 mmol) to fully consume the starting material. The reaction was quenched and the product extracted and chromatographed by elution with EtOAc which afforded the product as a yellow oil (113 mg, 46%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (d, J = 8.0 Hz, 1H, H7''), 6.69 (d, J = 1.5 Hz, 1H, H4''), 6.64 (dd, J = 8.0, 1.5 Hz, 1H, H6''), 5.93–5.91 (m [AB system], 2H, H2''), 2.99 (septet, J = 6.0 Hz, 1H, H2), 2.77 (dd, J = 13.5, 5.5 Hz, 1H, H2a'), 2.67 (dd, J = 13.5, 6.5 Hz, 1H, H2b'), 2.02 (ddd, J = 8.5, 6.5, 5.5 Hz, 1H, H1'), 1.02 (d, J = 6.0 Hz, 3H, H1), 0.94 (d, J = 6.0 Hz, 3H, H3), 0.69–0.61 (m, 1H), 0.54–0.47 (m, 1H), 0.44–0.37 (m, 1H), 0.22–0.15 (m [app sextet], 1H), 0.02–-0.04 (m [app sextet], 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4 and 145.8

(C3a" and C7a"), 133.2 (C5"), 122.3 (C6"), 109.7 and 108.0 (C4" and C7"), 100.7 (C2"), 61.4 (C1'), 45.4 (C2), 41.7 (C2'), 23.6 and 23.1 (C1 and C3), 16.5 (C1'"), 4.5 and 2.5 (C2'" and C3'"). HRMS–EI (m/z): M^+ calcd for $C_{15}H_{21}NO_2$, 247.1572; found, 247.1579.

[00112] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as colourless rods (mp 156–159 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.55–9.32 (m [app br d], 2H, NH_2), 6.77–6.70 (m, 3H, H4"+H6"+H7"), 5.95–5.91 (m [AB system], 2H, H2"), 3.70–3.60 (m [app septet], 1H, H2), 3.56 (dd, J = 13.5, 4.5 Hz, 1H, H2a'), 3.20 (dd, J = 13.5, 9.5 Hz, 1H, H2b'), 2.56–2.46 (m, 1H, H1'), 1.56 (d, J = 6.5 Hz, 3H, H1), 1.46 (d, J = 6.5 Hz, 3H, H3), 1.27–1.18 (m, 1H), 0.71–0.63 (m, 1H), 0.49–0.41 (m, 1H), 0.38–0.31 (m [app sextet], 1H), -0.20–-0.27 (m [app sextet], 1H). Anal. Calcd for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.56; H, 8.05; N, 4.85.

N-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]cyclopropanamine (UWA-037, MNG6028, GAP-068, "Compound 1E")



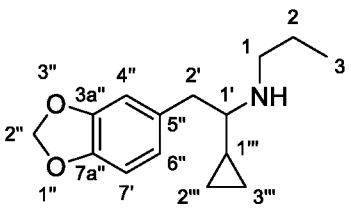
[00113] Following an adapted literature method,[5] to a suspension of freshly activated sieves (ca 100 mg) in anhydrous MeOH (2 mL) was added Compound 1A (202 mg, 0.984 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (200 µL, 0.995 mmol). The mixture was stirred under N_2 for 1 h then sodium cyanoborohydride (94 mg, 1.50 mmol) was added and the mixture heated at 50 °C for 20 h. The reaction was quenched, extracted and the product was then eluted with 4:1 EtOAc/hexanes followed by EtOAc to afford the desired product as a colourless oil (56 mg, 23%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (d, J = 8.0 Hz, 1H, H7"), 6.70 (d, J = 1.5 Hz, 1H, H4"), 6.65 (dd, J = 8.0, 1.5 Hz, 1H, H6"), 5.93 (s, 2H, H2"), 2.81 (dd, J = 13.5, 5.0 Hz, 1H, H2a'), 2.74 (dd, J = 13.5, 7.5 Hz, 1H, H2b'), 2.12–2.07 (m, 1H, H1), 1.99 (ddd, J = 9.0, 7.5, 5.5 Hz, 1H, H1'), 1.70 (br s, 1H, NH+H_2O), 0.73–0.64 (m, 1H), 0.59–0.52 (m, 1H), 0.52–0.24 (m, 6H), 0.02–-0.04 (m,1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 145.8 (C3a" and C7a"), 133.3 (C5"), 122.2 (C6"), 109.6 and 108.0 (C4" and C7"), 100.8 (C2"), 65.6 (C1'), 41.7 (C2'), 29.3 and 16.1 (C1 and C1'"), 7.5, 6.4, 5.0, 2.6 (C2, C3, C2'", C3'"). HRMS–EI (m/z): M^+ calcd for $C_{15}H_{19}NO_2$, 245.1416; found, 245.1414.

[00114] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol/Et_2O as a colourless amorphous powder (mp 128–131 °C). ^{1}H NMR (500 MHz. $CDCl_3$): δ 9.84 (br s, 1H, NHa), 9.62 (br s, 1H, NHb), 6.75 (dd, J = 7.5, 1.5 Hz, 1H, H6"), 6.73 (d, J = 1.5 Hz, 1H, H4"), 6.71 (d, J = 7.5 Hz, 1H, H7"), 5.94–5.91 (m [AB system], 2H, H2"), 3.55 (dd, J = 13.5, 3.5 Hz, 1H,

H2a'), 3.09 (dd, J = 13.5, 9.5 Hz, 1H, H2b'), 2.67–2.67 (m, 1H), 2.58–2.50 (m, 1H), 1.48–1.41 (m, 1H), 1.34–1.26 (m, 1H), 1.18–1.09 (m, 1H), 0.93–0.78 (m, 2H), 0.69–0.61 (m, 1H), 0.57–0.49 (m, 1H), 0.49–0.42 (m, 1H), -0.21–-0.29 (m, 1H). Anal. Calcd for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 64.05; H, 7.43; N, 4.89.

[00115] Alternatively, following general procedure 1, Cyclopropylamine (2.10 mL, 30.3 mmol) and AcOH (1.90 mL, 33.2 mmol) were added successively to a cold (0°C), stirred mixture of ketone K1 (623 mg, 3.05 mmol) and 3A sieves (652 mg) in 1:1 THF/MeOH (18 mL). Sodium cyanoborohydride (216 mg, 3.44 mmol) was added and the reaction vessel was flushed with N_2, sealed and stirred at 50 °C for 96 h before being cooled to room temperature and quenched with 4 M HCl (15 mL). The resulting mixture was vacuum filtered through a pad of Celite, washing through with water (50 mL) and MeOH (3 × 50 mL). The filtrate was concentrated under reduced pressure and the residue was basified with 4 M NaOH (30 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The extract was washed with brine (60 mL), dried and evaporated, and the residue was subjected to flash chromatography. Gradient elution with 1:3 EtOAc/hexanes → 1:1 EtOAc/hexanes → 1:49:50 NEt_3/EtOAc/hexanes afforded the secondary amine **1E** as a colourless oil (635 mg, 85%). The spectroscopic data for **1E** synthesised via this method match those obtained previously.

N-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]propan-1-amine (UWA-031, MNG5166, "Compound 1F")

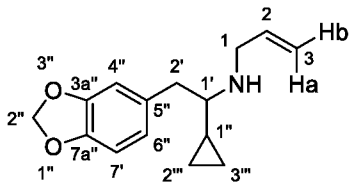


[00116] Following the general procedure 1, reaction of the ketone K1 (204 mg, 1.00 mmol) with n-propylamine (822 µL, 10.0 mmol) and elution with 2:3 EtOAc/hexanes followed by EtOAc afforded the product as a pale yellow oil (105 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (d, J = 7.5 Hz, 1H, H7''), 6.69 (d, J = 1.5 Hz, 1H, H4''), 6.65 (dd, J = 8.0, 1.5 Hz, 1H, H6''), 5.92 (s, 2H, H2''), 2.81 (dd, J = 8.5, 5.0 Hz, 1H, H2a'), 2.74 (ddd, J = 11.0, 8.5, 6.0 Hz, 1H, H1a), 2.67 (dd, J = 13.5, 8.0 Hz, 1H, H2b'), 2.49 (ddd, J = 11.5, 8.5, 6.0 Hz, 1H, H1b), 1.87 (ddd, J = 9.0, 8.0, 5.0 Hz, 1H, H1'), 1.80–1.20 (m, 3H, H2+NH+H_2O), 0.85 (t, J = 7.5 Hz, 3H, H3), 0.73–0.64 (m, 1H), 0.58–0.51 (m, 1H), 0.44–0.37 (m, 1H), 0.25–0.18 (m [app sextet], 1H), 0.02–-0.05 (m [app sextet], 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 145.8 (C3a'' and C7a''), 133.3 (C5''), 122.2 (C6''), 109.6 and 108.0 (C4'' and C7''), 100.7 (C2''), 64.9 (C1'), 49.8 and 41.7 (C1 and C2'), 23.3 (C2), 16.0 and 11.7 (C3 and C1'''), 4.8 and 2.0 (C2''' and C3'''). HRMS–EI (m/z): M^+ calcd for $C_{15}H_{21}NO_2$, 247.1572; found, 247.1525.

[00117] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol/Et_2O as colourless rods (mp 157–158 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.66 (br s, 1H, NHa),

9.38 (br s, 1H, NHb), 6.77–6.70 (m, 3H, H4"+H6"+H7"), 5.95–5.92 (m [AB system], 2H, C2"), 3.52 (dd, J = 13.5, 4.5 Hz, 1H, H2a'), 3.17–3.04 (m, 2H, H1a+H2b'), 3.00–2.90 (m, 1H, H1b), 2.54–2.46 (m, 1H, H1'), 2.03–1.94 (m [app sextet], 2H, H2), 1.14–1.05 (m, 1H), 0.99 (t, J = 7.0 Hz, 3H, H3), 0.70–0.62 (m, 1H), 0.55–0.45 (m, 2H), -0.14–-0.22 (m, 1H). Anal. Calcd for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.59; H, 8.02; N, 4.88.

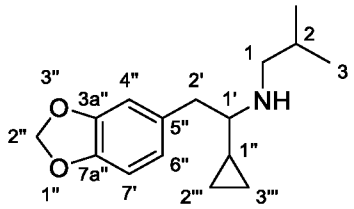
N-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]prop-2-en-1-amine (UWA-032, MNG6006, "Compound 1G")



[00118] Following the general procedure 1, reaction of the ketone K1 (204 mg, 1.00 mmol) with allylamine (750 µL, 10.0 mmol) and elution with EtOAc afforded the product as a pale yellow oil (172 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (d, J = 7.5 Hz, 1H, H7"), 6.69 (d, J = 1.5 Hz, 1H, H4"), 6.65 (dd, J = 8.0, 1.5 Hz, 1H, H6"), 5.93 (s, 2H, H2"), 5.88–5.78 (m, 1H, H2), 5.09 (dddd [app dq], J = 17.0, 1.5, 1.5, 1.5 Hz, 1H, H3a), 5.06–5.02 (m [app dq], 1H, H3b), 3.43 (dddd, J = 14.0, 6.0, 1.5, 1.5 Hz, 1H, H1a), 3.23 (dddd, J = 14.5, 6.5, 1.5, 1.5 Hz, 1H, H1b), 2.83 (dd, J = 14.0, 5.0 Hz, 1H, H2a'), 2.70 (dd, J = 14.0, 8.0 Hz, 1H, H2b'), 1.94 (ddd, J = 8.5, 8.0, 5.0 Hz, 1H, H1'), 1.59 (br s, 1H, NH+H_2O), 0.73–0.64 (m, 1H), 0.60–0.53 (m, 1H), 0.46–0.39 (m, 1H), 0.27–0.20 (m [app sextet], 1H), 0.03–-0.04 (m [app sextet], 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 145.9 (C3a" and C7a"), 137.2 (C2), 133.1 (C5"), 122.3 (C6"), 115.5 (C3), 109.6 and 108.1 (C4" and C7"), 100.8 (C2"), 63.9 (C1'), 50.1 and 41.8 (C1 and C2'), 15.9 (C1'"), 5.0 and 2.0 (C2'" and C3'"). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{15}H_{19}NO_2$, 246.1494; found, 246.1496.

[00119] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol/Et_2O as a colourless amorphous powder (mp 148–150 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.90–9.68 (m [app br d], 2H, NH_2), 6.76–6.71 (m, 3H, H4"+H6"+H7"), 6.20–6.11 (m, 1H, H2), 5.95–5.92 (m [AB system], 2H, H2"), 5.47–5.40 (m, 2H, H3a+H3b), 3.80–3.68 (m, 2H, H1), 3.44 (dd, J = 13.5, 4.5 Hz, 1H, H2a'), 3.09 (dd, J = 13.5, 9.0 Hz, 1H, H2b'), 2.55–2.45 (m [app octet], 1H, H1'), 1.19–1.10 (m, 1H), 0.73–0.65 (m, 1H), 0.54–0.41 (m, 2H), -0.13–-0.20 (m, 1H). Anal. Calcd for C15 $H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 63.88; H, 7.16; N, 4.94.

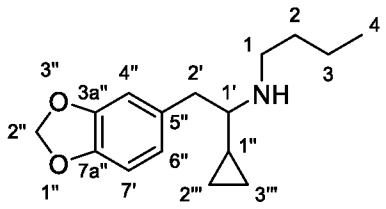
[00120] ***N-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]-2-methylpropan-1-amine (UWA-035, MNG6018, "Compound 1H")***



[00121] Following the general procedure 1, reaction of the ketone K1 (203 mg, 0.994 mmol) with isobutylamine (993 µL, 9.99 mmol) and elution with 2:3 EtOAc/hexanes followed by EtOAc afforded the product as a colourless oil (93 mg, 36%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (d, J = 8.0 Hz, 1H, H7"), 6.70 (d, J = 1.5 Hz, 1H, H4"), 6.65 (dd, J = 8.0, 1.5 Hz, 1H, H6"), 5.92 (s, 1H, H2"), 2.80 (dd, J = 13.5, 5.0 Hz, 1H, H2a'), 2.67 (dd, J = 13.5, 7.5 Hz, 1H, H2b'), 2.57 (dd, J = 11.5, 7.0 Hz, 1H, H1a), 2.34 (dd, J = 11.5, 6.5 Hz, 1H, H1b), 1.85 (ddd, J = 9.0, 7.5, 5.0 Hz, 1H, H1'), 1.72–1.60 (m [app nonet], 1H, H2), 1.49 (br s, 1H, NH+H_2O), 0.85–0.80 (m [app dd], 6H, 2×CH_3) 0.72–0.64 (m, 1H), 0.57–0.50 (m, 1H), 0.44–0.37 (m, 1H), 0.24–0.17 (m [app sextet], 1H), 0.02–-0.05 (m [app sextet], 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 145.8 (C3a" and C7a"), 133.4 (C5"), 122.2 (C6"), 109.7 and 108.0 (C4" and C7"), 100.7 (C2"), 64.9 (C1'), 55.9 and 41.6 (C1 and C2'), 28.2, 20.7, 20.6, 16.1 (C2, 2×CH_3, C1'''), 4.7 and 2.1 (C2''' and C3'''). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{23}NO_2$, 262.1807; found, 262.1803.

[00122] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as a colourless amorphous powder (mp 185–187 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.64 (br s, 1H, NHa), 8.97 (br s, 1H, NHb), 6.79–6.75 (m, 2H, H4"+H6"), 6.71 (d, J = 8.0 Hz, 1H, H7"), 5.95–5.92 (m [AB system], 2H, H2"), 3.57 (dd, J = 13.5, 4.5 Hz, 1H, H2a'), 3.07 (dd, J = 13.5, 9.5 Hz, 1H, H2b'), 3.00–2.91 (m, 1H, H1a), 2.88–2.79 (m, 1H, H1b), 2.64–2.56 (m, 1H, H1'), 2.37–2.25 (m [app nonet], 1H, H2), 1.15–1.06 (m, 7H, 2×CH_3+cyclopropyl), 0.68–0.61 (m, 2H), 0.56–0.48 (m, 1H), -0.09–-0.16 (m, 1H). Anal. Calcd for $C_{16}H_{24}ClNO_2$: C, 64.53; H, 8.12; N, 4.70. Found: C, 64.60; H, 8.36; N, 4.62.

N-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]butan-1-amine (UWA-036, MNG6026, "Compound 1l")

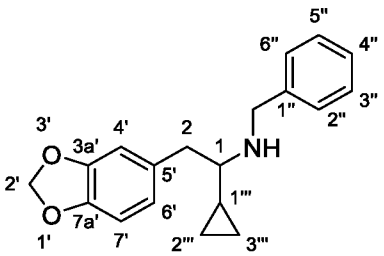


[00123] Following the general procedure 1, reaction of the ketone K1 (203 mg, 0.994 mmol) with n-butylamine (852 µL, 8.62 mmol) and elution with 3:7 EtOAc/hexanes followed by EtOAc afforded the product as a colourless oil (223 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (d, J = 8.0 Hz, 1H, H7"), 6.67 (d, J = 1.5 Hz, 1H, H4"), 6.63 (dd, J = 8.0, 1.5 Hz, 1H, H6"), 5.90 (s, 2H, H2"), 2.82–2.72 (m [app

dd+ddd], 2H, H1a+H2a'), 2.66 (dd, J = 13.5, 7.5 Hz, 1H, H2b'), 2.50 (ddd, J = 11.5, 8.5, 6.5 Hz, 1H, H1b), 1.85 (ddd, J = 9.0, 7.5, 5.0 Hz, 1H, H1'), 1.53 (br s, NH+H_2O), 1.45–1.31 (m, 2H, H2), 1.30–1.21 (m, 2H, H3), 0.85 (t, J = 7.0 Hz, 3H, H4), 0.71–0.63 (m, 1H), 0.55–0.49 (m, 1H), 0.42–0.36 (m, 1H), 0.23–0.17 (m, 1H), 0.00–-0.06 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4 and 145.8 (C3a" and C7a"), 133.2 (C5"), 122.2 (C6"), 109.6 and 108.0 (C4" and C7"), 100.7 (C2"), 65.0 (C1'), 47.6, 41.6, 32.3, 20.4 (C1, C2, C3, C2'), 16.0 and 13.9 (C4 and C1'"), 4.7 and 2.0 (C2'" and C3'"). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{23}NO_2$, 262.1807; found, 262.1800.

[00124] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol/Et_2O as a colourless amorphous powder (mp 163–165 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 9.65 (br s, 1H, NH_a), 6.50 (br s, 1H, NHb), 6.77–6.73 (m, 2H, H4"+H6"), 6.71 (d, J = 8.0 Hz, 1H, H7"), 5.94–5.91 (m [AB system], 2H, H2"), 3.54 (dd, J = 13.5, 3.5 Hz, 1H, H2a'), 3.20–3.10 (m, 1H, H1a), 3.07 (dd, J = 13.5, 10.5 Hz, 1H, H2b'), 3.02–2.92 (m, 1H, H1b), 2.54–2.46 (m, 1H, H1'), 1.99–1.89 (m, 2H, H2), 1.44–1.35 (m [app sextet], 2H, H3), 1.13–1.04 (m, 1H), 0.91 (t, J = 7.0 Hz, 3H, H4), 0.68–0.61 (m, 1H), 0.53–0.42 (m, 2H), -0.18–-0.26 (m, 1H). Anal. Calcd for $C_{16}H_{24}ClNO_2$: C, 64.53; H, 8.12; N, 4.70. Found: C, 64.52; H, 8.22; N, 4.64.

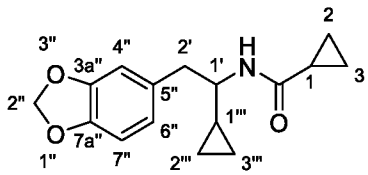
2-(1,3-Benzodioxol-5-yl)-N-benzyl-1-cyclopropylethanamine (UWA-034, MNG6016, "Compound 1J")



[00125] Following the general procedure 1, reaction of the ketone K1 (209 mg, 1.02 mmol) with benzylamine (1.09 mL, 9.98 mmol) and elution with 2:3 EtOAc/hexanes afforded the product as a pale yellow oil (261 mg, 86%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.31–7.17 (m, 5H, H2", H3", H4", H5"and H6"), 6.73 (d, J = 8.0 Hz, 1H, H7'), 6.68 (d, J = 1.5 Hz, 1H, H4'), 6.65 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.94–5.92 (m [AB system], 2H, H2'), 3.93 (d, J = 13.5 Hz, 1H, NCHaH), 3.80 (d, J = 13.5 Hz, 1H, NCHHb), 2.85 (dd, J = 13.5, 5.0 Hz, 1H, H2a), 2.73 (dd, J = 13.5, 7.5 Hz, 1H, H2b), 1.95 (ddd, J = 9.0, 8.0, 5.0 Hz, 1H, H1), 1.71 (br s, NH+H_2O), 0.79–0.70 (m, 1H), 0.56 (dddd, J = 9.0, 8.0, 5.5, 4.5 Hz, 1H), 0.42 (dddd, J = 9.0, 8.0, 5.5, 4.5 Hz, 1H), 0.23–0.16 (m [app sextet], 1H), 0.01–-0.06 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 145.9 (C3a' and C7a'), 140.5 (C1"), 133.1 (C5'), 128.3, 127.9, 126.8 (C2", C3", C4", C5", C6"), 122.3 (C6'), 109.7 and 108.1 (C4' and C7'), 100.8 (C2'), 63.7 (C1), 51.6 and 41.6 (C2 and NCH_2), 15.9 (C1'"), 4.8 and 2.0 (C2'" and C3'"). HRMS–EI (m/z): $[M+H]^+$ calcd for $C_{19}H_{21}NO_2$, 296.1645; found, 296.1648.

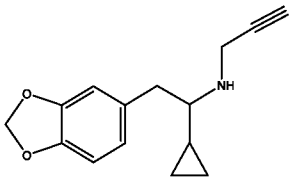
[00126] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol/Et_2O as a colourless amorphous powder (mp 144–146 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 9.95 (br s, 2H, NH_2), 7.63–7.59 (m [app d], 2H, H2" and H6"), 7.38–7.33 (m [app t], 2H, H3" and H5"), 7.31–7.27 (m, 1H, H4"), 6.70 (d, J = 8.0 Hz, 1H, H7'), 6.63 (dd, J = 8.0, 1.5 Hz, 2H, H6'), 6.61 (d, J = 1.5 Hz, 1H, H4'), 5.95–5.92 (m [AB system], 2H, H2"), 4.16–4.03 (m, 2H, NCH_2), 3.38 (dd, J = 13.5, 4.0 Hz, 1H, H2a), 3.00 (dd, J = 13.5, 9.5 Hz, 1H, H2b), 2.26–2.18 (m, 1H, H1), 1.15–1.06 (m, 1H), 0.63–0.60 (m, 1H), 0.44–0.36 (m, 1H), 0.29–0.22 (m [app sextet], 1H), -0.33–-0.39 (m, 1H). Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.78; H, 6.70; N, 4.19.

N-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]cyclopropanecarboxamide (MNG6022, "Compound 1K")



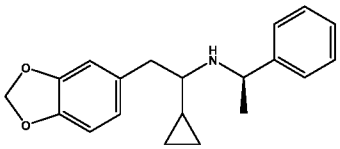
[00127] Following an adapted literature procedure,[6] to a stirred solution of Compound 1A (310 mg, 1.51 mmol) and NEt_3 (210 µL, 1.51 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at 0 °C under N_2 slowly added a solution of cyclopropanecarbonyl chloride (53, 172 mg, 1.65 mmol) in CH_2Cl_2 (2.5 mL). The solution was then allowed to warm to rt. After 2 h, the mixture was diluted with CH_2Cl_2 (20 mL), then washed with water (20 mL), 1 M HCl (20 mL), saturated $NaHCO_3$ solution (20 mL), water (20 mL), brine (20 mL), dried and evaporated to afford a white solid. This material was recrystallised from EtOAc/hexanes as colourless rods (244 mg, 59%): mp 128–129 °C. IR (dry film) $\bar{\nu}$ max (cm^{-1}): 3302 (m, N–H), 1632 (s, C–O). ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 (d, J = 8.0 Hz, 1H, H7"), 6.72 (d, J = 1.5 Hz, 1H, H4"), 6.66 (dd, J = 8.0, 1.5 Hz, 1H, H6"), 5.95–5.92 (m [AB system], 2H, H2"), 5.52 (br d, J = 7.5 Hz, 1H, NH), 3.44–3.36 (m, 1H, H1'), 2.85 (d, J = 6.0 Hz, 2H, H2'), 1.32–1.25 (m, 1H), 0.99–0.90 (m, 2H), 0.81–0.68 (m, 3H), 0.54–0.47 (m, 1H), 0.46–0.39 (m, 1H), 0.36–0.28 (m [app sextet], 1H), 0.19–0.12 (m [app sextet], 1H). ^{13}C NMR (125 MHz, CDCl3): δ 172.7 (C=O), 147.4 and 146.0 (C3a" and C7a"), 131.7 (C5"), 122.7 (C6"), 110.2 and 108.0 (C4" and C7"), 100.8 (C2"), 55.0 (C1'), 40.5 (C2'), 15.0 and 14.9 (C1 and C1'"), 7.0, 6.9, 4.0, 3.2 (C2, C3, C2'", C3'"). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{19}NO_3$, 274.1443; found, 274.1438. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.17; H, 7.18; N, 5.06.

N-(2-(benzo[d][1,3]dioxol-5-yl)-1-cyclopropylethyl)prop-2-yn-1-amine (UWA-005, "Compound 1L")



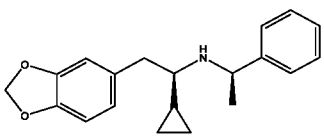
[00128] Compound 1L is a known compound, obtained by the previously reported procedure.[2 – page 86]

2-(benzo[d][1,3]dioxol-5-yl)-1-cyclopropyl-N-((R)-1-phenylethyl)ethan-1-amine ("Compound 1M")



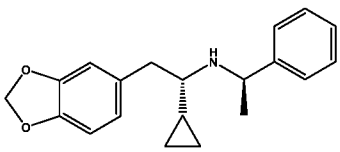
[00129] Compound 1M is a known compound, obtained by the previously reported procedure.[2 – page 115]

(R)-2-(benzo[d][1,3]dioxol-5-yl)-1-cyclopropyl-N-((R)-1-phenylethyl)ethan-1-amine ("Compound 1MR")



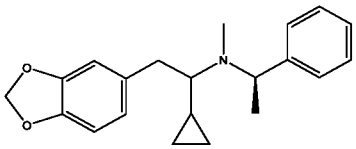
[00130] Compound 1MR is a known compound, obtained by the previously reported procedure.[2 – page 115]

(S)-2-(benzo[d][1,3]dioxol-5-yl)-1-cyclopropyl-N-((R)-1-phenylethyl)ethan-1-amine ("Compound 1MS")



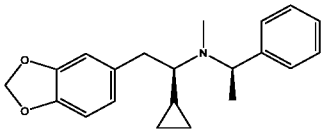
[00131] Compound 1MS is a known compound, obtained by the previously reported procedure.[2 – page 115]

2-(benzo[d][1,3]dioxol-5-yl)-1-cyclopropyl-N-methyl-N-((R)-1-phenylethyl)ethan-1-amine ("Compound 1N")



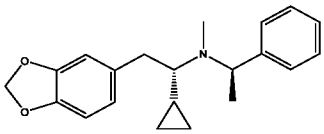
[00132] Compound 1N is a known compound, obtained by the previously reported procedure.[2 – page 116]

(R)-2-(benzo[d][1,3]dioxol-5-yl)-1-cyclopropyl-N-methyl-N-((R)-1-phenylethyl)ethan-1-amine ("Compound 1NR")



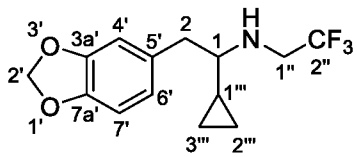
[00133] Compound 1NR is a known compound, obtained by the previously reported procedure.[2 – page 116]

(S)-2-(benzo[d][1,3]dioxol-5-yl)-1-cyclopropyl-N-methyl-N-((R)-1-phenylethyl)ethan-1-amine ("Compound 1NS")



[00134] Compound 1NS is a known compound, obtained by the previously reported procedure.[2 – page 116]

2-(1,3-Benzodioxol-5-yl)-1-cyclopropyl-N-(2,2,2-trifluoroethyl)ethan-1-amine (UWA-044, JLK2098, "Compound 1O")

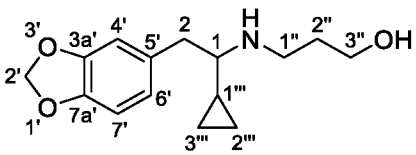


[00135] A sealed mixture of freshly activated 3 Å sieves (ca 300 mg), ketone K1 (205 mg, 1.00 mmol), 2,2,2-trifluoroethylamine hydrochloride (1.36 g, 10.0 mmol), sodium acetate (820 mg, 10.0 mmol) and sodium cyanoborohydride (63 mg, 1.0 mmol) in anhydrous THF (2 mL) was stirred at 50 °C for 3 d. The reaction was quenched with conc. HCl, filtered through a pad of Celite with H_2O, basified and extracted with DCM (3 × 50 mL). The extract was washed with H_2O (2 × 50 mL) and brine (50 mL), dried and evaporated, and the residue was subjected to flash chromatography. Elution with 1:9 EtOAc/Hex then 3:7 EtOAc/Hex afforded the secondary

amine **1O** as a colourless oil (48 mg, 17 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, J = 7.9 Hz, 1H, H7'), 6.69 (d, J = 1.5 Hz, 1H, H4'), 6.65 (dd, J = 7.9, 1.6 Hz, 1H, H6'), 5.93 (s, 2H, H2'), 3.37–3.26 (m, 1H, H1"a), 3.26–3.15 (m, 1H, H1"b), 2.83 (dd, J = 13.8, 4.9 Hz, 1H, H2a), 2.66 (dd, J = 13.8, 7.7 Hz, 1H, H2b), 2.10–2.02 (m, 1H, H1), 0.73–0.55 (m, 2H), 0.50–0.41 (m, 1H), 0.29–0.20 (m [app. sextet], 1H), 0.08 to –0.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8 and 146.2 (C3a' and C7a'), 132.4 (C5'), 125.7 (q, J = 279.4 Hz, C2"), 122.4 (C6'), 109.7 (C4'), 108.3 (C7'), 101.0 (C2'), 63.5 (C1), 48.1 (q, J = 30.9 Hz, C1"), 41.9 (C2), 15.7 (C1'"), 4.9 and 1.9 (C2'" and C3'"). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}F_3NO_2^+$ 288.1206; found, 288.1205.

[00136] The free base was converted to the hydrochloride salt, which crystallised from DCM/Hexane as off-white rhomboids. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.39 (br. s, 2H, NH_2), 6.80–6.71 (m, 3H, H4'/6'/7'), 5.94 (m [AB], 2H, H2'), 3.89–3.67 (m, 2H, H1"), 3.50 (dd, J = 13.4, 3.7 Hz, 1H, H2a), 3.13 (dd, J = 13.4, 9.2 Hz, 1H, H2b), 2.81–2.69 (m, 1H, H1), 1.18–1.06 (m, 1H), 0.77–0.66 (m, 1H), 0.61–0.51 (m, 2H), –0.02 to –0.13 (m, 1H).

2-(1,3-Benzodioxol-5-yl)-1-cyclopropyl-N-(3-hydroxypropyl)ethan-1-amine (UWA-047, JLK2100, "Compound 1P")

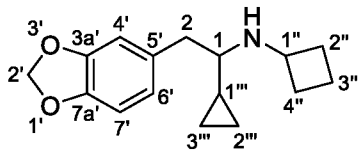


[00137] Following the general procedure 1, ketone K1 (204 mg, 1.00 mmol) was reacted with propanolamine (765 µL, 10.0 mmol) and the crude product was subjected to flash chromatography. Elution with 35:65:1 EtOAc/Hex/NEt_3 afforded the secondary amine **1P** as a pale-yellow oil (233 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, J = 7.9 Hz, 1H, H7'), 6.66 (d, J = 1.6 Hz, 1H, H4'), 6.62 (dd, J = 7.8, 1.6 Hz, 1H, H6'), 5.91 (s, 2H, H2'), 3.80–3.70 (m, 2H, H3"), 3.03 (ddd, J = 11.7, 6.9, 5.0 Hz, 1H, H1"a), 3.00 (br. s, 2H, OH + NH), 2.85–2.73 (m, 2H, H1"b/2a), 2.65 (dd, J = 13.7, 7.7 Hz, 1H, H2b), 1.87 (ddd, J = 8.6, 7.8, 5.0 Hz, 1H, H1), 1.71–1.57 (m, 2H, H2"), 0.72–0.61 (m, 1H, H1'"), 0.61–0.53 (m, 1H), 0.49–0.40 (m, 1H), 0.29–0.21 (m [app. sextet], 1H), 0.05 to –0.03 (m [app. sextet], 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7 and 146.1 (C3a' and C7a'), 132.7 (C5'), 122.4 (C6'), 109.7 (C4'), 108.3 (C7'), 100.9 (C2'), 65.1 (C1), 64.4 (C3"), 47.8 (C1"), 41.7 (C2), 31.5 (C2"), 15.9 (C1'"), 5.3 and 2.3 (C2'" and C3'"). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_3^+$ 264.1594; found, 264.1593.

[00138] The free base was converted to the hydrochloride salt, which crystallised from *i*-PrOH/Et_2O as white plates. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (br. s, 1H, NH), 9.04 (br. s, 1H, NH), 6.79–6.72 (m, 3H, H4'/6'/7'), 5.94 (s, 2H, H2'), 3.91–3.79 (m, 2H, H3"), 3.54–3.42 (m, 1H, H1"a), 3.34 (dd, J = 13.8, 6.0 Hz, 1H, H2a), 3.22–3.07 (m, 2H, H1"b/2b), 2.54–2.43 (m, 1H, H1),

2.15–1.99 (m, 2H, H2''), 1.24–1.13 (m, 1H), 0.78–0.68 (m, 1H), 0.63–0.53 (m, 1H), 0.50–0.41 (m [app. sextet], 1H), 0.01 to –0.08 (m [app. sextet], 1H).

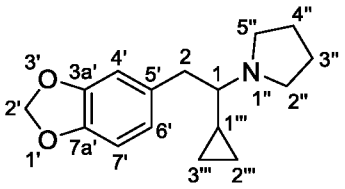
2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl*-N-*cyclobutanamine; *N-(2-(benzo[d][1,3]dioxol-5-yl)-1-cyclopropylethyl)cyclobutanamine; (UWA-055, JLK2043, "Compound 1Q")



[00139] Following general procedure 1 but using half the excess of amine, ketone K1 (102 mg, 0.500 mmol) was reacted with cyclobutylamine (0.21 mL, 2.5 mmol). The reaction was quenched with conc. HCl and filtered through a pad of Celite with H_2O. The solution was washed with DCM (3 × 50 mL), then basified and extracted with EtOAc (3 × 20 mL). The organic extracts were combined and washed with H_2O (2 × 20 mL) and brine (20 mL), then dried and evaporated to give the secondary amine **1Q** as a pale brown oil (111 mg, 86 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (d, J = 7.8 Hz, 1H, H7'), 6.67 (d, J = 1.5 Hz, 1H, H4'), 6.64 (dd, J = 7.9, 1.6 Hz, 1H, H6'), 5.93 (s, 2H, H2'), 3.54–3.44 (m, 1H, H1''), 2.79 (dd, J = 13.6, 5.1 Hz, 1H, H2a), 2.62 (dd, J = 13.6, 8.0 Hz, 1H, H2b), 2.26–2.09 (m, 2H), 1.88–1.81 (m, 1H, H1), 1.63–1.51 (m, 3H), 1.45–1.34 (m, 1H), 0.71–0.60 (m, 1H, H1'''), 0.58–0.49 (m, 1H), 0.45–0.36 (m, 1H), 0.23–0.14 (m [app. sextet], 1H), 0.01 to –0.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7 and 146.0 (C3a' and C7a'), 133.4 (C5'), 122.4 (C6'), 109.7 (C4'), 108.2 (C7'), 100.9 (C2'), 62.3 (C1), 51.8 (C1''), 42.1 (C2), 32.0 and 31.8 (C2'' and C4''), 16.3 (C1'''), 14.6 (C3''), 5.0 and 2.3 (C2''' and C3'''). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_2^+$ 260.1645; found, 260.1643.

[00140] The free base was converted to the hydrochloride salt, which crystallised from PhMe (toluene) as white granules. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (br. s, 2H, NH_2), 6.76–6.68 (m, 3H, H4'/6'/7'), 5.93 (m [AB], 2H, H2'), 3.96 (dddd [app. pentet], $J_1 = J_2 = J_3 = J_4$ = 8.2 Hz, 1H, H1''), 3.52 (dd, J = 13.4, 3.8 Hz, 1H, H2a), 3.05 (dd, J = 13.4, 10.3 Hz, 1H, H2b), 2.43–2.19 (m, 3H), 2.05–1.93 (m, 1H), 1.88–1.72 (m, 1H), 1.11–0.99 (m, 1H), 0.68–0.58 (m, 1H), 0.49–0.35 (m, 2H), –0.23 to –0.34 (m, 1H).

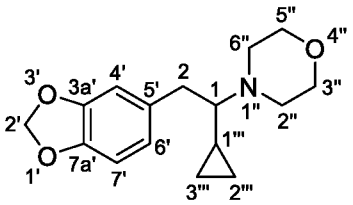
1-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]pyrrolidine (UWA-048, JLK2101, "Compound 1R")



[00141] Following general procedure 1, ketone K1 (205 mg, 1.00 mmol) was reacted with pyrrolidine (727 µL, 10.0 mmol) and the crude product was subjected to flash chromatography. Elution with 1:4 EtOAc/Hex followed by 20:80:1 EtOAc/Hex/NEt_3 afforded the tertriary amine **1R** as a pale-yellow oil (230 mg, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (d, J = 1.2 Hz, 1H, H4'), 6.65 (dd, J = 7.8, 0.3 Hz, 1H, H7'), 6.63 (dd, J = 7.9, 1.4 Hz, 1H, H6'), 5.85 (m [AB], 2H, H2'), 2.91 (dd, J = 13.7, 4.5 Hz, 1H, H2a), 2.74 (dd, J = 13.7, 7.0 Hz, 1H, H2b), 2.71–2.60 (m, 4H, H2"/5"), 1.78–1.67 (m, 4H, H3"/4"), 1.51 (ddd, J = 11.6, 7.0, 4.5 Hz, 1H, H1), 0.73–0.61 (m, 1H, H1'"), 0.51–0.41 (m, 1H), 0.31–0.22 (m, 1H), 0.20–0.10 (m [app. sextet], 1H), –0.25 to –0.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1 and 145.5 (C3a' and C7a'), 134.2 (C5'), 122.5 (C6'), 110.1 (C4'), 107.7 (C7'), 100.6 (C2'), 70.9 (C1), 52.2 (C2"/5"), 40.9 (C2), 23.3 (C3"/4"), 14.6 (C1'"), 6.1 and 3.0 (C2'" and C3'"). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_2^+$ 260.1645; found, 260.1643.

[00142] The free base was converted to the hydrochloride salt, which crystallised from *i*-PrOH/Et_2O as colourless plates. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75–6.72 (m, 3H, H4'/6'/7'), 5.95 (m [AB], 2H, H2'), 3.94–3.84 (m, 1H), 3.78–3.68 (m, 1H), 3.44 (dd, J = 14.0, 4.6 Hz, 1H, H2a), 3.15 (dd, J = 14.0, 8.8 Hz, 1H, H2b), 3.01–2.85 (m, 2H), 2.51–2.42 (m, 1H, H1), 2.34–2.19 (m, 2H, H3"a/4"a), 2.08–1.93 (m, 2H, H3"b/4"b), 1.29–1.18 (m, 1H), 0.80–0.72 (m, 1H), 0.60–0.51 (m, 1H), 0.44–0.35 (m, 1H), –0.12 to –0.21 (m, 1H).

4-[2-(1,3-Benzodioxol-5-yl)-1-cyclopropylethyl]morpholine (UWA-049, JLK2102, "Compound 1S")

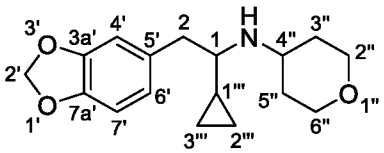


[00143] Following general procedure 1 ketone K1 (205 mg, 1.00 mmol) was reacted with morpholine (872 µL, 10.0 mmol) and the crude product was subjected to flash chromatography. Elution with 5:95:1 EtOAc/Hex/NEt_3 afforded the tertiary amine **1S** as a colourless oil (206 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (d, J = 1.6 Hz, 1H, H4'), 6.70 (d, J = 7.9 Hz, 1H, H7'), 6.65 (dd, J = 7.9, 1.6 Hz, 1H, H6'), 5.91 (m [AB], 2H, H2'), 3.74–3.64 (m, 4H, H2"/6"), 2.83 (dd, J = 13.1, 6.9 Hz, 1H, H2a), 2.82–2.74 (m, 2H, H3"a/5"a), 2.70 (dd, J = 13.9, 6.5 Hz, 1H, H2b),

2.65–2.58 (m, 2H, H3"b/5"b), 1.75 (ddd [app. dt], *J* = 9.5, 6.3, 6.3 Hz, 1H, H1), 0.77–0.66 (m, 1H, H1'"), 0.58–0.49 (m, 1H), 0.39–0.30 (m, 1H), 0.28–0.19 (m [app. sextet], 1H), –0.17 to –0.26 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 147.3 and 145.6 (C3a' and C7a'), 134.6 (C5'), 122.4 (C6'), 110.0 (C4'), 107.9 (C7'), 100.8 (C2'), 71.8 (C1), 67.7 (C2"/6"), 50.6 (3"/5"), 38.4 (C2), 11.7 (C1'"), 5.5 and 2.7 (C2'" and C3'"). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_3^+$ 276.1594; found, 276.1592.

[00144] The free base was converted to the crude hydrochloride salt, which precipitated from *i*-PrOH/Et_2O as white rhomboids. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.82 (d, *J* = 1.6 Hz, 1H, H4'), 6.78 (dd, *J* = 7.9, 1.6 Hz, 1H, H6'), 6.72 (d, *J* = 7.9 Hz, 1H, H7'), 5.94 (m [AB], 2H, H2'), 4.49–4.35 (m, 2H), 4.06–3.92 (m, 2H), 3.68 (dd, *J* = 13.3, 3.3 Hz, 1H, H2a), 3.58–3.50 (m, 1H), 3.37–3.24 (m, 2H), 3.17–3.05 (m, 1H), 2.97 (dd, *J* = 13.3, 9.6 Hz, 1H, H2b), 2.58 (dddd [app. tt], $J_1 = J_2$ = 10.2 Hz, $J_3 = J_4$ = 3.4 Hz, 1H, H1), 1.05–0.94 (m, 1H), 0.82–0.72 (m, 1H), 0.62–0.52 (m, 1H), 0.48–0.39 (m, 1H), –0.14 to –0.23 (m, 1H).

2-(1,3-Benzodioxol-5-yl)-1-cyclopropyl*-N-*(oxan-4-yl)ethan-1-amine (UWA-046, JLK2103, "Compound 1T")

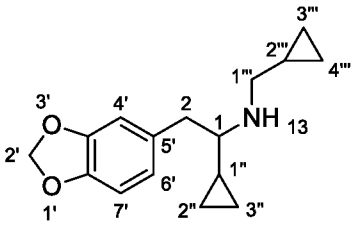


[00145] Following general procedure 1, ketone K1 (204 mg, 1.00 mmol) was reacted with 4-aminotetrahydropyran (570 µL, 10.0 mmol) and the crude product was subjected to flash chromatography. Elution with 3:7 EtOAc/Hex followed by 30:70:1 EtOAc/Hex/NEt_3 afforded the secondary amine **1T** as a pale-yellow oil (240 mg, 83 %). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.66 (d, *J* = 7.9 Hz, 1H, H7'), 6.63 (d, *J* = 1.6 Hz, 1H, H4'), 6.58 (dd, *J* = 7.9, 1.6 Hz, 1H, H6'), 5.85 (s, 2H, H2'), 3.90–3.77 (m, 2H, H2"a/6"a), 3.36–3.21 (dddd [app. tdd], *J* = 15.5, 11.5, 11.5, 2.3 Hz, 2H, H2"b/6"b), 2.82–2.69 (m, 2H, H2a/4"), 2.63–2.53 (dd, *J* = 13.6, 7.4 Hz, 1H, H2b), 2.05 (ddd, *J* = 8.6 7.4, 5.2 Hz, 1H, H1), 1.81–1.73 (m, 1H, H3"a or H5"a), 1.72–1.64 (m, 1H, H3"a or H5"a), 1.28–1.15 (m, 1H, H3"b or H5"b), 1.13–1.00 (m, 1H, H3"b or H5"b), 0.69–0.57 (m, 1H, H1'"), 0.52–0.42 (m, 1H), 0.42–0.32 (m, 1H), 0.16–0.07 (m [app. sextet], 1H), 0.01 to –0.08 (m [app. sextet], 1H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 147.5 and 145.8 (C3a' and C7a'), 132.9 (C5'), 122.2 (C6'), 109.3 (C4'), 108.0 (C7'), 100.7 (C2'), 67.0 and 66.9 (C2" and C6"), 60.3 (C1), 50.6 (C4"), 41.9 (C2), 34.7 and 33.9 (C3" and C5"), 16.5 (C1'"), 4.5 and 2.4 (C2'" and C3'"). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{17}H_{24}NO_3^+$ 290.1751; found, 290.1749.

[00146] The free base was converted to the hydrochloride salt, which precipitated from *i*-PrOH/Et_2O as white granules. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.76 (br. s, 1H, NH), 9.65 (br. s,

1H, NH), 6.76–6.69 (m, 3H, H4'/6'/7'), 5.93 (m [AB], 2H, H2'), 4.08–3.96 (m, 2H, H2"a/6"a), 3.64–3.45 (m, 2H, H2a/4"), 3.38–3.24 (m, 2H, H2"b/6"b), 3.16 (dd, *J* = 13.4, 9.8 Hz, 1H, H2b), 2.65–2.53 (m, 1H, H1), 2.26–2.10 (m, 3H), 2.03–1.94 (m, 1H), 1.28–1.16 (m, 1H), 0.75–0.64 (m, 1H), 0.53–0.42 (m, 1H), 0.38–0.29 (m [app. sextet], 1H), –0.18 to –0.27 (m [app. sextet], 1H).

2-(Benzo[d][1,3]dioxol-5-yl)-1-cyclopropyl-N-(cyclopropylmethyl)ethanamine (UWA-050, GAP-045, "Compound 1U")

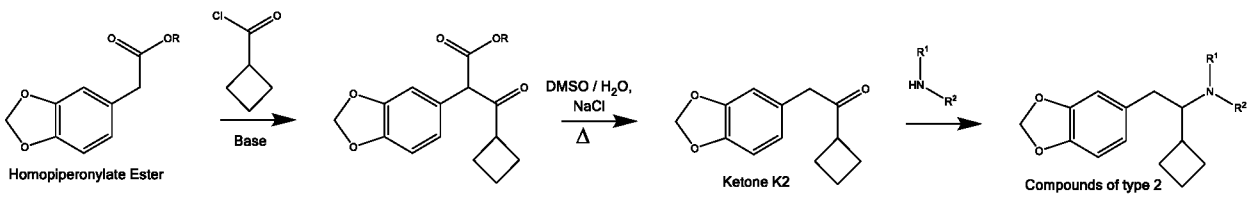


Following general procedure 1, a sealed mixture of freshly activated 3A sieves (144 mg), ketone K1 (103 mg, 0.504 mmol), cyclopropylmethanamine hydrochloride (570 mg, 5.30 mmol), sodium acetate (433 mg, 5.28 mmol) and sodium cyanoborohydride (33 mg, 0.53 mmol) in anhydrous THF (2.5 mL) was stirred at 50 °C for 3 d. The reaction mixture was cooled to room temperature, quenched with 1 M HCl (10 mL) and vacuum filtered through a pad of Celite, washing through with MeOH (3 × 25 mL). The filtrate was concentrated under reduced pressure and the residue was basified with 1 M NaOH (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The extract was washed with brine (30 mL), dried and evaporated, and the residue was subjected to flash chromatography. Elution with 1:1 EtOAc/hexanes then 1:49:50 NEt_3/EtOAc/hexanes afforded amine 1U as a colourless oil (89 mg, 68 %). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.73 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 1.5 Hz, 1H), 6.66 (dd, *J* = 7.8, 1.6 Hz, 1H), 5.93 (s, 2H), 2.81 (dd, *J* = 13.6, 5.3 Hz, 1H), 2.73–2.63 (m, 2H), 2.35 (dd, *J* = 11.8, 7.0 Hz, 1H), 1.89 (ddd, *J* = 9.0, 7.6, 5.3 Hz, 1H), 0.95–0.84 (m, 1H), 0.75–0.66 (m, 1H), 0.57–0.50 (m, 1H), 0.46–0.37 (m, 3H), 0.20 (m [app. sextet], *J* = 5.0 Hz, 1H), 0.09–0.04 (m, 1H), 0.02–(–0.06) (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 147.6, 146.0, 133.3, 122.4, 109.8, 108.2, 100.9, 65.1, 53.2, 41.7, 16.2, 11.5, 4.8, 3.6, 3.4, 2.4 ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_2^+$ 260.1645; found, 260.1642.

[00147] The free base was converted to the crude hydrochloride and was recrystallised from PhMe as colourless rosettes. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.70 (br s, 1H), 9.57 (br s, 1H), 6.77–6.73 (m, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.93 (d [AB], *J* = 1.4 Hz, 1H), 5.92 (d [AB], *J* = 1.4 Hz, 1H), 3.55 (dd, *J* = 13.4, 4.1 Hz, 1H), 3.11 (dd, *J* = 13.4, 9.9 Hz, 1H), 2.99 (br d, *J* = 6.8 Hz, 2H), 2.64–2.55 (m, 1H), 1.38–1.28 (m, 1H), 1.17–1.06 (m, 1H), 0.69–0.61 (m, 3H), 0.54–0.42 (m, 4H), (–0.15)–(–0.23) (m, 1H) ppm.

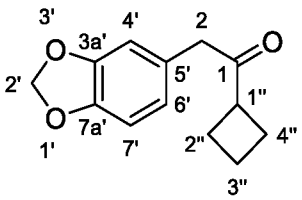
Compounds of type 2

[00148] Compounds of type 2 may be synthesised via the following general procedure 2;



wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 2 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

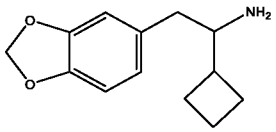
2-(1,3-Benzodioxol-5-yl)-1-cyclobutylethanone ("Ketone K2")



[00149] Following a modified literature procedure[7], to a freshly prepared solution of piperonylcuprate in THF (150 mM, 180 mL) at −70 °C was slowly added a solution of cyclobutanecarbonyl chloride (3.07 g, 25.9 mmol) in THF (5 mL). The reaction mixture was allowed to warm to rt over 2.5 h then quenched by addition of 1 M HCl (40 mL). The mixture was diluted with Et_2O (100 mL) and water (200 mL) then filtered through a Celite pad. The aqueous layer was separated, shaken with further Et_2O (100 mL) and both phases passed through a Celite pad to remove the evolved precipitate. This process was repeated once further. The combined organic extract was washed with water until no more precipitate evolved and then washed with saturated $NaHCO_3$ solution (50 mL), brine (50 mL), dried and evaporated to afford a pale yellow oil. The crude material was purified using flash chromatography (1:10 Et_2O/hexanes) which gave the product as a pale yellow oil (2.79 g, 48%). IR (thin film) $\bar{\nu}_{max}$ (cm^{-1}): 1709 (s, C−O). ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 (d, J = 8.0 Hz, 1H, H7'), 6.67 (d, J = 1.5 Hz, 1H, H4'), 6.62 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.93 (s, 2H, H2'), 3.55–3.53 (m, 2H, H2), 3.33 (dtt [app doublet of quintets], J = 8.5, 8.5, 1.0 Hz, 1H, H1''), 2.27–2.17 (m, 2H), 2.11-2.02

(m, 2H), 1.98–1.87 (m, 1H), 1.84–1.75 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.2 (C1), 147.8 and 146.5 (C3a' and C7a'), 127.9 (C5'), 122.5 (C6'), 109.8 and 108.3 (C4' and C7'), 101.0 (C2'), 47.1 (C1), 44.6 (C1"), 24.5 (C2" and C4"), 17.6 (C3"). HRMS–EI (m/z): M^+ calcd for $C_{13}H_{14}O_3$, 218.0943; found, 218.0948.

2-(benzo[d][1,3]dioxol-5-yl)-1-cyclobutylethan-1-amine (UWA-045, JLK2097, "Compound 2A")

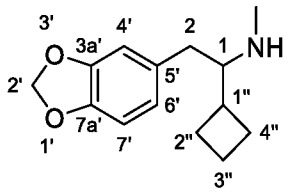


[00150] Compound 2A may be obtained via the following adaptation of the procedure for the preparation of compound 1A using ketone K2 instead of ketone K1.

[00151] To freshly activated 3 Å sieves (ca 150 mg) was added a solution of the ketone K2 (218 mg, 1.00 mmol) in anhydrous THF (2 mL), ammonium acetate (771 mg, 10.0 mmol) and sodium cyanoborohydride (63 mg, 1.00 mmol). The mixture was stirred stoppered at 50 °C for 16 h. The reaction was quenched with conc. HCl, filtered through a pad of Celite with H_2O, basified and extracted with DCM (3 × 50 mL). The extract was washed with H_2O (2 × 50 mL) and brine (50 mL), dried and evaporated, and the residue was subjected to flash chromatography. Elution with 40:60:1 EtOAc/Hex/AcOH followed by 60:40:1 EtOAc/Hex/NEt_3 gave the primary amine **2A** as a pale-yellow oil (87 mg, 40 %). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.74 (d, *J* = 7.9 Hz, 1H, H7'), 6.68 (d, *J* = 1.6 Hz, 1H, H4'), 6.63 (dd, *J* = 7.9, 1.6 Hz, 1H, H6'), 5.92 (s, 2H, H2'), 2.82 (ddd [app. td], $J_1 = J_2 = 8.8$, $J_3 = 3.9$ Hz, 1H, H1), 2.68 (dd, *J* = 13.5, 3.9 Hz, 1H, H2a), 2.25–2.17 (m, 2H), 2.10-1.68 (m, 6H), 0.97 (br. s, 2H, NH_2). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 147.7 and 146.0 (C3a' and C7a'), 133.5 (C5'), 122.3 (C6'), 109.7 (C4'), 108.3 (C7'), 100.9 (C2'), 58.6 (C1), 42.1 (C1"), 41.1 (C2), 25.7, 25.6, 17.8 (C2", C3" and C4"). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_2^+$ 220.1332; found, 220.1330.

[00152] The free base was converted to the crude hydrochloride, which crystallised from DCM/Hex as colourless rhomboids. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.37 (br. s, 3H, NH_3), 6.76 (d, *J* = 1.3 Hz, 1H, H7'), 6.73 (d, *J* = 7.9 Hz, 1H, H4'), 6.69 (dd, *J* = 7.9, 1.3 Hz, 1H, H6'), 5.91 (s, 2H, H2'), 3.42–3.26 (m, 1H, H1), 3.05 (dd, *J* = 14.0, 5.7 Hz, 1H, H2a), 2.79 (dd, *J* = 14.0, 7.9 Hz, 1H, H2b), 2.66–2.52 (m, 1H), 2.22–2.02 (m, 2H), 1.93–1.71 (m, 4H).

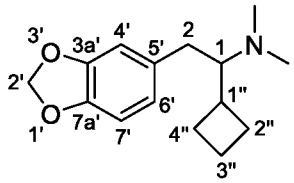
2-(1,3-Benzodioxol-5-yl)-1-cyclobutyl-N-methylethanamine (UWA-038, MNG6050, "Compound 2B")



[00153] Following the general procedure 2, reaction of the ketone K2 (221 mg, 1.02 mmol) with 8.03 M methylamine in EtOH (1.25 ml, 10.0 mmol) and elution with 2:3 EtOAc/hexanes followed by 1:9 MeOH/EtOAc afforded the product as a pale yellow oil (159 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (d, J = 8.0 Hz, 1H, H7'), 6.67 (d, J = 1.5 Hz, 1H, H4'), 6.61 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.93–5.91 (m, 2H, H2'), 2.62 (dd, J = 13.5, 4.5 Hz, 1H, H2a), 2.54 (ddd, J = 9.0, 7.5, 4.5 Hz, 1H, H1), 2.41 (dd, J = 14.0, 7.5 Hz, 1H, H2b), 2.36 (s, 3H, NCH_3), 2.34–2.22 (m, 1H), 2.10–1.68 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 145.8 (C3a' and C7a'), 133.2 (C5'), 122.2 (C6'), 109.6 and 108.1 (C4' and C7'), 100.7 (C2'), 66.4 (C1), 40.2 and 34.5 (NCH_3 and C1''), 36.9 (C2), 27.2, 26.3, 18.2 (C2'', C3'', C4''). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{19}NO_2$, 234.1494; found, 234.1486.

[00154] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as a colourless amorphous powder (mp 165–166 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.5–9.1 (2×br s, 2H, NH_2), 6.78–6.73 (m, 3H, H4'+H6'+H7'), 5.94–5.93 (m [AB system], 2H, H2'), 3.23–3.15 (br m, 1H), 3.12 (dd, J = 14.0, 6.5 Hz, 1H, H2a), 2.83 (dd, J = 14.0, 7.0 Hz, 1H, H2b), 2.78–2.68 (m, 1H), 2.59–2.54 (m [app br t], 3H, NCH_3), 2.29–2.21 (m, 1H), 2.14–2.04 (m, 1H), 1.93–1.82 (m, 2H), 1.81–1.66 (m, 2H). Anal. Calcd for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19. Found: C, 62.35; H, 7.59; N, 5.15.

***2-(1,3-Benzodioxol-5-yl)-1-cyclobutyl*-N,N-*dimethylethan-1-amine* (UWA-016, JLK2094, GAP-070, "Compound 2C")**

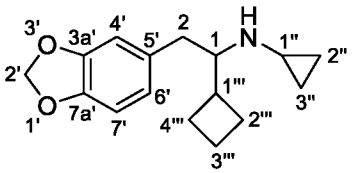


[00155] To freshly activated 3 Å sieves (ca 150 mg) was added a solution of the ketone K2 (109 mg, 0.50 mmol) in anhydrous THF (2 Ml), dimethylamine hydrochloride (408 mg, 5.00 mmol), sodium acetate (411 mg, 5.01 mmol) and sodium cyanoborohydride (32 mg, 0.51 mmol). The mixture was stirred stoppered at 50 °C for 16 h. The reaction was quenched with conc. HCl, filtered through a pad of Celite with H_2O, basified and extracted with DCM (3 × 50 Ml). The extract was washed with H_2O (2 × 50 Ml) and brine (50 Ml), dried and evaporated, and the residue was subjected to flash chromatography. Elution with 40:60:1 EtOAc/Hex/AcOH then 40:60:1 EtOAc/Hex/Net_3 gave the tertiary amine **2C** as a yellow oil (87 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.71–6.66 (m, 2H, H4'/7'), 6.62 (dd, *J* = 7.9, 1.3 Hz, H6'), 5.90 (s, 2H, H2'),

2.69–2.60 (m, 2H, H1/2a), 2.52–2.40 (m, 1H, H1”), 2.37–2.30 (m, 1H, H2b), 2.27 (s, 6H, 2 × CH_3), 2.05–1.94 (m, 1H), 1.89–1.60 (m, 4H), 1.55–1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4 and 145.5 (C3a’ and C7a’), 135.4 (C5’), 122.0 (C6’), 109.6 (C4’), 108.0 (C7’), 100.8 (C2’), 71.7 (C1), 41.2 (CH_3), 39.1 (C1”), 33.3 (C2), 28.6 and 28.4 (C2” and C4”), 18.8 (C3”). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_2^+$ 248.1645; found, 248.1643.

[00156] The free base was converted to the hydrochloride salt and evaporated to leave a pale brown gum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.85 (br. S, 1H, NH), 6.78–6.71 (m, 3H, H4’/6’/7’), 5.94 (s, 2H, H2’), 3.47–3.36 (m, 1H, H1), 3.15 (dd, J = 14.6, 4.8 Hz, 1H, H2a), 2.78 (dd, J = 14.6, 7.1 Hz, 1H, H2b), 2.72 (d, J = 4.4 Hz, 3H, CH_3), 2.68 (d, J = 4.4 Hz, 3H, CH_3), 2.23–2.07 (m, 2H), 1.98–1.79 (m, 3H), 1.78–1.61 (m, 2H).

2-(1,3-Benzodioxol-5-yl)-1-cyclobutylethyl*-N-*cyclopropanamine; *N-(2-(benzo[d][1,3]dioxol-5-yl)-1-cyclobutylethyl)cyclopropanamine; (UWA-054, JLK2045, “Compound 2D”)

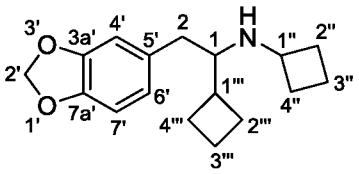


[00157] Following general procedure 2, ketone K2 (220 mg, 1.01 mmol) was reacted with cyclopropylamine (572 Ml, 10.0 mmol). The reaction was quenched with conc. HCl and filtered through a pad of Celite with H_2O. The solution was washed with DCM (3 × 50 Ml), then basified and extracted with EtOAc (3 × 30 Ml). The organic extracts were combined and washed with H_2O (2 × 30 Ml) and brine (30 Ml), then dried and evaporated to give the secondary amine **2D** as a pale brown oil (233 mg, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.73 (d, J = 8.0 Hz, 1H, H7’), 6.69 (d, J = 1.4 Hz, 1H, H4’), 6.62 (dd, J = 7.9, 1.5 Hz, 1H, H6’), 5.93 (s, 2H, H2’), 2.77–2.71 (m, 1H, H1), 2.64 (dd, J = 13.7, 4.7 Hz, 1H, H2a), 2.48 (dd, J = 13.7, 7.6 Hz, 1H, H2b), 2.34–2.24 (m, 1H, H1”), 2.08–1.99 (m, 2H), 1.94–1.86 (m, 1H), 1.86–1.78 (m, 2H), 1.76–1.66 (m, 2H), 0.42–0.38 (m, 2H, H2” or H3”), 0.25–0.21 (m, 2H, H2” or H3”). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6 and 145.9 (C3a” and C7a”), 133.6 (C5’), 122.4 (C6’), 109.8 (C4’), 108.2 (C7’), 100.9 (C2’), 65.4 (C1), 40.6 (C1”), 38.1 (C2), 29.3 (C1”’), 27.3 and 26.3 (C2”’ and C4”’), 18.2 (C3”’), 7.4 and 7.1 (C2” and C3”). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_2^+$ 260.1645; found, 260.1643.

[00158] The free base was converted to the hydrochloride salt, which crystallised from *i*-PrOH/Et_2O as white rosettes. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81–6.75 (m, 2H, H4’/H6’), 6.75–6.70 (m, 1H, H7’), 5.93 (s, 2H, H2’), 3.38–3.25 (m, 2H, H1/2a), 2.92–2.75 (m, 2H, 1”/H2b),

2.37–2.22 (m, 2H), 2.13–2.01 (m, 1H), 1.92–1.79 (m, 2H), 1.77–1.58 (m, 2H), 1.36–1.17 (m, 2H), 0.80–0.70 (m, 2H).

2-(1,3-Benzodioxol-5-yl)-1-cyclobutylethyl*-N-*cyclobutanamine; N-(2-(benzo[d][1,3]dioxol-5-yl)-1-cyclobutylethyl)cyclobutanamine; (UWA-056, JLK2044, "Compound 2E")

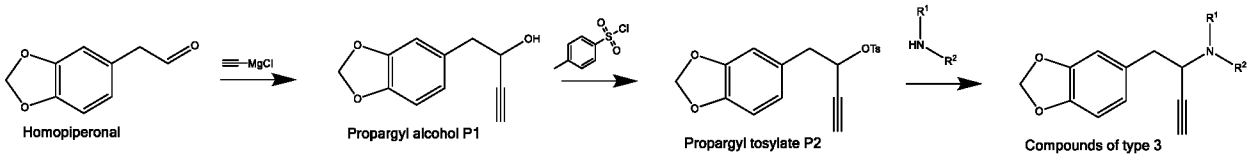


[00159] Following general procedure 2 but using half the excess of amine, ketone K2 (111 mg, 0.51 mmol) was reacted with cyclobutylamine (213 Ml, 2.50 mmol). The reaction was quenched with conc. HCl and filtered through a pad of Celite with H_2O. The solution was washed with DCM (3 × 50 Ml), then basified and extracted with EtOAc (3 × 20 Ml). The organic extracts were combined and washed with H_2O (2 × 20 Ml) and brine (20 Ml), then dried and evaporated to give the secondary amine **2E** as a pale brown oil (109 mg, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, J = 7.9 Hz, 1H, H7'), 6.67 (d, J = 1.1 Hz, 1H, H4'), 6.61 (dd, J = 7.9, 1.1 Hz, 1H, H6'), 5.93 (s, 2H, H2'), 3.30–3.20 (m, 1H, H1''), 2.64–2.54 (m, 2H, H1/H2a), 2.39–2.30 (m, 1H, H2b), 2.29–2.20 (m, 1H, H1'''), 2.20–2.10 (m, 2H, H2'' or H4''), 2.09–1.98 (m, 1H), 1.93–1.64 (m, 5H), 1.61–1.34 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6 and 145.9 (C3a' and C7a'), 133.6 (C5'), 122.3 (C6'), 109.7 (C4'), 108.2 (C7'), 100.9 (C2'), 62.0 (C1), 52.1 (C1''), 40.9 (C1'''), 38.4 (C2), 32.03 and 31.95 (C2'' and C4''), 27.2 and 26.3 (C2''' and C4'''), 18.2 (C3'''), 14.6 (C3''). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{17}H_{24}NO_2^+$ 274.1802; found, 274.1799.

[00160] The product was converted to the hydrochloride salt, which precipitated from *i*-PrOH/Et_2O as white granules. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (br. S, 1H, NH), 9.35 (br. S, 1H, NH), 6.79 (dd, J = 7.9, 1.5 Hz, 1H, H6'), 6.77 (d, J = 1.4 Hz, 1H, H4'), 6.74 (d, J = 7.9 Hz, 1H, H7'), 5.95 (m [AB], 2H, H2'), 3.61–3.48 (m, 1H, H1''), 3.25 (dd, J = 14.5, 6.2 Hz, 1H, H2a), 3.16–3.05 (m, 1H, H1), 2.87–2.71 (m, 2H, H1'''/2b), 2.70–2.57 (m, 1H), 2.56–2.43 (m, 1H), 2.41–2.30 (m, 1H), 2.27–2.16 (m, 2H), 2.07–1.79 (m, 4H), 1.79–1.56 (m, 3H).

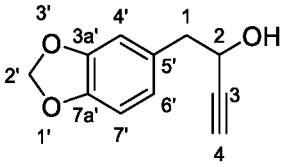
Compounds of type 3

[00161] Compounds of type 3 may be synthesised via the following general procedure 3;



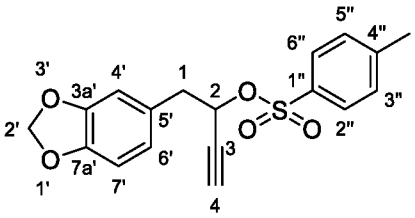
wherein R^1 and R^2 are as defined for the compound of Formula II'.

1-(1,3-Benzodioxol-5-yl)but-3-yn-2-ol ("Propargyl alcohol P1")



[00162] Propargyl alcohol P1 is a known compound previously synthesised by other methods.[8] Following an adapted literature procedure[7], to a stirring solution of 0.5 M ethynylmagnesium chloride in THF (41 Ml, 20 mmol) at 0 °C was added dropwise a solution of freshly prepared homopiperonal[9] (57, 3.34 g, 20.3 mmol) in THF (100 Ml) over 45 min. The resulting solution was stirred at 0 °C for 0.5 h then allowed to warm to rt. The mixture was quenched with saturated NH_4Cl solution (50 Ml) then stirred for a further 5 min. The aqueous layer was separated and extracted with further Et_2O (3×50 Ml). The combined organic extract was washed with water (2×100 Ml), brine (50 Ml), dried and evaporated which gave a crude orange oil. This material was adsorbed onto silica gel and purified by flash chromatography (1:9 EtOAc/hexanes followed by 1:4 EtOAc/hexanes) to afford a yellow oil (2.96 g, 76%). The characterisation data was consistent with that found in the literature.[8]

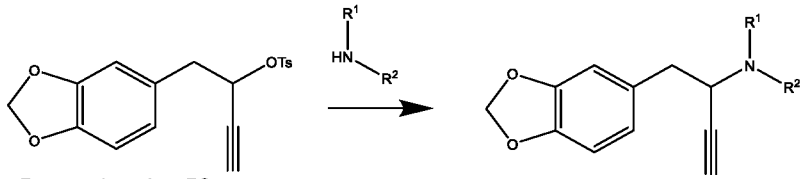
1-(1,3-Benzodioxol-5-yl)but-3-yn-2-yl 4-methylbenzenesulfonate ("Propargyl tosylate P2")



[00163] Following an adapted literature procedure[10], to a stirred solution of the propargyl alcohol P1 (2.96 g, 15.6 mmol), Net_3 (4.35 Ml, 31.2 mmol), 4-(dimethylamino)pyridine (95 mg, 0.78 mmol) in anhydrous CH_2Cl_2 (50 Ml) at 0 °C was added tosyl chloride (3.06 g, 16.1 mmol). The reaction mixture was stirred at rt under a $CaCl_2$ guard tube for 1 h. The reaction mixture was washed with 1 M HCl (2×20 Ml), saturated $NaHCO_3$ solution (10 Ml), water (10 Ml), brine (10 Ml), dried and evaporated to give a white solid, which discoloured pink upon standing overnight. The crude material was triturated with hexanes. The liquid was separated and allowed to cool affording the desired product as white crystals (4.07 g, 76%). A sample was recrystallised from CH_2Cl_2/hexanes as a white amorphous solid: mp 71–72 °C. IR (dry film) $\tilde{\nu}_{max}$ (cm^{-1}): 3290 (s, C≡C–H), 2125 (w, C≡CH), 1363 (vs, SO_2), 1176 (vs, SO_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.71–7.66 (m, 2H, H2" and H6"), 7.28–7.23 (m, 2H, H3" and H5"), 6.69–6.66 (m, 1H), 6.63–6.59 (m, 2H), 5.93–5.91 (m [AB system], 2H, H2'), 5.10 (ddd [app dt], J = 6.8,

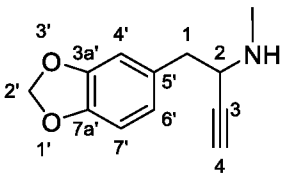
6.8, 2.2 Hz, 1H, H2), 3.03 (dd, J = 14.0, 7.0 Hz, 1H, H1a), 2.99 (dd, J = 14.0, 6.6 Hz, 1H, H1b), 2.47 (d, J = 2.2 Hz, 1H, H4), 2.42 (s, 3H, $ArCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 146.8, 144.8(C3a', C7a', C1"), 133.5 (C5'), 129.6 (C3"+C5"), 128.1 (C4"), 128.0 (C2"+C6"), 123.0 (C6'), 110.0 and 108.2 (C4' and C7'), 101.0 (C2'), 78.7 (C3), 76.9 (C4), 71.4 (C2), 41.7 (C1), 21.6 (CH_3). HRMS–EI (m/z): M^+ calcd for $C_{18}H_{16}O_5S$, 344.0718; found, 344.0720. Anal. Calcd for $C_{18}H_{16}O_5S$: C, 62.78; H, 4.68; N, 0.00. Found: C, 62.67; H, 4.60; N, 0.02.

General method for the final step of general procedure 3



[00164] The propargyl tosylate P2 (0.90–1.00 mmol) is dissolved in the appropriate amine (3–20 eq.) and stirred overnight under N_2 at rt. The reaction is poured onto 1M NaOH (20 Ml) and extracted with EtOAc (3×20 Ml). The combined organic extract is dried, evaporated and purified by RSF chromatography to afford the desired product.

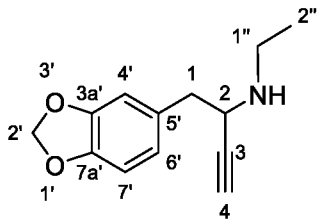
1-(1,3-Benzodioxol-5-yl)-N-methylbut-3-yn-2-amine (UWA-017, MNG016, "Compound 3A")



[00165] To a solution of the propargyl tosylate P2 (517 mg, 1.50 mmol) in dry THF (10 mL) was added a solution of 8.03 M methylamine in EtOH (3.74 mL, 30.0 mmol) and the solution was stirred overnight under N_2 at rt. The following day TLC analysis revealed that only partial conversion had been effected so the reaction was heated at reflux for 3 h. The reaction was worked up and purified as per the general procedure 3. Elution with 2:3 EtOAc/hexanes followed by EtOAc gave the desired amine as a yellow oil (213 mg, 70%). IR (thin film) $\bar{\nu}$ max (cm^{-1}): 3289 (s, C≡C–H). ^1H NMR (500 MHz, $CDCl_3$): δ 6.79 (d, J = 1.5 Hz, 1H, H4'), 6.74 (d, J = 8.0 Hz, 1H, H7'), 6.72 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.93 (s, 2H, H2'), 3.50 (ddd [app dt], J = 6.5, 6.5, 2.0 Hz, 1H, H2), 2.91–2.82 (m [AB part of ABX system], 2H, H1a+H1b), 2.48 (s, 3H, NCH_3), 2.31 (d, J = 2.5 Hz, 2H, H4). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4 and 146.3 (C3a' and C7a'), 131.1 (C5'), 122.6 (C6'), 109.9 and 108.1 (C4' and C7'), 100.8 (C2'), 84.4 (C3), 72.5 (C4), 53.0 (C2), 41.4 (C1), 33.9 (NCH_3). HRMS–ESI (m/z): $[M+H]^+$calcd for $C_{12}H_{12}NO_2$, 204.1025; found, 204.1021.

[00166] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as a colourless amorphous powder (mp 184–189 °C). ^{1}H NMR (500 MHz, D2O): δ 6.93 (d, J = 1.5 Hz, 1H, H4'), 6.90 (d, J = 7.5 Hz, 1H, H7'), 6.87 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.98 (s, 2H, H2'), 4.33 (ddd, J = 8.5, 6.0, 2.0 Hz, 1H, H2), 3.17 (dd, J = 14.0, 6.0 Hz, 1H, H1a), 3.15–3.08 (m [app dd+d], 2H, H1b +H4), 2.83 (s, 3H, NCH3). Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; N, 5.84. Found: C, 60.01; H, 5.75; N, 5.69.

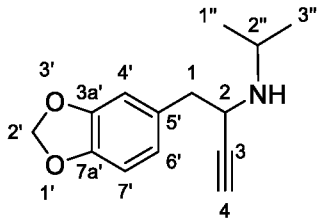
1-(1,3-Benzodioxol-5-yl)-N-ethylbut-3-yn-2-amine (UWA-024, MNG5130, "Compound 3B")



[00167] The propargyl tosylate P2 (344 mg, 1.00 mmol) was dissolved in a solution of 2.0 M ethylamine in MeOH (10.0 mL, 20.0 mmol) and the solution was stirred under N_2 at rt for 7 d. The reaction was worked up as per the general procedure 3 using 2:3 EtOAc/hexanes followed by EtOAc for chromatography to give the desired amine as a yellow oil (174 mg, 80%). IR (thin film) $\bar{\nu}$ max (cm^{-1}): 3290 (s, C≡C–H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (d, J = 2.0 Hz, 1H, H4'), 6.75 (d, J = 8.0 Hz, 1H, H7'), 6.73 (dd, J = 8.0, 2.0 Hz, 1H, H6'), 5.95–5.93 (m, 2H, H2'), 2.39 (ddd, J = 7.0, 6.0, 2.0 Hz, 1H, H2), 2.95–2.88 (m, 2H, H1a+H1a"), 2.84 (dd, J = 13.5, 7.0 Hz, 1H, H1b), 2.62 (dq, J = 11.5, 7.0 Hz, 1H, H1b "), 2.29 (d, J = 2.5 Hz, 1H, H4), 1.10 (t, J = 7.5 Hz, 3H, H2"). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 146.3 (C3a' and C7a'), 131.2 (C5'), 122.6 (C6'), 109.9 and 108.1 (C4' and C7'), 100.9 (C2'), 84.8 (C3), 72.3 (C4), 51.2 (C2), 41.63 and 41.60 (C1 and C1"), 15.0 (C2"). HRMS–EI (m/z): M^+ calcd for $C_{13}H_{15}NO_2$, 217.1103; found, 217.1098.

[00168] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as a colourless amorphous powder (mp 203–206 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.1 (br s, 2H, NH2), 6.83 (d, J = 1.5 Hz, 1H, H4'), 6.80 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 6.73 (d, J = 8.0 Hz, 1H, H7'), 5.94–5.92 (m [AB system], 2H, H2'), 4.02–3.97 (m [app dq], 1H, H2), 3.59 (dd, J = 8.0, 3.5 Hz, 1H, H1a), 3.38 (dq, J = 12.5, 7.0 Hz, 1H, H1a"), 3.23–3.0 (m, 2H, H1b +H1b "), 2.59 (d, J = 1.5 Hz, 1H, H4), 1.52 (t, J = 7.0 Hz, 3H, H2"). Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.36; N, 5.52. Found: C, 61.40; H, 6.61; N, 5.44.

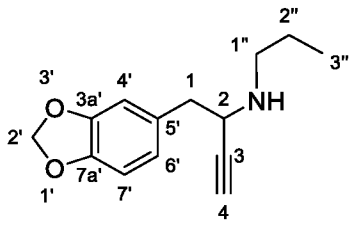
1-(1,3-Benzodioxol-5-yl)-N-(propan-2-yl)but-3-yn-2-amine (UWA-026, MNG5136, "Compound 3C")



[00169] Following the general procedure 3, reaction of the propargyl tosylate P2 (343 mg, 1.00 mmol) with isopropylamine (1.64 mL, 19.3 mmol) and elution with 1:19 EtOAc/hexanes followed by 1:5 EtOAc/hexanes afforded the product as a dark tan oil (197 mg, 86%). IR (thin film) $\tilde{\nu}_{max}$ (cm^{-1}): 3290 (s, C≡C–H). ^1H NMR (500 MHz, $CDCl_3$): δ 6.83–6.81 (m, 1H), 6.77–6.72 (m, 2H), 5.95–5.92 (m, 2H, H2'), 3.67 (ddd, J = 8.0, 5.5, 2.0 Hz, 1H, H2), 3.16 (septet, J = 6.0 Hz, 1H, H2''), 2.93 (dd, J = 13.5, 5.5 Hz, 1H, H1a), 2.81 (dd, J = 13.5, 8.0 Hz, 1H, H1b), 2.29 (d, J = 2.0 Hz, 1H, H4), 1.97 (br s, NH+H_2O), 1.10 (d, J = 6.5 Hz, 3H, H1''), 1.01 (d, J = 6.0 Hz, 3H, H3''). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4 and 146.4 (C3a' and C7a'), 130.9 (C5'), 122.7 (C6'), 110.0 and 108.1 (C4' and C7'), 100.9 (C2'), 84.2 (C3), 72.8 (C4), 48.7 and 46.2 (C2 and C2''), 41.6 (C1), 23.7 and 21.2 (C1'' and C3''). HRMS–EI (m/z): M^+ calcd for $C_{14}H_{17}NO_2$, 231.1259; found, 231.1264.

[00170] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as a colourless amorphous powder (mp 197–199 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 10.22 (br s, 1H, NHa), 9.81 (br s, 1H, NHb), 6.84 (d, J = 1.5 Hz, 1H, H4'), 6.80 (dd, J = 8.0, 2.0 Hz, 1H, H6'), 6.73 (d, J = 7.5 Hz, 1H, H7'), 5.94–5.92 (m [AB system], 2H, C2'), 4.05–3.98 (m, 1H, H2), 3.81–3.71 (m, 1H, H2''), 3.66 (dd, J = 12.5, 3.5 Hz, 1H, $H1_a$), 3.33 (dd [app t], J = 12.0, 12.0 Hz, 1H, $H1_b$), 2.57 (d, J = 2.0 Hz, 1H, H4), 1.64 (d, J = 6.5 Hz, 3H, H1''), 1.43 (d, J = 6.5 Hz, 3H, H3''). Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.62; H, 7.00; N, 5.17.

1-(1,3-Benzodioxol-5-yl)-N-propylbut-3-yn-2-amine (UWA-025, MNG5134, "Compound 3D")

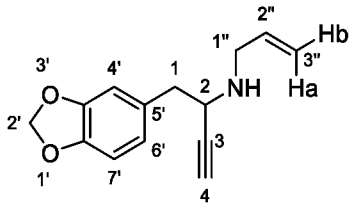


[00171] Following the general procedure 3, reaction of the propargyl tosylate P2 (344 mg, 1.00 mmol) with n-propylamine (1.64 Ml, 19.9 mmol) and elution with 2:3 EtOAc/hexanes afforded the product as a dark tan oil (181 mg, 85%). IR (thin film) $\tilde{\nu}_{max}$ (cm^{-1}): 3292 (s, C≡C–H). ^1H NMR (600 MHz, $CDCl_3$): δ 6.79 (d, J = 1.8 Hz, 1H, H4'), 6.74 (d, J = 7.8 Hz, 1H, H7'), 6.71 (dd, J = 7.8, 1.8 Hz, 1H, H6'), 5.92 (s, 2H, H2'), 3.58–3.54 (m, 1H, H2), 2.81 (dd, J = 13.2, 6.0 Hz, 1H, H1a), 2.85–2.77 (m [app dd+ddd], 2H,

H1b and H1a"), 2.55 (ddd, J = 10.8, 8.4, 6.0 Hz, 1H, H1b"), 2.29 (d, J = 2.4 Hz, 1H, H4), 1.55–1.35 (m, 3H, H2"+NH+H_2O), 0.89 (t, J = 7.2 Hz, 3H, H3"). ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.4 and 146.3 (C3a' and C7a'), 131.2 (C5'), 122.6 (C6'), 109.9 and 108.0 (C4' and C7'), 100.8 (C2'), 84.2 (C3), 72.2 (C4), 51.3 (C2), 49.2 and 41.5 (C1 and C1"), 23.0 (C2"), 11.7 (C3"). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{17}NO_2$, 232.1338; found, 232.1334.

[00172] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol/Et_2O as a colourless amorphous powder (mp 171–173 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 10.05 (br s, 2H, NH_2), 6.83 (d, J = 1.5 Hz, 1H, H4'), 6.80 (dd, J = 8.0, 2.0 Hz, 1H, H6'), 6.73 (d, J = 8.0 Hz, 1H, H7'), 5.94–5.92 (m [AB system], 2H, H2'), 4.02 (ddd, J = 11.0, 3.5, 2.0 Hz, 1H, H2), 3.61 (dd, J = 13.0, 3.5 Hz, 1H, H1a), 3.24–3.14 (m [app ddd+dd], 2H, H1b+H1a"), 3.03 (ddd, J = 12.0, 9.0, 7.0 Hz, 1H, H1b"), 2.59 (d, J = 2.5 Hz, 1H, H4), 2.04–1.93 (m, 2H, H2"), 1.03 (t, J = 7.5 Hz, 1H, H3"). Anal. Calcd for $C_{14}H_{18}ClNO_2$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.83; H, 6.95; N, 5.15.

1-(1,3-Benzodioxol-5-yl)-N-(prop-2-en-1-yl)but-3-yn-2-amine (UWA-028, "Compound 3E")

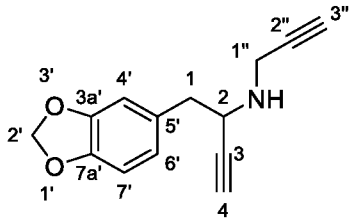


[00173] Following the general procedure 3, reaction of the propargyl tosylate P2 (310 mg, 0.90 mmol) with allylamine (675 µL, 9.00 mmol) and elution with 1:5 EtOAc/hexanes followed by 2:3 EtOAc/hexanes afforded the product as a pale yellow oil (174 mg, 84%). IR (thin film) $\tilde{\nu}_{max}$ (cm^{-1}): 3292 (s, C≡C–H) 1643 (w, HC-CH_2). ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (d, J = 1.5 Hz, 1H, H4'), 6.75 (d, J = 8.0 Hz, 1H, H7'), 6.73 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.94–5.92 (m, 2H, H2'), 5.87 (dddd, J = 17.0, 10.5, 6.5, 5.5 Hz, 1H, H2"), 5.18 (dddd, J = 17.0, 1.5, 1.5, 1.5 Hz, 1H, H3a"), 5.08 (dddd, J = 10.5, 1.5, 1.5, 1.5 Hz, 1H, H3b"), 3.60 (ddd, J = 7.0, 6.0, 2.0 Hz, 1H, H2), 3.47 (dddd, J = 14.0, 5.5, 1.5, 1.5 Hz, 1H, H1a"), 3.26 (dddd, J = 14.0, 6.5, 1.5, 1.5 Hz, 1H, H1b"), 2.90 (dd, J = 13.5, 6.0 Hz, 1H, H1a), 2.85 (dd, J = 13.5, 7.0 Hz, 1H, H1b), 2.31 (d, J = 2.5 Hz, 1H, H4), 1.6 (br s, NH+H_2O). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5 and 146.3 (C3a' and C7a'), 136.1 (C2"), 131.0 (C5'), 122.6 (C6'), 116.4 (C3"), 109.9 and 108.1 (C4' and C7'), 100.8 (C2'), 84.5 (C3), 72.6 (C4), 50.5 (C2), 49.8 and 41.6 (C1 and C1"). HRMS–EI (m/z): M^+ calcd for $C_{14}H_{15}NO_2$, 229.1103; found, 229.1104.

[00174] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as colourless rods (mp 183–185 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 10.3 (br s, 2H, NH_2), 6.83 (d, J = 2.0 Hz, 1H, H4'), 6.79 (dd, J = 8.0, 2.0 Hz, 1H, H6'), 6.74 (d, J = 8.0 Hz, 1H, H7'), 6.14 (dddd, J = 17.0, 10.0, 8.5, 6.0 Hz, 1H, H2"), 5.94–5.92 (m [AB system], 2H, H2'), 5.59–5.54 (m, 1H, H3a"), 5.49–5.45 (m,

1H, H3b"), 3.99 (ddd, J = 11.0, 4.0, 2.0 Hz, 1H, H2), 3.95–3.89 (m [app dd], 1H, H1a"), 3.72 (dd, J = 13.5, 8.5 Hz, 1H, H1b"), 3.56 (dd, J = 13.0, 4.0 Hz, 1H, H1a), 3.21 (dd, J = 13.0, 11.0 Hz, 1H, H1b), 2.62 (d, J = 2.0 Hz, 1H, H4). Anal. Calcd for $C_{14}H_{16}ClNO_2$: C, 63.28; H, 6.07; N, 5.27. Found: C, 63.21; H, 6.30; N, 5.23.

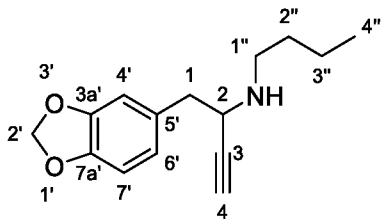
1-(1,3-Benzodioxol-5-yl)-N-(prop-2-yn-1-yl)but-3-yn-2-amine (UWA-029, MNG5152, "Compound 3F")



[00175] Following the general procedure 3, reaction of the propargyl tosylate P2 (220 mg, 0.658 mmol) with propargylamine (421 µL, 0.657 mmol) and elution with 1:5 EtOAc/hexanes afforded the product as a pale yellow oil (118 mg, 79%). IR (thin film) $\tilde{\nu}_{max}$ (cm^{-1}): 3288 (s, C≡C–H). ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (d, J = 1.5 Hz, 1H, H4'), 6.75 (d, J = 8.0 Hz, 1H, H7'), 6.73 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.94 (s, 2H, H2'), 3.81 (ddd [app dt], J = 7.0, 7.0, 2.0 Hz, 1H, H2), 3.60 (dd, J = 17.0, 2.5 Hz, 1H, H1a"), 3.53 (dd, J = 16.5, 2.0 Hz, 1H, $H1_b$"), 2.94–2.86 (m [AB part of ABX system], 2H, H1a+H1b), 2.32 (d, J = 2.0 Hz, 1H, H4), 2.21(dd [app t], J = 2.5, 2.5 Hz, 1H, H3"). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6 and 146.5 (C3a' and C7a'), 130.6 (C5'), 122.6 (C6'), 109.8 and 108.2 (C4' and C7'), 100.9 (C2'), 83.5 and 81.3 (C3 and C2"), 73.0 and 71.7 (C4 and C3"), 49.8 (C2), 41.3 and 36.0 (C1 and C1"). HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{13}NO_2$, 228.1025; found, 228.1029.

[00176] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as colourless needles (mp 190–191 °C). ^1H NMR (500 MHz, D2O): δ 6.95 (d, J = 1.0 Hz, 1H, H4'), 6.92 (d, J = 7.5 Hz, 1H, H7'), 6.88 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 6.00 (s, 2H, H2'), 4.53 (ddd, J = 8.0, 6.0, 2.5 Hz, 1H, H2), 4.15 (dd, J = 16.5, 2.5 Hz, 1H, H1a"), 4.08 (dd, J = 16.5, 2.5 Hz, 1H, H1b"), 3.22 (dd, J = 14.0, 6.0 Hz, 1H, H1a), 3.18–3.11 (m [app d+dd], 2H, H4+H1b"), 3.03 (t, J = 2.5 Hz, 1H, H3"). Anal. Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.83; H, 5.56; N, 5.22.

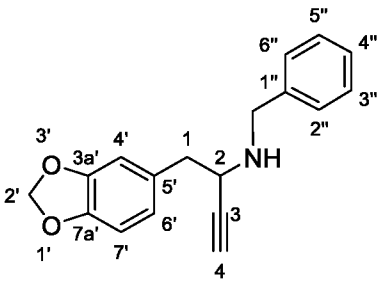
1-(1,3-Benzodioxol-5-yl)-N-butylbut-3-yn-2-amine (UWA-027, MNG5146, "Compound 3G")



[00177] Following the general procedure 3, reaction of the propargyl tosylate P2 (310 mg, 0.900 mmol) with n- butylamine (889 µL, 9.00 mmol) and elution with 1:5 EtOAc/hexanes followed by 2:3 EtOAc/hexanes afforded the product as a pale brown oil (183 mg, 84%). IR (thin film) $\tilde{\nu}_{max}$ (cm^{-1}): 3292 (s, C≡C–H). ^1H NMR (500 MHz, $CDCl_3$): δ 6.78 (d, J = 1.5 Hz, 1H, H4'), 6.73 (d, J = 8.0 Hz, 1H, H7'), 6.70 (dd, J = 8.0, 1.5 Hz, 1H, H6''), 5.91 (s, 2H, H2'), 3.56–3.52 (m, 1H, H2), 2.88 (dd, J = 13.5, 6.0 Hz, 1H, H1a), 2.85–2.78 (m, 2H, H1b+H1a''), 2.53 (ddd, J = 11.0, 9.0, 5.5 Hz, 1H, H1b''), 2.29 (d, J = 2.0 Hz, 1H, H4), 1.6–1.0 (m, 5H, NH+H2''+H3''), 0.87 (t, J = 7.5 Hz, 3H, H4''). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.2 and 16.1 (C3a' and C7a'), 130.8 (C5'), 122.5 (C6'), 109.8 and 108.0 (C4' and C7'), 100.7 (C2'), 84.5 (C3), 72.4 (C4), 51.2 (C2), 47.0, 41.3, 31.8, 20.3 (C1, C1'', C2'', C3''), 13.9 (C4''). HRMS–EI (m/z): M^+ calcd for $C_{15}H_{19}NO_2$, 245.1416; found, 245.1427.

[00178] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as colourless rods (mp 166–168 °C). ^1H NMR (500 MHz, $CDCl_3$): δ 10.6–9.5 (2×br s, 2H, NH_2), 6.83 (d, J = 1.5 Hz, 1H, H4'), 6.80 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 6.73 (d, J = 8.0 Hz, 1H, H7'), 5.95–5.92 (m [AB system], 2H, H2'), 4.04–3.95 (m [app dt], 1H, H2), 3.63 (dd, J = 13.0, 3.5 Hz, 1H, H1a), 3.28–3.15 (m [app m+dd], 2H, H1b+H1a''), 3.09–3.01 (m, 1H, H1b''), 2.59 (d, J = 2.5 Hz, 1H, H4), 2.00–1.87 (m, 2H, H2''), 1.50–1.36 (m, 2H, H3''), 0.92 (t, J = 7.5 Hz, 3H, H4''). Anal. Calcd for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 63.75; H, 7.34; N, 4.86.

1-(1,3-Benzodioxol-5-yl)-N-benzylbut-3-yn-2-amine (UWA-087, "Compound 3H")



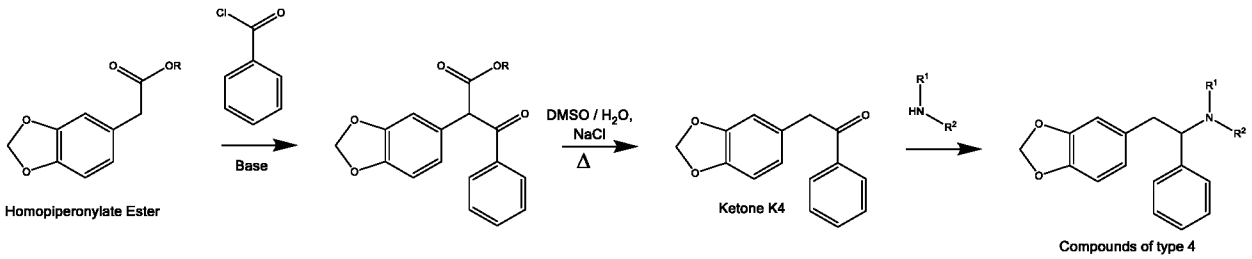
[00179] Following the general procedure 3, reaction of the propargyl tosylate P2 (310 mg, 0.900 mmol) with benzylamine (2.56 mL, 2.44 mmol) and elution with 1:5 EtOAc/hexanes followed by 2:3 EtOAc/hexanes afforded the product as a pale yellow oil which solidified upon standing (202 mg, 80%). IR (thin film) $\tilde{\nu}_{max}$ (cm^{-1}): 3288 (s, C≡C–H). ^1H NMR (500 MHz, $CDCl_3$): δ 7.36–7.23 (m, 5H, H2'', H3'', H4'', H5'', H6''), 6.80 (d, J = 1.5 Hz, 1H, H4'), 6.76 (d, J = 8.0 Hz, 1H, H7'), 6.73 (dd, J = 8.0, 1.5 Hz, 1H, H6'), 5.94–5.93 (m, 2H, H2'), 4.04 (d, J = 13.0 Hz, 1H, NCHaH), 3.83 (d, J = 13.0 Hz, 1H, NCHHb), 3.59 (ddd, J = 7.0, 6.5, 2.0 Hz, 1H, H2), 2.92 (dd, J = 13.5, 6.5 Hz, 1H, H1a), 2.89 (dd, J = 13.5, 7.0 Hz, 1H, H1b), 2.38 (d, J = 2.5 Hz, 1H, H4), 1.48 (br s, NH+H_2O). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.4 and 146.3 (C3a' and C7a'), 139.7 (C1''), 131.1 (C5'), 128.3 and 128.2 (C2''+C6'' and C3''+C5''), 127.0

(C4"), 122.6 (C6'), 109.9 and 108.0 (C4' and C7'), 100.8 (C2'), 84.6 (C3), 72.6 (C4), 51.1 (NCH_2), 50.4 (C2), 41.5 (C1). HRMS–EI (m/z): M^+ calcd for $C_{18}H_{17}NO_2$, 279.1259; found, 279.1273.

[00180] The free base was converted to the crude hydrochloride and was recrystallised from 2-propanol as a colourless amorphous powder (mp 196–199 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.5 (br s, 2H, NH_2), 7.67–7.62 (m [app d], 2H, H2"+H6"), 7.38–7.32 (m [app t], 2H, H3"+H5"), 7.28–7.23 (m, 1H, H4"), 6.76–6.69 (m, 3H, H4', H6', H7'), 5.93–5.91 (m [AB system], 2H, H2'), 4.26 (d, J = 13.0 Hz, 1H, NCHaH), 4.13 (d, J = 13.0 Hz, 1H, NCHHb), 3.73 (ddd, J = 11.5, 4.0, 2.0 Hz, 1H, H2), 3.39 (dd, J = 13.0, 4.0 Hz, 1H, $H1_a$), 3.08 (dd, J = 13.0, 11.0 Hz, 1H, $H1_b$), 2.68 (d, J = 2.5 Hz, 1H, H4). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.12; H, 5.58; N, 4.30.

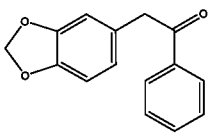
Compounds of type 4

[00181] Compounds of type 4 may be synthesised via the following general procedure 4;



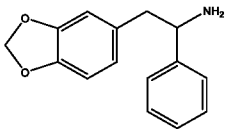
[00182] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 4 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethan-1-one ("Ketone K4")



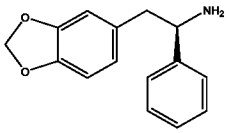
[00183] Ketone K4 is a known compound, also obtainable by the previously reported method.[4]

2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethan-1-amine (UWA-074, "Compound 4A")

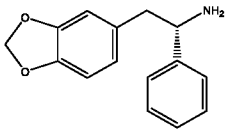


[00184] Compound 4A is a known compound, also obtainable by the previously published method.[2 – page 78]

(R)-2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethan-1-amine ("Compound 4AR") and (S)-2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethan-1-amine ("Compound 4AS")



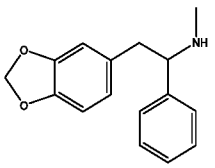
4AR



4AS

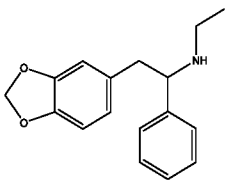
[00185] Compounds 4AR and 4AS are obtainable via crystallization of diastereomeric tartrate salts of compound 4A or via chiral column chromatography.

2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-phenylethan-1-amine (UWA-001, "Compound 4B")



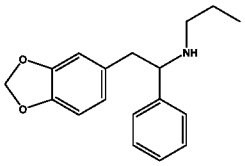
[00186] Compound 4B is a known compound, also obtainable by the previously published method.[4]

2-(benzo[d][1,3]dioxol-5-yl)-N-ethyl-1-phenylethan-1-amine (UWA-066, "Compound 4C")



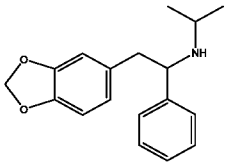
[00187] Compound 4C is a known compound, also obtainable by the previously published method.[2 – page 78]

N-(2-(3a,4-dihydrobenzo[d][1,3]dioxol-5-yl)-1-phenylethyl)propan-1-amine (UWA-068, "Compound 4D")



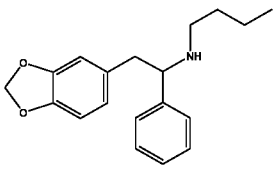
[00188] Compound 4D is a known compound, also obtainable by the previously published method. [2 – page 79]

N-(2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethyl)propan-2-amine (UWA-065, "Compound 4E")



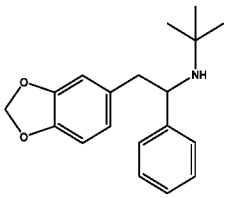
[00189] Compound 4E is a known compound, also obtainable by the previously published method. [2 – page 81]

N-(2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethyl)butan-1-amine (UWA-064, "Compound 4F")



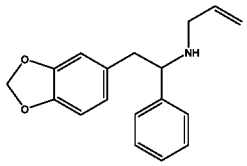
[00190] Compound 4F is a known compound, also obtainable by the previously published method. [2 – page 80]

N-(2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethyl)-2-methylpropan-2-amine ("Compound 4G")



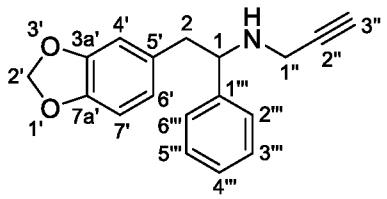
[00191] Compound 4G is a known compound, also obtainable by the previously published method.[2]

N-(2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethyl)prop-2-en-1-amine (UWA-069, "Compound 4H")



[00192] Compound 4H is a known compound, also obtainable by the previously published method.[2 – page 82]

N-(2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethyl)prop-2-yn-1-amine (UWA-070, "Compound 4I")

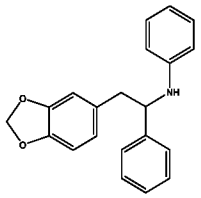


[00193] Following the general procedure 4, reaction of the ketone K4 (144 mg, 0.60 mmol) with propargylamine (384 µL, 6.00 mmol) and elution with 20:80:1 EtOAc/Hex/NEt_3 afforded the secondary amine **4I** as a colourless gum (138 mg, 82 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.23 (m, 5H, Ph), 6.71 (d, J = 7.8 Hz, 1H, H7'), 6.68 (d, J = 1.6 Hz, 1H, H4'), 6.61 (dd, J = 7.9, 1.6 Hz, 1H, H6'), 5.92 (s, 2H, H2'), 4.06 (dd, J = 8.7, 5.5 Hz, 1H, H1), 3.31 (dd, J = 17.2, 2.5 Hz, 1H, H1"a), 3.05 (dd, J = 17.2, 2.4 Hz, 1H, H1"b), 2.90 (dd, J = 13.7, 5.4 Hz, 1H, H2a), 2.79 (dd, J = 13.7, 8.7 Hz, 1H, H2b), 2.17 (t, J = 2.4 Hz, 1H, H3"). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8 and 146.3 (C3a' and C7a'), 142.5 (C1'"), 132.2 (C5'), 128.6 (C3'"/5'"), 127.6 (C2'"/6'"), 127.5 (C4'"), 122.4 (C6'), 109.5 (C4'), 108.3 (C7'), 101.0 (C2'), 82.1 (C2"), 71.5 (C3"), 62.6 (C1), 44.7 (C2), 35.9 (C1"). HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{18}H_{18}NO_2^+$ 280.1332; found, 280.1331.

[00194] The free base was converted to the crude hydrochloride and recrystallised from 2-propanol/Et_2O as colourless rhomboids. ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.99 (br. s, 2H, NH_2), 7.46–7.34 (m, 5H, Ph), 6.73 (d, J = 7.9 Hz, 1H, H7'), 6.60 (d, J = 1.6 Hz, 1H, H4'), 6.47 (dd, J = 7.9, 1.6 Hz, 1H, H6'), 5.93 (s, 2H, H2'), 4.51–4.37 (m, 1H, H1), 3.76–3.61 (m, 2H, H1"), 3.46–3.36 (m, 2H, H2), 3.06 (t, J = 11.8 Hz, 1H, H3").

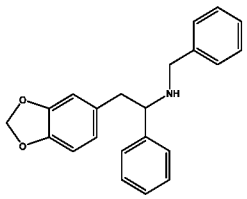
[00195] Compound 4I is a known compound, also obtainable by the previously published method.[2 – page 83]

N-(2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethyl)aniline (UWA-067, "Compound 4J")

[00196] 

[00197] Compound 4J is a known compound, also obtainable by the previously published method.[2 – page 85]

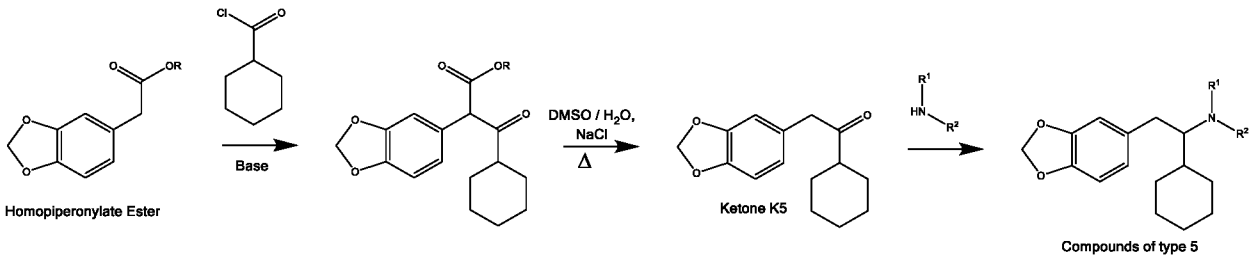
2-(benzo[d][1,3]dioxol-5-yl)-N-benzyl-1-phenylethan-1-amine (UWA-063, "Compound 4K")

[00198] 

[00199] Compound 4K is a known compound, also obtainable by the previously published method.[2 – page 84]

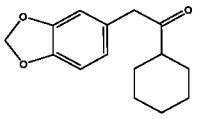
Compounds of type 5

[00200] Compounds of type 5 may be synthesised via the following general procedure 5;



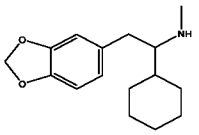
[00201] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 5 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-cyclohexylethan-1-one ("Ketone K5")



[00202] Ketone K5 is a known compound, also obtainable by the previously published method.[4]

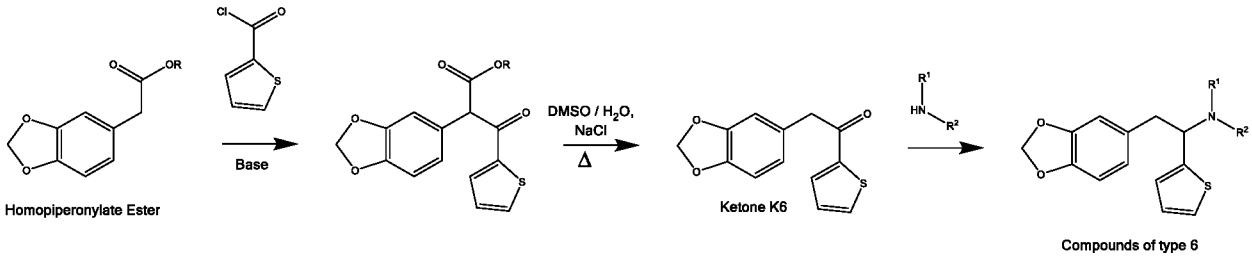
2-(benzo[d][1,3]dioxol-5-yl)-1-cyclohexyl-N-methylethan-1-amine (UWA-079, "Compound 5A")



[00203] Compound 5A is a known compound, also obtainable by the previously published method.[4]

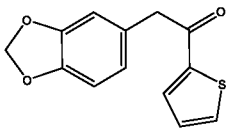
Compounds of type 6

[00204] Compounds of type 6 may be synthesised via the following general procedure 6;



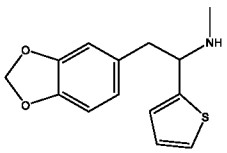
[00205] wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 6 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(thiophen-2-yl)ethan-1-one ("Ketone K6")



[00206] Ketone K6 is a known compound, also obtainable by the previously published method. [2 – page 44]

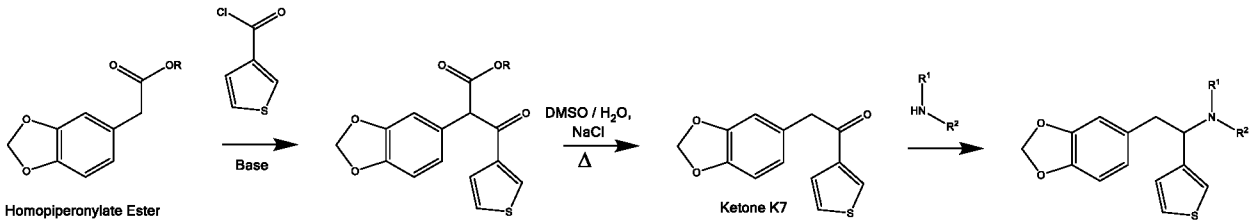
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(thiophen-2-yl)ethan-1-amine (UWA-059, "Compound 6A")



[00207] Compound 6A is a known compound, also obtainable by the previously published method.[2 – page 49]

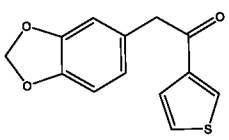
Compounds of type 7

[00208] Compounds of type 7 may be synthesised via the following general procedure 7;



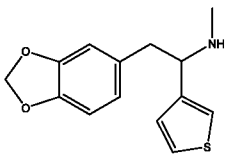
[00209] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 7 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(thiophen-3-yl)ethan-1-one ("Ketone K7")



[00210] Ketone K7 is a known compound, also obtainable by the previously published method. [2 – pages 44 and 45]

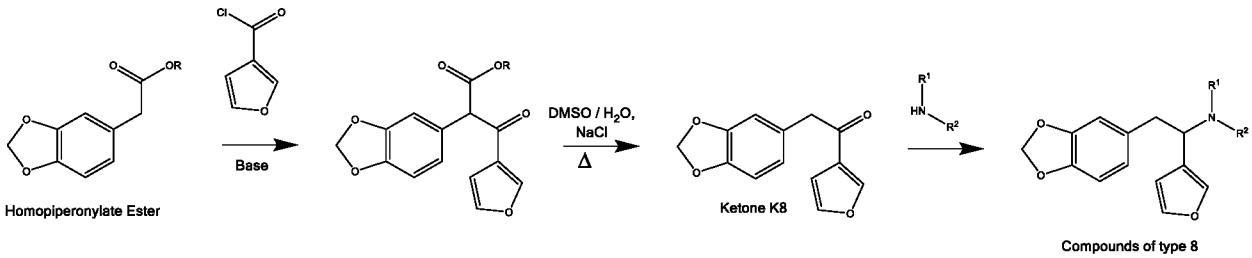
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(thiophen-3-yl)ethan-1-amine ("Compound 7A")



[00211] Compound 7A is a known compound, also obtainable by the previously published method.[2 – pages 49 and 50]

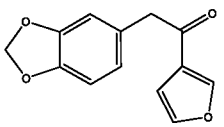
Compounds of type 8

[00212] Compounds of type 8 may be synthesised via the following general procedure 8;



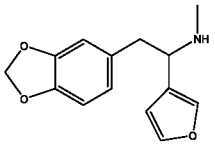
[00213] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 8 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(furan-3-yl)ethan-1-one ("Ketone K8")



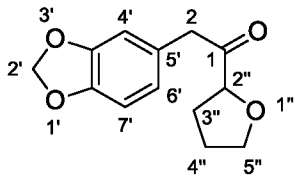
[00214] Ketone K8 is a known compound, also obtainable by the previously published method. [2 – page 44]

2-(benzo[d][1,3]dioxol-5-yl)-1-(furan-3-yl)-N-methylethan-1-amine (UWA-071, "Compound 8A")



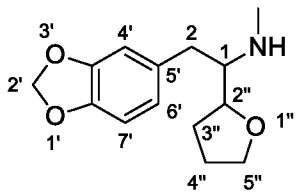
[00215] Compound 8A is a known compound, also obtainable by the previously published method.[2 – page 50]

2-(Benzo[d][1,3]dioxol-5-yl)-1-(tetrahydrofuran-2-yl)ethanone ("Ketone K8TH")



[00216] A solution of 1.0 M LiHMDS in THF (12.4 mL, 12.4 mmol) was added to a stirred solution of methyl homopiperonylate (2.32 g, 12.0 mmol) in anhydrous THF (15 mL) at –78 °C under N_2. The reaction solution was stirred at –78 °C for 1.5 h before being treated with methyl tetrahydrofuran-2-carboxylate (1.04 g, 8.01 mmol) added dropwise. The resulting solution was gradually warmed to room temperature overnight, quenched with half-saturated NH_4Cl (60 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The extract was washed with brine (30 mL), dried and evaporated and the crude residue subjected to flash chromatography. Gradient elution with 1:19 EtOAc/hexanes → 1:4 EtOAc/hexanes afforded partially purified β-ketoester as a yellow oil (1.45 g), which was dissolved in 8:8:1 water/AcOH/H_2SO_4 (17 mL). The resulting solution was stirred under reflux for 1.5 h, cooled to room temperature, diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine (50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:19 EtOAc/hexanes → 3:17 EtOAc/hexanes afforded the ketone K8TH as a pale yellow oil (436 mg, 23%).^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, J = 7.9 Hz, 1H, H7′), 6.71 (d, J = 1.5 Hz, 1H, H4′), 6.65 (dd, J = 7.9, 1.6 Hz, 1H, H6′), 5.94 (s, 2H, H2′), 4.39 (dd, J = 8.0, 5.9 Hz, 1H, H2″), 3.97–3.87 (m, 2H, H5″), 3.80 (d [AB], J = 15.8 Hz, 1H, H2), 3.74 (d [AB], J = 15.8 Hz, 1H, H2), 2.20–2.10 (m, 1H, H3″), 1.97–1.78 (m, 3H, H3″ & H4″) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 147.9, 146.7, 127.4, 122.9, 110.2, 108.5, 101.1, 83.1, 69.5, 45.1, 29.3, 25.8 ppm.

2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(tetrahydrofuran-2-yl)ethanamine (UWA-106, GAP-058, "Compound 8ATH")

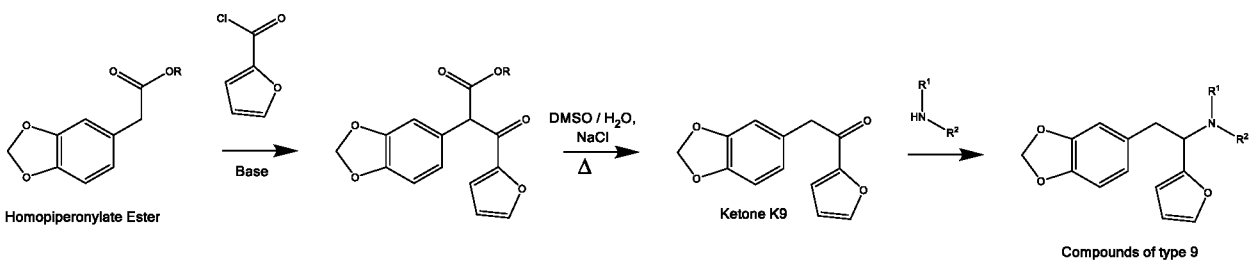


[00217] An 8.03 M solution of methylamine in EtOH (0.71 mL, 5.7 mmol) and AcOH (0.36 mL, 6.3 mmol) were added successively to a cold (0°C), stirred mixture of ketone K8TH (124 mg, 0.529 mmol) and 3A sieves (156 mg) in 2:1 THF/MeOH (3.0 mL). Sodium cyanoborohydride (41 mg, 0.65 mmol) was added and the reaction vessel was flushed with N_2, sealed and stirred at 50 °C for 48 h before being cooled to room temperature and quenched with 1 M HCl (15 mL). The resulting mixture was vacuum filtered through a pad of Celite, washing through with MeOH (3 × 25 mL). The filtrate was concentrated under reduced pressure and the residue was basified with 1 M NaOH (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The extract was washed with brine (30 mL), dried and evaporated, and the residue was subjected to flash chromatography. Gradient elution with 1:1 EtOAc/hexanes → 1:24:25 NEt_3/EtOAc/hexanes afforded amine 8ATH as a colourless oil (110 mg, 83 %) as a 1:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75–6.71 (m, 2H), 6.68–6.63 (m, 1H), 5.93 (s, 2H), 3.91–3.80 (m, 1H), 3.79–3.66 (m, 2H), 2.83–2.71 (m, 1H), 2.69–2.57 (m, 2H), 2.42 and 2.41 (s, 3H, NCH_3), 1.92–1.78 (m, 3H), 1.90–1.85 and 1.66–1.58 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.7, 146.04, 146.00, 133.4, 132.9, 122.34, 122.29, 109.8, 109.7, 108.31, 108.27, 101.0, 80.7, 80.5, 68.3, 68.1 65.1, 64.0, 36.63, 36.57, 35.1, 34.6, 28.5, 26.7, 26.3, 26.2 ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_3^+$ 250.1438; found, 250.1434.

[00218] The free base was converted to the crude hydrochloride and was recrystallised from PhMe as a 5*:4# mixture of diastereomers as colourless granules. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (br s, 1H)*, 9.48 (br s, 1H)#, 9.19 (br s, 1H)#, 8.52 (br s, 1H)*, 6.80–6.69 (m, 3H), 5.95 (s, 2H)*, 5.94 (s, 2H)#, 4.16–4.05 (m, 1H), 4.02–3.92 (m, 1H), 3.79–3.70 (m, 1H), 3.51–3.43 (m, 1H)*, 3.35–3.27 (m, 1H), 3.20 (br m, 1H)#, 2.95–2.89 (m, 1H), 2.72 (br s, 3H), 2.13–2.05 (m, 1H), 2.05–2.00 (m, 1H)*, 1.96–1.86 (m, 2H), 1.60–1.49 (m, 1H)# ppm.

Compounds of type 9

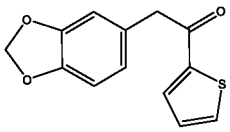
[00219] Compounds of type 9 may be synthesised via the following general procedure 9;



[00220] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will

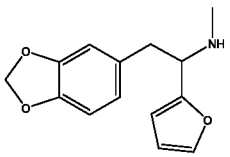
understand that the acid chloride precursor utilized in general procedure 9 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(furan-2-yl)ethan-1-one ("Ketone K9")



[00221] Ketone K9 is a known compound, also obtainable by the previously published method. [2 – page 43]

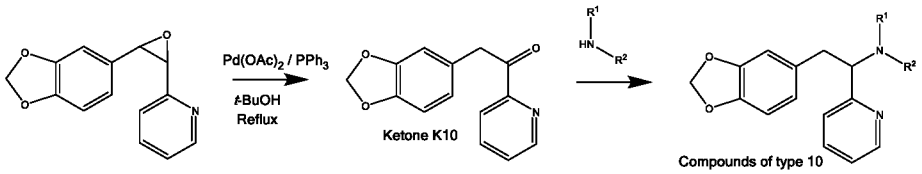
2-(benzo[d][1,3]dioxol-5-yl)-1-(furan-2-yl)-N-methylethan-1-amine ("Compound 9A")



[00222] Compound 9A is a known compound, also obtainable by the previously published method.[2 – page 51]

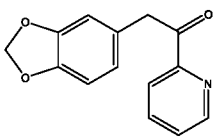
Compounds of type 10

[00223] Compounds of type 10 may be synthesised via the following general procedure 10;



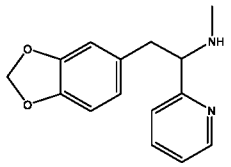
[00224] wherein R^1 and R^2 are as defined for the compound of Formula II'.

2-(benzo[d][1,3]dioxol-5-yl)-1-(pyridin-2-yl)ethan-1-one ("Ketone K10")



[00225] Ketone K10 is a known compound, obtained by the previously published method in accordance with general procedure 10. [17 – page 49]

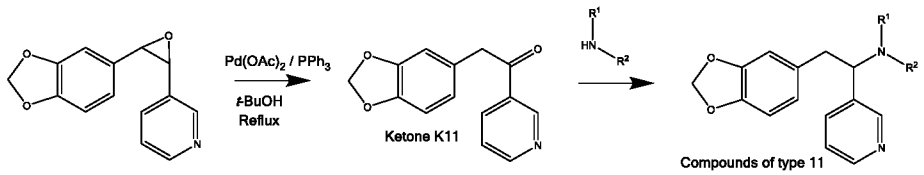
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(pyridin-2-yl)ethan-1-amine ("Compound 10A")



Compound 10A is a known compound, obtained by the previously published method in accordance with general procedure 10. [17 – page 59]

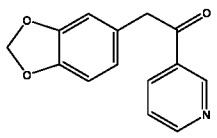
Compounds of type 11

[00226] Compounds of type 11 may be synthesised via the following general procedure 11;



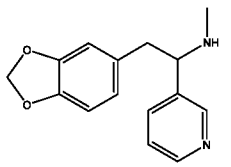
[00227] wherein R^1 and R^2 are as defined for the compound of Formula II'.

2-(benzo[d][1,3]dioxol-5-yl)-1-(pyridin-3-yl)ethan-1-one ("Ketone K11")



[00228] Ketone K11 is a known compound, obtained by the previously published method, in accordance with general procedure 11. [17 – page 49]

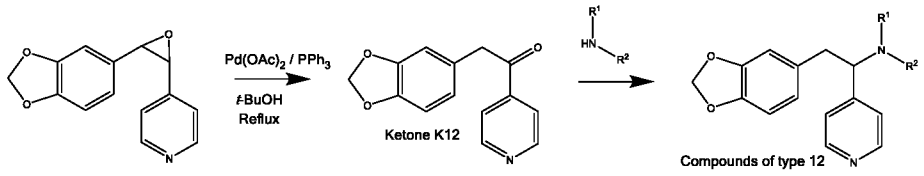
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(pyridin-3-yl)ethan-1-amine ("Compound 11A")



[00229] Compound 11A is a known compound, obtained by the previously published method in accordance with general procedure 11. [17 – page 60]

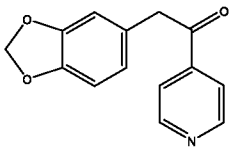
Compounds of type 12

[00230] Compounds of type 12 may be synthesised via the following general procedure 12;



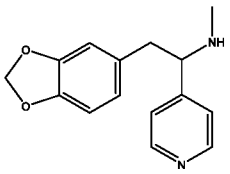
wherein R^1 and R^2 are as defined for the compound of Formula II'.

2-(benzo[d][1,3]dioxol-5-yl)-1-(pyridin-4-yl)ethan-1-one ("Ketone K12")



[00231] Ketone K12 is a known compound, obtained by the previously published method, in accordance with general procedure 12. [17 – page 50]

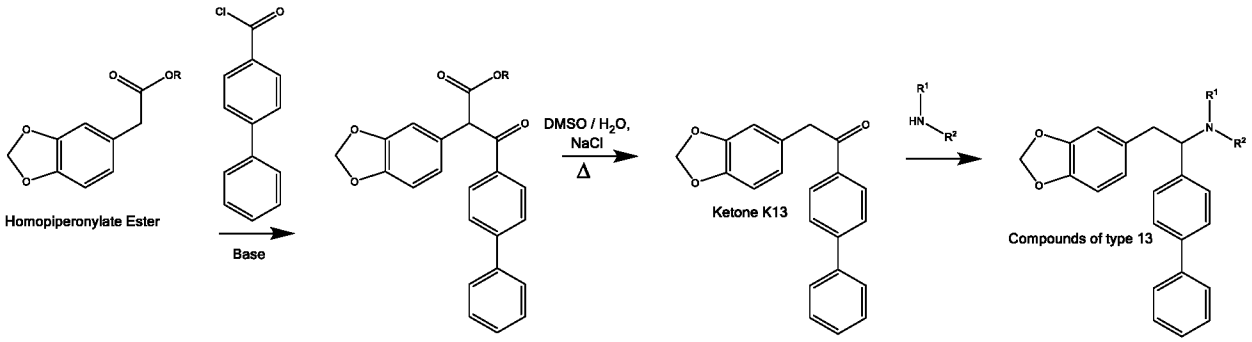
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(pyridin-4-yl)ethan-1-amine ("Compound 12A")



[00232] Compound 12A is a known compound, obtained by the previously published method in accordance with general procedure 12. [17 – page 61]

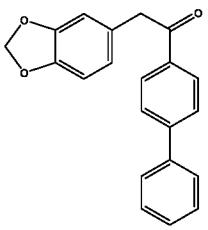
Compounds of type 13

[00233] Compounds of type 13 may be synthesised via the following general procedure 13;



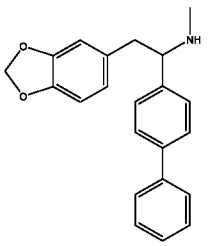
wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 13 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

1-([1,1'-biphenyl]-4-yl)-2-(benzo[d][1,3]dioxol-5-yl)ethan-1-one ("Ketone K13")



[00234] Ketone K13 is a known compound, also obtainable by the previously published method. [4]

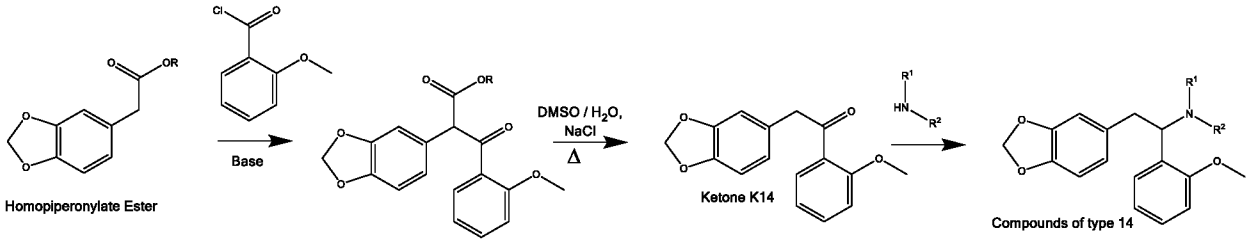
1-([1,1'-biphenyl]-4-yl)-2-(benzo[d][1,3]dioxol-5-yl)-N-methylethan-1-amine ("Compound 13A")



[00235] Compound 13A is a known compound, also obtainable by the previously published method.[4]

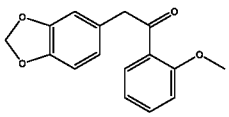
Compounds of type 14

[00236] Compounds of type 14 may be synthesised via the following general procedure 14;



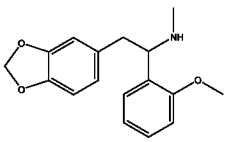
[00237] wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 14 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(2-methoxyphenyl)ethan-1-one ("Ketone K14")



[00238] Ketone K14 is a known compound, also obtainable by the previously published method. [4]

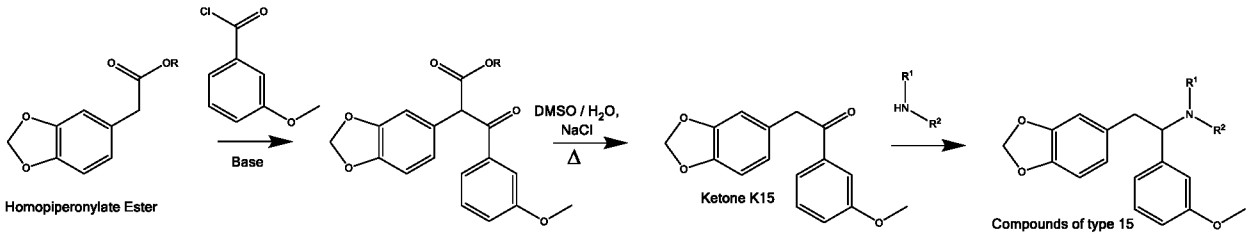
2-(benzo[d][1,3]dioxol-5-yl)-1-(2-methoxyphenyl)-N-methylethan-1-amine ("Compound 14A")



[00239] Compound 14A is a known compound, also obtainable by the previously published method.[4]

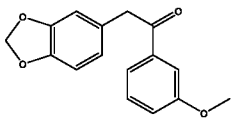
Compounds of type 15

[00240] Compounds of type 15 may be synthesised via the following general procedure 15;



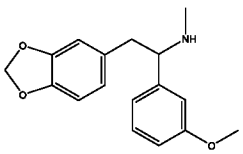
[00241] wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 15 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(3-methoxyphenyl)ethan-1-one ("Ketone K15")



[00242] Ketone K15 is a known compound, also obtainable by the previously published method. [4]

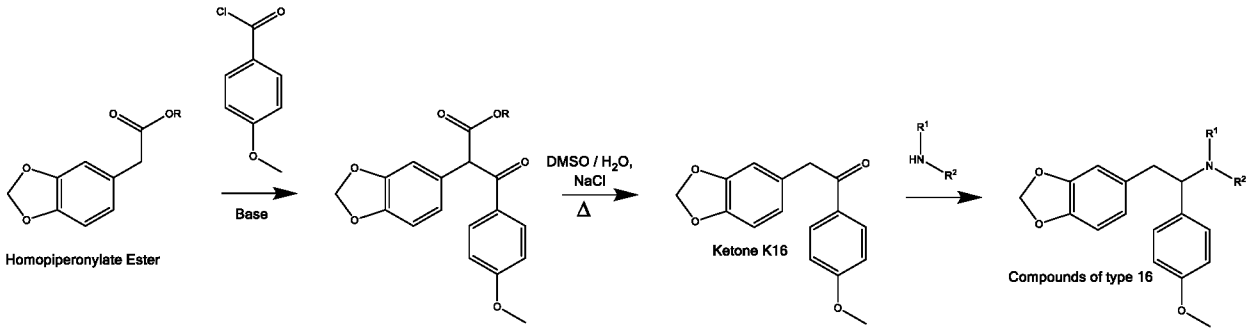
2-(benzo[d][1,3]dioxol-5-yl)-1-(3-methoxyphenyl)-N-methylethan-1-amine ("Compound 15A")



[00243] Compound 15A is a known compound, also obtainable by the previously published method.[4]

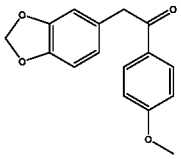
Compounds of type 16

[00244] Compounds of type 16 may be synthesised via the following general procedure 16;



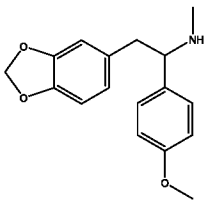
[00245] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 16 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)ethan-1-one ("Ketone K16")



[00246] Ketone K16 is a known compound, also obtainable by the previously published method. [4]

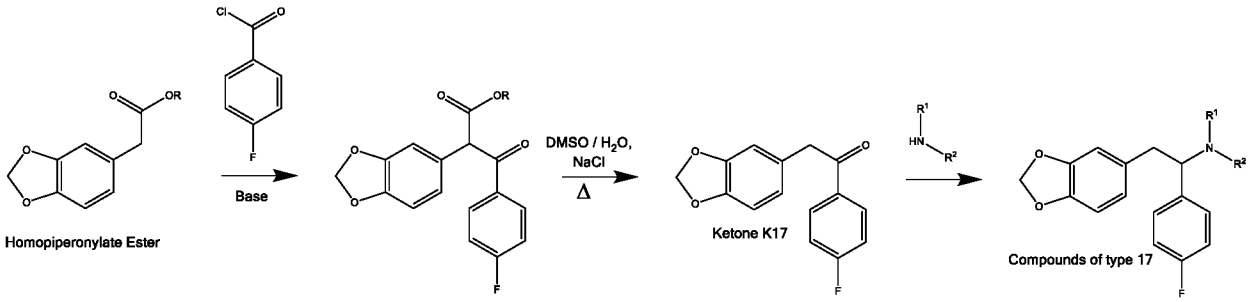
2-(benzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)-N-methylethan-1-amine ("Compound 16A")



[00247] Compound 16A is a known compound, also obtainable by the previously published method.[4]

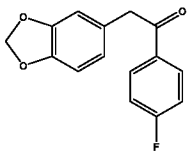
Compounds of type 17

[00248] Compounds of type 17 may be synthesised via the following general procedure 17;



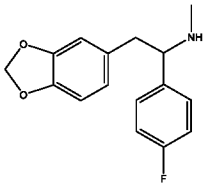
[00249] wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 17 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(4-fluorophenyl)ethan-1-one ("Ketone K17")



[00250] Ketone K17 is a known compound, also obtainable by the previously published method. [4]

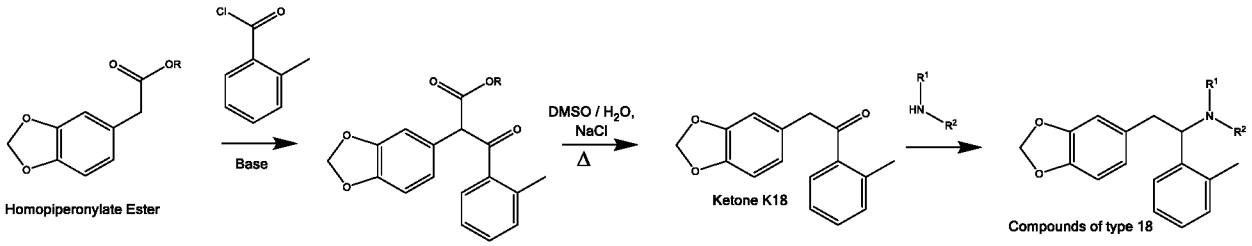
2-(benzo[d][1,3]dioxol-5-yl)-1-(4-fluorophenyl)-N-methylethan-1-amine (UWA-076, "Compound 17A")



[00251] Compound 17A is a known compound, also obtainable by the previously published method.[4]

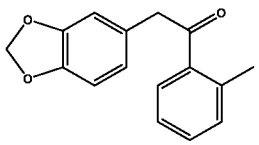
Compounds of type 18

[00252] Compounds of type 18 may be synthesised via the following general procedure 18;



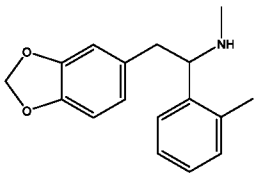
[00253] wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 18 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(o-tolyl)ethan-1-one ("Ketone K18")



[00254] Ketone K18 is a known compound, also obtainable by the previously published method. [4]

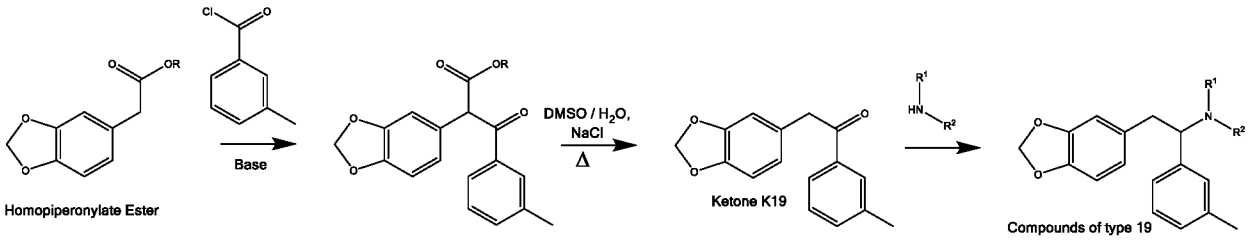
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(o-tolyl)ethan-1-amine ("Compound 18A")



[00255] Compound 18A is a known compound, also obtainable by the previously published method.[4]

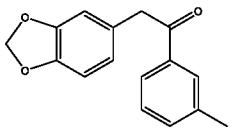
Compounds of type 19

[00256] Compounds of type 19 may be synthesised via the following general procedure 19;



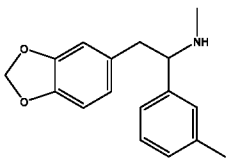
[00257] wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 19 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(m-tolyl)ethan-1-one ("Ketone K19")



[00258] Ketone K19 is a known compound, also obtainable by the previously published method. [4]

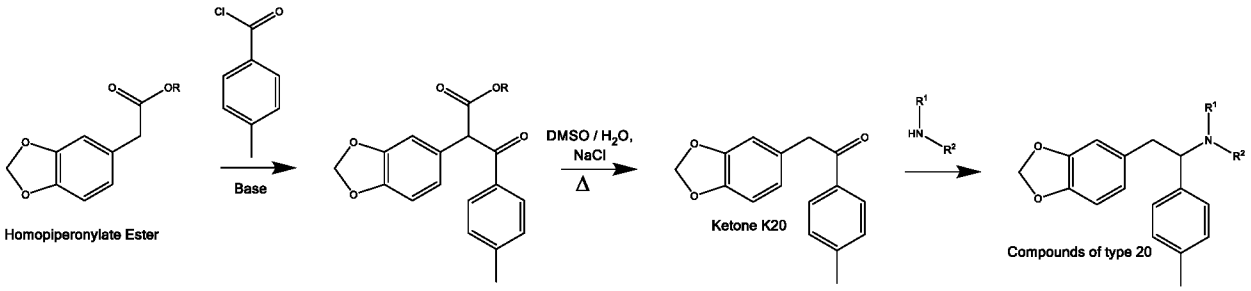
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(m-tolyl)ethan-1-amine ("Compound 19A")



[00259] Compound 19A is a known compound, also obtainable by the previously published method.[4]

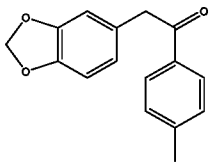
Compounds of type 20

[00260] Compounds of type 20 may be synthesised via the following general procedure 20;



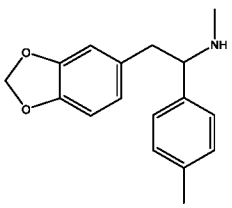
[00261] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 20 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(p-tolyl)ethan-1-one ("Ketone K20")



[00262] Ketone K20 is a known compound, also obtainable by the previously published method. [4]

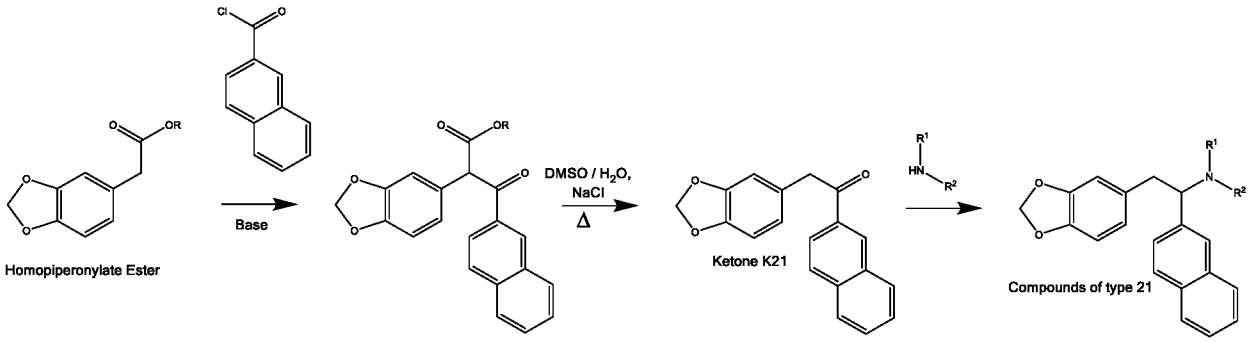
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(p-tolyl)ethan-1-amine ("Compound 20A")



[00263] Compound 20A is a known compound, also obtainable by the previously published method.[4]

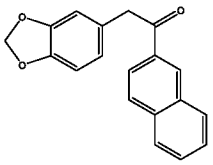
Compounds of type 21

[00264] Compounds of type 21 may be synthesised via the following general procedure 21;



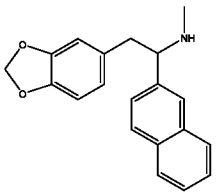
[00265] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 21 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(naphthalen-2-yl)ethan-1-one ("Ketone K21")



[00266] Ketone K21 is a known compound, also obtainable by the previously published method. [4]

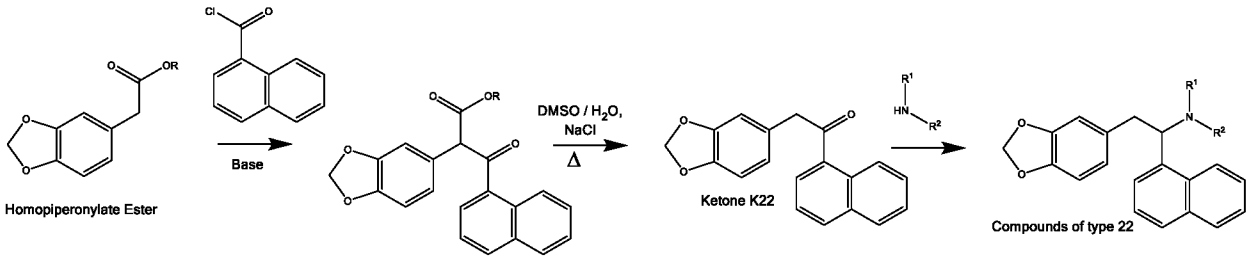
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(naphthalen-2-yl)ethan-1-amine ("Compound 21A")



[00267] Compound 21A is a known compound, also obtainable by the previously published method.[4]

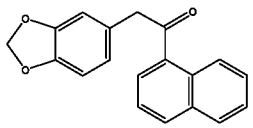
Compounds of type 22

[00268] Compounds of type 22 may be synthesised via the following general procedure 22;



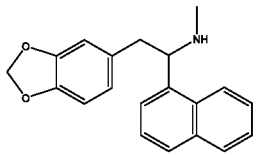
[00269] wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedure 22 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride.

2-(benzo[d][1,3]dioxol-5-yl)-1-(naphthalen-1-yl)ethan-1-one ("Ketone K22")



[00270] Ketone K22 is a known compound, also obtainable by the previously published method. [4]

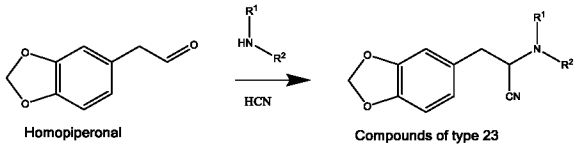
2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(naphthalen-1-yl)ethan-1-amine ("Compound 22A")



[00271] Compound 22A is a known compound, also obtainable by the previously published method.[4]

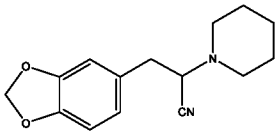
Compounds of type 23

[00272] Compounds of type 23 may be synthesised from homopiperonal via partial Strecker synthesis as previously reported,[18] by following general procedure 23;



[00273] wherein R^1 and R^2 are as defined for the compound of Formula II'.

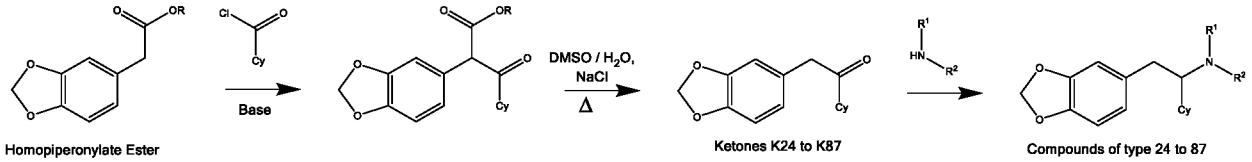
3-(benzo[d][1,3]dioxol-5-yl)-2-(piperidin-1-yl)propanenitrile ("Compound 23A")



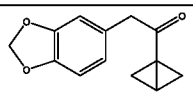
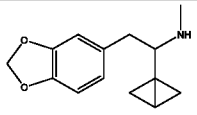
[00274] Compound 23A may be obtained via an adaptation of the previously published method using homopiperonal instead of 2-phenylacetaldehyde as starting material in accordance with general procedure 23.[18]

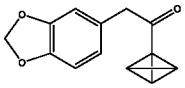
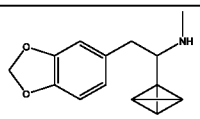
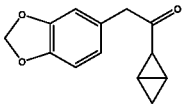
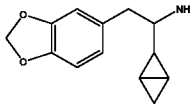
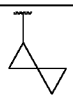
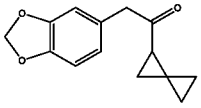
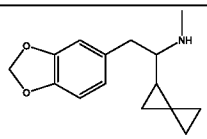
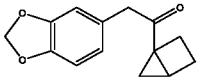
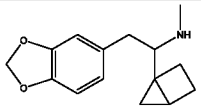
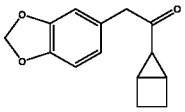
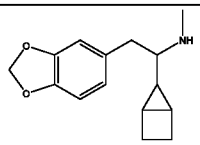
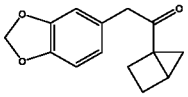
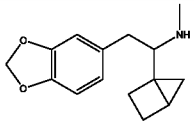
Compounds of type 24 to 87

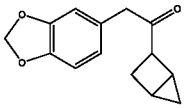
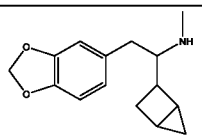
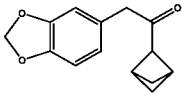
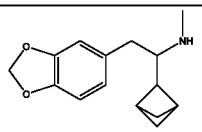
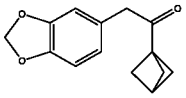
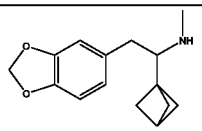
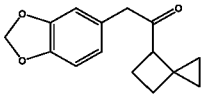
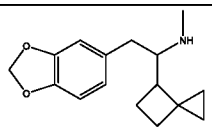
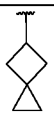
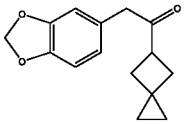
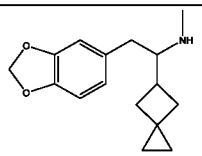
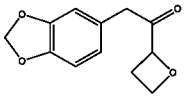
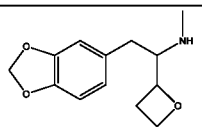
[00275] Compounds of type 24 to 87 may be synthesised via the following general procedures 24 to 87;

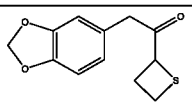
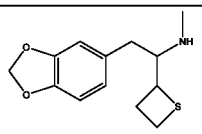
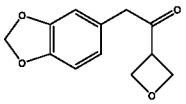
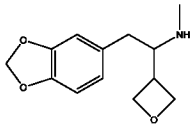
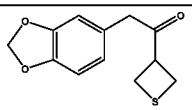
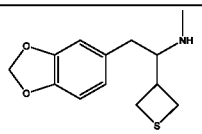
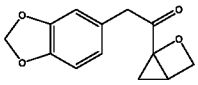
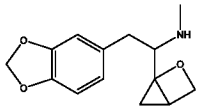
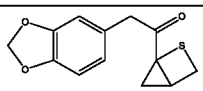
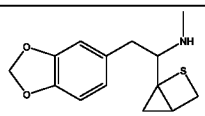
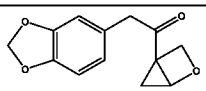
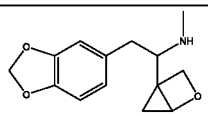


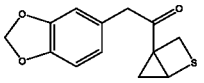
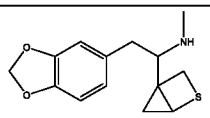
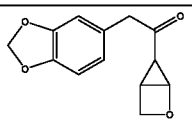
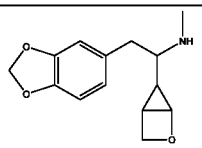
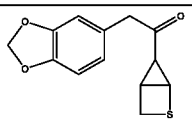
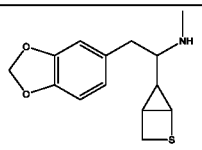
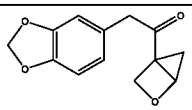
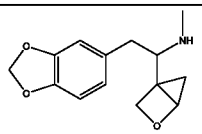
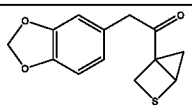
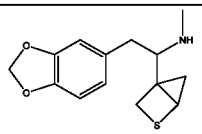
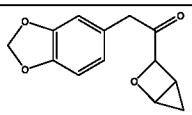
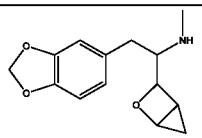
[00276] wherein R is selected from the group consisting of; methyl, ethyl, and -$C_{3\text{-}9}$alkyl, and R^1 and R^2 are as defined for the compound of Formula II'. The skilled addressee will understand that the acid chloride precursor utilized in general procedures 24 to 87 may be interchanged with a corresponding acid anhydride precursor or mixed acid anhydride precursor. The skilled addressee will also understand that the sodium chloride utilized in the Krapcho decarboxylation step may be substituted with an alternative source of chloride ions, such as lithium chloride, or potassium chloride. The substituent "Cy" in general procedures 24 to 87 may be selected from the group consisting of Cy24 to Cy87, and thereby produce ketones K24 to K87 and corresponding compounds of type 24 to 87, examples of which are compounds 24A to 87A, produced by reductive amination of ketones K24 to K87 with methylamine, as summarized in the following table;

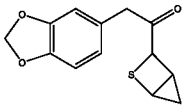
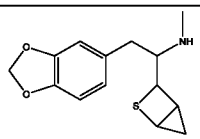
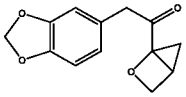
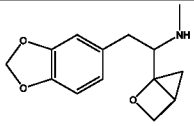
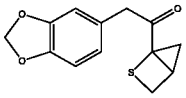
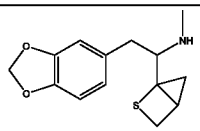
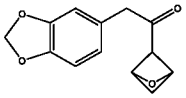
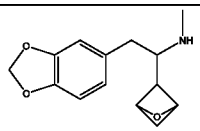
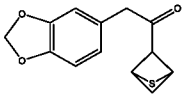
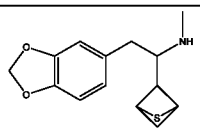
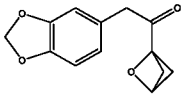
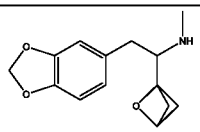
Cy	Ketone	Exemplary compound
Cy24 	K24  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[1.1.0]butan-1-yl)ethan-1-one	24A  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[1.1.0]butan-1-yl)-N-methylethan-1-amine

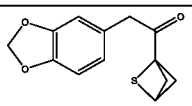
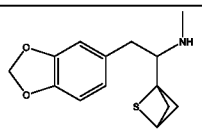
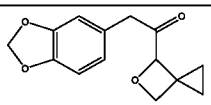
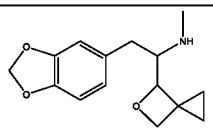
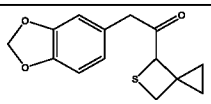
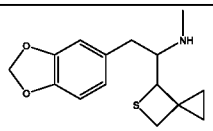
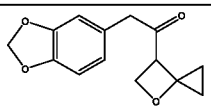
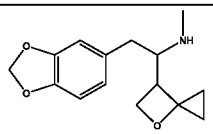
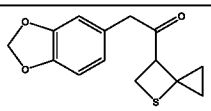
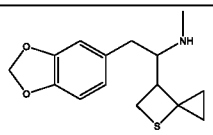
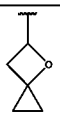
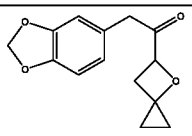
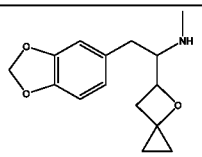
Cy	Ketone	Exemplary compound
Cy25 	K25  2-(benzo[d][1,3]dioxol-5-yl)-1-(tricyclo[1.1.0.02,4]butan-1-yl)ethan-1-one	25A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(tricyclo[1.1.0.02,4]butan-1-yl)ethan-1-amine
Cy26 	K26  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[1.1.0]butan-2-yl)ethan-1-one	26A  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[1.1.0]butan-2-yl)-N-methylethan-1-amine
Cy27 	K27  2-(benzo[d][1,3]dioxol-5-yl)-1-(spiro[2.2]pentan-1-yl)ethan-1-one	27A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(spiro[2.2]pentan-1-yl)ethan-1-amine
Cy28 	K28  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[2.1.0]pentan-1-yl)ethan-1-one	28A  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[2.1.0]pentan-1-yl)-N-methylethan-1-amine
Cy29 	K29  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[2.1.0]pentan-5-yl)ethan-1-one	29A  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[2.1.0]pentan-5-yl)-N-methylethan-1-amine
Cy30 	K30  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[2.1.0]pentan-1-yl)ethan-1-one	30A  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[2.1.0]pentan-1-yl)-N-methylethan-1-amine

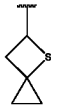
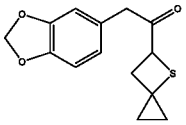
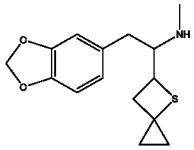
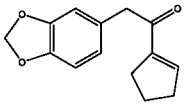
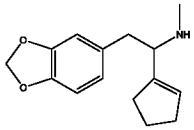
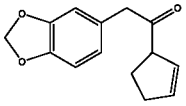
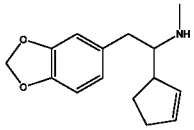
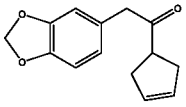
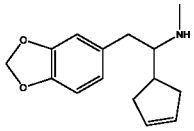
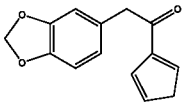
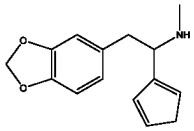
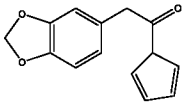
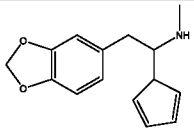
Cy	Ketone	Exemplary compound
Cy31 	K31  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[2.1.0]pentan-2-yl)ethan-1-one	31A  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[2.1.0]pentan-2-yl)-N-methylethan-1-amine
Cy32 	K32  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[1.1.1]pentan-2-yl)ethan-1-one	32A  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[1.1.1]pentan-2-yl)-N-methylethan-1-amine
Cy33 	K33  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[1.1.1]pentan-1-yl)ethan-1-one	33A  2-(benzo[d][1,3]dioxol-5-yl)-1-(bicyclo[1.1.1]pentan-1-yl)-N-methylethan-1-amine
Cy34 	K34  2-(benzo[d][1,3]dioxol-5-yl)-1-(spiro[2.3]hexan-4-yl)ethan-1-one	34A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(spiro[2.3]hexan-4-yl)ethan-1-amine
Cy35 	K35  2-(benzo[d][1,3]dioxol-5-yl)-1-(spiro[2.3]hexan-5-yl)ethan-1-one	35A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(spiro[2.3]hexan-5-yl)ethan-1-amine
Cy36 	K36  2-(benzo[d][1,3]dioxol-5-yl)-1-(oxetan-2-yl)ethan-1-one	36A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(oxetan-2-yl)ethan-1-amine

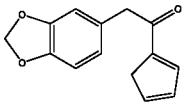
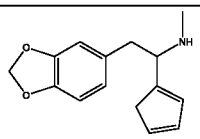
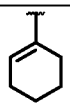
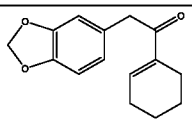
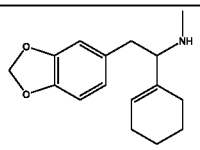
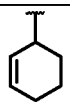
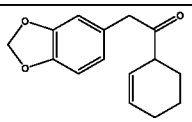
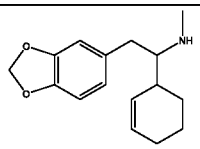
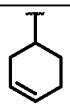
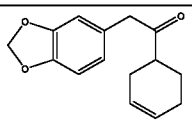
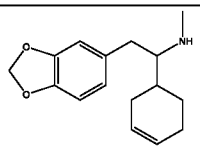
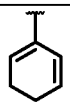
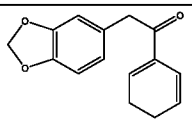
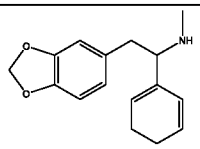
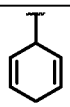
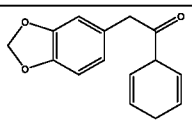
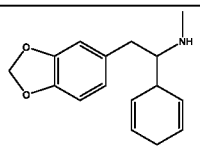
Cy	Ketone	Exemplary compound
Cy37 	K37  2-(benzo[d][1,3]dioxol-5-yl)-1-(thietan-2-yl)ethan-1-one	37A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(thietan-2-yl)ethan-1-amine
Cy38 	K38  2-(benzo[d][1,3]dioxol-5-yl)-1-(oxetan-3-yl)ethan-1-one	38A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(oxetan-3-yl)ethan-1-amine
Cy39 	K39  2-(benzo[d][1,3]dioxol-5-yl)-1-(thietan-3-yl)ethan-1-one	39A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(thietan-3-yl)ethan-1-amine
Cy40 	K40  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-1-yl)ethan-1-one	40A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-1-yl)-N-methylethan-1-amine
Cy41 	K41  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-1-yl)ethan-1-one	41A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-1-yl)-N-methylethan-1-amine
Cy42 	K42  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-4-yl)ethan-1-one	42A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-4-yl)-N-methylethan-1-amine

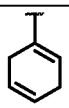
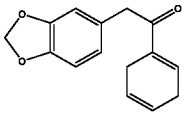
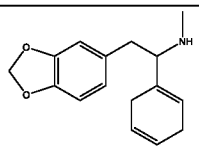
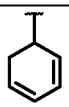
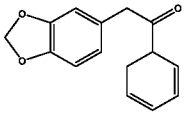
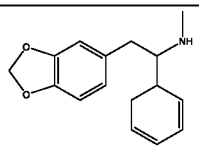
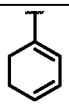
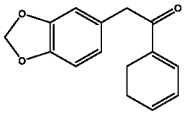
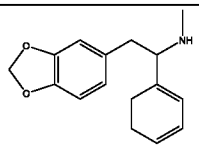
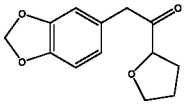
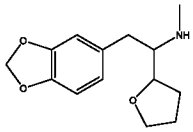
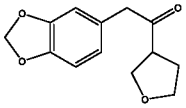
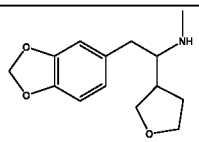
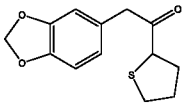
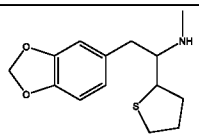
Cy	Ketone	Exemplary compound
Cy43 	K43  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-4-yl)ethan-1-one	43A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-4-yl)-N-methylethan-1-amine
Cy44 	K44  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-5-yl)ethan-1-one	44A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-5-yl)-N-methylethan-1-amine
Cy45 	K45  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-5-yl)ethan-1-one	45A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-5-yl)-N-methylethan-1-amine
Cy46 	K46  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-4-yl)ethan-1-one	46A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-4-yl)-N-methylethan-1-amine
Cy47 	K47  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-4-yl)ethan-1-one	47A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-4-yl)-N-methylethan-1-amine
Cy48 	K48  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-3-yl)ethan-1-one	48A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-3-yl)-N-methylethan-1-amine

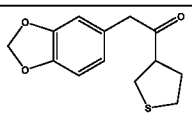
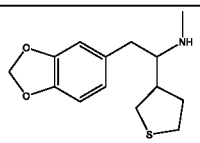
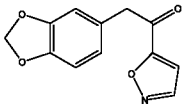
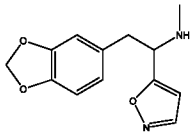
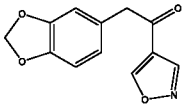
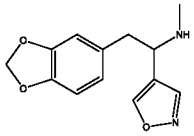
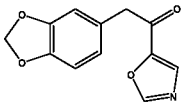
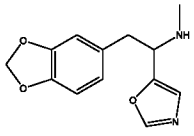
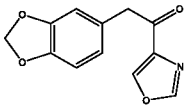
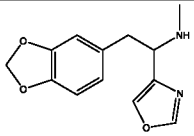
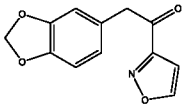
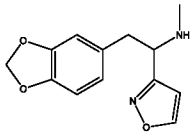
Cy	Ketone	Exemplary compound
Cy49 	K49  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-3-yl)ethan-1-one	49A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-3-yl)-N-methylethan-1-amine
Cy50 	K50  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-1-yl)ethan-1-one	50A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[2.1.0]pentan-1-yl)-N-methylethan-1-amine
Cy51 	K51  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-1-yl)ethan-1-one	51A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[2.1.0]pentan-1-yl)-N-methylethan-1-amine
Cy52 	K52  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[1.1.1]pentan-4-yl)ethan-1-one	52A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[1.1.1]pentan-4-yl)-N-methylethan-1-amine
Cy53 	K53  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[1.1.1]pentan-4-yl)ethan-1-one	53A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[1.1.1]pentan-4-yl)-N-methylethan-1-amine
Cy54 	K54  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[1.1.1]pentan-1-yl)ethan-1-one	54A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-oxabicyclo[1.1.1]pentan-1-yl)-N-methylethan-1-amine

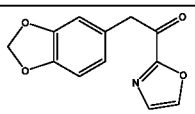
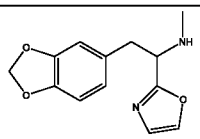
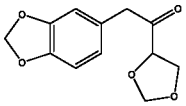
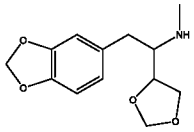
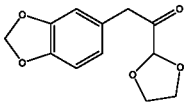
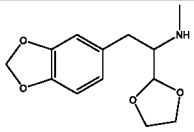
Cy	Ketone	Exemplary compound
Cy55 	K55  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[1.1.1]pentan-1-yl)ethan-1-one	55A  2-(benzo[d][1,3]dioxol-5-yl)-1-(2-thiabicyclo[1.1.1]pentan-1-yl)-N-methylethan-1-amine
Cy56 	K56  2-(benzo[d][1,3]dioxol-5-yl)-1-(5-oxaspiro[2.3]hexan-4-yl)ethan-1-one	56A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(5-oxaspiro[2.3]hexan-4-yl)ethan-1-amine
Cy57 	K57  2-(benzo[d][1,3]dioxol-5-yl)-1-(5-thiaspiro[2.3]hexan-4-yl)ethan-1-one	57A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(5-thiaspiro[2.3]hexan-4-yl)ethan-1-amine
Cy58 	K58  2-(benzo[d][1,3]dioxol-5-yl)-1-(4-oxaspiro[2.3]hexan-6-yl)ethan-1-one	58A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(4-oxaspiro[2.3]hexan-6-yl)ethan-1-amine
Cy59 	K59  2-(benzo[d][1,3]dioxol-5-yl)-1-(4-thiaspiro[2.3]hexan-6-yl)ethan-1-one	59A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(4-thiaspiro[2.3]hexan-6-yl)ethan-1-amine
Cy60 	K60  2-(benzo[d][1,3]dioxol-5-yl)-1-(4-oxaspiro[2.3]hexan-5-yl)ethan-1-one	60A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(4-oxaspiro[2.3]hexan-5-yl)ethan-1-amine

Cy	Ketone	Exemplary compound
Cy61 	K61  2-(benzo[d][1,3]dioxol-5-yl)-1-(4-thiaspiro[2.3]hexan-5-yl)ethan-1-one	61A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(4-thiaspiro[2.3]hexan-5-yl)ethan-1-amine
Cy62 	K62  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopent-1-en-1-yl)ethan-1-one	62A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopent-1-en-1-yl)-N-methylethan-1-amine
Cy63 	K63  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopent-2-en-1-yl)ethan-1-one	63A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopent-2-en-1-yl)-N-methylethan-1-amine
Cy64 	K64  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopent-3-en-1-yl)ethan-1-one	64A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopent-3-en-1-yl)-N-methylethan-1-amine
Cy65 	K65  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopenta-1,4-dien-1-yl)ethan-1-one	65A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopenta-1,4-dien-1-yl)-N-methylethan-1-amine
Cy66 	K66  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopenta-2,4-dien-1-yl)ethan-1-one	66A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopenta-2,4-dien-1-yl)-N-methylethan-1-amine

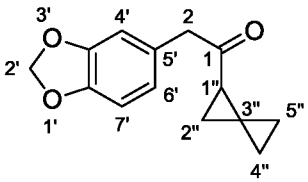
Cy	Ketone	Exemplary compound
Cy67 	K67  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopenta-1,3-dien-1-yl)ethan-1-one	67A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclopenta-1,3-dien-1-yl)-N-methylethan-1-amine
Cy68 	K68  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohex-1-en-1-yl)ethan-1-one	68A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohex-1-en-1-yl)-N-methylethan-1-amine
Cy69 	K69  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohex-2-en-1-yl)ethan-1-one	69A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohex-2-en-1-yl)-N-methylethan-1-amine
Cy70 	K70  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohex-3-en-1-yl)ethan-1-one	70A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohex-3-en-1-yl)-N-methylethan-1-amine
Cy71 	K71  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-1,5-dien-1-yl)ethan-1-one	71A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-1,5-dien-1-yl)-N-methylethan-1-amine
Cy72 	K72  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-2,5-dien-1-yl)ethan-1-one	72A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-2,5-dien-1-yl)-N-methylethan-1-amine

Cy	Ketone	Exemplary compound
Cy73 	K73  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-1,4-dien-1-yl)ethan-1-one	73A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-1,4-dien-1-yl)-N-methylethan-1-amine
Cy74 	K74  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-2,4-dien-1-yl)ethan-1-one	74A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-2,4-dien-1-yl)-N-methylethan-1-amine
Cy75 	K75  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-1,3-dien-1-yl)ethan-1-one	75A  2-(benzo[d][1,3]dioxol-5-yl)-1-(cyclohexa-1,3-dien-1-yl)-N-methylethan-1-amine
Cy76 	K76  2-(benzo[d][1,3]dioxol-5-yl)-1-(tetrahydrofuran-2-yl)ethan-1-one	76A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(tetrahydrofuran-2-yl)ethan-1-amine
Cy77 	K77  2-(benzo[d][1,3]dioxol-5-yl)-1-(tetrahydrofuran-3-yl)ethan-1-one	77A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(tetrahydrofuran-3-yl)ethan-1-amine
Cy78 	K78  2-(benzo[d][1,3]dioxol-5-yl)-1-(tetrahydrothiophen-2-yl)ethan-1-one	78A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(tetrahydrothiophen-2-yl)ethan-1-amine

Cy	Ketone	Exemplary compound
Cy79 	K79  2-(benzo[d][1,3]dioxol-5-yl)-1-(tetrahydrothiophen-3-yl)ethan-1-one	79A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(tetrahydrothiophen-3-yl)ethan-1-amine
Cy80 	K80  2-(benzo[d][1,3]dioxol-5-yl)-1-(isoxazol-5-yl)ethan-1-one	80A  2-(benzo[d][1,3]dioxol-5-yl)-1-(isoxazol-5-yl)-N-methylethan-1-amine
Cy81 	K81  2-(benzo[d][1,3]dioxol-5-yl)-1-(isoxazol-4-yl)ethan-1-one	81A  2-(benzo[d][1,3]dioxol-5-yl)-1-(isoxazol-4-yl)-N-methylethan-1-amine
Cy82 	K82  2-(benzo[d][1,3]dioxol-5-yl)-1-(oxazol-5-yl)ethan-1-one	82A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(oxazol-5-yl)ethan-1-amine
Cy83 	K83  2-(benzo[d][1,3]dioxol-5-yl)-1-(oxazol-4-yl)ethan-1-one	83A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(oxazol-4-yl)ethan-1-amine
Cy84 	K84  2-(benzo[d][1,3]dioxol-5-yl)-1-(isoxazol-3-yl)ethan-1-one	84A  2-(benzo[d][1,3]dioxol-5-yl)-1-(isoxazol-3-yl)-N-methylethan-1-amine

Cy	Ketone	Exemplary compound
Cy85 	K85  2-(benzo[d][1,3]dioxol-5-yl)-1-(oxazol-2-yl)ethan-1-one	85A  2-(benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(oxazol-2-yl)ethan-1-amine
Cy86 	K86  2-(benzo[d][1,3]dioxol-5-yl)-1-(1,3-dioxolan-4-yl)ethan-1-one	86A  2-(benzo[d][1,3]dioxol-5-yl)-1-(1,3-dioxolan-4-yl)-N-methylethan-1-amine
Cy87 	K87  2-(benzo[d][1,3]dioxol-5-yl)-1-(1,3-dioxolan-2-yl)ethan-1-one	87A  2-(benzo[d][1,3]dioxol-5-yl)-1-(1,3-dioxolan-2-yl)-N-methylethan-1-amine

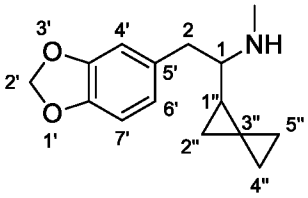
2-(Benzo[d][1,3]dioxol-5-yl)-1-(spiro[2.2]pentan-1-yl)ethanone ("Ketone K27")



[00277] A stirred solution of spiro[2.2]pentane-1-carboxylic acid (12 mg, 0.11 mmol) in PhMe (0.2 mL) was treated with oxalyl chloride (10 µL, 0.12 mmol) followed by one drop of DMF. The resulting solution was stirred at room temperature under N_2 for 2.5 h. Concurrently, and in a separate flask, a 1.0 M solution of LiHMDS in THF (0.22 mL, 0.22 mmol) was added to a stirred solution of methyl homopiperonylate (19 mg, 0.10 mmol) in anhydrous THF (0.4 mL) at –78 °C under N_2. This solution was stirred at –78 °C for 1.5 h before being treated dropwise via syringe with the PhMe solution of *in situ* generated acid chloride. The reaction mixture was warmed gradually to room temperature over 2 h, quenched with half-saturated NH_4Cl (15 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The extract was washed with brine (20 mL), dried and evaporated to give a pale brown oil (34 mg), which was dissolved in 9:1 DMSO/water (0.60 mL). The resulting solution was degassed and stirred at 120 °C under N_2 for 64 h. The reaction solution was cooled to room temperature, diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The extract was washed with brine (15 mL), dried and evaporated and the crude

residue was subjected to preparative thin-layer chromatography. Development with 3:17 EtOAc/hexanes afforded ketone K27 as a colourless oil (17 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (d, J = 7.9 Hz, 1H), 6.67 (d, J = 1.5 Hz, 1H), 6.62 (dd, J = 7.9, 1.5 Hz, 1H), 5.94 (s, 2H), 3.63 (d [AB], J = 15.1 Hz, 1H), 3.59 (d [AB], J = 15.1 Hz, 1H), 2.29 (dd, J = 7.3, 4.4 Hz, 1H), 1.61 (dd [app. t], J = 4.0 Hz, 1H), 1.38 (dd, J = 7.3, 3.6 Hz, 1H), 0.95–0.90 (m, 1H), 0.86–0.75 (m, 2H), 0.66–0.61 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 147.9, 146.6, 128.0, 122.6, 109.9, 108.5, 101.1, 49.7, 28.2, 22.0, 16.9, 6.9, 5.4 ppm.

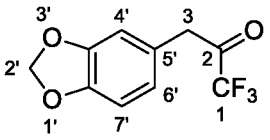
2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(spiro[2.2]pentan-1-yl)ethanamine (UWA-115, GAP-146, "Compound 27A")



[00278] According to General Procedure A; ketone K27 (15 mg, 65 µmol) was reacted for 20 h to afford amine 27A as a 11*:9$^{\#}$ mixture of diastereomers as a pale yellow oil (13 mg, 81%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 (d, J = 7.8 Hz, 1H)$^{\#}$, 6.72 (d, J = 1.6 Hz, 1H)$^{\#}$, 6.71 (d, J = 7.8 Hz, 1H)*, 6.67 (dd, J = 7.8, 1.6 Hz, 1H)$^{\#}$, 6.62 (d, J = 1.6 Hz, 1H)*, 6.58 (dd, J = 7.8, 1.6 Hz, 1H)*, 5.921 (s, 2H)$^{\#}$, 5.918 (s, 2H)*, 2.87 (dd, J = 13.7, 4.5 Hz, 1H)$^{\#}$, 2.67 (dd, J = 13.7, 8.0 Hz, 1H)$^{\#}$, 2.64 (dd, J = 13.5, 7.0 Hz, 1H)*, 2.55 (dd, J = 13.5, 5.9 Hz, 1H)*, 2.48 (s, 3H)*, 2.26 (s, 3H)$^{\#}$, 2.21 (ddd, J = 8.5, 8.5, 4.5 Hz, 1H)$^{\#}$, 2.14 (ddd, J = 9.1, 7.0, 6.1 Hz, 1H)*, 1.12–1.03 (m, 1H)$^{\#,*}$, 0.99 (dd, J = 7.7, 4.0 Hz, 1H)*, 0.93 (dd, J = 8.2, 4.2 Hz, 1H)$^{\#}$, 0.81–0.71 (m, 4H)$^{3\times\#,*}$, 0.69–0.66 (m, 1H)*, 0.63–0.58 (m, 1H)$^{\#,*}$, 0.57–0.54 (m, 1H)*, 0.47 (dd [app. t], J = 4.5 Hz, 1H)$^{\#}$, 0.31–0.27 (m, 1H)* ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 147.6, 146.03, 146.00, 133.3, 133.2, 122.43, 122.38, 109.9, 109.8, 108.2, 100.9, 65.7, 64.4, 41.4, 41.1, 34.8, 34.4, 22.9, 22.4, 15.0, 12.9, 12.1, 10.2, 6.1, 5.6, 5.1, 3.7 ppm. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{15}H_{20}NO_2^+$ 246.1489; found, 246.1487.

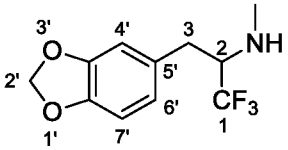
[00279] The free base was converted to the crude hydrochloride and was crystallised from Et_2O as a 3*:2$^{\#}$ mixture of diastereomers as colourless granules. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (br s, 1H)*, 9.57 (br s, 1H)*, 9.40 (br s, 2H)$^{\#}$, 6.83–6.80 (m, 2H)$^{\#}$, 6.76 (d, J = 8.4 Hz, 1H)$^{\#}$, 6.73 (d, J = 7.8 Hz, 1H)*, 6.66 (d, J = 1.0 Hz, 1H)*, 6.64 (dd, J = 7.9, 1.0 Hz, 1H)*, 5.94 (s, 2H)$^{\#,*}$, 3.37 (dd, J = 13.9, 6.1 Hz, 1H)$^{\#}$, 3.32 (br d, J = 10 Hz, 1H)*, 3.16 (dd, J = 14.0, 7.8 Hz, 1H)$^{\#}$, 2.89–2.81 (m, 2H)*, 2.78 (br s, 3H)*, 2.78–2.70 (m, 1H)$^{\#}$, 2.53 (br s, 3H)$^{\#}$, 1.58–1.54 (m, 1H)$^{\#}$, 1.48–1.43 (m, 1H)*, 1.19–1.15 (m, 1H)*, 1,14–1.08 (m, 1H)$^{\#,*}$, 1.03–0.98 (m, 2H)$^{\#}$, 0.84–0.79 (m, 1H)$^{\#}$, 0.77–0.72 (m, 1H)$^{\#}$, 0.65–0.59 (m, 1H)*, 0.46–0.38 (m, 2H)*, 0.33 (dd [app. t], J = 4.6 Hz, 1H)$^{\#}$, (–0.46)–(–0.51) (m, 1H)* ppm.

3-(Benzo[d][1,3]dioxol-5-yl)-1,1,1-trifluoropropan-2-one ("Ketone K88")



[00280] A solution of 1.0 M LiHMDS in THF (8.1 mL, 8.1 mmol) was added to a stirred solution of methyl homopiperonylate (750 mg, 3.86 mmol) in anhydrous THF (8 mL) at –78 °C under N_2. The reaction solution was stirred at –78 °C for 1.5 h before being treated with trifluoroacetic anhydride (0.64 mL, 4.6 mmol) added dropwise. The resulting solution was gradually warmed to room temperature overnight, quenched with 0.5 M HCl (80 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was washed with brine (40 mL), dried and evaporated to give a yellow oil (1039 mg), which was dissolved in 9:1 DMSO/water (15 mL). The resulting solution was degassed and stirred at 130 °C under N_2 for 18 h. The reaction solution was cooled to room temperature, diluted with water (120 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine (2 × 50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:19 EtOAc/hexanes → 3:17 EtOAc/hexanes afforded a 7:3 mixture of ketone K88 and its hydrate as a pale yellow oil (296 mg). This oil was dissolved in anhydrous CH_2Cl_2 and treated with anhydrous $MgSO_4$ (502 mg). The resulting mixture was stirred under reflux under N_2 for 4 h before being filtered and evaporated to afford ketone K88 as a pale yellow oil (281 mg, 31%). .^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.5 Hz, 1H), 6.66 (dd, J = 7.9, 1.8 Hz, 1H), 5.97 (s, 2H), 3.92 (s, 2H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –78.2 (s, 3F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (q, J = 34.8 Hz), 148.3, 147.6, 123.8, 123.1, 115.9 (q, J = 291 Hz), 110.0, 108.8, 101.4, 42.8 ppm.

3-(Benzo[d][1,3]dioxol-5-yl)-1,1,1-trifluoro-N-methylpropan-2-amine (UWA-132, GAP-145, "Compound 88A")

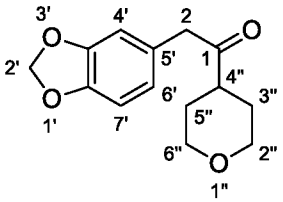


According to General Procedure A; ketone K88 (114 mg, 0.492 mmol) was reacted for 72 h to afford amine 88A as a colourless oil (17 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 1.6 Hz, 1H), 6.67 (dd, J = 7.9, 1.6 Hz, 1H), 5.95 (s, 2H), 3.10 (ddq, J = 10.2, 3.6, 7.1 Hz, 1H), 3.00 (dd, J = 14.3, 3.6 Hz, 1H), 2.58 (dd, J = 14.3, 10.2 Hz, 1H), 2.42 (q, J = 1.0 Hz, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –74.6 (s, 3F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 146.8, 130.3, 126.9 (q, J = 282 Hz), 122.4, 109.3, 108.6, 101.2, 62.8 (q, J =

26.8 Hz), 35.7 (q, *J* = 1.1 Hz), 34.5 (q, *J* = 2.4 Hz) ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}F_3NO_2^+$ 248.0893; found, 248.0890.

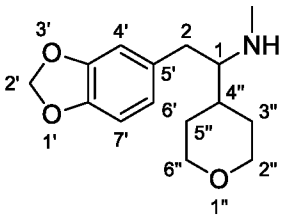
[00281] The free base was converted to the crude hydrochloride and was recrystallised from *i*PrOH/PhMe as colourless granules. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (br s, 2H), 6.86–6.82 (m, 2H), 6.78 (dd, *J* = 7.1, 1.4 Hz, 1H), 5.96 (s, 2H), 3.86 (m [app. sextet] = 7.0 Hz, 1H), 3.46 (dd, *J* = 14.8, 5.9 Hz, 1H), 3.19 (dd, *J* = 14.7, 7.7 Hz, 1H), 2.76 (s, 3H) ppm.

2-(Benzo[d][1,3]dioxol-5-yl)-1-(tetrahydro-2H-pyran-4-yl)ethanone ("Ketone K89")



[00282] A solution of 1.0 M LiHMDS in THF (8.4 mL, 8.4 mmol) was added to a stirred solution of methyl homopiperonylate (767 mg, 3.95 mmol) in anhydrous THF (8 mL) at –78 °C under N_2. The reaction solution was stirred at –78 °C for 1.5 h before being treated dropwise with oxane-4-carbonyl chloride (645 mg, 4.34 mmol). The resulting solution was gradually warmed to room temperature overnight, quenched with saturated NH_4Cl (60 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was washed with brine (40 mL), dried and evaporated to give a pale brown oil (1.37 g), which was dissolved in 9:1 DMSO/water (14 mL) and treated with NaCl (941 mg, 16.1 mmol). The resulting mixture was degassed and stirred at 140 °C under N_2 for 20 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine (2 × 50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:9 EtOAc/hexanes → 1:3 EtOAc/hexanes afforded ketone K89 as a pale yellow solid (871 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.7 Hz, 1H), 6.62 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.95 (s, 2H), 3.98 (ddd [app. dt], *J* = 11.4, 3.4 Hz, 2H), 3.65 (s, 2H), 3.45–3.34 (m, 2H), 2.72–2.60 (m, 1H), 1.77–1.67 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 148.1, 146.8, 127.6, 122.6, 109.9, 108.6, 101.2, 67.3, 47.3, 46.8, 28.4 ppm.

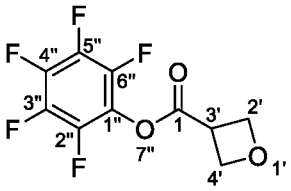
2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(tetrahydro-2H-pyran-4-yl)ethanamine (UWA-141, GAP-114, "Compound 89A")



[00283] According to General Procedure A; ketone K89 (125 mg, 0.503 mmol) was reacted for 40 h to afford amine 89A as a colourless oil (116 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 1.6 Hz, 1H), 6.63 (dd, J = 7.9, 1.6 Hz, 1H), 5.94 (s, 2H), 4.06–3.98 (m, 2H), 3.41–3.32 (m, 2H), 2.75–2.67 (m, 1H), 2.50–2.42 (m, 2H), 2.33 (s, 3H), 1.77–1.68 (m, 1H), 1.62–1.56 (m, 2H), 1.55–1.43 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.1, 133.6, 122.2, 109.4, 108.4, 101.0, 68.52, 68.49, 65.6, 37.5, 36.5, 34.7, 29.5, 29.0 ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_3^+$ 264.1594; found, 264.1591.

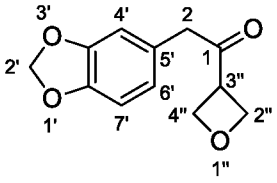
[00284] The free base was converted to the crude hydrochloride and was recrystallised from PhMe as colourless microneedles. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (br s, 2H), 6.81 (dd, J = 8.0, 1.6 Hz, 1H), 6.79–6.75 (m, 2H), 5.96 (s, 2H), 4.05–3.99 (m, 2H), 3.43–3.35 (m, 2H), 3.10 (dd, J = 13.1, 6.7 Hz, 1H), 3.06–2.94 (m, 2H), 2.53 (s, 3H), 2.26–2.15 (m, 1H), 1.83–1.75 (m, 2H), 1.74–1.67 (m, 1H), 1.66–1.55 (m, 1H) ppm.

Perfluorophenyl oxetane-3-carboxylate (Ester E90)



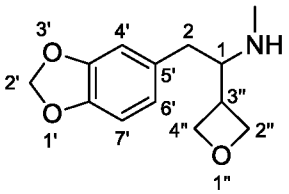
[00285] A solution of *N,N'*-Dicyclohexylcarbodiimide (1.08 g, 5.23 mmol) and DMAP (53 mg, 0.43 mmol) in CH_2Cl_2 (5 mL) was added to a cold (0 °C) stirred mixture of oxetane-3-carboxylic acid (403 mg, 3.95 mmol) and pentafluorophenol (910 mg, 4.94 mmol) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 24 h and vacuum filtered through a pad of Celite, washing through with CH_2Cl_2 (3 × 30 mL). The filtrate was concentrated and the crude residue was subjected to flash chromatography. Repeated gradient elution with 1:49 EtOAc/hexanes → 1:9 EtOAc/hexanes afforded a 17:3 mixture of ester E90 and pentafluorophenol as a pale yellow oil (339 mg, 29% by qNMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (d, J = 7.6 Hz, 4H), 4.21 (quintet, J = 7.6 Hz, 1H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ (–152.8)–(–153.0) (m, 2F), –157.1 (t, J = 21.7 Hz, 1F), (–161.7)–(–161.9) (m, 2F) ppm.

2-(Benzo[d][1,3]dioxol-5-yl)-1-(oxetan-3-yl)ethanone ("Ketone K90")



[00286] A solution of 1.0 M LiHMDS in THF (1.28 mL, 1.28 mmol) was added to a stirred solution of methyl homopiperonylate (236 mg, 1.22 mmol) in anhydrous THF (2.5 mL) at –78 °C under N_2. The reaction solution was stirred at –78 °C for 1.5 h before being treated dropwise with a solution of ester E90 and pentafluorophenol (17:3 mixture, 151 mg; contained 0.50 mmol E90 by qNMR) in THF (2.0 mL). The resulting solution was gradually warmed to room temperature overnight and quenched with half-saturated NH_4Cl (30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The extract was washed with brine (30 mL), dried and evaporated and the crude residue subjected to flash chromatography. Gradient elution with 1:9 EtOAc/hexanes → 1:4 EtOAc/hexanes afforded partially purified β-ketoester as a pale yellow oil (139 mg), which was dissolved in 9:1 DMSO/water (5 mL). The resulting solution was degassed and stirred at 110 °C under N_2 for 14 h. The reaction solution was cooled to room temperature, diluted with water (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extract was washed with brine (20 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:9 EtOAc/hexanes → 1:3 EtOAc/hexanes afforded ketone K90 as a colourless solid (54 mg, 48%).^{1}H NMR (600 MHz, $CDCl_3$): δ 6.77 (d, J = 7.9 Hz, 1H), 6.65 (d, J = 1.6 Hz, 1H), 6.61 (dd, J = 7.9, 1.6 Hz, 1H), 5.96 (s, 2H), 4.75 (dd, J = 6.7, 6.2 Hz, 2H), 4.66 (dd, J = 8.8, 6.2 Hz, 2H), 4.05–3.99 (m, 1H), 3.60 (s, 2H) ppm. ^{13}C NMR (600 MHz, $CDCl_3$) δ 205.5, 148.2, 147.1, 126.7, 122.7, 109.8, 108.8, 101.3, 72.5, 48.4, 44.6 ppm.

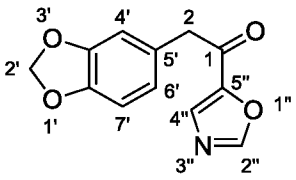
2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(oxetan-3-yl)ethanamine (UWA-142 GAP-167, "Compound 90A")



[00287] An 8.03 M solution of methylamine in EtOH (0.26 mL, 2.1 mmol) and AcOH (0.13 mL, 2.3 mmol) were added successively to a cold (0°C), stirred mixture of ketone K90 (47 mg, 0.21 mmol) and 3A sieves (54 mg) in 2:1 THF/MeOH (1.5 mL). Sodium cyanoborohydride (16 mg, 0.25 mmol) was added and the reaction vessel was flushed with N_2, sealed and stirred at 50 °C for 14 h before being cooled to room temperature, quenched with 1 M NaOH (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extract was vacuum filtered through a pad of Celite, washing through with CH_2Cl_2 (3 × 15 mL). The filtrate was dried and evaporated to afford the

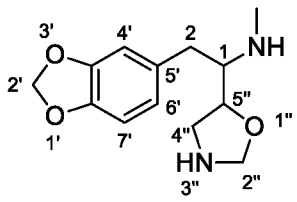
secondary amine 90A as a colourless oil (47 mg, 94%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.73 (d, J = 7.9 Hz, 1H), 6.62 (d, J = 1.6 Hz, 1H), 6.56 (dd, J = 7.9, 1.6 Hz, 1H), 5.93 (s, 2H), 4.73 (dd, J = 7.6, 6.1 Hz, 1H), 4.63–4.58 (m, 2H), 4.39 (dd [app. t], J = 6.3 Hz, 1H), 3.03–2.95 (m, 2H), 2.57 (dd, J = 13.8, 4.7 Hz, 1H), 2.53 (dd, J = 13.8, 6.5 Hz, 1H), 2.37 (s, 3H) ppm.^{13}C NMR (150 MHz, $CDCl_3$) δ 147.9, 146.3, 131.9, 122.3, 109.6, 108.4, 101.1, 76.1, 75.0, 63.6, 39.8, 37.3, 34.3 ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_3^+$ 236.1281; found, 236.1279.

2-(Benzo[d][1,3]dioxol-5-yl)-1-(oxazol-5-yl)ethanone ("Ketone K91")



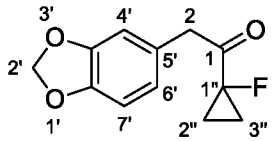
[00288] A stirred solution of oxazole-5-carboxylic acid (154 mg, 1.36 mmol) in PhMe (2.5 mL) was treated with oxalyl chloride (0.12 mL, 1.40 mmol) followed by two drops of DMF. The resulting solution was stirred at room temperature under N_2 for 5 h. Concurrently, and in a separate flask, a 1.0 M solution of LiHMDS in THF (2.9 mL, 2.9 mmol) was added to a stirred solution of methyl homopiperonylate (253 mg, 1.30 mmol) in anhydrous THF (4 mL) at –78 °C under N_2. This solution was stirred at –78 °C for 1.5 h before being treated dropwise via syringe with the PhMe solution of *in situ* generated acid chloride. The reaction mixture was warmed gradually to room temperature overnight, quenched with half-saturated NH_4Cl (70 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was washed with brine (40 mL), dried and evaporated to give an orange residue (356 mg), which was dissolved in 4:1 trifluoroacetic acid/water (15 mL). The resulting solution was degassed and stirred at 80 °C under N_2 for 24 h. The reaction solution was cooled to room temperature, diluted with water (50 mL), basified with saturated $NaHCO_3$ (180 mL) and extracted with EtOAc (3 × 50 mL). The extract was washed with brine (50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:9 EtOAc/hexanes → 3:7 EtOAc/hexanes afforded ketone K91 as a beige solid (60 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.77 (s, 1H), 6.79–6.76 (m, 2H), 6.73 (dd, J = 8.0, 1.6 Hz, 1H), 5.95 (s, 2H), 4.02 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 153.4, 148.2, 147.2, 133.5, 126.4, 122.9, 110.0, 108.7, 101.3, 46.1 ppm.

[00289] 2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(oxazolidin-5-yl)ethanamine (UWA-143, GAP-156, "Compound 91A")



[00290] An 8.03 M solution of methylamine in EtOH (0.13 mL, 1.0 mmol) and AcOH (60 µL, 1.0 mmol) were added successively to a cold (0°C), stirred mixture of ketone K91 (24 mg, 0.10 mmol) and 3A sieves (34 mg) in 2:1 THF/MeOH (1.5 mL). Sodium cyanoborohydride (9.0 mg, 0.14 mmol) was added and the reaction vessel was flushed with N_2, sealed and stirred at 50 °C for 18 h before being cooled to room temperature, quenched with 1 M NaOH (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extract was vacuum filtered through a pad of Celite, washing through with CH_2Cl_2 (3 × 15 mL). The filtrate was dried and evaporated to give a brown oil (23 mg) which was dissolved in dry MeOH (1.5 mL) and treated with $NaBH_4$ (27 mg, 0.71 mmol). The resulting mixture was stirred at room temperature under N_2 for 96 h before being quenched with brine (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extract was dried and evaporated and the yellow crude residue was subjected to preparative thin-layer chromatography. Development with 3:3:94 NEt_3/MeOH/CH_2Cl_2 afforded amine 91A as a pale yellow solid (10 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.75–6.72 (m, 2H), 6.70 (dd, J = 7.9, 1.3 Hz, 1H), 5.92 (s, 2H), 3.77 (d, J = 11.3 Hz, 1H), 3.22 (d, J = 1.4 Hz, 1H), 3.10 (d, J = 11.3 Hz, 1H), 3.00–2.93 (m, 2H), 2.66 (dd, J = 13.0, 10.8 Hz, 1H), 2.63 (dd, J = 14.0, 1.5 Hz, 1H), 2.48 (br s, 2H), 2.28 (s, 3H), 2.28–2.23 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.8, 146.2, 131.5, 122.7, 110.1, 108.4, 101.0, 72.0, 68.7, 63.1, 51.7, 38.9, 35.2 ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{19}N_2O_3^+$ 251.1390; found, 251.1386.

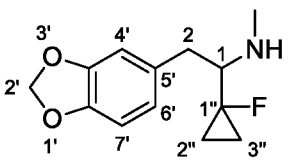
2-(Benzo[d][1,3]dioxol-5-yl)-1-(1-fluorocyclopropyl)ethanone ("Ketone K92")



[00291] A stirred solution of 1-fluorocyclopropanecarboxylic acid (454 mg, 4.36 mmol) in PhMe (4.4 mL) was treated with oxalyl chloride (0.38 mL, 4.40 mmol) followed by two drops of DMF. The resulting solution was stirred at room temperature under N_2 for 2 h. Concurrently, and in a separate flask, a 1.0 M solution of LiHMDS in THF (8.7 mL, 8.7 mmol) was added to a stirred solution of methyl homopiperonylate (774 mg, 3.98 mmol) in anhydrous THF (12 mL) at –78 °C under N_2. This solution was stirred at –78 °C for 1.5 h before being treated dropwise via syringe with the PhMe solution of *in situ* generated acid chloride. The reaction mixture was warmed gradually to room temperature overnight, quenched with 0.5 M HCl (80 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was washed with brine (40 mL), dried and

evaporated to give a dark yellow oil (1.13 g), which was dissolved 9:1 DMSO/water (16 mL) and treated with NaCl (1.05 g, 18.0 mmol). The resulting mixture was degassed and stirred at 140 °C under N_2 for 40 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine (2 × 50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:49 EtOAc/hexanes → 1:19 EtOAc/hexanes afforded ketone K92 as a colourless oil (375 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 1.6 Hz, 1H), 6.68 (dd, J = 7.9, 1.6 Hz, 1H), 5.95 (s, 2H), 4.00 (d, J = 3.4 Hz, 2H), 1.41–1.38 (m, 2H), 1.37–1.34 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ –196.9 ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4 (d, J = 24.9 Hz), 147.9, 146.8, 126.8, 123.0, 110.3, 108.5, 101.2, 82.8 (d, J = 230 Hz), 45.4, 17.3 (d, J = 10.2 Hz) ppm.

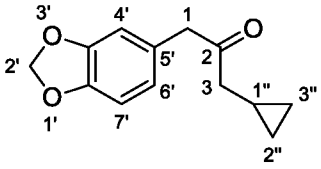
2-(Benzo[d][1,3]dioxol-5-yl)-1-(1-fluorocyclopropyl)-N-methylethanamine (UWA-144, GAP-128, "Compound 92A")



[00292] According to General Procedure A; ketone K92 (112 mg, 0.504 mmol) was reacted for 24 h to afford amine 92A as a colourless oil (94 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 1.6 Hz, 1H), 6.68 (dd, J = 7.8, 1.7 Hz, 1H), 5.93 (s, 2H), 2.95 (dd, J = 13.8, 6.1 Hz, 1H), 2.81 (dd, J = 13.8, 8.1 Hz, 1H), 2.49 (s, 3H), 2.34 (ddd, J = 24.7, 8.1, 6.1 Hz, 1H), 1.16–1.03 (m, 1H), 0.95–0.82 (m, 1H), 0.71–0.60 (m, 1H), 0.35–0.24 (m, 1H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –196.5 ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 146.2, 132.9, 122.4, 109.7, 108.3, 101.0, 78.7 (d, J = 219 Hz), 65.3 (d, J = 19.8 Hz), 38.3 (d, J = 1.6 Hz), 35.0, 10.6 (d, J = 12.3 Hz), 8.3 (d, J = 11.5 Hz) ppm. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{13}H_{17}FNO_2^+$ 238.1238; found, 238.1235.

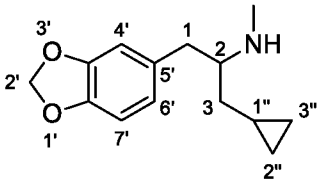
[00293] The free base was converted to the crude hydrochloride and was recrystallised from *i*PrOH/PhMe as colourless granules. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (br s, 1H), 9.92 (br s, 1H), 6.81 (d, J = 1.5 Hz, 1H), 6.79 (dd, J = 7.9, 1.5 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 5.95 (d [AB], J = 1.4 Hz, 1H), 5,94 (d [AB], J = 1.4 Hz, 1H), 3.38 (dd, J = 13.2, 4.4 Hz, 1H), 3.28 (dd, J = 13.2, 11.0 Hz, 1H), 3.14–3.00 (m, 1H), 2.86 (dd, J = 5.6, 4.8 Hz, 3H), 1.28–1.06 (m, 2H), 1.01–0.87 (m, 1H), 0.29–0.18 (m, 1H) ppm.

1-(Benzo[d][1,3]dioxol-5-yl)-3-cyclopropylpropan-2-one ("Ketone K93")



[00294] A stirred solution of cyclopropylacetic acid (445 mg, 4.44 mmol) in PhMe (4.4 mL) was treated with oxalyl chloride (0.39 mL, 4.5 mmol) followed by one drop of DMF. The resulting solution was stirred at room temperature under N_2 for 2.5 h. Concurrently, and in a separate flask, a 1.0 M solution of LiHMDS in THF (8.7 mL, 8.7 mmol) was added to a stirred solution of methyl homopiperonylate (770 mg, 3.96 mmol) in anhydrous THF (12 mL) at –78 °C under N_2. This solution was stirred at –78 °C for 1.5 h before being treated dropwise via syringe with the PhMe solution of *in situ* generated acid chloride. The reaction mixture was warmed gradually to room temperature overnight, quenched with 0.5 M HCl (80 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was washed with brine (40 mL), dried and evaporated to give a yellow oil (1.24 g), which was dissolved 9:1 DMSO/water (16 mL) and treated with NaCl (1.21 g, 20.7 mmol). The resulting mixture was degassed and stirred at 140 °C under N_2 for 16 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine (2 × 50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:49 EtOAc/hexanes → 1:19 EtOAc/hexanes afforded ketone K93 as a colourless oil (674 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 1.4 Hz, 1H), 6.63 (dd, J = 7.9, 1.7 Hz, 1H), 5.94 (s, 2H), 3.64 (s, 2H), 2.32 (d, J = 7.0 Hz, 1H), 1.04–0.92 (m, 1H), 0.60–0.50 (m, 2H), 0.11–0.02 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 148.0, 146.8, 128.0, 122.7, 110.0, 108.6, 101.2, 49.4, 47.2, 6.4, 4.7 ppm.

1-(Benzo[d][1,3]dioxol-5-yl)-3-cyclopropyl-N-methylpropan-2-amine (UWA-145, GAP-125, "Compound 93A")

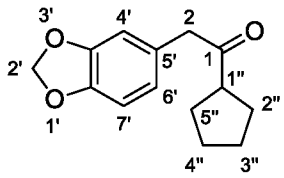


[00295] According to General Procedure A; ketone K93 (112 mg, 0.513 mmol) was reacted for 24 h to afford amine 93A as a colourless oil (112 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 1.6 Hz, 1H), 6.64 (dd, J = 7.8, 1.6 Hz, 1H), 5.93 (s, 2H), 2.76–2.66 (m, 2H), 2.65–2.58 (m, 1H), 2.39 (s, 3H), 1.38–1.25 (m, 2H), 0.76–0.66 (m, 1H), 0.51–0.42 (m, 2H), 0.10–0.00 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 146.0,

133.6, 122.3, 109.6, 108.3, 100.9, 62.0, 40.4, 38.5, 34.1, 7.9, 4.9, 4.6 ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{20}NO_2^+$ 234.1489; found, 234.1485.

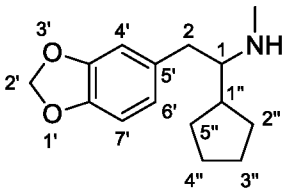
[00296] The free base was converted to the crude hydrochloride and was recrystallised from PhMe as colourless granules. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (br s, 1H), 9.50 (br s, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.74–6.70 (m, 2H), 5.95 (s, 2H), 3.33–3.24 (m, 2H), 2.94 (dd, J = 15.2, 10.3 Hz, 1H), 2.68 (dd [app. t], J = 5.6 Hz, 3H), 1.79 (ddd [app. dt], J = 14.8, 6.4 Hz, 1H), 1.53 (ddd, J = 14.8, 7.3, 5.5 Hz, 1H), 0.96–0.84 (m, 1H), 0.63–0.51 (m, 2H), 0.18–0.11 (m, 1H), 0.06–(–0.01) (m, 1H) ppm.

2-(Benzo[d][1,3]dioxol-5-yl)-1-cyclopentylethanone ("Ketone K94")



[00297] A solution of 1.0 M LiHMDS in THF (9.4 mL, 9.4 mmol) was added to a stirred solution of methyl homopiperonylate (869 mg, 4.47 mmol) in anhydrous THF (9 mL) at –78 °C under N_2. The reaction solution was stirred at –78 °C for 1.5 h before being treated dropwise with cyclopentanecarbonyl chloride (661 mg, 4.99 mmol). The resulting solution was gradually warmed to room temperature overnight, quenched with 0.5 M HCl (80 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was washed with brine (40 mL), dried and evaporated to give a yellow oil (1.67 g), which was dissolved in 9:1 DMSO/water (15 mL) and treated with NaCl (1.07 g, 18.4 mmol). The resulting mixture was degassed and stirred at 140 °C under N_2 for 18 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with water (50 mL) and brine (2 × 50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:49 EtOAc/hexanes → 1:19 EtOAc/hexanes afforded ketone K94 as a colourless oil (952 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.6 Hz, 1H), 6.64 (dd, J = 7.9, 1.7 Hz, 1H), 5.94 (s, 2H), 3.64 (s, 2H), 2.96 (quintet, J = 8.0 Hz, 1H), 1.82–1.49 (m, 8H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 147.9, 146.7, 128.3, 122.7, 110.0, 108.5, 101.1, 50.6, 48.9, 29.3, 26.2 ppm.

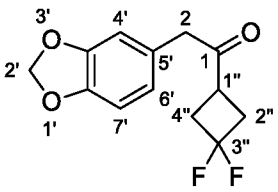
2-(Benzo[d][1,3]dioxol-5-yl)-1-cyclopentyl-N-methylethanamine (UWA-146, GAP-116, "Compound 94A")



[00298] According to General Procedure A; ketone K94 (119 mg, 0.512 mmol) was reacted for 60 h to afford amine 94A as a colourless oil (109 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 1.6 Hz, 1H), 6.64 (dd, J = 7.8, 1.7 Hz, 1H), 5.92 (s, 2H), 2.70 (dd, J = 13.6, 4.6 Hz, 1H), 2.56 (dd, J = 13.6, 7.6 Hz, 1H), 2.52–2.48 (m, 1H), 2.36 (s, 3H), 1.98–1.87 (m, 1H), 1.82–1.69 (m, 2H), 1.66–1.47 (m, 4H), 1.35–1.24 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.9, 133.9, 122.2, 109.7, 108.2, 100.9, 65.5, 43.2, 38.0, 34.1, 29.7, 29.4, 25.8, 25.7 ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}NO_2^+$ 248.1645; found, 248.1642.

[00299] The free base was converted to the crude hydrochloride and was recrystallised from *i*PrOH/PhMe as colourless granules. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (br s, 1H), 8.99 (br s, 1H), 6.82 (dd, J = 7.9, 1.6 Hz, 1H), 6.78 (d, J = 1.5 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 5.95 (s, 2H), 3.21–3.12 (m, 2H), 2.96 (ddd [app. q], J = 8.5 Hz, 1H), 2.55 (dd [app. t], J = 5.3 Hz, 3H), 2.37–2.26 (m, 1H), 2.12–2.02 (m, 1H), 1.88–1.79 (m, 1H), 1.77–1.40 (m, 6H) ppm.

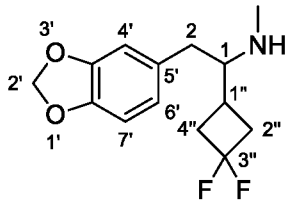
2-(Benzo[d][1,3]dioxol-5-yl)-1-(3,3-difluorocyclobutyl)ethanone ("Ketone K95")



[00300] A stirred solution of 3,3-difluorocyclobutanecarboxylic acid (607 mg, 4.46 mmol) in PhMe (4.4 mL) was treated with oxalyl chloride (0.38 mL, 4.4 mmol) followed by two drops of DMF. The resulting solution was stirred at room temperature under N_2 for 2 h. Concurrently, and in a separate flask, a 1.0 M solution of LiHMDS in THF (8.8 mL, 8.8 mmol) was added to a stirred solution of methyl homopiperonylate (779 mg, 4.01 mmol) in anhydrous THF (12 mL) at –78 °C under N_2. This solution was stirred at –78 °C for 1.5 h before being treated dropwise via syringe with the PhMe solution of *in situ* generated acid chloride. The reaction mixture was warmed gradually to room temperature overnight, quenched with 0.5 M HCl (80 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was washed with brine (40 mL), dried and evaporated to give a yellow oil (1.59 g), which was dissolved 9:1 DMSO/water (14 mL) and treated with NaCl (1.01 g, 17.3 mmol). The resulting mixture was degassed and stirred at 140 °C under N_2 for 18 h. The reaction mixture was cooled to room temperature, diluted with water

(100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine (2 × 50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:19 Et_2O/hexanes → 3:17 Et_2O/hexanes afforded ketone K95 as a colourless oil (628 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 7.8 Hz, 1H), 6.66 (d, J = 1.5 Hz, 1H), 6.63 (dd, J = 7.9, 1.7 Hz, 1H), 5.96 (s, 2H), 3.63 (s, 2H), 3.13 (quintet of doublets, J = 8.7, 2.6 Hz, 1H), 2.81–2.66 (m, 2H), 2.65–2.52 (m, 2H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –82.4 (d, J = 192 Hz, 1F), –97.5 (d, J = 192 Hz, 1F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5 (dd [app. t], J = 1.8 Hz), 148.2, 147.1, 126.9, 122.7, 118.5 (dd, J = 284, 268 Hz), 109.8, 108.8, 101.3, 48.4 (d, J = 1.1 Hz), 38.0 (dd [app. t], J = 24.2 Hz), 32.2 (dd, J = 13.5, 4.5 Hz) ppm.

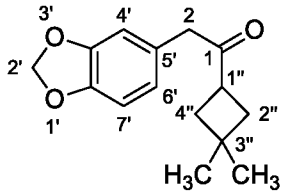
2-(Benzo[d][1,3]dioxol-5-yl)-1-(3,3-difluorocyclobutyl)-N-methylethanamine (UWA-147, GAP-119, "Compound 95A")



[00301] According to General Procedure A; ketone K95 (128 mg, 0.503 mmol) was reacted for 40 h to afford amine 95A as a colourless oil (121 mg, 89%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 1.6 Hz, 1H), 6.59 (dd, J = 7.8, 1.7 Hz, 1H), 5.94 (s, 2H), 2.68–2.47 (m, 5H), 2.43–2.31 (m, 1H), 2.39 (s, 3H), 2.30–2.17 (m, 1H), 2.13–2.00 (m, 1H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –81.5 (d, J = 192 Hz, 1F), –98.3 (d, J = 192 Hz, 1F) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.3, 132.1, 122.3, 119.9 (dd, J = 284, 269 Hz), 109.6, 108.5, 101.1, 65.1 (dd, J = 2.6, 2.0 Hz), 39.2 (dd, J = 22.9, 21.1 Hz), 38.2 (dd, J = 23.2, 21.4 Hz), 37.3, 34.4, 27.7 (dd, J = 13.6, 4.2 Hz) ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}F_2NO_2^+$ 270.1300; found, 270.1297.

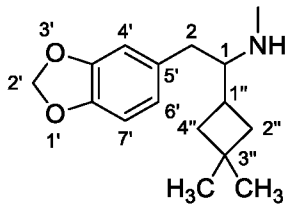
[00302] The free base was converted to the crude hydrochloride and was recrystallised from PhMe as colourless granules. ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (br s, 1H), 9.58 (br s, 1H), 6.79–6.72 (m, 3H), 5.97 (s, 2H), 3.34–3.21 (m, 2H), 2.95–2.72 (m, 3H), 2.60 (dd [app. t], J = 5.6 Hz, 3H), 2.59–2.42 (m, 2H), 2.26–2.12 (m, 1H) ppm.

2-(Benzo[d][1,3]dioxol-5-yl)-1-(3,3-dimethylcyclobutyl)ethanone ("Ketone K96")



[00303] A stirred solution of 3,3-dimethylcyclobutanecarboxylic acid (448 mg, 3.49 mmol) in PhMe (3.5 mL) was treated with oxalyl chloride (0.31 mL, 3.6 mmol) followed by two drops of DMF. The resulting solution was stirred at room temperature under N_2 for 2 h. Concurrently, and in a separate flask, a 1.0 M solution of LiHMDS in THF (7.0 mL, 7.0 mmol) was added to a stirred solution of methyl homopiperonylate (615 mg, 3.17 mmol) in anhydrous THF (9.5 mL) at –78 °C under N_2. This solution was stirred at –78 °C for 1.5 h before being treated dropwise via syringe with the PhMe solution of *in situ* generated acid chloride. The reaction mixture was warmed gradually to room temperature overnight, quenched with 0.5 M HCl (80 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The extract was washed with brine (40 mL), dried and evaporated to give a yellow oil (1.11 g), which was dissolved 9:1 DMSO/water (12 mL) and treated with NaCl (838 mg, 14.3 mmol). The resulting mixture was degassed and stirred at 140 °C under N_2 for 18 h. The reaction mixture was cooled to room temperature, diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine (2 × 50 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:49 EtOAc/hexanes → 1:19 EtOAc/hexanes afforded ketone K96 as a colourless oil (629 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 7.9 Hz, 1H), 6.67 (d, J = 1.5 Hz, 1H), 6.62 (dd, J = 7.9, 1.7 Hz, 1H), 5.94 (s, 2H), 3.54 (s, 2H), 3.23 (quintet, J = 8.9 Hz, 1H), 2.03–1.96 (m, 2H), 1.87–1.80 (m, 2H), 1.14 (s, 3H), 1.03 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 147.9, 146.7, 128.2, 122.7, 110.0, 108.5, 101.1, 47.5, 38.2, 37.1, 31.5, 30.1, 28.8 ppm.

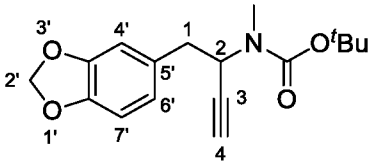
2-(Benzo[d][1,3]dioxol-5-yl)-1-(3,3-dimethylcyclobutyl)-N-methylethanamine (UWA-148, GAP-133, "Compound 96A")



According to General Procedure A; ketone K96 (124 mg, 0.503 mmol) was reacted for 24 h to afford amine 96A as a colourless oil (90 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 1.6 Hz, 1H), 6.61 (dd, J = 7.8, 1.6 Hz, 1H), 5.93 (s, 2H), 2.62 (dd, J = 13.5, 4.3 Hz, 1H), 2.51 (ddd, J = 9.0, 7.5, 4.3 Hz, 1H), 2.39 (dd, J = 13.5, 7.5 Hz, 1H), 2.35 (s, 3H), 2.22–2.10 (m, 1H), 1.90–1.83 (m, 1H), 1.80–1.72 (m, 1H), 1.58 (dd [app. t], J = 9.9 Hz, 1H), 1.48 (dd [app. t], J = 10.0 Hz, 1H), 1.13 (s, 3H), 1.03 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.9, 133.4, 122.3, 109.7, 108.2, 100.9, 67.3, 40.1, 39.1, 37.4, 34.8, 33.2, 31.6, 31.2, 28.5 ppm. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{24}NO_2^+$ 262.1802; found, 262.1799.

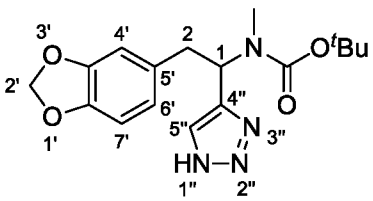
[00304] The free base was converted to the crude hydrochloride and was recrystallised from PhMe as colourless microneedles. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (br s, 1H), 9.20 (br s, 1H), 6.80–6.73 (m, 3H), 5.95 (s, 2H), 3.20–3.08 (m, 2H), 2.88–2.80 (m, 1H), 2.71–2.58 (m, 1H), 2.54 (dd [app. t], J = 5.6 Hz, 3H), 2.16–2.07 (m, 1H), 1.83 (dd, J = 11.1, 9.6 Hz, 1H), 1.76–1.69 (m, 1H), 1.41 (dd, J = 11.0, 9.5 Hz, 1H), 1.13 (s, 3H), 1.04 (s, 3H) ppm.

tert-*Butyl (1-(benzo[d][1,3]dioxol-5-yl)but-3-yn-2-yl)(methyl)carbamate ("Carbamate CX97")*



[00305] A stirred solution of UWA-017•HCl ("Compound 3A•HCl"; 50 mg, 0.21 mmol) in water (1.6 mL) was treated with Na_2CO_3 (80 mg, 0.75 mmol) followed by di-*tert*-butyl dicarbonate (164 mg, 0.751 mmol). The resulting mixture was stirred at room temperature for 48 h, diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The extract was washed with brine (15 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with hexanes → 1:9 EtOAc/hexanes afforded carbamate CX97 as a colourless oil (61 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$; rotameric mixture) δ 6.73 (d, J = 7.8 Hz, 1H), 6.72–6.60 (br m, 2H), 5.92 (q [AB], J = 1.3 Hz, 2H), 5.19 and 5.00 (2 × br s, 1H, rotamers), 2.91–2.79 (br m, 5H), 2.36 and 2.32 (2 × br s, 1H, rotamers), 1.40 and 1.34 (2 × br s, 9H, rotamers) ppm. ^{13}C NMR (100 MHz, $CDCl_3$; rotameric mixture) δ 154.6 (br), 147.6, 146.6, 130.8, 122.5, 109.9, 108.3, 101.0, 81.6 (br), 80.2, 73.4, 50.1 and 49.2 (2 × br, rotamers), 40.1 and 39.7 (2 × br, rotamers), 29.9 and 29.2 (2 × br, rotamers), 28.4 ppm.

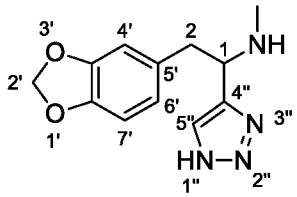
tert-*Butyl (2-(benzo[d][1,3]dioxol-5-yl)-1-(1H-1,2,3-triazol-4-yl)ethyl)(methyl)carbamate ("Carbamate CY97")*



[00306] CuI (4.0 mg, 0.021 mmol, 12 mol%), iPr$_2$NEt (50 µL, 0.29 mmol) and $TMSN_3$ (45 µL, 0.34 mmol) were added to a stirred solution of carbamate CX97 (55 mg, 0.18 mmol) in 9:1 DMF/MeOH (2.0 mL). The reaction vessel was flushed with argon, sealed and the reaction mixture stirred at 80 °C for 20 h. The resulting mixture was cooled to room temperature, diluted with water (20 mL) and extracted with $CHCl_3$ (3 × 20 mL). The extract was washed with

saturated NH_4Cl (2 × 20 mL), dried and evaporated and the crude residue was subjected to flash chromatography. Gradient elution with 1:4 EtOAc/hexanes → 1:39:60 NEt_3/EtOAc/hexanes afforded carbamate CY97 as a pale yellow oil (49 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$, rotameric mixture) δ 7.63 and 7.60 (2 × br s, 1H, rotamers), 6.74–6.63 (br m, 3H), 5.90 (s, 2H), 5.66 and 5.55 (2 × br s, 1H, rotamers), 3.37–3.25 (br m, 1H), 3.24–3.05 (br m, 1H), 2.69 (s, 3H), 1.39 and 1.35 (2 × br s, 9H, rotamers) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 and 155.6 (2 × br, rotamers), 147.7, 146.3, 131.6 (br), 131.3, 122.2, 109.6, 108.4, 101.0, 80.4, 53.8 and 52.4 (2 × br, rotamers), 36.9, 30.4 and 29.3 (2 × br, rotamers), 28.4 ppm. Note: A ^{13}C signal for C4″ was not observed due to rotameric and tautomeric broadening.

2-(Benzo[d][1,3]dioxol-5-yl)-N-methyl-1-(1H-1,2,3-triazol-4-yl)ethanamine (UWA-149, GAP-168, "Compound 97A")



A solution of carbamate CY97 (14 mg, 41 μmol) in MeOH (0.6 mL) was treated with 4.0 M HCl in dioxane (0.15 mL, 0.60 mmol) and stirred at 40 °C for 3 h. The resulting solution was cooled to room temperature and evaporated and the residue was triturated with Et_2O to afford the dihydrochloride 97A•2HCl as a beige solid (12 mg, 93%). ^{1}H NMR (600 MHz, CD_3OD) δ 7.75 (s, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.64 (d, J = 1.7 Hz, 1H), 6.58 (dd, J = 7.9, 1.7 Hz, 1H), 5.90 (q [AB], J = 1.3 Hz, 2H), 4.67 (dd, J = 9.6, 5.6 Hz, 1H), 3.34 (dd, J = 13.4, 5.6 Hz, 1H), 3.22 (dd, J = 13.4, 9.8 Hz, 1H), 2.60 (s, 3H) ppm.

[00307] A sample of the dihydrochloride 97A•2HCl was dissolved in saturated $NaHCO_3$ and extracted with EtOAc. The extract was dried and evaporated to afford amine 97A as a colourless solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.58 (br s, 1H), 6.65 (d, J = 7.9 Hz, 1H), 6.57 (d, J = 1.3 Hz, 1H), 6.53 (dd, J = 7.9, 1.2 Hz, 1H), 5.86 (q [AB], J = 1.4 Hz, 2H), 4.03 (dd, J = 8.1, 6.6 Hz, 1H), 3.05 (dd, J = 13.3, 6.4 Hz, 1H), 2.96 (br dd, J = 13.0, 8.0 Hz, 1H), 2.25 (s, 3H) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 149.0, 147.6, 146.9 (br), 132.7, 129.3 (br), 123.4, 110.4, 109.0, 102.1, 59.1, 42.5, 33.9 ppm. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{12}H_{15}N_4O_2^+$ 247.1190; found, 247.1188.

Biological Activity Screening Tests

[00308] Particularly preferred compounds of the present invention were subjected to the following biological screening tests to determine their activity profiles.

Serotonin Transporter (SERT) activity

[00309] The Na^+/Cl^- dependent neurotransporters, which represent a gene superfamily, are essential for controlling neurotransmitter function. Serotonin's function is terminated in part by the plasma-membrane norepinephrine transporter (SERT), which transports serotonin into presynaptic serotonergic neurones. Psychostimulants and antidepressants have a high affinity for monoamine transporters like SERT. These drugs increase extracellular neurotransmitter concentrations in both the central and peripheral nervous systems by inhibiting transporters and thereby impeding neuronal uptake, which contributes to their behavioural and autonomic effects.

[00310] The screening procedure follows that reported in the literature,[11(a),(b)] whereby a modified Tris-HCl buffer pH 7.4, human recombinant serotonin transporter expressed in human HEK-293 cells is employed. For 60 minutes at 25°C, a 9 µg aliquot is incubated with 0.4 nM [^{3}H]Paroxetine. In the presence of 10 µM imipramine (as an exemplary compound), non-specific binding is estimated. The transporters are filtered and washed, and the filters are counted to determine [^{3}H]Paroxetine specifically bound. Compounds were screened at a concentration of 10 µM. A standard reference agent used for this screening test is Fluoxetine, which has IC_{50} (nM) = 8.6, Ki (nM) = 1.4, and nH = 0.9.

Dopamine Transporter (DAT) activity

[00311] The Na^+/Cl^- dependent neurotransporters, which represent a gene superfamily, are essential for controlling neurotransmitter function. Dopamine's function is terminated in part by the plasma-membrane norepinephrine transporter (DAT), which transports dopamine into presynaptic dopaminergic neurones. Psychostimulants and antidepressants have a high affinity for monoamine transporters like DAT. These drugs increase extracellular neurotransmitter concentrations in both the central and peripheral nervous systems by inhibiting transporters and thereby impeding neuronal uptake, which contributes to their behavioural and autonomic effects.

[00312] The screening procedure follows that reported in the literature,[12(a),(b)] whereby human recombinant dopamine transporters expressed in CHO-S cells are used in modified Tris-HCl buffer pH 7.4. A 0.4 µg aliquot is incubated with 0.15 nM [^{125}I]RTI-55 for 3 hours at 4°C. Non-specific binding is estimated in the presence of 10 µM nomifensine (as an exemplary compound). Transporters are filtered and washed, the filters are then counted to determine [^{125}I]RTI-55 specifically bound. Compounds are screened at 10 µM. A standard reference agent used for this screening test is GBR-12909 (1-[2[bis(4-fluorophenyl)methoxy]ethyl]-4-[3-phenylpropyl]piperazine dihydrochloride), which has IC_{50} (nM) = 1.7, Ki (nM) = 1.3, and nH = 0.9.

Norepinephrine Transporter (NET) activity

[00313] The Na^+/Cl^- dependent neurotransporters, which represent a gene superfamily, are essential for controlling neurotransmitter function. Norepinephrine's function is terminated in part by the plasma-membrane norepinephrine transporter (NET), which transports norepinephrine into presynaptic noradrenergic neurones. Psychostimulants and antidepressants have a high affinity for monoamine transporters like NET. These drugs increase extracellular neurotransmitter concentrations in both the central and peripheral nervous systems by inhibiting transporters and thereby impeding neuronal uptake, which contributes to their behavioural and autonomic effects.

[00314] The screening procedure follows that reported in the literature,[13] whereby human recombinant norepinephrine transporters expressed in dog kidney MDCK cells are used in modified Tris-HCl buffer pH 7.4. A 40 µg aliquot is incubated with 0.2 nM [^{125}I]RTI-55 for 3 hours at 4°C. Non-specific binding is estimated in the presence of 10 µM desipramine (as an exemplary compound). Transporters are filtered and washed, the filters are then counted to determine [^{125}I]RTI-55 specifically bound. Compounds are screened at 10 µM. A standard reference agent used for this screening test is Desipramine, which has IC_{50} (nM) = 0.93, Ki (nM) = 0.92, and nH = 0.6.

Monoamine Oxidase A (MAO-A) activity

[00315] Monoamine Oxidase (MAO, E.C.1.4.3.4) catalyses the removal of an amine group via oxidative deamination from a variety of substrates including endogenous substances and neurotransmitters (norepinephrine, epinephrine, dopamine, tyramine, serotonin) and many amine drugs. MAO provides an important protective mechanism against exogenous, biologically active amines. There are at least two types of MAO which display varying preferences for substrates and differing sensitivities to selective inhibitors. Relatively selective inhibitors of MAO-A (e.g. Clorgyline) are correlated with efficacy in the treatment of major depression, and relatively selective MAO-B inhibitors are correlated with beneficial effects on Parkinson's disease and dyskinesia.

[00316] The screening procedure follows that reported in the literature,[14(a),(b)] whereby Human recombinant MAO-A expressed in insect cells is used. Test compound and/or vehicle is preincubated with 4.2 µg/ml enzyme in phosphate buffer pH 7.4 for 15 minutes at 37°C. The reaction is initiated by addition of 50 µM Kynuramine (as substrate) for another 60 minute incubation period and terminated by further addition of 1.2 N NaOH. Determination of the amount of 4-hydroxyquinoline formed is read spectrofluorimetrically at 325 nm/465 nm. Compounds are screened at 10 µM. A standard reference agent used for this screening test is Clorgyline, which has IC_{50} (µM) = 0.0022.

Serotonin Receptor (5-HT2B) activity

[00317] Evaluation of the agonist and antagonist activities of compounds at the human 5-HT2B receptor expressed in transfected CHO cells, is determined by measuring their effects on IP1 production using the Homogeneous Time Resolved Fluorescence (HTRF) detection method.

[00318] The screening procedure follows that reported in the literature,[15] whereby the CHO cells are suspended in a buffer containing 10 mM Hepes/NaOH (pH 7.4), 4.2 mM KCl, 146 mM NaCl, 1 mM $CaCl_2$, 0.5 mM $MgCl_2$, 5.5 mM glucose and 50 mM LiCl, then distributed in microplates at a density of about 2.10^4 cells/well and incubated for 30 min at 37°C in the presence of buffer (basal control), test compound, reference agonist or reference antagonist.

[00319] For stimulated control measurement, separate assay wells contain 1 µM 5-HT. For basal control measurements, separate assay wells do not contain 5-HT.

[00320] Following incubation, the cells are lysed and the fluorescence acceptor (D2-labeled IP1) and fluorescence donor (anti-IP1 antibody labelled with europium cryptate) are added. After 60 min at room temperature, the fluorescence transfer is measured at λex=337 nm and λem=620 and 665 nm using a microplate reader (Envision, Perkin Elmer). The IP1 concentration is determined by dividing the signal measured at 665 nm by that measured at 620 nm (ratio).

[00321] The agonist results are expressed as a percent of the control response to 1 µM 5-HT. The antagonist results are expressed as a percent inhibition of the control response to 30 nM 5-HT.

[00322] The standard reference agonist is 5-HT (serotonin), which is tested in each experiment at several concentrations to generate a concentration-response curve from which its EC_{50} value is calculated.

[00323] The standard reference antagonist is SB 206553 (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-f]indole), which is tested in each experiment at several concentrations to generate a concentration-response curve from which its IC50 value is calculated.

Human Potassium Channel (HERG) activity

[00324] The HERG potassium channel is mediates the delayed rectifier current (I_{Kr}) underlying cardiac repolarization. Due to either genetic defects in its pore-forming subunit or adverse drug effects, decreased HERG activity lengthens the QT interval and can lead to the

potentially lethal ventricular arrhythmia Torsades de pointes. The implication of (I_{Kr}) in cardiac arrhythmias and in anti-arrhythmic/pro-arrhythmic actions of drugs has driven intensive research interests in its structure-function relationship, the linkage between LQT-associated mutations and changes in channel function, and the mechanism of drug actions.

[00325] The screening procedure for HERG binding follows that reported in the literature,[16(a),(b)] whereby Human recombinant potassium channel HERG expressed in human HEK-293 cells are used in modified Tris-HCl buffer pH 7.4. A 7.5 µg aliquot is incubated with 3 nM [^{3}H]Dofetilide for 60 minutes at 25oC. Non-specific binding is estimated in the presence of 10 µM Dofetilide. Channel proteins are filtered and washed, the filters are then counted to determine [^{3}H]Dofetilide specifically bound. Compounds are screened at 10 µM. A standard reference agent used in this screen is Dofetilide, which has IC_{50} (nM) = 2.5, Ki (nM) = 1.7 and nH = 1.0.

DAT / NET / SERT Inhibition Results

[00326] The results of the screening tests for DAT, NET and SERT are presented in the table below, as (10 uM) concentration % displacement of radioligand by the MDMA analogue compounds at the three monoamine transporters, as a measure of affinity (shading) and % inhibition (values) of the compounds to the transporters. In addition to compounds of the invention, the following known compounds were screened for comparison; MDA = 3,4-Methylenedioxyamphetamine; MDDM = 3,4-Methylenedioxy-N,N-dimethylamphetamine; MDMA = racemic 3,4-methylenedioxy-N-methylamphetamine; R-MDMA = enantiomerically pure 3,4-methylenedioxy-N-methylamphetamine of absolute configuration Rectus; S-MDMA = enantiomerically pure 3,4-methylenedioxy-N-methylamphetamine of absolute configuration Sinister:

Compound	DAT Inhibition	NET Inhibition	SERT Inhibition
1A	60.3	55.8	2.45
1B	71.55	43.05	17.05
1BR	72.35	54.9	18
1BS	79.6	40.95	12.7
1C	93.8	84.85	27.45
1D	97.95	66.6	21.8
1E	100.45		32.05
1F	95.35	60.95	20.7
1G	93.85	70.2	34.25
1H	94.6	46.75	14.2
1I	94.1	45.35	22.15
1J	96.9	76.85	50.05
1L	88.75	54.4	7.75

Compound	DAT Inhibition	NET Inhibition	SERT Inhibition
2B	93.45	63.5	35.4
3A	34.25	37.2	9.25
3B	67.85	24.05	-1.25
3C	65.9	11.25	10.8
3D	54.2	3.25	18.75
3E	63.55	37.6	9.1
3F	46.4	27.45	-7.65
3G	57.95	37.3	-1.65
3H	77.05	83.75	32.2
4A	87.65	73	32.55
4B	89.55	78.45	40.75
4C	97.15	77.9	57.15
4D	96.15	83.05	21.85
4E	98.55	57.55	12.35
4F	89.2	88.9	0.3
4H	97.7	89.65	42.35
4J	94.65	64.05	-5.55
4K	98.45	96.8	37.35
5A	96.55	80.4	71.95
6A	90.75	76	30.55
8A	78.9	42.35	10.8
17A	75.8	70.35	32.75
MDA	23.15	32.65	13
MDDM	22.35	28.65	-8.4
MDMA	42.45	46.05	1
R-MDMA	38.15	28.9	-1
S-MDMA	40.55	26.85	2.75

Legend:

- 75% Affinity and above
- 50% - 74.99% Affinity
- 25% - 49.99% Affinity
- 0% - 24.99% Affinity

[00327] Dose-response data for selected compounds of embodiments of the invention, compared to known compounds (MDA = 3,4-Methylenedioxyamphetamine; MDDM = 3,4-Methylenedioxy-N,N-dimethylamphetamine; MDMA = racemic 3,4-methylenedioxy-N-methylamphetamine; R-MDMA = enantiomerically pure 3,4-methylenedioxy-N-methylamphetamine of absolute configuration Rectus; S-MDMA = enantiomerically pure 3,4-methylenedioxy-N-methylamphetamine of absolute configuration Sinister) are presented in the table below:

Compound	NET			DAT			SERT		
	IC_{50} (uM)	K_i (uM)	n_H	IC_{50} (uM)	K_i (uM)	n_H	IC_{50} (uM)	K_i (uM)	n_H
4B	2.29	2.27	1.19				20.0	3.27	1.07
MDDM	30.1	29.9	1.15	32.0	25.4	0.81	186	30.4	1.35
1D				0.41	0.33	1.07			
MDA	49.6	49.2	1.35	32.0	25.5	1.19	114	18.6	1.07
MDMA	37.5	37.2	0.98	20.9	16.6	1.08	187	30.5	1.16
R-MDMA	34.3	34.0	1.04	27.3	21.7	1.10			
S-MDMA	27.8	27.5	0.90	15.0	11.9	1.05	173	28.2	0.87
3A	43.3	43.0	1.02	21.7	17.2	0.92			
1C	1.08	1.07	1.39	0.51	0.40	1.12			
1F	12.1	12.0	0.67	0.40	0.32	0.98	60.1	9.81	0.85
1G							41.1	6.71	0.78
1J				0.33	0.27	1.13	9.06	1.48	1.01
1H				0.49	0.39	1.01			
1I	46.5	46.2	3.95	0.55	0.43	0.94	133	21.7	0.69
1E	1.78	1.76	1.19				30.2	4.94	0.91
2B	7.44	7.38	1.03	0.88	0.70	1.00	27.3	4.45	0.89
4K	16.7	16.6	0.83	0.32	0.25	1.15	19.6	3.2	0.66
4F	2.18	2.16	1.56						
4D	2.02	2.0	1.17						
4H	0.65	0.65	1.12	0.37	0.29	1.29	14.1	2.29	0.79
5A	2.77	2.75	1.09	0.4	0.32	0.92	3.47	0.57	0.93
3H	1.27	1.26	1.15						
1B	20.7	20.5	0.91	5.41	4.30	1.04	92.6	15.1	0.87
1BR	13.0	12.9	0.97	5.71	4.54	0.82	41.1	6.71	0.54
1BS	38.5	38.2	1.12	4.37	3.47	0.98	146	23.7	0.91

GENERAL

[00328] Each document, reference, patent application or patent cited in this text is expressly incorporated herein in their entirety by reference, which means that it should be read and considered by the reader as part of this text. That the document, reference, patent application or patent cited in this text is not repeated in this text is merely for reasons of conciseness.

[00329] It should be appreciated that throughout this specification, any reference to any prior publication, including prior patent publications and non-patent publications, is not an acknowledgment or admission that any of the material contained within the prior publication referred to was part of the common general knowledge as at the priority date of the application.

[00330] Any manufacturer's instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein,

are hereby incorporated herein by reference, and may be employed in the practice of the invention.

[00331] The invention described herein may include one or more range of values (eg. size, displacement and field strength etc). A range of values will be understood to include all values within the range, including the values defining the range, and values adjacent to the range which lead to the same or substantially the same outcome as the values immediately adjacent to that value which defines the boundary to the range.

[00332] The present invention is not to be limited in scope by any of the specific embodiments described herein. These embodiments are intended for the purpose of exemplification only. Functionally equivalent products, formulations and methods are clearly within the scope of the invention as described herein.

[00333] Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. The invention includes all such variation and modifications. The invention also includes all of the steps, features, formulations and compounds referred to or indicated in the specification, individually or collectively and any and all combinations or any two or more of the steps or features.

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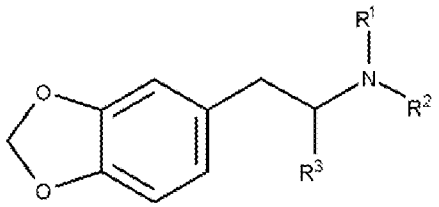
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CLAIMS

1. A compound of Formula I;



Formula I

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula I may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

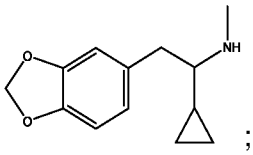
R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

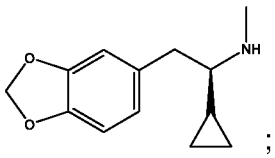
R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, $-OR^a$, $-SR^a$, $-NR^bR^c$, methyl, ethyl, $-C_{3\text{-}9}$alkyl, $-C_{1\text{-}9}$haloalkyl, $-C_{2\text{-}9}$alkenyl, $-C_{2\text{-}9}$haloalkenyl, $-C_{2\text{-}9}$alkynyl, $-C_{2\text{-}9}$haloalkynyl, $-C_{3\text{-}9}$cycloalkyl, $-C_{6\text{-}12}$bicycloalkyl, $-C_{6\text{-}12}$spirocycloalkyl, $-C_{3\text{-}9}$cyclohaloalkyl, $-C_{6\text{-}12}$bicyclohaloalkyl, $-C_{6\text{-}12}$spirocyclohaloalkyl, $-C_{3\text{-}9}$cycloalkenyl, $-C_{6\text{-}12}$bicycloalkenyl, $-C_{6\text{-}12}$spirocycloalkenyl, $-C_{3\text{-}9}$cyclohaloalkenyl, $-C_{6\text{-}12}$bicyclohaloalkenyl, $-C_{6\text{-}12}$spirocyclohaloalkenyl, $-C_{8\text{-}12}$cycloalkynyl, $-C_{9\text{-}14}$bicycloalkynyl, $-C_{9\text{-}14}$spirocycloalkynyl, $-C_{8\text{-}12}$cyclohaloalkynyl, $-C_{9\text{-}14}$bicycloalkynyl, $-C_{9\text{-}14}$spirocycloalkynyl, aryl, heteroaryl, $-C_{1\text{-}5}$alkyl-aryl, $-C_{2\text{-}5}$alkenyl-aryl, $-C_{2\text{-}5}$alkynyl-aryl, $-C_{1\text{-}5}$alkyl-heteroaryl, $-C_{2\text{-}5}$alkenyl-heteroaryl, $-C_{2\text{-}5}$alkynyl-heteroaryl, $-C_{1\text{-}5}$haloalkyl-aryl, $-C_{2\text{-}5}$haloalkenyl-aryl, $-C_{2\text{-}5}$haloalkynyl-aryl, $-C_{1\text{-}5}$haloalkyl-heteroaryl, $-C_{2\text{-}5}$haloalkenyl-heteroaryl, $-C_{2\text{-}5}$haloalkynyl-heteroaryl, $-C(=O)R^a$, $-C_{1\text{-}8}$alkyl-$C(=O)R^a$, $-C_{2\text{-}8}$alkenyl-$C(=O)R^a$, $-C_{2\text{-}8}$alkynyl-$C(=O)R^a$, $-C_{1\text{-}8}$haloalkyl-$C(=O)R^a$, $-C_{2\text{-}8}$haloalkenyl-$C(=O)R^a$, $-C_{2\text{-}8}$haloalkynyl-$C(=O)R^a$, $-CO_2R^a$, $-C_{1\text{-}8}$alkyl-CO_2R^a, $-C_{2\text{-}8}$alkenyl-CO_2R^a, $-C_{2\text{-}8}$alkynyl-CO_2R^a, $-C_{1\text{-}8}$haloalkyl-CO_2R^a, $-C_{2\text{-}8}$haloalkenyl-CO_2R^a, $-C_{2\text{-}8}$haloalkynyl-CO_2R^a, $-SO_2R^a$, $-C_{1\text{-}8}$alkyl-SO_2R^a, $-C_{2\text{-}8}$alkenyl-SO_2R^a, $-C_{2\text{-}8}$alkynyl-SO_2R^a, $-C_{1\text{-}8}$haloalkyl-SO_2R^a, $-C_{2\text{-}8}$haloalkenyl-SO_2R^a, $-C_{2\text{-}8}$haloalkynyl-SO_2R^a, $-C(=O)NR^bR^c$, $-C_{1\text{-}8}$alkyl-$C(=O)NR^bR^c$, $-C_{2\text{-}8}$alkynyl-$C(=O)NR^bR^c$, $-C_{2\text{-}8}$alkenyl-$C(=O)NR^bR^c$, $-C_{1\text{-}8}$haloalkyl-$C(=O)NR^bR^c$, $-C_{2\text{-}8}$haloalkynyl-$C(=O)NR^bR^c$, $-C_{2\text{-}8}$haloalkenyl-$C(=O)NR^bR^c$, -CN, $-C_{1\text{-}8}$alkyl-CN, $-C_{2\text{-}8}$alkenyl-CN, $-C_{2\text{-}8}$alkynyl-CN, $-C_{1\text{-}8}$haloalkyl-CN, $-C_{2\text{-}8}$haloalkenyl-CN, $-C_{2\text{-}8}$haloalkynyl-CN, $-CH_2$-O-R^a, $-C_{2\text{-}9}$alkyl-O-R^a, $-C_{2\text{-}9}$alkenyl-O-R^a, $-C_{2\text{-}9}$alkenyl-O-R^a, $-C_{2\text{-}9}$haloalkyl-O-R^a, $-C_{2\text{-}9}$haloalkenyl-O-R^a, $-C_{2\text{-}9}$haloalkenyl-O-R^a, $-CH_2$-S-R^a, $-C_{2\text{-}9}$alkyl-S-R^a, $-C_{2\text{-}9}$alkenyl-S-R^a, $-C_{2\text{-}9}$alkenyl-S-R^a, $-C_{2\text{-}9}$haloalkyl-S-R^a, $-C_{2\text{-}9}$haloalkenyl-S-R^a, and $-C_{2\text{-}9}$haloalkenyl-S-R^a;

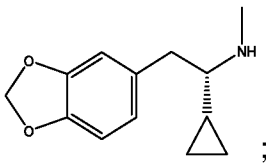
or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

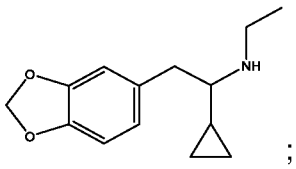
R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl;

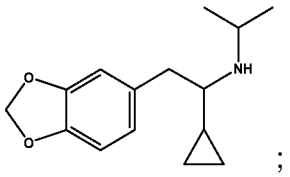
wherein the compound of Formula I is not a compound selected from the group comprising;

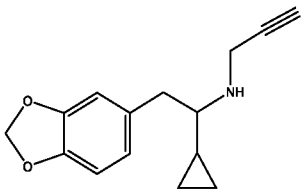

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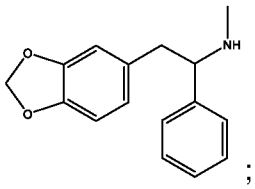

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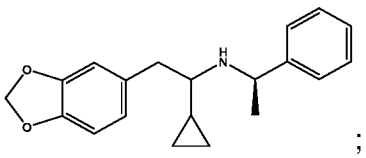

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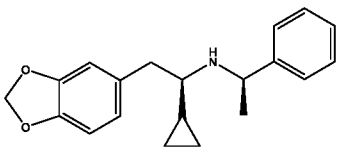

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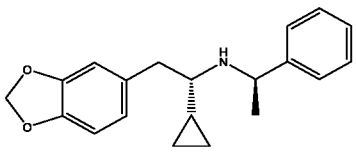

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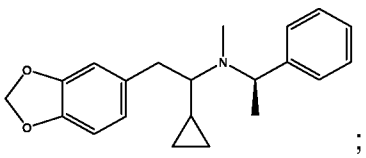

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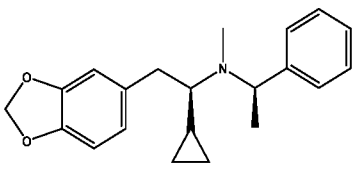

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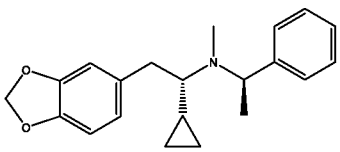

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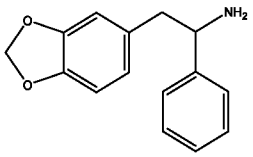

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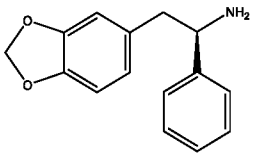

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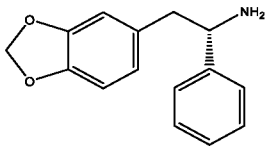

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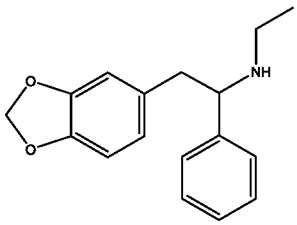

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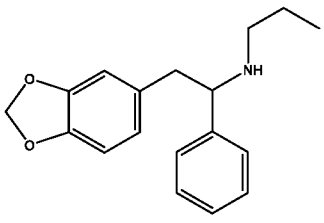

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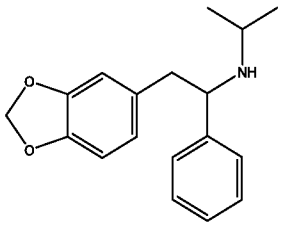

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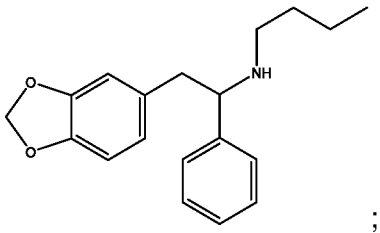
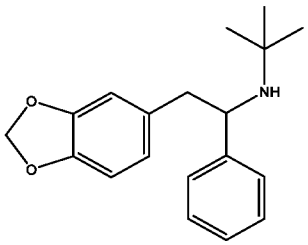
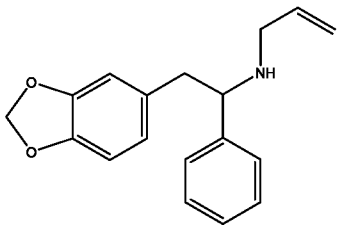
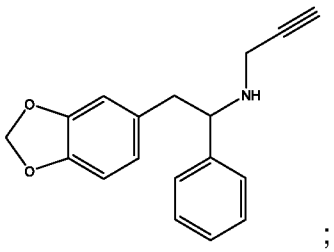
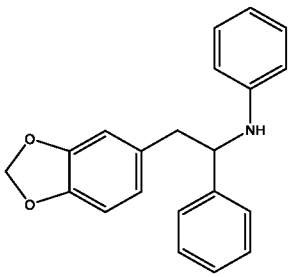
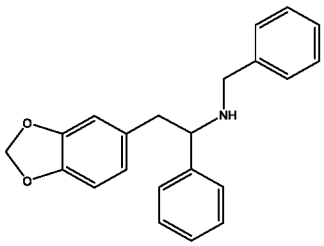
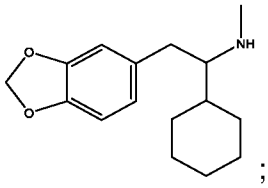
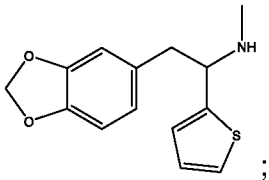
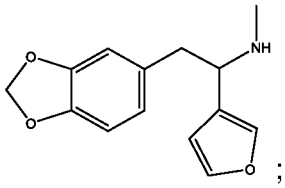
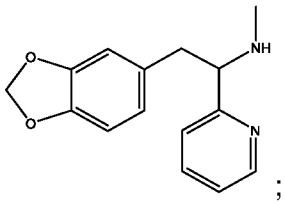
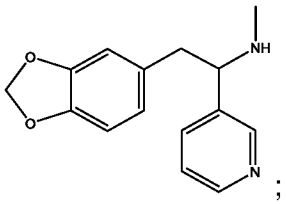
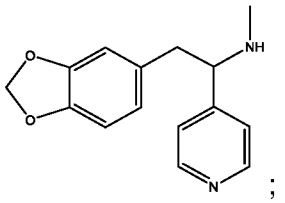
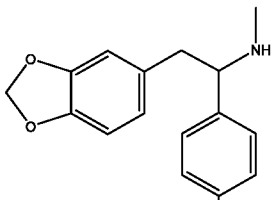
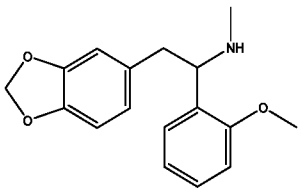
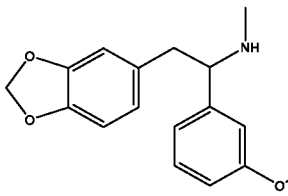
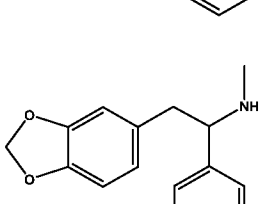
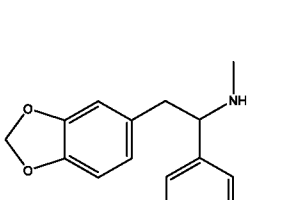
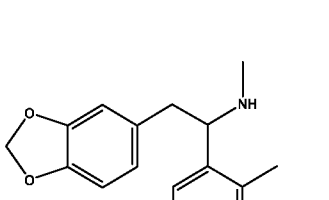

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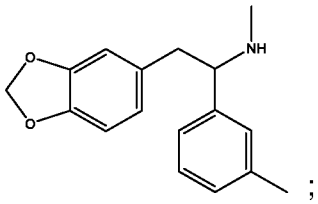
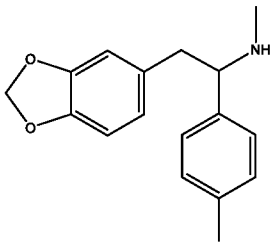
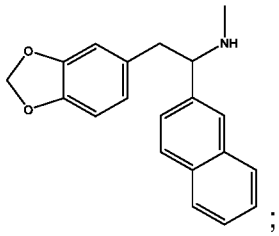

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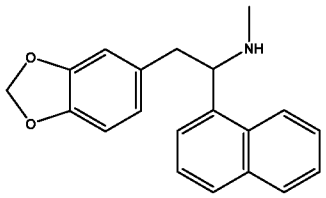
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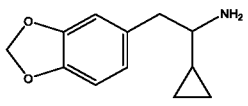
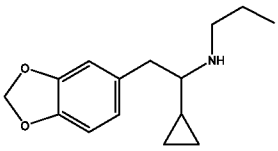
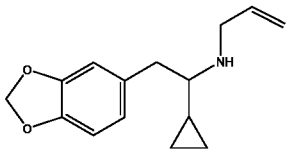
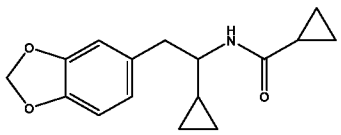
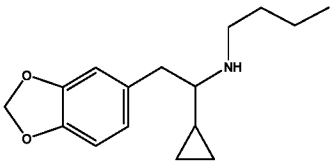
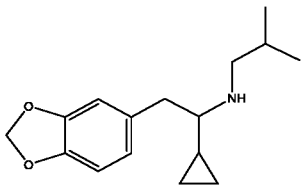
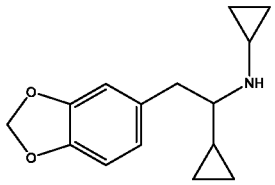
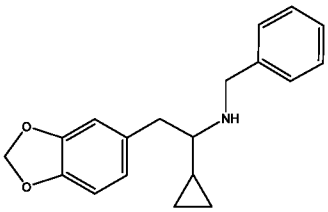
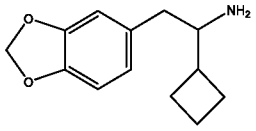
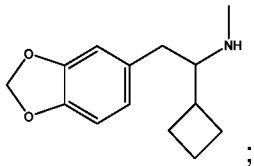
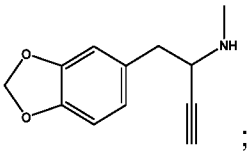
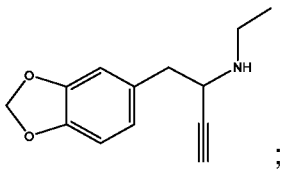
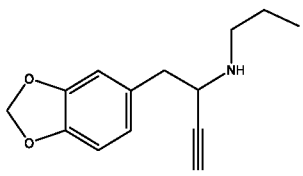
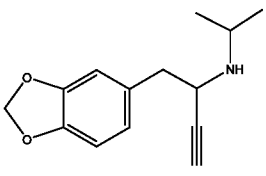
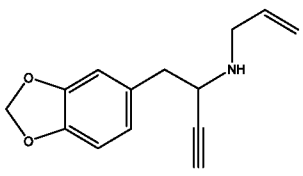
2. A compound according to claim 1, wherein R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, propyl, isopropyl, allyl, cyclopropylmethyl, propargyl, butyl, isobutyl, *t*-butyl, cyclobutyl, -C_{1-9}haloalkyl, -C_{2-9}alkyl-O-R^a, -C_{3-9}heterocycloalkyl, cyclopropyl, phenyl, benzyl, and 1-phenylethyl; or wherein R^1 and R^2 together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring.

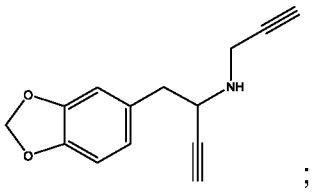
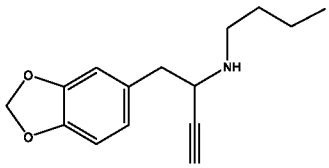
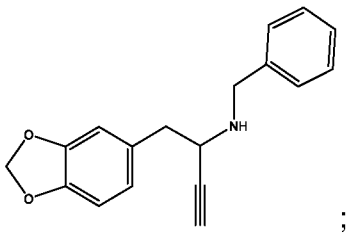
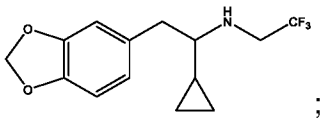
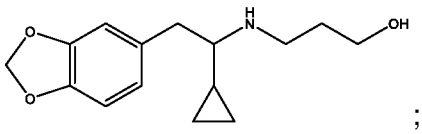
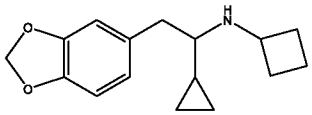
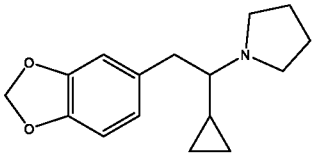
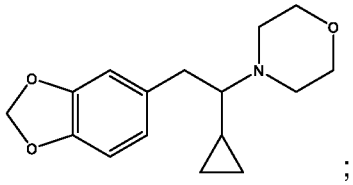
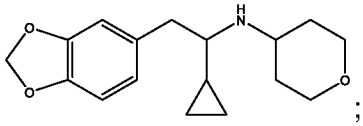
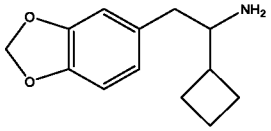
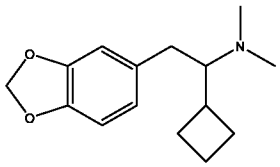
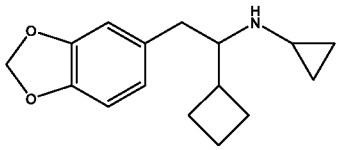
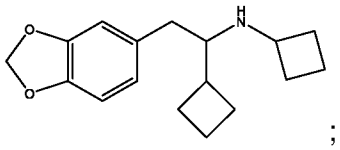
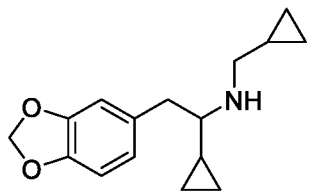
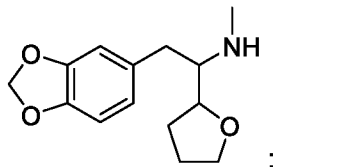
3. A compound according to claim 1 or claim 2, wherein R^1 is H or methyl, and R^2 is selected from the group consisting of; methyl, ethyl, propyl, isopropyl, allyl, cyclopropylmethyl, propargyl, butyl, isobutyl, *t*-butyl, -CH_2CF_3, -C_3alkyl-OH, oxanyl, cyclopropyl, cyclobutyl, phenyl, benzyl, and 1-phenylethyl; or wherein R^1 and R^2 together form a pyrrolidinyl or morpholinyl ring.

4. A compound according to any one of claims 1 to 3, wherein R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, fluorocyclopropyl, 1-fluorocyclopropan-1-yl, cyclobutyl, fluorocyclobutyl, difluorocyclobutyl, 3,3-difluorocyclobutan-1-yl, methylcyclobutyl, dimethylcyclobutyl, 3,3-dimethylcyclobutan-1-yl, cyclopentyl, vinyl, allyl, acetylenyl, cyclohexyl, propargyl, cyanomethyl, thiophen-2-yl, thiophen-3-yl, furan-2-yl, furan-3-yl, triazol-1-yl, triazol-4-yl, triazol-5-yl, oxan-4-yl, oxan-3-yl, oxan-2-yl, pyridine-2-yl, pyridine-3-yl, pyridine-4-yl, phenyl, 1,1'-biphenyl, 1,2'-biphenyl, 1,3'-biphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, o-tolyl, m-tolyl, p-tolyl, naphthalen-1-yl, naphthalen-2-yl, cyclopent-1-en-1-yl, cyclopent-1-en-3-yl, cyclopent-1-en-4-yl, cyclopenta-1,3-dien-2-yl, cyclopenta-1,3-dien-1-yl, cyclopenta-1,3-dien-5-yl, cyclohex-1-en-1-yl, cyclohex-1-en-3-yl, cyclohex-1-en-5-yl, cyclohexa-1,3-dien-1-yl, cyclohexa-1,3-dien-2-yl, cyclohexa-1,3-dien-5-yl, cyclohexa-1,4-dien-1-yl, cyclohexa-1,4-dien-3-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothiophene-2-yl, tetrahydrothiophene-3-yl, oxazolidin-5-yl, oxazolidin-4-yl, oxazolidin-2-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, 1,3-dioxolan-2-yl, 1,3-dioxolan-4-yl, bicyclo[1.1.0]butan-1-yl, tricyclo[1.1.0.$0^{2,4}$]butan-1-yl,

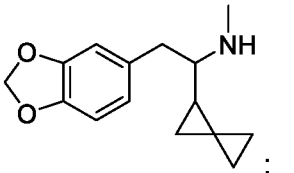
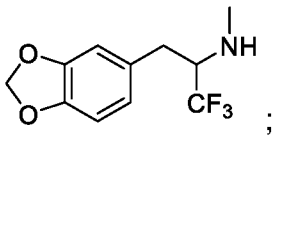
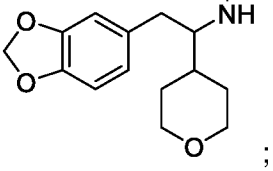
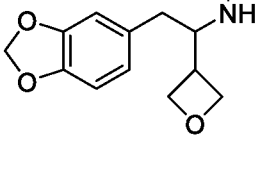
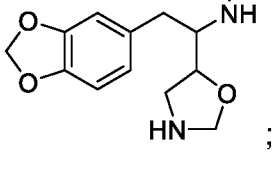
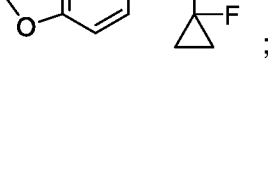
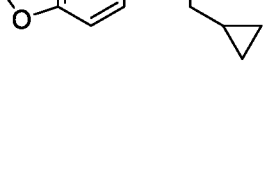
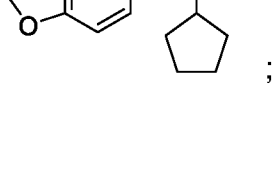
bicyclo[1.1.0]butan-2-yl, spiro[2.2]pentan-1-yl, bicyclo[2.1.0]pentan-1-yl, bicyclo[2.1.0]pentan-5-yl, bicyclo[2.1.0]pentan-1-yl, bicyclo[2.1.0]pentan-2-yl, bicyclo[1.1.1]pentan-2-yl, bicyclo[1.1.1]pentan-1-yl, spiro[2.3]hexan-4-yl, spiro[2.3]hexan-5-yl, oxetan-2-yl, thietane-2-yl, oxetan-3-yl, thietane-3-yl, 2-oxabicyclo[2.1.0]pentan-1-yl, 2-thiabicyclo[2.1.0]pentan-1-yl, 2-oxabicyclo[2.1.0]pentan-5-yl, 2-thiabicyclo[2.1.0]pentan-5-yl, 2-oxabicyclo[2.1.0]pentan-4-yl, 2-thiabicyclo[2.1.0]pentan-4-yl, 2-oxabicyclo[2.1.0]pentan-3-yl, 2-thiabicyclo[2.1.0]pentan-3-yl, 2-oxabicyclo[2.1.0]pentan-4-yl, 2-thiabicyclo[2.1.0]pentan-4-yl, oxabicyclo[2.1.0]pentan-5-yl, 2-thiabicyclo[2.1.0]pentan-5-yl, 2-oxabicyclo[2.1.0]pentan-1-yl, 2-thiabicyclo[2.1.0]pentan-1-yl, 2-oxabicyclo[1.1.1]pentan-4-yl, 2-oxabicyclo[1.1.1]pentan-1-yl, 5-oxaspiro[2.3]hexan-4-yl, 4-oxaspiro[2.3]hexan-5-yl, 2-thiabicyclo[1.1.1]pentan-4-yl, 2-thiabicyclo[1.1.1]pentan-1-yl, 5-thiaspiro[2.3]hexan-4-yl, 4-thiaspiro[2.3]hexan-5-yl, 4-oxaspiro[2.3]hexan-6-yl, and 4-thiaspiro[2.3]hexan-6-yl.

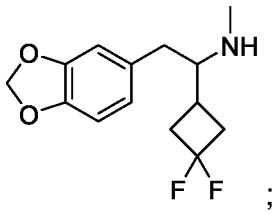
5. A compound according to any one of claims 1 to 4, wherein the compound is selected from the group consisting of;


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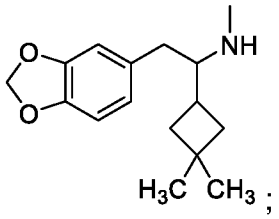

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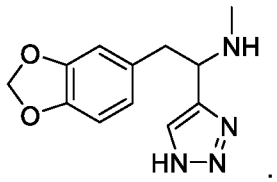


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and

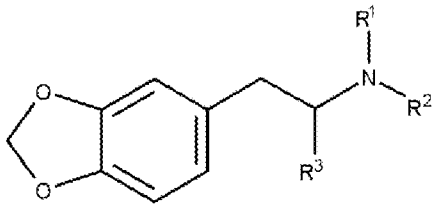


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6. A compound of any one of claims 1 to 5 for use, as a medicament.

7. A composition comprising a compound according to any one of claims 1 to 6, and one or more pharmaceutically acceptable carrier(s) and/or diluent(s) and/or excipient(s).

8. Use of a compound of Formula II;



Formula II

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula II may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c,

-C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, -OR^a, -SR^a, -NR^bR^c, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c,

-C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl;

for the manufacture of a medicament for the treatment or prevention of a disease, disorder, injury or trauma; preferably wherein the disease, disorder, injury or trauma may be treated or prevented via the modulation of;

(i) Serotonin Transporter (SERT) activity; and/or
(ii) Dopamine Transporter (DAT) activity; and/or
(iii) Norepinephrine Transporter (NET) activity; and/or
(iv) Monoamine Oxidase A (MAO-A) activity; and/or
(v) Serotonin Receptor (5-HT2B) activity;

more preferably wherein the disease, disorder, injury or trauma, is a disease, disorder, injury or trauma associated with the central nervous system;

most preferably wherein the disease, disorder, injury or trauma associated with the central nervous system is selected from the group consisting of; dementia in Alzheimer disease (including early onset, late onset, atypical, mixed, or unspecified), vascular dementia (including arteriosclerotic, acute onset, multi-infarct, subcortical, mixed cortical or unspecified), dementia in Pick disease, dementia in Creutzfeldt-Jakob disease, dementia in Huntington disease, dementia in Parkinson disease, dementia in human immunodeficiency virus [HIV] disease, dementia in cerebral lipidosis, dementia in epilepsy, dementia in hepatolenticular degeneration, dementia in hypercalcaemia, dementia in hypothyroidism, dementia in intoxications, dementia in Lewy Body disease, dementia in Multiple Sclerosis, dementia in neurosyphilis, dementia in niacin deficiency, dementia in polyarteritis nodosa, dementia in systemic lupus erythematosus, dementia in trypanosomiasis, dementia in uraemia, dementia in vitamin b_{12} deficiency,

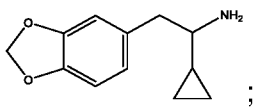
unspecified dementia (including dementia not otherwise specified, psychosis not otherwise specified, senile, delirium, depressed, paranoid, or acute confusional state), organic amnesic syndrome, Korsakov psychosis, Korsakov syndrome, delirium, brain syndrome, confusional state, infective psychosis, organic reaction, psycho-organic syndrome, organic hallucinosis, organic catatonic disorder, organic delusional [schizophrenia-like] disorder, organic mood [affective] disorders, organic anxiety disorder, organic dissociative disorder, organic emotionally labile [asthenic] disorder, mild cognitive disorder, epileptic psychosis, brain syndrome not otherwise specified, mental disorder not otherwise specified, organic personality disorder, pseudopsychopathic personality disorder, pseudoretarded personality disorder, frontal lobe syndrome, limbic epilepsy personality syndrome, lobotomy syndrome, postleucotomy syndrome, postencephalitic syndrome, postconcussional syndrome, postcontusional syndrome (encephalopathy), post-traumatic brain syndrome, nonpsychotic, right hemispheric organic affective disorder, organic psychosyndrome, mental and behavioural disorders due to use of alcohol, mental and behavioural disorders due to use of opioids, mental and behavioural disorders due to use of cannabinoids, mental and behavioural disorders due to use of sedatives or hypnotics, mental and behavioural disorders due to use of cocaine, mental and behavioural disorders due to use of stimulants including caffeine, mental and behavioural disorders due to use of hallucinogens, mental and behavioural disorders due to use of tobacco, mental and behavioural disorders due to use of volatile solvents, mental and behavioural disorders due to use of other psychoactive substances (including any combination of psychoactive substances), schizophrenia, paranoid schizophrenia, paraphrenic schizophrenia, hebephrenic schizophrenia, hebephrenia, disorganized schizophrenia, catatonic schizophrenia, catatonic stupor, schizophrenic catalepsy, schizophrenic catatonia, schizophrenic flexibilitas cerea, undifferentiated schizophrenia, atypical schizophrenia, post-schizophrenic depression, residual schizophrenia, chronic undifferentiated schizophrenia, schizophrenic Restzustand, simple schizophrenia, cenesthopathic schizophrenia, schizophreniform disorder, schizophreniform psychosis, schizophrenia not otherwise specified, schizotypal disorder, latent schizophrenic reaction, borderline schizophrenia, latent schizophrenia, prepsychotic schizophrenia, prodromal schizophrenia, pseudoneurotic schizophrenia, pseudopsychopathic schizophrenia, schizotypal personality disorder, persistent delusional disorder, delusional disorder, paranoia, paranoid psychosis, paranoid state, paraphrenia (late), Sensitiver Beziehungswahn, delusional dysmorphophobia, involutional paranoid state, paranoia querulans, acute and transient psychotic disorder, acute polymorphic psychotic disorder without symptoms of schizophrenia, acute polymorphic psychotic disorder with symptoms of schizophrenia, Bouffée délirante, cycloid psychosis, acute schizophrenia-like psychotic disorder, acute (undifferentiated) schizophrenia, brief schizophreniform disorder, brief schizophreniform psychosis, oneirophrenia, schizophrenic reaction, paranoid reaction, psychogenic paranoid psychosis, acute transient psychotic disorders, induced delusional disorder, Folie à deux, induced paranoid disorder,

induced psychotic disorder, schizoaffective disorder (including manic, depressive, mixed and unspecified), nonorganic psychotic disorder, chronic hallucinatory psychosis, manic episode disorder, bipolar disorder, single manic episode disorder, hypomania, mania without psychotic symptoms, mania with psychotic symptoms, mania with mood-congruent psychotic symptoms, mania with mood-incongruent psychotic symptoms, manic stupor, mania not otherwise specified, bipolar affective disorder, manic depression, manic-depressive illness, manic-depressive psychosis, manic-depressive reaction, bipolar II disorder, depression, psychogenic depression, reactive depression, mild depression, moderate depression, severe depression, agitated depression, major depression, vital depression, atypical depression, monopolar depression, depressive disorder not otherwise specified, recurrent depressive disorder, seasonal depressive disorder, cyclothymia, affective personality disorder, cycloid personality, cyclothymic personality, dysthymia, depressive neurosis, depressive personality disorder, neurotic depression, persistent anxiety depression, phobic anxiety disorder, agoraphobia, panic disorder, social phobia, anthropophobia, social neurosis, acrophobia, animal phobia, claustrophobia, simple phobia, phobic state not otherwise specified, episodic paroxysmal anxiety, generalized anxiety disorder, anxiety hysteria, anxiety not otherwise specified, obsessive-compulsive disorder, anankastic neurosis, obsessive-compulsive neurosis, predominantly obsessional thoughts or ruminations, predominantly compulsive acts [obsessional rituals], acute stress reaction, acute crisis reaction, acute reaction to stress, combat fatigue, crisis state, psychic shock, post-traumatic stress disorder (PTSD), traumatic neurosis, adjustment disorder, culture shock, grief reaction, paediatric hospitalism, dissociative [conversion] disorder, conversion hysteria, conversion reaction, dissociative amnesia, dissociative fugue, dissociative stupor, trance disorder, possession disorder, dissociative motor disorder, psychogenic aphonia, psychogenic dysphonia, dissociative convulsions, dissociative anaesthesia, dissociative sensory loss, ganser syndrome, multiple personality dissociative disorder, psychogenic confusion, psychogenic twilight state, somatoform disorder, somatization disorder, briquet disorder, multiple psychosomatic disorder, undifferentiated somatoform disorder, undifferentiated psychosomatic disorder, hypochondriacal disorder, body dysmorphic disorder, dysmorphophobia (nondelusional), hypochondriacal neurosis, hypochondriasis, nosophobia, somatoform autonomic dysfunction, cardiac neurosis, da costa syndrome, gastric neurosis, neurocirculatory asthenia, psychogenic aerophagy, psychogenic cough, psychogenic diarrhoea, psychogenic dyspepsia, psychogenic dysuria, psychogenic flatulence, psychogenic hiccough, psychogenic hyperventilation, psychogenic increased frequency of micturition, psychogenic irritable bowel syndrome, psychogenic pylorospasm, persistent somatoform pain disorder, psychalgia, psychogenic backache, psychogenic headache, somatoform pain disorder, psychogenic dysmenorrhoea, psychogenic dysphagia, globus hystericus, psychogenic pruritus, psychogenic torticollis, psychogenic teeth-grinding, psychosomatic disorder not otherwise specified, neurasthenia, fatigue syndrome, depersonalization-derealization syndrome, Dhat

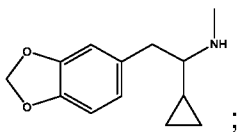
syndrome, occupational neurosis, writer cramp neurosis, psychasthenia, psychasthenic neurosis, psychogenic syncope, neurosis not otherwise specified, eating disorder, anorexia nervosa, atypical anorexia nervosa, bulimia nervosa, bulimia not otherwise specified, hyperorexia nervosa, atypical bulimia nervosa, overeating associated with other psychological disturbances, psychogenic overeating, vomiting associated with other psychological disturbances, psychogenic vomiting, pica, psychogenic loss of appetite, nonorganic sleep disorder, nonorganic insomnia, nonorganic hypersomnia, nonorganic disorder of the sleep-wake schedule, psychogenic inversion of circadian rhythm, psychogenic inversion of nyctohemeral rhythm, psychogenic inversion of sleep rhythm, sleepwalking [somnambulism], sleep terrors [night terrors], nightmares, dream anxiety disorder, emotional sleep disorder not otherwise specified, sexual dysfunction not caused by organic disorder or disease, lack or loss of sexual desire, frigidity, hypoactive sexual desire disorder, sexual aversion, lack of sexual enjoyment, sexual anhedonia, failure of genital response, female sexual arousal disorder, male erectile disorder, psychogenic impotence, orgasmic dysfunction, inhibited orgasm, psychogenic anorgasmy, premature ejaculation, psychogenic vaginismus, nonorganic dyspareunia, psychogenic dyspareunia, nymphomania, satyriasis, sexual dysfunction not otherwise specified, postnatal depression, postpartum depression, puerperal psychosis, puerperal mental disorder, psychological and behavioural factors associated with physical disorders or diseases (including but not limited to asthma, dermatitis, gastric ulcer, irritable bowel syndrome, ulcerative colitis, and urticaria), abuse of non-dependence-producing substances (including but not limited to antacids, herbal remedies, folk remedies, steroids, hormones, vitamins, and laxatives), psychogenic physiological dysfunction not otherwise specified, paranoid personality disorder, expansive paranoid personality disorder, fanatic paranoid personality disorder, querulant paranoid personality disorder, sensitive paranoid personality disorder, schizoid personality disorder, dissocial personality disorder, amoral personality disorder, antisocial personality disorder, asocial personality disorder, psychopathic personality disorder, sociopathic personality disorder, emotionally unstable personality disorder, aggressive personality disorder, borderline personality disorder, explosive personality disorder, histrionic personality disorder, hysterical personality disorder, psychoinfantile personality disorder, anankastic personality disorder, compulsive personality disorder, obsessional personality disorder, obsessive-compulsive personality disorder, anxious [avoidant] personality disorder, dependent personality disorder, asthenic personality disorder, inadequate personality disorder, passive personality disorder, self-defeating personality disorder, eccentric personality disorder, haltlose type personality disorder, immature personality disorder, narcissistic personality disorder, passive-aggressive personality disorder, psychoneurotic personality disorder, character neurosis not otherwise specified, pathological personality not otherwise specified, mixed personality disorders, personality and behavioural disorder due to brain disease, personality and behavioural disorder due to brain damage, personality and behavioural disorder due to brain dysfunction, enduring

personality change after catastrophic experience (including but not limited to concentration camp experiences, disasters, prolonged captivity with an imminent possibility of being killed, prolonged exposure to life-threatening situations such as being a victim of terrorism, or prolonged torture), enduring personality change after psychiatric illness, chronic pain personality syndrome, enduring personality change unspecified, habit disorder, impulse disorder, pathological gambling, compulsive gambling, pathological fire-setting [pyromania], pathological stealing [kleptomania], trichotillomania, intermittent explosive disorder, gender identity disorder, transsexualism, dual-role transvestism, gender-role disorder, sexual preference disorder, fetishism, fetishistic transvestism, exhibitionism, voyeurism, paedophilia, sadomasochism, frotteurism, necrophilia, sexual deviation not otherwise specified, sexual maturation disorder, egodystonic sexual orientation, sexual relationship disorder, psychosexual development disorder, elaboration of physical symptoms for psychological reasons, compensation neurosis, intentional production or feigning of symptoms or disabilities, either physical or psychological [factitious disorder], hospital hopper syndrome, Münchhausen syndrome, peregrinating patient, character disorder not otherwise specified, relationship disorder not otherwise specified, hyperkinetic disorder, disturbance of activity and attention, attention deficit disorder with hyperactivity, attention deficit hyperactivity disorder, attention deficit syndrome with hyperactivity, hyperkinetic conduct disorder, hyperkinetic syndrome not otherwise specified, conduct disorder, unsocialized conduct disorder, socialized conduct disorder, oppositional defiant disorder, depressive conduct disorder, separation anxiety disorder, sibling rivalry disorder, overanxious disorder, childhood emotional disorder not otherwise specified, elective mutism, selective mutism, reactive attachment disorder, disinhibited attachment disorder, affectionless psychopathy, institutional syndrome, childhood disorder of social functioning, tic disorder, transient tic disorder, chronic motor tic disorder, chronic vocal tic disorder, combined vocal and multiple motor tic disorder [de la Tourette], Tourette's syndrome, nonorganic enuresis, functional enuresis, psychogenic enuresis, urinary incontinence of nonorganic origin, nonorganic encopresis, functional encopresis, incontinence of faeces of nonorganic origin, psychogenic encopresis, feeding disorder of infancy and childhood, rumination disorder of infancy, stereotyped movement disorder, stuttering [stammering], cluttering, attention deficit disorder without hyperactivity, excessive masturbation, nail-biting, nose-picking, thumb-sucking, and mental disorders not otherwise specified.

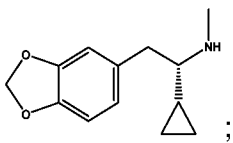
9. The use of claim 8, wherein the compound is selected from the group consisting of;



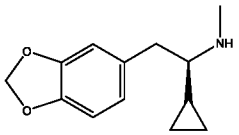
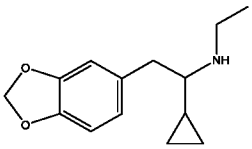
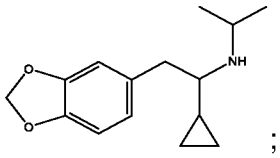
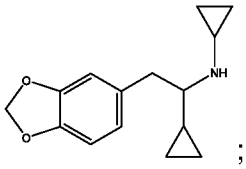
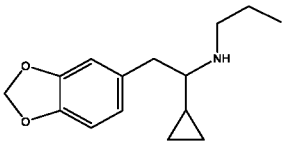
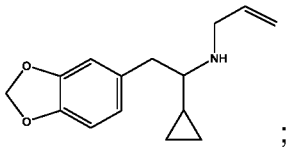
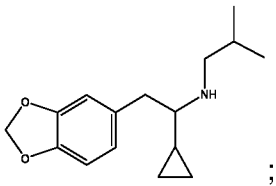
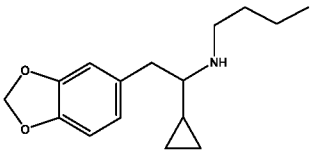
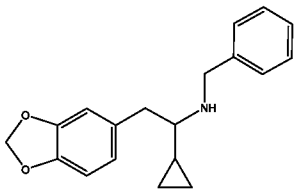
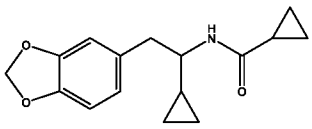
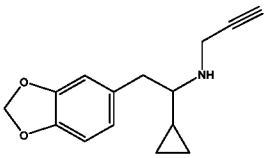
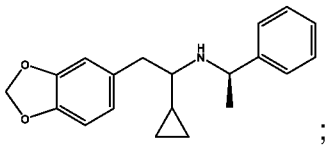
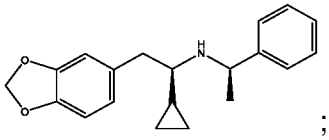
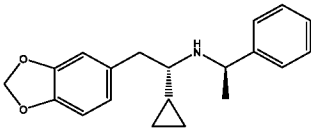
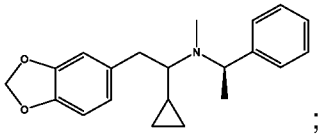
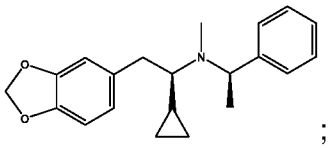
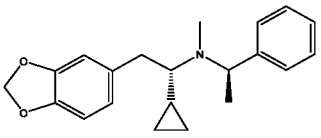
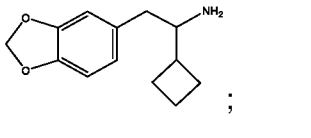
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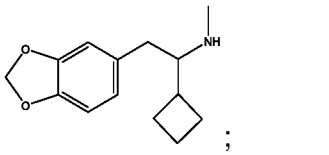
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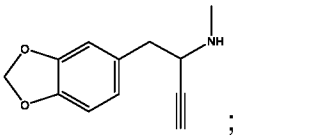
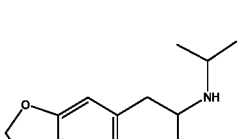
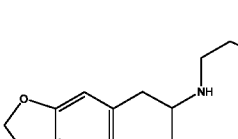
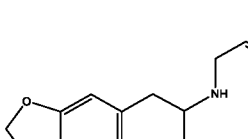
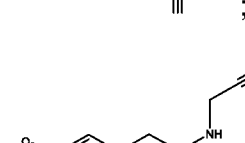
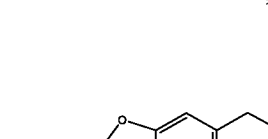
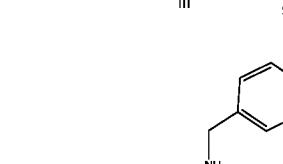
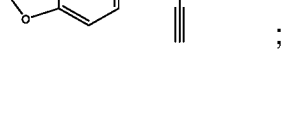
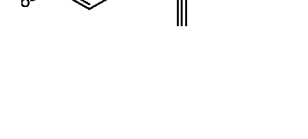
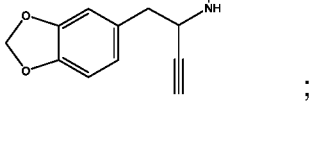


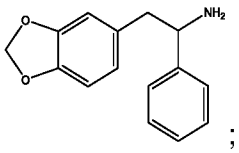
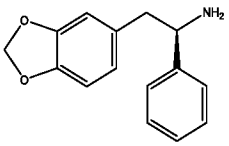
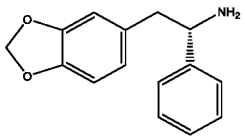
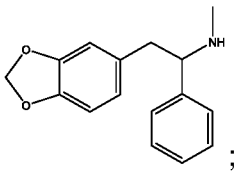
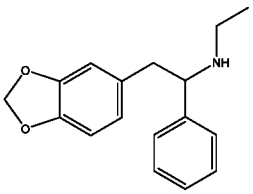
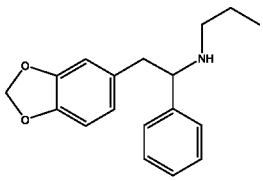
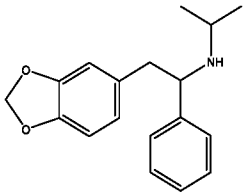
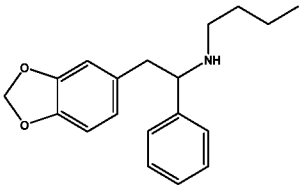
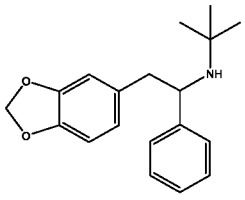
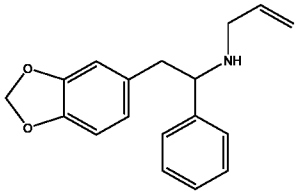
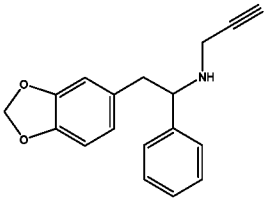
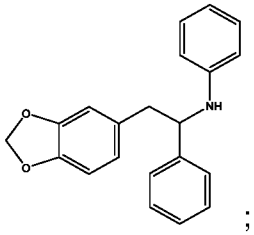
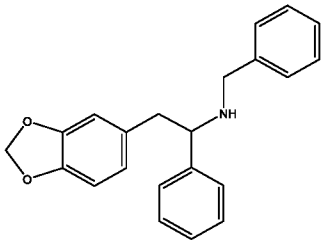
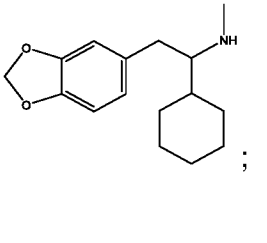
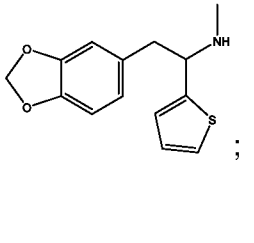
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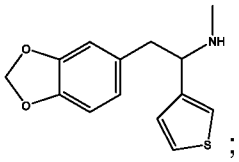
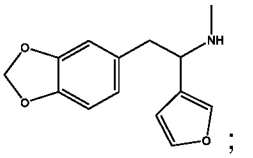
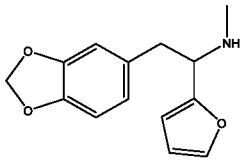
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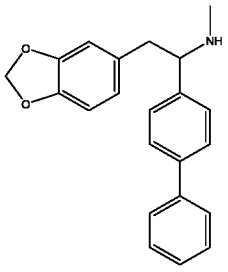
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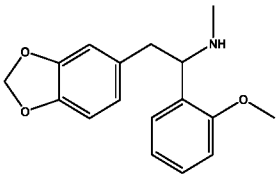
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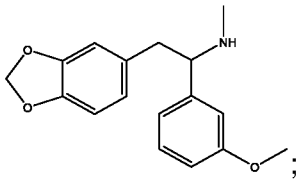
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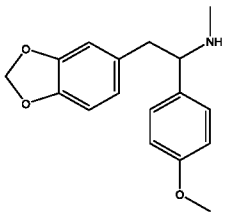
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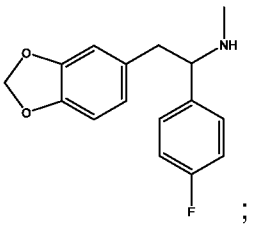
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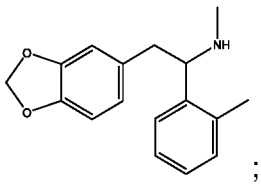

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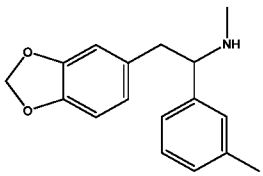

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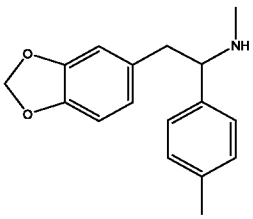

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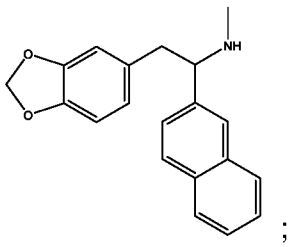

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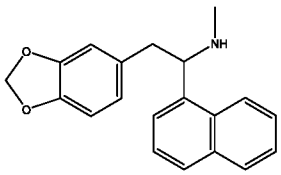

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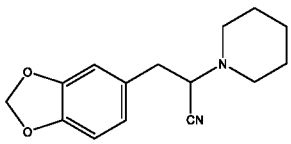

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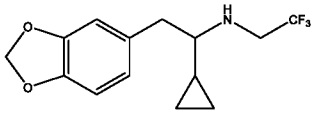

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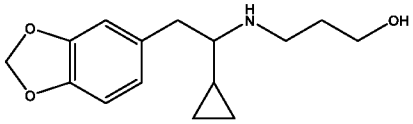

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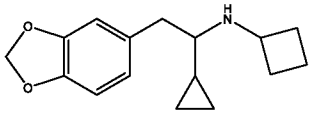

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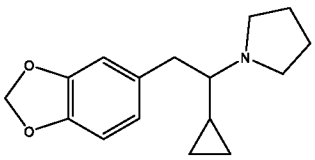

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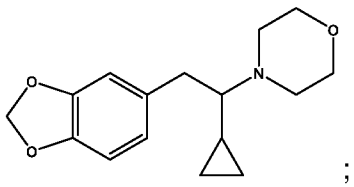

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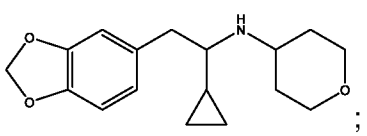

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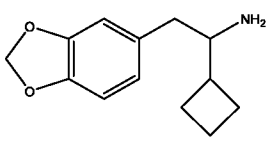

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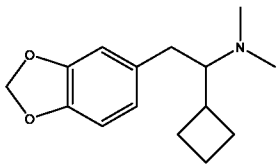

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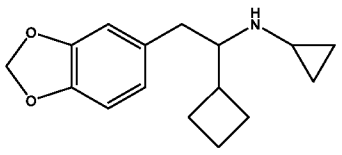

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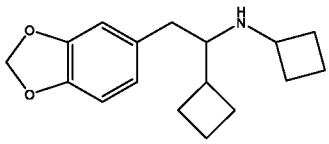

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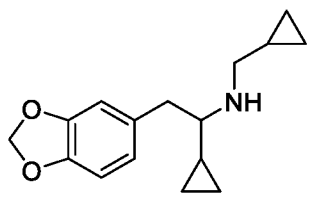

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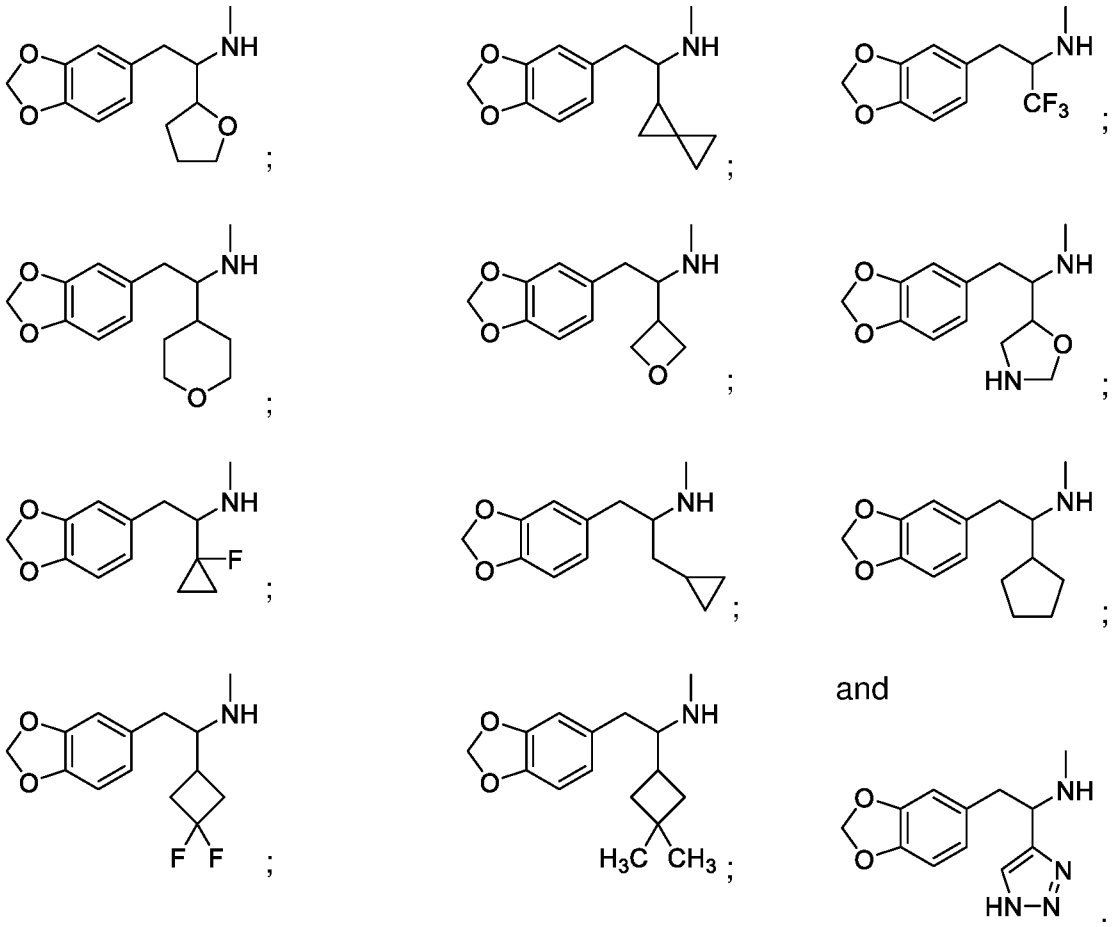

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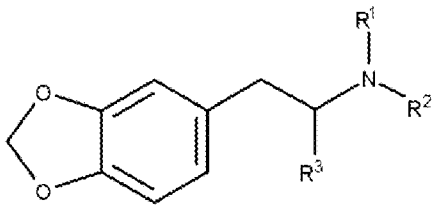

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and

10. A method of treating or preventing a disease, disorder, injury or trauma, comprising the administration of an effective amount of a compound of Formula II to a subject in need thereof;



Formula II

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula II may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl,

-C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, -OR^a, -SR^a, -NR^bR^c, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, -C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl,

-C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl and -C_{2-5}haloalkynyl-heteroaryl;

preferably wherein the disease, disorder, injury or trauma may be treated or prevented via the modulation of;

(a) Serotonin Transporter (SERT) activity; and/or

(b) Dopamine Transporter (DAT) activity; and/or

(c) Norepinephrine Transporter (NET) activity; and/or

(d) Monoamine Oxidase A (MAO-A) activity; and/or

(e) Serotonin Receptor (5-HT2B) activity;

more preferably wherein the disease, disorder, injury or trauma, is a disease, disorder, injury or trauma associated with the central nervous system;

most preferably wherein the disease, disorder, injury or trauma associated with the central nervous system is selected from the group consisting of; dementia in Alzheimer disease (including early onset, late onset, atypical, mixed, or unspecified), vascular dementia (including arteriosclerotic, acute onset, multi-infarct, subcortical, mixed cortical or unspecified), dementia in Pick disease, dementia in Creutzfeldt-Jakob disease, dementia in Huntington disease, dementia in Parkinson disease, dementia in human immunodeficiency virus [HIV] disease, dementia in cerebral lipidosis, dementia in epilepsy, dementia in hepatolenticular degeneration, dementia in hypercalcaemia, dementia in hypothyroidism, dementia in intoxications, dementia in Lewy Body disease, dementia in Multiple Sclerosis, dementia in neurosyphilis, dementia in niacin deficiency, dementia in polyarteritis nodosa, dementia in systemic lupus erythematosus, dementia in trypanosomiasis, dementia in uraemia, dementia in vitamin b_{12} deficiency, unspecified dementia (including dementia not otherwise specified, psychosis not otherwise specified, senile, delirium, depressed, paranoid, or acute confusional state), organic amnesic syndrome, Korsakov psychosis, Korsakov syndrome, delirium, brain syndrome, confusional state, infective psychosis, organic reaction, psycho-organic syndrome, organic hallucinosis, organic catatonic disorder, organic delusional [schizophrenia-like] disorder, organic mood [affective] disorders, organic anxiety disorder, organic dissociative disorder, organic emotionally labile [asthenic] disorder, mild cognitive disorder, epileptic psychosis, brain syndrome not otherwise specified, mental disorder not otherwise specified, organic personality disorder, pseudopsychopathic personality disorder, pseudoretarded personality disorder, frontal lobe syndrome, limbic epilepsy personality syndrome, lobotomy syndrome, postleucotomy syndrome, postencephalitic syndrome, postconcussional syndrome, postcontusional syndrome (encephalopathy), post-traumatic brain syndrome, nonpsychotic, right hemispheric organic affective disorder, organic psychosyndrome, mental and behavioural disorders due to use of alcohol, mental and behavioural disorders due to use of opioids, mental and behavioural disorders due to use of cannabinoids, mental and behavioural disorders due to use of sedatives or hypnotics, mental and behavioural disorders due to use of cocaine, mental and behavioural disorders due to use of stimulants including caffeine, mental and behavioural disorders due to use of hallucinogens, mental and behavioural disorders due to use of tobacco, mental and behavioural disorders due to use of volatile solvents, mental and behavioural disorders due to use of other psychoactive substances (including any combination of psychoactive substances), schizophrenia, paranoid schizophrenia, paraphrenic schizophrenia, hebephrenic schizophrenia, hebephrenia, disorganized schizophrenia, catatonic schizophrenia, catatonic stupor, schizophrenic catalepsy, schizophrenic catatonia, schizophrenic flexibilitas cerea, undifferentiated schizophrenia, atypical schizophrenia, post-schizophrenic depression, residual schizophrenia, chronic undifferentiated schizophrenia, schizophrenic Restzustand, simple schizophrenia, cenesthopathic schizophrenia, schizophreniform disorder, schizophreniform psychosis, schizophrenia not otherwise specified, schizotypal disorder, latent schizophrenic

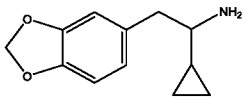
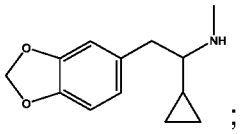
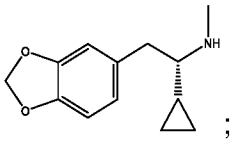
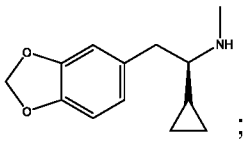
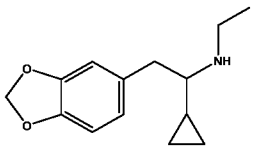
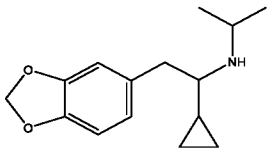
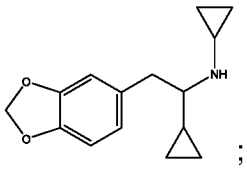
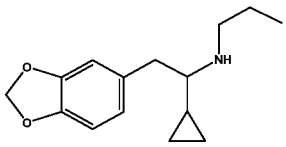
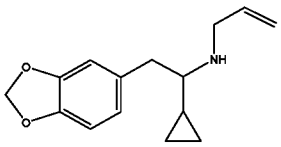
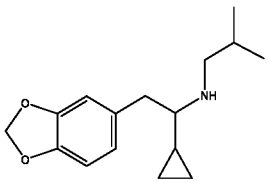
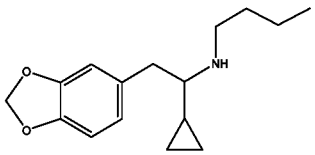
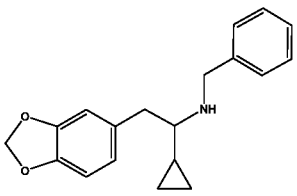
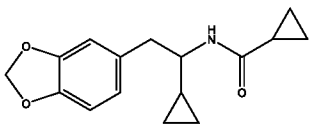
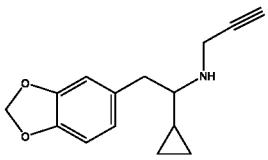
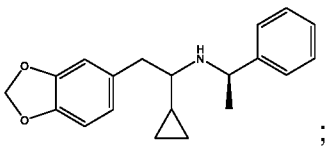
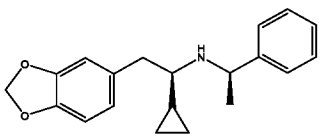
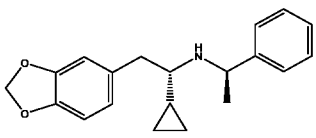
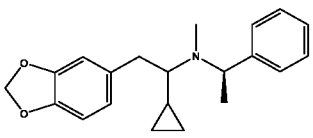
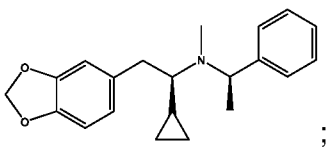
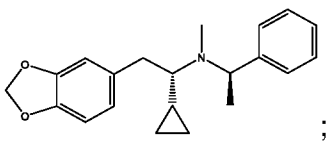
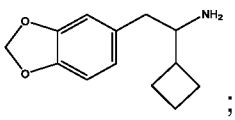
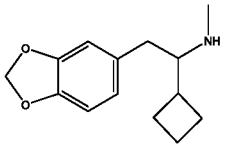
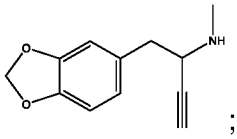
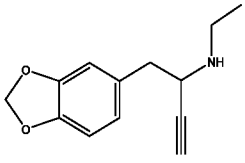
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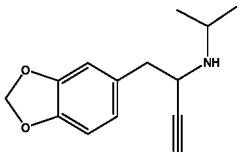
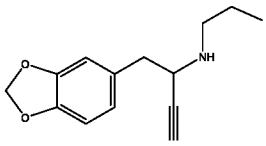
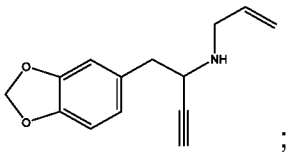
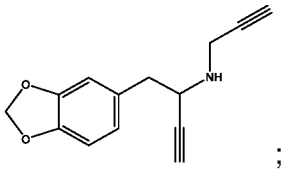
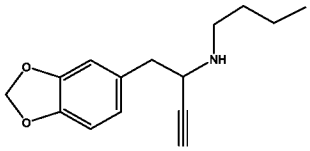
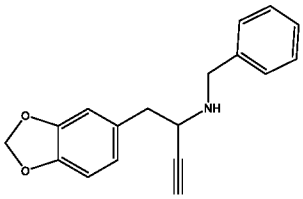
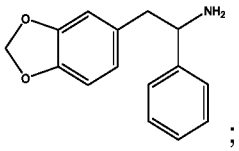
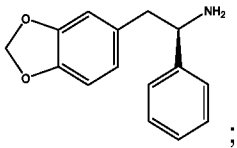
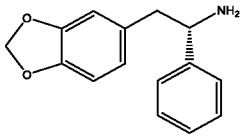
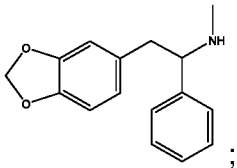
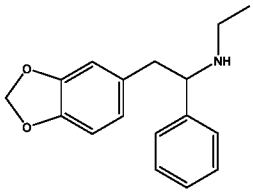
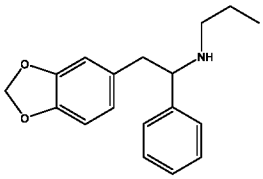
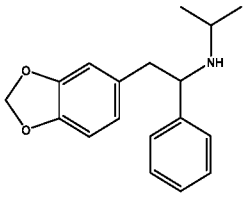
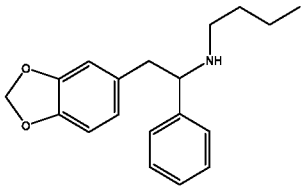
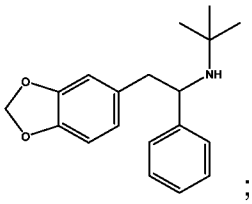
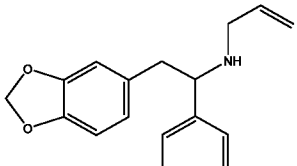
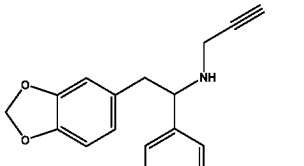
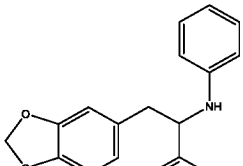
disorder, undifferentiated psychosomatic disorder, hypochondriacal disorder, body dysmorphic disorder, dysmorphophobia (nondelusional), hypochondriacal neurosis, hypochondriasis, nosophobia, somatoform autonomic dysfunction, cardiac neurosis, da costa syndrome, gastric neurosis, neurocirculatory asthenia, psychogenic aerophagy, psychogenic cough, psychogenic diarrhoea, psychogenic dyspepsia, psychogenic dysuria, psychogenic flatulence, psychogenic hiccough, psychogenic hyperventilation, psychogenic increased frequency of micturition, psychogenic irritable bowel syndrome, psychogenic pylorospasm, persistent somatoform pain disorder, psychalgia, psychogenic backache, psychogenic headache, somatoform pain disorder, psychogenic dysmenorrhoea, psychogenic dysphagia, globus hystericus, psychogenic pruritus, psychogenic torticollis, psychogenic teeth-grinding, psychosomatic disorder not otherwise specified, neurasthenia, fatigue syndrome, depersonalization-derealization syndrome, Dhat syndrome, occupational neurosis, writer cramp neurosis, psychasthenia, psychasthenic neurosis, psychogenic syncope, neurosis not otherwise specified, eating disorder, anorexia nervosa, atypical anorexia nervosa, bulimia nervosa, bulimia not otherwise specified, hyperorexia nervosa, atypical bulimia nervosa, overeating associated with other psychological disturbances, psychogenic overeating, vomiting associated with other psychological disturbances, psychogenic vomiting, pica, psychogenic loss of appetite, nonorganic sleep disorder, nonorganic insomnia, nonorganic hypersomnia, nonorganic disorder of the sleep-wake schedule, psychogenic inversion of circadian rhythm, psychogenic inversion of nyctohemeral rhythm, psychogenic inversion of sleep rhythm, sleepwalking [somnambulism], sleep terrors [night terrors], nightmares, dream anxiety disorder, emotional sleep disorder not otherwise specified, sexual dysfunction not caused by organic disorder or disease, lack or loss of sexual desire, frigidity, hypoactive sexual desire disorder, sexual aversion, lack of sexual enjoyment, sexual anhedonia, failure of genital response, female sexual arousal disorder, male erectile disorder, psychogenic impotence, orgasmic dysfunction, inhibited orgasm, psychogenic anorgasmy, premature ejaculation, psychogenic vaginismus, nonorganic dyspareunia, psychogenic dyspareunia, nymphomania, satyriasis, sexual dysfunction not otherwise specified, postnatal depression, postpartum depression, puerperal psychosis, puerperal mental disorder, psychological and behavioural factors associated with physical disorders or diseases (including but not limited to asthma, dermatitis, gastric ulcer, irritable bowel syndrome, ulcerative colitis, and urticaria), abuse of non-dependence-producing substances (including but not limited to antacids, herbal remedies, folk remedies, steroids, hormones, vitamins, and laxatives), psychogenic physiological dysfunction not otherwise specified, paranoid personality disorder, expansive paranoid personality disorder, fanatic paranoid personality disorder, querulant paranoid personality disorder, sensitive paranoid personality disorder, schizoid personality disorder, dissocial personality disorder, amoral personality disorder, antisocial personality disorder, asocial personality disorder, psychopathic personality disorder, sociopathic personality disorder, emotionally unstable personality disorder, aggressive personality disorder, borderline

personality disorder, explosive personality disorder, histrionic personality disorder, hysterical personality disorder, psychoinfantile personality disorder, anankastic personality disorder, compulsive personality disorder, obsessional personality disorder, obsessive-compulsive personality disorder, anxious [avoidant] personality disorder, dependent personality disorder, asthenic personality disorder, inadequate personality disorder, passive personality disorder, self-defeating personality disorder, eccentric personality disorder, haltlose type personality disorder, immature personality disorder, narcissistic personality disorder, passive-aggressive personality disorder, psychoneurotic personality disorder, character neurosis not otherwise specified, pathological personality not otherwise specified, mixed personality disorders, personality and behavioural disorder due to brain disease, personality and behavioural disorder due to brain damage, personality and behavioural disorder due to brain dysfunction, enduring personality change after catastrophic experience (including but not limited to concentration camp experiences, disasters, prolonged captivity with an imminent possibility of being killed, prolonged exposure to life-threatening situations such as being a victim of terrorism, or prolonged torture), enduring personality change after psychiatric illness, chronic pain personality syndrome, enduring personality change unspecified, habit disorder, impulse disorder, pathological gambling, compulsive gambling, pathological fire-setting [pyromania], pathological stealing [kleptomania], trichotillomania, intermittent explosive disorder, gender identity disorder, transsexualism, dual-role transvestism, gender-role disorder, sexual preference disorder, fetishism, fetishistic transvestism, exhibitionism, voyeurism, paedophilia, sadomasochism, frotteurism, necrophilia, sexual deviation not otherwise specified, sexual maturation disorder, egodystonic sexual orientation, sexual relationship disorder, psychosexual development disorder, elaboration of physical symptoms for psychological reasons, compensation neurosis, intentional production or feigning of symptoms or disabilities, either physical or psychological [factitious disorder], hospital hopper syndrome, Münchhausen syndrome, peregrinating patient, character disorder not otherwise specified, relationship disorder not otherwise specified, hyperkinetic disorder, disturbance of activity and attention, attention deficit disorder with hyperactivity, attention deficit hyperactivity disorder, attention deficit syndrome with hyperactivity, hyperkinetic conduct disorder, hyperkinetic syndrome not otherwise specified, conduct disorder, unsocialized conduct disorder, socialized conduct disorder, oppositional defiant disorder, depressive conduct disorder, separation anxiety disorder, sibling rivalry disorder, overanxious disorder, childhood emotional disorder not otherwise specified, elective mutism, selective mutism, reactive attachment disorder, disinhibited attachment disorder, affectionless psychopathy, institutional syndrome, childhood disorder of social functioning, tic disorder, transient tic disorder, chronic motor tic disorder, chronic vocal tic disorder, combined vocal and multiple motor tic disorder [de la Tourette], Tourette's syndrome, nonorganic enuresis, functional enuresis, psychogenic enuresis, urinary incontinence of nonorganic origin, nonorganic encopresis, functional encopresis, incontinence of faeces of nonorganic origin,

psychogenic encopresis, feeding disorder of infancy and childhood, rumination disorder of infancy, stereotyped movement disorder, stuttering [stammering], cluttering, attention deficit disorder without hyperactivity, excessive masturbation, nail-biting, nose-picking, thumb-sucking, and mental disorders not otherwise specified.

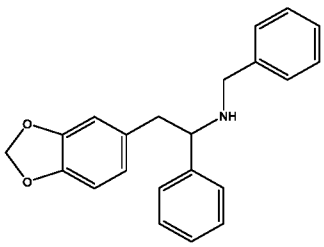
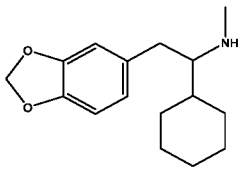
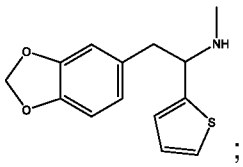
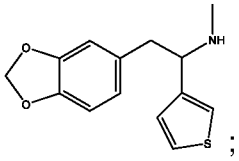
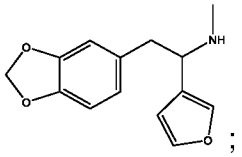
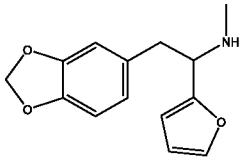
11. The method of claim 10, wherein the compound is selected from the group consisting of;

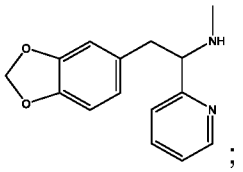
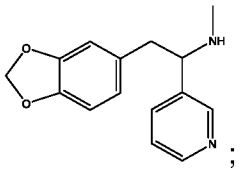
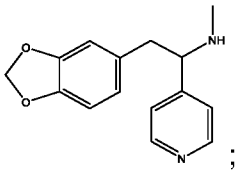
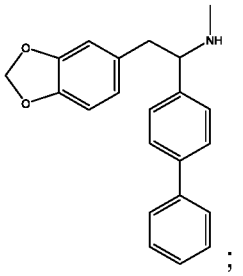
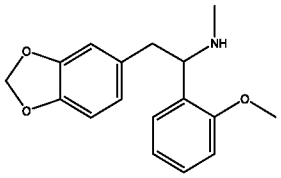
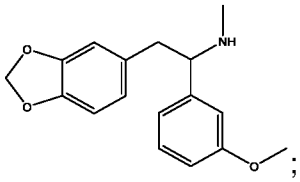
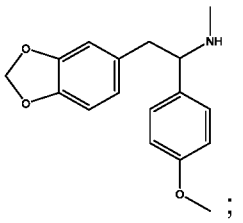
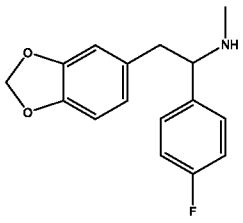
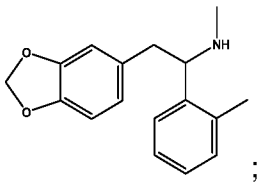
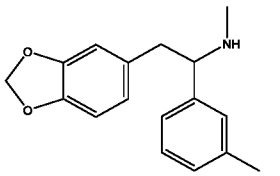
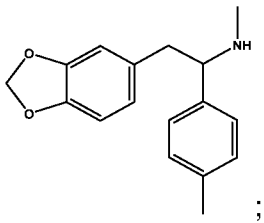
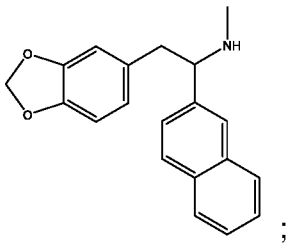
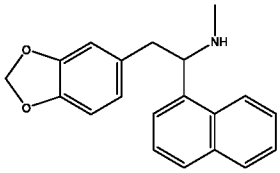
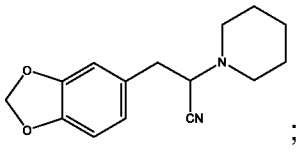
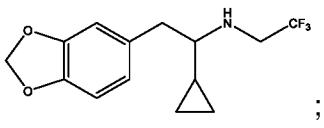
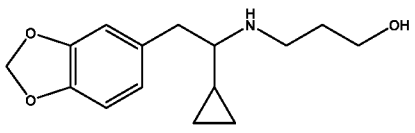
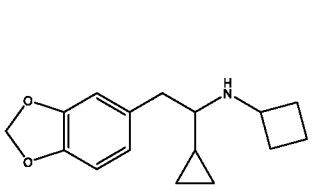
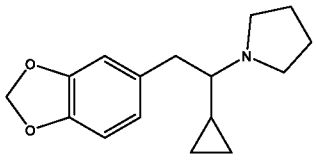
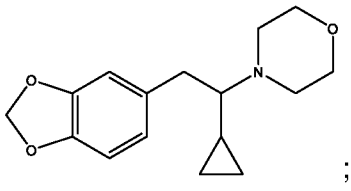

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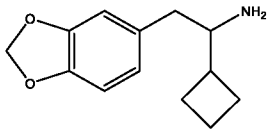
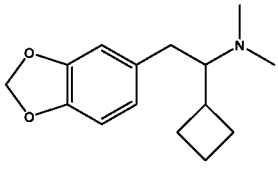

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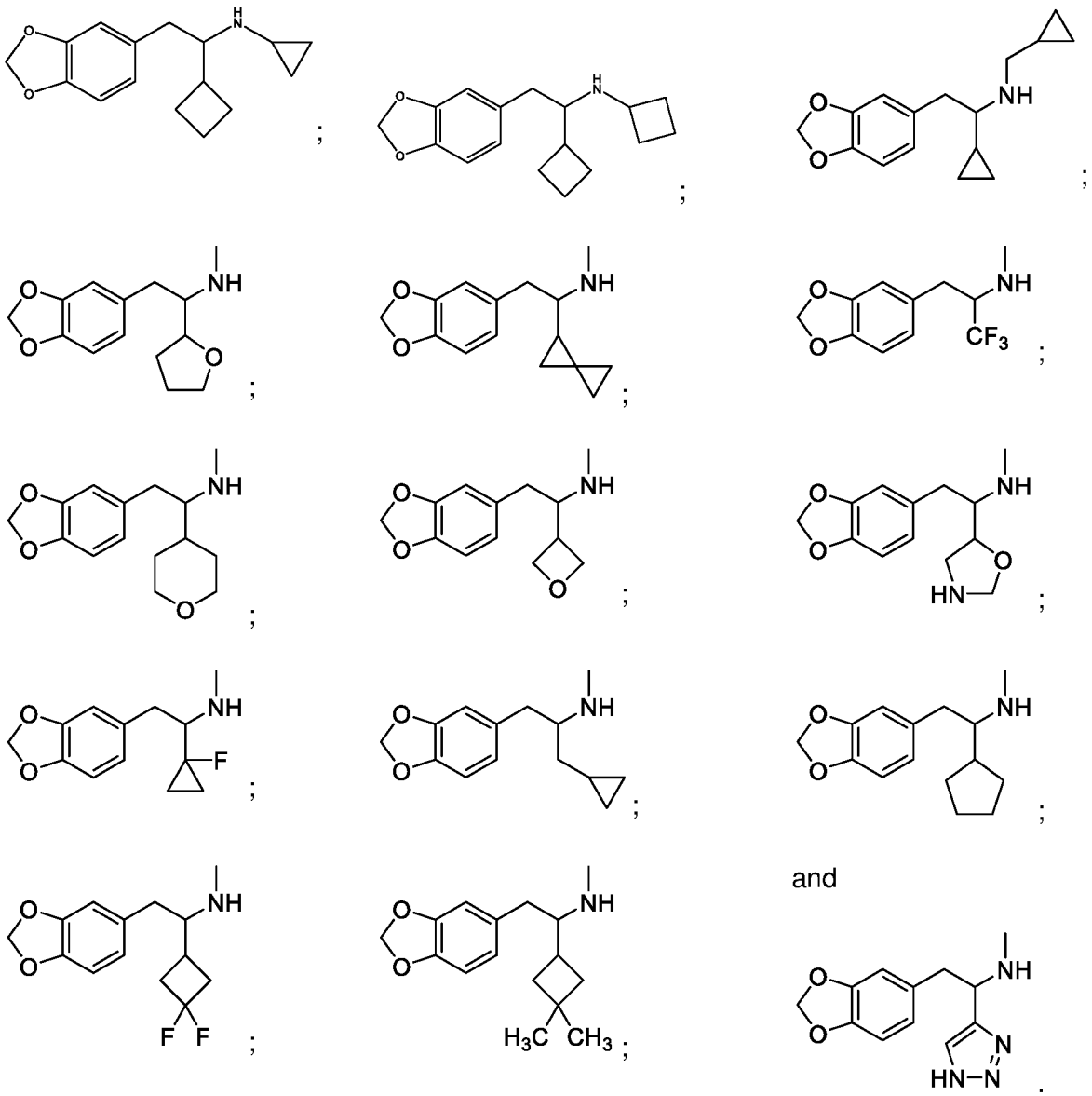
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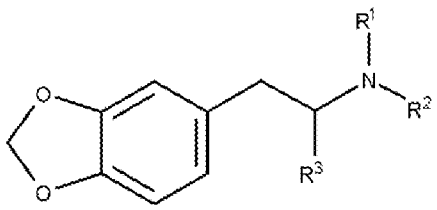

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and

12. A process for the preparation of a compound according to Formula II';



Formula II'

including stereoisomers, individual enantiomers, racemates, non-racemic mixtures, isotopologues, prodrugs and/or pharmaceutically acceptable salts thereof, wherein;

one or more hydrogen atoms in the compound of Formula II' may be replaced by fluorine;

R^1 and R^2 are independently selected from the group consisting of; H, methyl, ethyl, -C_{3-9}alkyl, -C_{1-9}haloalkyl, -C_{2-9}alkenyl, -C_{2-9}haloalkenyl, -C_{2-9}alkynyl, -C_{2-9}haloalkynyl, -C_{3-9}cycloalkyl,

-C_{6-12}bicycloalkyl, -C_{6-12}spirocycloalkyl, -C_{3-9}cyclohaloalkyl, -C_{6-12}bicyclohaloalkyl, -C_{6-12}spirocyclohaloalkyl, -C_{3-9}cycloalkenyl, -C_{6-12}bicycloalkenyl, -C_{6-12}spirocycloalkenyl, -C_{3-9}cyclohaloalkenyl, -C_{6-12}bicyclohaloalkenyl, -C_{6-12}spirocyclohaloalkenyl, -C_{8-12}cycloalkynyl, -C_{9-14}bicycloalkynyl, -C_{9-14}spirocycloalkynyl, -C_{8-12}cyclohaloalkynyl, -C_{9-14}bicyclohaloalkynyl, -C_{9-14}spirocyclohaloalkynyl, -C_{3-9}heterocycloalkyl, -C_{6-12}heterobicycloalkyl, -C_{6-12}heterospirocycloalkyl, aryl, heteroaryl, -C_{1-5}alkyl-aryl, -C_{2-5}alkenyl-aryl, -C_{2-5}alkynyl-aryl, -C_{1-5}alkyl-heteroaryl, -C_{2-5}alkenyl-heteroaryl, -C_{2-5}alkynyl-heteroaryl, -C_{1-5}haloalkyl-aryl, -C_{2-5}haloalkenyl-aryl, -C_{2-5}haloalkynyl-aryl, -C_{1-5}haloalkyl-heteroaryl, -C_{2-5}haloalkenyl-heteroaryl, -C_{2-5}haloalkynyl-heteroaryl, -C(=O)R^a, -C_{1-8}alkyl-C(=O)R^a, -C_{2-8}alkenyl-C(=O)R^a, -C_{2-8}alkynyl-C(=O)R^a, -C_{1-8}haloalkyl-C(=O)R^a, -C_{2-8}haloalkenyl-C(=O)R^a, -C_{2-8}haloalkynyl-C(=O)R^a, -CO_2R^a, -C_{1-8}alkyl-CO_2R^a, -C_{2-8}alkenyl-CO_2R^a, -C_{2-8}alkynyl-CO_2R^a, -C_{1-8}haloalkyl-CO_2R^a, -C_{2-8}haloalkenyl-CO_2R^a, -C_{2-8}haloalkynyl-CO_2R^a, -SO_2R^a, -C_{1-8}alkyl-SO_2R^a, -C_{2-8}alkenyl-SO_2R^a, -C_{2-8}alkynyl-SO_2R^a, -C_{1-8}haloalkyl-SO_2R^a, -C_{2-8}haloalkenyl-SO_2R^a, -C_{2-8}haloalkynyl-SO_2R^a, -C(=O)NR^bR^c, -C_{1-8}alkyl-C(=O)NR^bR^c, -C_{2-8}alkynyl-C(=O)NR^bR^c, -C_{2-8}alkenyl-C(=O)NR^bR^c, -C_{1-8}haloalkyl-C(=O)NR^bR^c, -C_{2-8}haloalkynyl-C(=O)NR^bR^c, -C_{2-8}haloalkenyl-C(=O)NR^bR^c, -CN, -C_{1-8}alkyl-CN, -C_{2-8}alkenyl-CN, -C_{2-8}alkynyl-CN, -C_{1-8}haloalkyl-CN, -C_{2-8}haloalkenyl-CN, -C_{2-8}haloalkynyl-CN, -CH_2-O-R^a, -C_{2-9}alkyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}alkenyl-O-R^a, -C_{2-9}haloalkyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -C_{2-9}haloalkenyl-O-R^a, -CH_2-R^a, -CH_2-S-R^a, -C_{2-9}alkyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}alkenyl-S-R^a, -C_{2-9}haloalkyl-S-R^a, -C_{2-9}haloalkenyl-S-R^a, and -C_{2-9}haloalkenyl-S-R^a;

wherein R^1 and R^2 may together form a 3, 4, 5, 6, or 7 membered, heterocycloalkyl ring, or heterocycloalkenyl ring, or a 6 membered heteroaryl ring, each of which rings may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^3 is selected from the group consisting of; CF_3, CN, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclobutylmethyl, cyclopentyl, cyclopentylmethyl, vinyl, allyl, acetylenyl, cyclohexyl, cyclopentenyl, cyclohexenyl, propargyl, cyanomethyl, oxetanyl, thienyl, furyl, tetrahydrothienyl, tetrahydrofuryl, oxazolinyl, oxazolidinyl, isoxazolinyl, isoxazolidinyl, triazolyl, oxanyl, dioxolanyl, pyridinyl, naphthyl and phenyl; each of which may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5; or

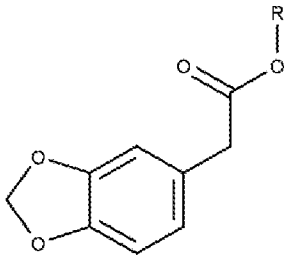
R^3 is a 4-6 membered fused ring system or a 4-6 membered spirocyclic ring system, each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems are saturated carbocyclic ring systems containing 0 heteroatoms or saturated heterocyclic ring systems containing 1 heteroatom, selected from O or S, and each of which 4-6 membered fused ring systems or 4-6 membered spirocyclic ring systems may be unsubstituted, or substituted by one or more groups selected from R^4 or R^5;

R^4 and R^5 are independently selected in each instance from the group consisting of; halogen, $-OR^a$, $-SR^a$, $-NR^bR^c$, methyl, ethyl, $-C_{3-9}$alkyl, $-C_{1-9}$haloalkyl, $-C_{2-9}$alkenyl, $-C_{2-9}$haloalkenyl, $-C_{2-9}$alkynyl, $-C_{2-9}$haloalkynyl, $-C_{3-9}$cycloalkyl, $-C_{6-12}$bicycloalkyl, $-C_{6-12}$spirocycloalkyl, $-C_{3-9}$cyclohaloalkyl, $-C_{6-12}$bicyclohaloalkyl, $-C_{6-12}$spirocyclohaloalkyl, $-C_{3-9}$cycloalkenyl, $-C_{6-12}$bicycloalkenyl, $-C_{6-12}$spirocycloalkenyl, $-C_{3-9}$cyclohaloalkenyl, $-C_{6-12}$bicyclohaloalkenyl, $-C_{6-12}$spirocyclohaloalkenyl, $-C_{8-12}$cycloalkynyl, $-C_{9-14}$bicycloalkynyl, $-C_{9-14}$spirocycloalkynyl, $-C_{8-12}$cyclohaloalkynyl, $-C_{9-14}$bicycloalkynyl, $-C_{9-14}$spirocycloalkynyl, aryl, heteroaryl, $-C_{1-5}$alkyl-aryl, $-C_{2-5}$alkenyl-aryl, $-C_{2-5}$alkynyl-aryl, $-C_{1-5}$alkyl-heteroaryl, $-C_{2-5}$alkenyl-heteroaryl, $-C_{2-5}$alkynyl-heteroaryl, $-C_{1-5}$haloalkyl-aryl, $-C_{2-5}$haloalkenyl-aryl, $-C_{2-5}$haloalkynyl-aryl, $-C_{1-5}$haloalkyl-heteroaryl, $-C_{2-5}$haloalkenyl-heteroaryl, $-C_{2-5}$haloalkynyl-heteroaryl, $-C(=O)R^a$, $-C_{1-8}$alkyl-$C(=O)R^a$, $-C_{2-8}$alkenyl-$C(=O)R^a$, $-C_{2-8}$alkynyl-$C(=O)R^a$, $-C_{1-8}$haloalkyl-$C(=O)R^a$, $-C_{2-8}$haloalkenyl-$C(=O)R^a$, $-C_{2-8}$haloalkynyl-$C(=O)R^a$, $-CO_2R^a$, $-C_{1-8}$alkyl-CO_2R^a, $-C_{2-8}$alkenyl-CO_2R^a, $-C_{2-8}$alkynyl-CO_2R^a, $-C_{1-8}$haloalkyl-CO_2R^a, $-C_{2-8}$haloalkenyl-CO_2R^a, $-C_{2-8}$haloalkynyl-CO_2R^a, $-SO_2R^a$, $-C_{1-8}$alkyl-SO_2R^a, $-C_{2-8}$alkenyl-SO_2R^a, $-C_{2-8}$alkynyl-SO_2R^a, $-C_{1-8}$haloalkyl-SO_2R^a, $-C_{2-8}$haloalkenyl-SO_2R^a, $-C_{2-8}$haloalkynyl-SO_2R^a, $-C(=O)NR^bR^c$, $-C_{1-8}$alkyl-$C(=O)NR^bR^c$, $-C_{2-8}$alkynyl-$C(=O)NR^bR^c$, $-C_{2-8}$alkenyl-$C(=O)NR^bR^c$, $-C_{1-8}$haloalkyl-$C(=O)NR^bR^c$, $-C_{2-8}$haloalkynyl-$C(=O)NR^bR^c$, $-C_{2-8}$haloalkenyl-$C(=O)NR^bR^c$, -CN, $-C_{1-8}$alkyl-CN, $-C_{2-8}$alkenyl-CN, $-C_{2-8}$alkynyl-CN, $-C_{1-8}$haloalkyl-CN, $-C_{2-8}$haloalkenyl-CN, $-C_{2-8}$haloalkynyl-CN, $-CH_2$-O-R^a, $-C_{2-9}$alkyl-O-R^a, $-C_{2-9}$alkenyl-O-R^a, $-C_{2-9}$alkenyl-O-R^a, $-C_{2-9}$haloalkyl-O-R^a, $-C_{2-9}$haloalkenyl-O-R^a, $-C_{2-9}$haloalkenyl-O-R^a, $-CH_2$-S-R^a, $-C_{2-9}$alkyl-S-R^a, $-C_{2-9}$alkenyl-S-R^a, $-C_{2-9}$alkenyl-S-R^a, $-C_{2-9}$haloalkyl-S-R^a, $-C_{2-9}$haloalkenyl-S-R^a, and $-C_{2-9}$haloalkenyl-S-R^a;

or, where two of R^4 and/or R^5 are attached to the same carbon atom, said two of R^4 and/or R^5 may together from a carbonyl group; and

R^a, R^b and R^c are independently selected, in each instance, from the group consisting of; H, methyl, ethyl, $-C_{3-9}$alkyl, $-C_{1-9}$haloalkyl, $-C_{2-9}$alkenyl, $-C_{2-9}$haloalkenyl, $-C_{2-9}$alkynyl, $-C_{2-9}$haloalkynyl, $-C_{3-9}$cycloalkyl, aryl, heteroaryl, $-C_{1-5}$alkyl-aryl, $-C_{1-5}$haloalkyl-aryl, $-C_{2-5}$alkenyl-aryl, $-C_{2-5}$haloalkenyl-aryl, $-C_{2-5}$alkynyl-aryl, $-C_{2-5}$haloalkynyl-aryl, $-C_{1-5}$alkyl-heteroaryl, $-C_{1-5}$haloalkyl-heteroaryl, $-C_{2-5}$alkenyl-heteroaryl, $-C_{2-5}$haloalkenyl-heteroaryl, $-C_{2-5}$alkynyl-heteroaryl and $-C_{2-5}$haloalkynyl-heteroaryl;

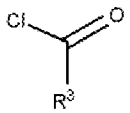
wherein the process comprises; reacting a compound according to Formula III;



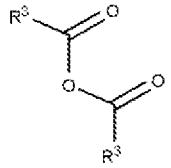
Formula III

wherein R is selected from the group consisting of; methyl, ethyl, and -C_{3-9}alkyl;

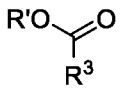
with a compound according to Formula IVa, or Formula IVb, or Formula IVc;



Formula IVa;



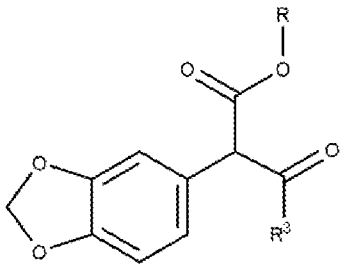
Formula IVb;



Formula IVc;

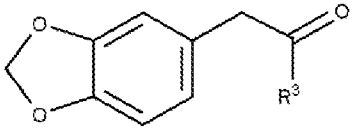
wherein R^3 is as defined for the compound of Formula II', and wherein, for the compound of Formula IVb, each R^3 may be the same or different, and wherein R' is selected from the group consisting of; methyl, ethyl, -C_{3-9}alkyl, aryl and haloaryl;

under a first set of reaction conditions, to produce a compound of Formula V;



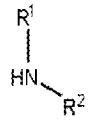
Formula V

followed by subjecting the compound of Formula V to a second set of reaction conditions to produce a ketone intermediate of Formula VI;



Formula VI

and subsequent reductive amination of the compound of Formula VI with a compound of Formula VII;



Formula VII

wherein R^1 and R^2 are as defined for the compound of Formula II';

under a third set of reaction conditions, to produce the compound of Formula II'.

13. The process of claim 12, wherein the first set of reaction conditions comprises reacting 1 equivalent of a compound of Formula III with an excess of a compound of Formula IVa or Formula IVb or Formula IVc, in an organic solvent, in the presence of an excess of a base;

preferably wherein the organic solvent is a polar aprotic solvent, and the base is a lithium base;

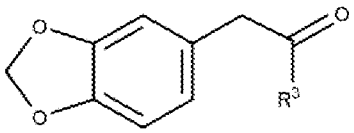
most preferably wherein the organic solvent is THF, and the base is LiHMDS.

14. The process of claim 12 or claim 13, wherein the second set of reaction conditions comprises heating a solution of the compound of Formula V in a mixture of DMSO and water, in the presence of NaCl; and/or

wherein the third set of reaction conditions comprises reductive amination of the compound of Formula VI with a compound of Formula VII, preferably in the presence of acetic acid and sodium cyanoborohydride in a mixture of anhydrous THF and anhydrous methanol.

15. A compound of Formula II', as defined in claim 8 or claim 10, when made via the process of any one of claims 12 to 14.

16. A compound according to Formula VI;



Formula VI

wherein R^3 is as defined for the compound of Formula II' according to claim 8 or claim 10, when the compound of Formula VI is made via the process of any one of claims 12 to 14.