



(51) International Patent Classification:

C07D 451/06 (2006.01) C07D 211/44 (2006.01)
 C07D 487/04 (2006.01) A61K 31/437 (2006.01)
 C07D 487/08 (2006.01) A61K 31/438 (2006.01)
 C07D 211/14 (2006.01) A61K 31/445 (2006.01)
 C07D 211/58 (2006.01) A61K 31/4468 (2006.01)
 C07D 413/04 (2006.01) A61K 31/46 (2006.01)
 C07D 241/04 (2006.01) A61K 31/496 (2006.01)
 C07D 207/08 (2006.01) A61P 25/00 (2006.01)

(21) International Application Number:

PCT/US2018/000352

(22) International Filing Date:

20 August 2018 (20.08.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/548,320 21 August 2017 (21.08.2017) US

(71) Applicant: ACADIA PHARMACEUTICALS INC.
 [US/US]; 3611 Valley Centre Drive, Suite 300, San Diego,
 CA 92130 (US).

(72) Inventors: BURSTEIN, Ethan, S.; 4168 Sturgeon
 Court, San Diego, CA 92130 (US). OLSSON, Roger;
 Klagshamnsvägen 99 A, SE-218 38 Bunkeflostrand (SE).
 JANSSON, Karl, Erik; Spannmålsvägen 11, SE-247 55
 Dalby (SE). BERGNER, Magnus Gustav, Wilhelm; Fyn-
 dvägen 18, SE-224 80 Lund (SE). SKÖLD, Niklas, Patrik;
 Grisslevägen 3, SE-227 32 Lund (SE). VON WACHEN-
 FELDT, Henrik; Hässleholmsgatan 2b, SE-214 43 Malmö
 (SE). POPOV, Kyrylo; Kattfotsgränden 14, SE-247 56
 Dalby (SE). KOVALENKO, Oleksandr; Jaktstigen 2,
 Lgh. 1103, SE-226 52 Lund (SE). KLINGSTEDT, Per,
 Tomas; Rudeboksvägen 341, SE-226 55 Lund (SE).
 BORGSTRÖM, Björn, Gustav; Uardavägen 52 B, Lgh
 1101, SE-224 71 Lund (SE). WAHLSTRÖM, Larisa, Yu-
 dina; Västerlånggatan 50B, SE-241 31 Eslöv (SE).

(74) Agent: RICH, Roger, C. et al.; Jones Day, 250 Vesey
 Street, New York, NY 10281-1047 (US).

(81) Designated States (unless otherwise indicated, for every
 kind of national protection available): AE, AG, AL, AM,
 AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,
 CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,
 DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,
 HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP,
 KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME,
 MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
 OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA,

SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
 TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

— without international search report and to be republished
 upon receipt of that report (Rule 48.2(g))

(54) Title: COMPOUNDS, SALTS THEREOF AND METHODS FOR TREATMENT OF DISEASES

(57) Abstract: The present disclosure relates to compounds according to Formula (I), treating diseases.

COMPOUNDS, SALTS THEREOF AND METHODS FOR TREATMENT OF DISEASES

FIELD

[0001] Provided herein are compounds and their pharmaceutically acceptable salts for treatment of diseases and conditions associated with the serotonin receptor 5-HT.

BACKGROUND

[0002] Serotonin or 5-hydroxytryptamine (5-HT) plays a significant role in the functioning of the mammalian body. In the central nervous system, 5-HT is an important neurotransmitter and neuromodulator that is implicated in such diverse behaviors and responses as sleeping, eating, locomotion, perceiving pain, learning and memory, sexual behavior, controlling body temperature and blood pressure. In the spinal column, serotonin plays an important role in the control systems of the afferent peripheral nociceptors (Moullignier, *Rev. Neurol.* 150:3-15, (1994)). Peripheral functions in the cardiovascular, hematological and gastrointestinal systems have also been ascribed to 5-HT. 5-HT has been found to mediate a variety of contractile, secretory, and electrophysiologic effects including vascular and nonvascular smooth muscle contraction, and platelet aggregation. (Fuller, *Biology of Serotonergic Transmission*, 1982; Boullin, *Serotonin In Mental Abnormalities* 1:316 (1978); Barchas, et al., *Serotonin and Behavior*, (1973)). The 5-HT_{2A} receptor subtype (also referred to as subclass) is widely yet discretely expressed in the human brain, including many cortical, limbic, and forebrain regions postulated to be involved in the modulation of higher cognitive and affective functions. This receptor subtype is also expressed on mature platelets where it mediates, in part, platelet aggregation, one of the initial steps in the process of vascular thrombosis.

[0003] Given the broad distribution of serotonin within the body, it is understandable that tremendous interest in drugs that affect serotonergic systems exists (Gershon, et al., *The Peripheral Actions of 5-Hydroxytryptamine*, 246 (1989); Saxena, et al., *J. Cardiovascular Pharmacol.* 15: Supp. 7 (1990)). Serotonin receptors are members of a large human gene family of membrane-spanning proteins that function as transducers of intercellular communication. They exist on the surface of various cell types, including neurons and platelets, where, upon their activation by either their endogenous ligand serotonin or exogenously administered drugs, they change their conformational structure and subsequently

interact with downstream mediators of cellular signaling. Many of these receptors, including the 5-HT_{2A} subclass, are G-protein coupled receptors (GPCRs) that signal by activating guanine nucleotide binding proteins (G-proteins), resulting in the generation, or inhibition of, second messenger molecules such as cyclic AMP, inositol phosphates, and diacylglycerol. These second messengers then modulate the function of a variety of intracellular enzymes, including kinases and ion channels, which ultimately affect cellular excitability and function.

[0004] At least 14 genetically distinct 5-HT receptor subtypes have been identified and assigned to one of seven families (5-HT₁₋₇). Each subtype displays a unique distribution, preference for various ligands, and functional correlate(s).

[0005] Serotonin may be an important component in various types of pathological conditions such as certain psychiatric disorders (depression, aggressiveness, panic attacks, obsessive compulsive disorders, psychosis, schizophrenia, suicidal tendency), certain neurodegenerative disorders (Alzheimer-type dementia, Parkinsonism, Huntington's chorea), anorexia, bulimia, disorders associated with alcoholism, cerebral vascular accidents, and migraine (Meltzer, *Neuropsychopharmacology*, 21:106S-115S (1999); Barnes & Sharp, *Neuropharmacology*, 38:1083-1152 (1999); Glennon, *Neurosci. Biobehavioral Rev.*, 14:35 (1990)).

[0006] Given the broad distribution of serotonin within the body and its role in a wide range of physiological and pathological processes, it is understandable that there is tremendous interest in drugs that affect serotonergic systems (Gershon, et al., *The Peripheral Actions of 5-Hydroxytryptamine*, 246 (1989); Saxena, et al., *J. Cardiovascular Pharmacol.* 15: Supp. 7 (1990)).

[0007] The effects of serotonin are mediated by at least 14 genetically distinct 5-HT receptor subtypes have been identified and assigned to one of seven families (5-HT₁₋₇). Each subtype displays a unique distribution, preference for various ligands, and functional correlate(s). Serotonin receptors are members of a large human gene family of membrane-spanning proteins that function as transducers of intercellular communication. They exist on the surface of various cell types, including neurons and platelets, where, upon their activation by either their endogenous ligand serotonin or exogenously administered drugs, they change their conformational structure and subsequently interact with downstream mediators of cellular signaling. Many of these receptors, including the 5-HT_{2A} subclass, are G-protein coupled receptors (GPCRs) that signal by activating guanine nucleotide binding proteins (G-proteins), resulting in the generation, or inhibition of, second messenger molecules such as cyclic AMP, inositol phosphates, and diacylglycerol. These second messengers then

modulate the function of a variety of intracellular enzymes, including kinases and ion channels, which ultimately affect cellular excitability and function.

[0008] The 5-HT_{2A} receptor subtype (also referred to as subclass) is widely yet discretely expressed in the human brain, including many cortical, limbic, and forebrain regions postulated to be involved in the modulation of higher cognitive and affective functions. This receptor subtype is also expressed on mature platelets where it mediates, in part, platelet aggregation, one of the initial steps in the process of vascular thrombosis.

[0009] Antipsychotic drugs have been shown to interact with a large number of central monoaminergic neurotransmitter receptors, including dopaminergic, serotonergic, adrenergic, muscarinic, and histaminergic receptors. It is likely that the therapeutic and adverse effects of these drugs are mediated by distinct receptor subtypes. The high degree of genetic and pharmacological homology between these receptor subtypes has hampered the development of subtype-selective compounds, as well as the determination of the normal physiologic or pathophysiologic role of any particular receptor subtype. Thus there is a need to develop drugs that are selective for individual receptor classes and subclasses amongst monoaminergic neurotransmitter receptors.

[0010] The prevailing theory for the mechanism of action of antipsychotic drugs involves antagonism of dopamine D₂ receptors. Unfortunately, it is likely that antagonism of dopamine D₂ receptors also mediates the extrapyramidal side effects as well as some additional undesired effects of antipsychotic therapies such as a worsening of depression symptoms, anhedonia and impairment of cognitive processes. Antagonism of 5-HT_{2A} receptors is an alternate molecular mechanism for drugs with antipsychotic efficacy, possibly through antagonism of heightened or exaggerated signal transduction through serotonergic systems. 5-HT_{2A} antagonists are therefore good candidates for treating psychosis without extrapyramidal side effects or other undesired effects associated with blockade of dopamine D₂ receptors.

[0011] Traditionally, GPCRs such as the 5-HT_{2A} receptor have been assumed to exist in a quiescent state unless activated by the binding of an agonist (a drug that activates a receptor). It is now appreciated that many, if not most, of the GPCR monoamine receptors, including serotonin receptors, can exist in a partially activated state in the absence of their endogenous agonists. This increased basal activity (constitutive activity) can be inhibited by compounds called inverse agonists. Both agonists and inverse agonists possess intrinsic activity at a receptor, in that they alone can activate or inactivate these molecules, respectively. In contrast, classic or neutral antagonists compete against agonists and inverse

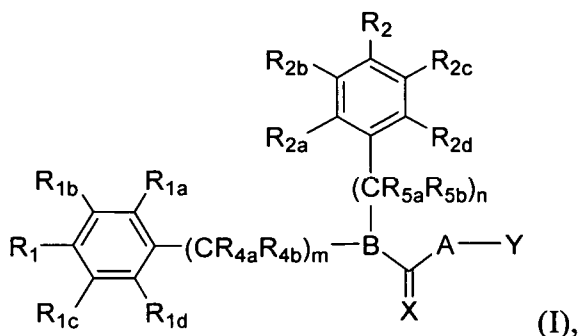
agonists for access to the receptor, but do not possess the intrinsic ability to inhibit elevated basal or constitutive receptor responses.

[0012] Consequently there is a need of new compounds for making antipsychotic drugs that target serotonin receptors.

SUMMARY

[0013] Provided herein are compounds according to Formula (I),

[0014] A compound according to Formula (I)



[0015] or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof, wherein:

[0016] m, and n are independently an integer selected from the group consisting of 0, 1, 2, and 3;

[0017] t is an integer selected from the group consisting of 0, 1, 2 and 3;

[0018] R₁, R_{1a}, R_{1b}, R_{1c} and R_{1d} are independently selected from the group consisting of hydrogen, deuterium, hydroxyl, -OD, halogen, cyano, amino, -SO₂R₁₀, -OC(=O)R₁₁, -C(=O)OR₁₁, unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₁₋₆ haloalkyl, unsubstituted or substituted C₁₋₆ hydroxyalkyl, unsubstituted or substituted C₁₋₆ aminoalkyl, unsubstituted or substituted C₂₋₆ alkenyl, unsubstituted or substituted C₁₋₆ alkoxy, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted C₃₋₆ heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein at least one of R₁, R_{1a}, R_{1b}, R_{1c} and R_{1d} is not hydrogen;

[0019] R₂, R_{2a}, R_{2b}, R_{2c} and R_{2d} are independently selected from the group consisting of hydrogen, deuterium, amino, hydroxyl, -OD, halogen, cyano, unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₁₋₆ haloalkyl, , unsubstituted or substituted C₁₋₆ hydroxyalkyl, unsubstituted or substituted C₂₋₆ alkenyl, unsubstituted or substituted C₁₋₆ alkoxy, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted C₃₋₆ heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein at least one of R₂, R_{2a}, R_{2b}, R_{2c} and R_{2d} is not selected from hydrogen;

[0020] R_{4a} , R_{4b} , R_{5a} , R_{5b} , R_{5c} , R_{5d} , R_{9a} , and R_{9b} , are independently selected from the group consisting of hydrogen, deuterium, and unsubstituted or substituted C_{1-6} alkyl;

[0021] A is selected from the group consisting of a bond, $-CR_{5c}R_{5d}-$, $-CR_{5c}R_{5d}O-$, $-S-$, $-O-$ and $-NH-$;

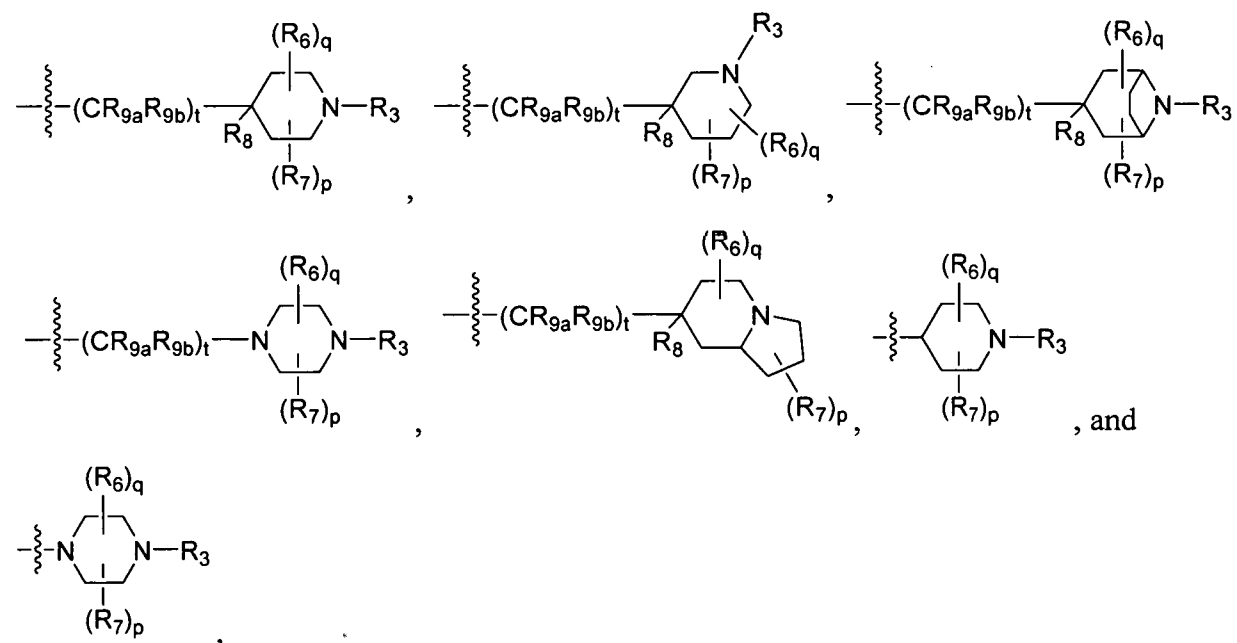
[0022] B is selected from the group consisting of $-N-$, $-NCH_2-$, $-CHNH-$, and $-CH-$;

[0023] R_{10} and R_{11} , independently are selected from the group consisting of hydrogen, amino, unsubstituted or substituted C_{1-6} alkyl;

[0024] X is O or S;

[0025] Y is $-(CR_{9a}R_{9b})_t-(\text{unsubstituted or substituted } C_{3-8} \text{ heteroalicycyl})$.

[0026] The following are also disclosed herein, compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer wherein Y is selected from the group consisting of



[0027] wherein t is an integer selected from the group consisting of 0, 1 and 2; p and q, are integers, independently selected from the group consisting of 0, 1, and 2;

[0028] R_3 is selected from hydrogen, deuterium, hydroxyl, $-OD$, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

[0029] R_6 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy, substituted or unsubstituted aryl;

[0030] R_7 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

[0031] R_8 is absent, or selected from the group consisting of hydrogen, deuterium, cyano, hydroxyl, -OD, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{2-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy, or R_8 taken together with R_{9a} or R_{9b} is forming a ring system.

[0032] Some embodiments disclosed herein relate to a method for treating a disease in a patient comprising administering to the patient an effective amount of a compound, pharmaceutically acceptable salt, polymorph or stereoisomer of a compound according to Formula (I), wherein the disease is selected from the group consisting of Abnormal hormonal activity, Alzheimer's disease, Alzheimer's disease dementia, Alzheimer's disease psychosis, Addiction (alcohol, cocaine, methamphetamine, nicotine and opioid), Addison's disease, ADHD, Alzheimer's disease psychosis, Affective disorders, Aggressiveness, Agitation, Akathisia, Alcohol addiction, Alcohol withdrawal, Amenorrhea, Amyotrophic lateral sclerosis, Anhedonia, Anorexia, Anti-NMDAR encephalitis, Anxiety, Appetite disorders, Asthma, Autism, Behavioral disorders, Behavioral disturbances associated with dementia, Binge eating disorder associated with impulse control disorder (ICD), Bipolar disorder, Blindness, Borderline disorder, Borderline personality disorder, Bradykinesia, Bulimia, Buying associated with ICD, Cardiac arrhythmia, Cerebral vascular accidents, Charles Bonnet disease, Chemotherapy-induced emesis, Childhood autism, Chronic pain, Chronic insomnia, cocaine addiction, Cognitive disorders, craniofacial pain, temporomandibular joint (TMJ) / temporomandibular disorder (TMD), Cushing's disease, Delusion, Dementia, Dementia with Lewy Body or Lewy Body dementia, dementia and psychosis associated with Creutzfeld-Jakob disease (CJD), Gerstmann-Strausser-Schenker disease (GSSD) and fatal familial insomnia (FFI), Depression, Diabetes mellitus (non-insulin dependent), Diabetic peripheral neuropathy, Drug addiction, Double vision, Down's syndrome, Dyskinesia, Dysthymia, Dystonia, Ejaculatory problem, Emphysema, Epilepsy, Extrapyrmidal disorder, Fibromyalgia, Frailty, Friedrich's Ataxia, Frontotemperal Dementia, Gambling associated with ICD, Galactorrhea, General anxiety disorder, Glaucoma, Hair loss or thinning,

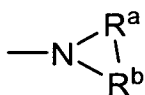
Hallucination, Headache, Hemorrhoids, Huntington's disease, Hyperprolactinemia, Hypertension, Hypersexuality associated with ICD, Hypotension, Hypoglutamateriga disorders, Impulse control disorder, Idiopathic thrombocytopenic purpura, Impotence, Incontinence, Increased intraocular pressure, Infertility, Inflammatory pain, Insomnia, Ischemia, Ischemic stroke, Lewy body disease (LBD), Learning disorders, Libido (decreased), Loss of libido, Low male fertility, Low sperm mobility, Lupus, Machado-Joseph disease, Major depression, Mania, Menopausal symptoms, Metabolic syndrome, methamphetamine addiction, Migraine, mild cognitive impairment (MCI), Motor tics, Multi-infarct dementia, Multiple sclerosis, Multiplex development disorder, Myocardial infarction, Myoclonus, Neuropathic pain, Neurodegenerative disorder, Neuropsychiatric disease, Nicotine addiction, Non motor symptoms of Parkinson's disease selected from dementia, depression, apathy, hallucinations, dribbling saliva (sialorrhea), constipation, pain, genitourinary problems and sleep disorders, Obsessive compulsive disorder, On/off phenomena, Opioid addiction, Osteoporosis, Pancreatitis, Panic attacks, Parkinson's disease, Parkinson's disease dementia, Parkinson's disease psychosis, Periodic limb movement during sleep (PLMS), Peripheral vascular disease, Pituitary tumor, Postherpetic neuralgia, Progressive Supranuclear Palsy, Prion disease including Creutzfeld-Jakob disease (CJD), Gerstmann-Strausser-Schenker disease (GSSD) and fatal familial insomnia (FFI), Prolactinoma, Pseudobulbar affect (PBA), Psychomotor slowing, Psychosis, Psychoses secondary to neurodegenerative disorders, Psychosomatic disorders, Psychotic depression, post-traumatic stress disorder (PTSD), Raynaud's disease, Reflex sympathetic dystrophy, Restless legs syndrome, Retinal disease, Schizoaffective disorders, Schizophrenia, negative symptoms of schizophrenia, cognitive impairment associated with schizophrenia, Sepsis, Serotonin syndrome, Sexual dysfunction, Sexual dysfunction associated with antidepressant use, Sleep apnea, Sleep disorders, Sleep maintenance insomnia, social anxiety disorder, Spinal injury, Spinocerebellar Atrophy, Suicidal tendency, Thrombosis, Thrombotic stroke, Thrombotic thrombocytopenic purpura, Tinnitus, Tiredness, Tourette's syndrome, Transient insomnia, Traumatic brain injury, Treatment-resistant depression, Treatment-resistant schizophrenia, Tremor, Vaginal dryness, Vasospasm Wakefulness, vascular dementia, Hallucinations associated with Parkinson's disease, Delusions associated with Parkinson's disease; cancer, brain cancer, glioma, Pancreatic cancer, Hypoactive sexual desire disorder, adult type 2 diabetes mellitus with Parkinson's disease or dementia and Liver fibrosis.

DETAILED DESCRIPTION

Definitions

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0034] As used herein, any “R” group(s) such as, without limitation, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, and R₁₀, represent substituents that can be attached to the indicated atom. A non-limiting list of R groups includes but is not limited to hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, and heteroalicycyl. If two “R” groups are covalently bonded to the same atom or to adjacent atoms, then they may be “taken together” or “combined” as defined herein to form a cycloalkyl, aryl, heteroaryl or heteroalicycyl group. For example, without limitation, if R_a and R_b of an NR_aR_b group are indicated to be “taken together” or “combined”, it means that they are covalently bonded to one another at their terminal atoms to form a ring that includes the nitrogen:



[0035] As readily recognized by the skilled person, any given atom with unsatisfied valences disclosed in the text, formulas, schemes, examples and figures herein is assumed to have a sufficient number of hydrogen atoms to satisfy the valency.

[0036] Whenever a group is described as being “unsubstituted or substituted,” if substituted, the substituent(s) (which may be present one or more times, such as 1, 2, 3 or 4 times) are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

[0037] When a substituent on a group is deemed to be “substituted,” the substituent itself is substituted with one or more of the indicated substituents. When the referenced substituent is substituted, it is meant that one or more hydrogen atoms on the referenced substituent may be replaced with a group(s) individually and independently selected from deuterium, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl,

aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. The protecting groups that may form the protective derivatives of the above substituents are known to those of skill in the art and may be found in references Greene and Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is hereby incorporated by reference in its entirety.

[0038] Whenever a group, such as an alkyl group, is described as “alkyl”, i.e. without the use of “unsubstituted or substituted”, it should be the same as “unsubstituted alkyl”. For example C₁₋₆ alkyl means an unsubstituted alkyl comprising 1 to 6 carbon atoms.

[0039] As used herein, “C_m to C_n,” “C_m-C_n” or “C_{m-n}” in which “m” and “n” are integers refers to the number of carbon atoms in the relevant group. That is, the group can contain from “m” to “n”, inclusive, carbon atoms. Thus, for example, a “C₁ to C₆ alkyl” group refers to all alkyl groups having from 1 to 6 carbons, that is, CH₃-, CH₃CH₂-, CH₃CH₂CH₂-, (CH₃)₂CH-, CH₃CH₂CH₂CH₂-, CH₃CH₂CH(CH₃)-, CH₃CH(CH₃)₃CH₂-, CH₃CH(CH₃)₃CH₂- and (CH₃)₃C-. If no “m” and “n” are designated with regard to a group, the broadest range described in these definitions is to be assumed.

[0040] As used herein, “alkyl” refers to a straight or branched hydrocarbon chain group that is fully saturated (no double or triple bonds). The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as “1 to 20” refers to each integer in the given range; *e.g.*, “1 to 20 carbon atoms” means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 10 carbon atoms, such as “C₁₋₆”. The alkyl group could also be a lower alkyl having 1 to 4 carbon atoms. The alkyl group of the compounds may be designated as “C₁-C₄ alkyl,” “C₁₋₄ alkyl” or similar designations. By way of example only, “C₁-C₄ alkyl” or “C₁₋₄ alkyl” indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like. When substituted, the substituent group(s) is(are) one or more group(s) individually and

independently selected from alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

[0041] As used herein, the term “optionally”, for example “optionally deuterated” means that group may be unsubstituted or substituted with one or more of the indicated substituents, e.g. one or more hydrogen(s) may be replaced by one or more deuterium(s).

[0042] As used herein, “alkenyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more double bonds. If more than one double bond is present, the double bonds may be conjugated or not conjugated. The alkenyl group may have 2 to 20 carbon atoms (whenever it appears herein, a numerical range such as “2 to 20” refers to each integer in the given range; *e.g.*, “2 to 20 carbon atoms” means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkenyl” where no numerical range is designated). When substituted, the substituent group(s) is(are) one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, mercapto, alkylthio, cyano, halogen, nitro, haloalkyl, haloalkoxy, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof.

[0043] As used herein, “alkynyl” refers to an alkyl group that contains in the straight or branched hydrocarbon chain one or more triple bonds. The alkynyl group may have 2 to 20 carbon atoms (whenever it appears herein, a numerical range such as “2 to 20” refers to each integer in the given range; *e.g.*, “2 to 20 carbon atoms” means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, *etc.*, up to and including 20 carbon atoms, although the present definition also covers the occurrence of the term “alkynyl” where no numerical range is designated). An alkynyl group may be unsubstituted or substituted. When substituted, the substituent(s) may be selected from the same groups disclosed above with regard to alkenyl group substitution.

[0044] As used herein, “hetero” refers to heteroatoms selected from nitrogen, oxygen, phosphorus and sulfur.

[0045] As used herein, “heteroalkyl,” by itself or in combination with another term, refers to a straight or branched alkyl group consisting of the stated number of carbon atoms, where one or more carbon atom(s), such as 1, 2, 3 or 4 carbon atom(s), and the associated hydrogen atom(s) have been independently replaced with the same or different heteroatoms selected from nitrogen, oxygen and sulfur. The carbon atom(s) being replace may be in the middle or at the end of the alkyl group. Examples of heteroalkyl include, but are not limited to, -S-alkyl, -O-alkyl, -NH-alkyl, -alkylene-O-alkyl, etc.

[0046] As used herein, “aryl” refers to a carbocyclic (all carbon) ring or two or more fused rings (rings that share two adjacent atoms) that have a fully delocalized pi-electron system. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted. When substituted, hydrogen atoms are replaced by substituent group(s) that is(are) one or more group(s) independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. When substituted, substituents on an aryl group may form a non-aromatic ring fused to the aryl group, including a cycloalkyl, cycloalkenyl, cycloalkynyl, and heterocyclyl.

[0047] As used herein, “heteroaryl” refers to a monocyclic or polycyclic aromatic ring system (a ring system with fully delocalized pi-electron system), in which at least one of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. Examples of monocyclic “heteroaryl” include, but are not limited to, furan, thiophene, phthalazine, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, triazole, thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, tetrazole, oxadiazole, and triazine. Examples of polycyclic “heteroaryl” include, but are not limited to, quinoline, isoquinoline, quinazoline, quinoxaline, indole, purines, benzofuran, benzothiophene, benzopyranones (e.g. coumarin, chromone, and isocoumarin). A heteroaryl may be substituted. When substituted, hydrogen atoms are replaced by substituent group(s) that is(are) one or more group(s) independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, carbonyl, thiocarbonyl, C-amido, N-amido, S-

sulfonamido, N-sulfonamido, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. When substituted, substituents on a heteroaryl group may form a non-aromatic ring fused to the aryl group, including a cycloalkyl, cycloalkenyl, cycloalkynyl, and heterocyclyl.

[0048] An “aralkyl” or “arylalkyl” is an aryl group connected, as a substituent, via an alkylene group. The alkylene and aryl group of an aralkyl may be substituted. Examples include but are not limited to benzyl, substituted benzyl, 2-phenylethyl, 3-phenylpropyl, and naphthylalkyl. In some cases, the alkylene group is a lower alkylene group.

[0049] A “heteroaralkyl” or “heteroarylalkyl” is heteroaryl group connected, as a substituent, via an alkylene group. The alkylene and heteroaryl group of heteroaralkyl may be substituted. Examples include but are not limited to 2-thienylmethyl, 3-thienylmethyl, furylmethyl, thienylethyl, pyrrolylalkyl, pyridylalkyl, isoxazolylalkyl, pyrazolylalkyl and imidazolylalkyl, and their substituted as well as benzo-fused analogs. In some cases, the alkylene group is a lower alkylene group.

[0050] An “alkylene” is a straight-chained tethering group, forming bonds to connect molecular fragments via their terminal carbon atoms. The alkylene may have 1 to 20 carbon atoms. The alkylene may also be a medium size alkylene having 1 to 10 carbon atoms, such as “C₁₋₆”. The alkylene could also be a lower alkylene having 1 to 4 carbon atoms. The alkylene may be designated as “C₁-C₄ alkylene”, “C₁₋₄ alkylene” or similar designations. Non-limiting examples include, methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), and butylene (-CH₂)₄- groups. In the case of methylene, the two connected fragments are connected to the same carbon atom. A lower alkylene group may be substituted.

[0051] As used herein, “heteroalkylene” by itself or in combination with another term refers to an alkylene group consisting of the stated number of carbon atoms in which one or more of the carbon atoms, such as 1, 2, 3 or 4 carbon atom(s), are independently replaced with the same or different heteroatoms selected from oxygen, sulfur and nitrogen. Examples of heteroalkylene include, but not limited to -CH₂-O-, -CH₂-CH₂-O-, -CH₂-CH₂-CH₂-O-, -CH₂-NH-, -CH₂-CH₂-NH-, -CH₂-CH₂-CH₂-NH-, -CH₂-CH₂-NH-CH₂-, -O-CH₂-CH₂-O-CH₂-CH₂-O-, -O-CH₂-CH₂-O-CH₂-CH₂-, and the like.

[0052] As used herein, “alkylidene” refers to a divalent group, such as =CR'R'', which is attached to one carbon of another group, forming a double bond. Alkylidene groups include, but are not limited to, methylenidene (=CH₂) and ethylenidene (=CHCH₃). As used herein,

“arylalkylidene” refers to an alkylidene group in which either R' or R'' is an aryl group. An alkylidene group may be substituted.

[0053] As used herein, “alkoxy” refers to the group –OR wherein R is an alkyl, e.g. methoxy, ethoxy, n-propoxy, cyclopropoxy, 1-methylethoxy (isopropoxy), n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, amoxy, tert-amoxy and the like. An alkoxy may be substituted.

[0054] As used herein, “alkylthio” refers to the formula –SR wherein R is an alkyl is defined as above, e.g. methylmercapto, ethylmercapto, n-propylmercapto, 1-methylethylmercapto (isopropylmercapto), n-butylmercapto, iso-butylmercapto, sec-butylmercapto, tert-butylmercapto, and the like. An alkylthio may be substituted.

[0055] As used herein, “aryloxy” and “arylthio” refers to RO- and RS-, in which R is an aryl as defined above, e.g., phenoxy, naphthalenyloxy, azulenyloxy, anthracenyloxy, naphthalenylthio, phenylthio and the like. Both an aryloxy and arylthio may be substituted.

[0056] As used herein, “alkenyloxy” refers to the formula –OR wherein R is an alkenyl as defined above, e.g., vinyloxy, propenyloxy, n-butenyloxy, iso-butenyloxy, sec-pentenylloxy, tert-pentenylloxy, and the like. The alkenyloxy may be substituted.

[0057] As used herein, “acyl” refers to a hydrogen, alkyl, alkenyl, alkynyl, or aryl connected, as substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted.

[0058] As used herein, “cycloalkyl” refers to a completely saturated (no double bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro-connected fashion. Cycloalkyl groups may range from C₃ to C₁₀, such as from C₃ to C₆. A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. If substituted, the substituent(s) may be an alkyl or selected from those indicated above with regard to substitution of an alkyl group unless otherwise indicated. When substituted, substituents on a cycloalkyl group may form an aromatic ring fused to the cycloalkyl group, including an aryl and a heteroaryl.

[0059] As used herein, “cycloalkenyl” refers to a cycloalkyl group that contains one or more double bonds in the ring although, if there is more than one, they cannot form a fully delocalized pi-electron system in the ring (otherwise the group would be “aryl,” as defined herein). When composed of two or more rings, the rings may be connected together in a fused, bridged or spiro-connected fashion. Cycloalkenyl groups may range from C₃ to C₁₀,

such as from C₃ to C₈ or from C₅ to C₁₀. For example, C₃₋₈ cycloalkenyl includes C₄₋₈ cycloalkenyl, C₅₋₈ cycloalkenyl or C₆₋₈ cycloalkenyl. A cycloalkenyl group may be unsubstituted or substituted. When substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated. When substituted, substituents on a cycloalkenyl group may form an aromatic ring fused to the cycloalkenyl group, including an aryl and a heteroaryl.

[0060] As used herein, “cycloalkynyl” refers to a cycloalkyl group that contains one or more triple bonds in the ring. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro-connected fashion. Cycloalkynyl groups may range from C₈ to C₁₂. A cycloalkynyl group may be unsubstituted or substituted. When substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated. When substituted, substituents on a cycloalkynyl group may form an aromatic ring fused to the cycloalkynyl group, including an aryl and a heteroaryl.

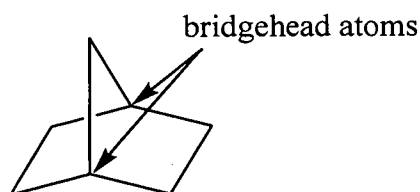
[0061] As used herein, “heteroalicyclic” or “heteroalicycyl” refers to a 3- to 18 membered ring which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. The heteroalicyclic or heteroalicycyl groups may range from C₂ to C₁₀, in some embodiments it may range from C₂ to C₉, and in other embodiments it may range from C₂ to C₈. The “heteroalicyclic” or “heteroalicycyl” may be monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may be joined together in a fused, bridged or spiro-connected fashion; and the nitrogen, carbon and sulfur atoms in the “heteroalicyclic” or “heteroalicycyl” may be oxidized; the nitrogen may be quaternized; and the rings may also contain one or more double bonds provided that they do not form a fully delocalized pi-electron system throughout all the rings, examples are 2H-benzo[b][1,4]oxazin-3(4H)-one, 3,4-dihydroquinolin-2(1H)-one, 1,2,3,4-tetrahydroquinoline, 3,4-dihydro-2H-benzo[b][1,4]oxazine, 2,3-dihydrobenzo[d]oxazole, 2,3-dihydro-1H-benzo[d]imidazole, indoline, and 1,3-dihydro-2H-benzo[d]imidazol-2-one, and benzo[d]oxazol-2(3H)-one. Heteroalicycyl groups may be unsubstituted or substituted. When substituted, the substituent(s) may be one or more groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicycyl, aralkyl, heteroaralkyl, (heteroalicycyl)alkyl, hydroxy, oxo, alkoxy, aryloxy, acyl, ester, O-carboxy, mercapto, alkylthio, arylthio, cyano, halogen, C-amido, N-amido, S-sulfonamido, N-sulfonamido, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, and

amino, including mono- and di-substituted amino groups, and the protected derivatives thereof. Examples of such “heteroalicyclic” or “heteroalicycyl” include but are not limited to, azepinyl, dioxolanyl, imidazolanyl, morpholinyl, oxetanyl, oxiranyl, piperidinyl *N*-Oxide, piperidinyl, piperazinyl, pyrrolidinyl, pyranyl, 4-piperidonyl, pyrazolidinyl, 2-oxopyrrolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone. When substituted, substituents on a heteroalicycyl group may form an aromatic ring fused to the heteroalicycyl group, including an aryl and a heteroaryl.

[0062] A “fused bicyclic ring” refers to a ring system where the two rings share two adjacent atoms. The two rings share one covalent bond. An example of a fused bicyclic ring is decalin.

[0063] A “spiro bicyclic ring” refers to a bicyclic ring wherein the two rings share one atom.

[0064] A “bridged ring system” refers to a ring system where two rings share three or more atoms. The two bridgehead atoms are separated by a bridge containing at least one atom, a specific example is norbornane, also known as bicyclo[2.2.1]heptane. The structure of bicyclo[2.2.1]heptane is shown below, also indicating the bridgehead atoms



[0065] A “(cycloalkyl)alkyl” is a cycloalkyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkyl of a (cycloalkyl)alkyl may be substituted. Examples include but are not limited cyclopropylmethyl, cyclobutylmethyl, cyclopropylethyl, cyclopropylbutyl, cyclobutylethyl, cyclopropylisopropyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, cycloheptylmethyl, and the like. In some cases, the alkylene group is a lower alkylene group.

[0066] A “(cycloalkenyl)alkyl” is a cycloalkenyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkenyl of a (cycloalkenyl)alkyl may be substituted. In some cases, the alkylene group is a lower alkylene group.

[0067] A “(cycloalkynyl)alkyl” is a cycloalkynyl group connected, as a substituent, via an alkylene group. The alkylene and cycloalkynyl of a (cycloalkynyl)alkyl may be substituted. In some cases, the alkylene group is a lower alkylene group.

[0068] As used herein, “halo” or “halogen” refers to F (fluoro), Cl (chloro), Br (bromo) or I (iodo).

[0069] As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl and 1-chloro-2-fluoromethyl, 2-fluoroisobutyl. A haloalkyl may be substituted.

[0070] As used herein, “haloalkoxy” refers to a RO-group in which R is a haloalkyl group. Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy and 1-chloro-2-fluoromethoxy, 2-fluoroisobutyloxy. A haloalkoxy may be substituted.

[0071] An “O-carboxy” group refers to a “RC(=O)O-” group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heteroalicyclic, aralkyl, or (heteroalicyclic)alkyl, as defined herein. An O-carboxy may be substituted.

[0072] A “C-carboxy” group refers to a “-C(=O)OR” group in which R can be the same as defined with respect to O-carboxy. A C-carboxy may be substituted.

[0073] A “trihalomethanesulfonyl” group refers to an “X₃CSO₂-” group wherein X is a halogen.

[0074] A dashed bond, ----, represents an optional unsaturation between the atoms forming the bond. This bond may be unsaturated (e.g. C=C, C=N, C=O) or saturated (e.g. C-C, C-N, C-O). When a dashed bond is present in a ring system it may form part of an aromatic ring system.

[0075] A “nitro” group refers to a “-NO₂” group.

[0076] A “cyano” group refers to a “-CN” group.

[0077] A “cyanato” group refers to an “-OCN” group.

[0078] An “isocyanato” group refers to a “-NCO” group.

[0079] A “thiocyanato” group refers to a “-SCN” group.

[0080] A “carbonyl” group refers to a “-C(=O)-” group.

[0081] A “thiocarbonyl” group refers to a “-C(=S)-” group.

[0082] An “oxo” group refers to a “=O” group.

[0083] A “hydroxy” group or “hydroxyl” group refers to an “-OH” group.

[0084] An “isothiocyanato” group refers to an “-NCS” group.

[0085] A “sulfinyl” group refers to an “-S(=O)-R” group in which R can be the same as defined with respect to O-carboxy. A sulfinyl may be substituted.

[0086] A “sulfonyl” group refers to an “SO₂R” group in which R can be the same as defined with respect to O-carboxy. A sulfonyl may be substituted.

[0087] An “S-sulfonamido” group refers to a “-SO₂NR_AR_B” group in which R_A and R_B independently of each other can be the same as defined with respect to the R group as defined for O-carboxy, or combined to form a ring system selected from the group consisting of substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted C₃₋₈ cycloalkenyl, substituted or unsubstituted heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A S-sulfonamido may be substituted.

[0088] An “N-sulfonamido” group refers to a “RSO₂N(R_A)-” group in which R and R_A independently of each other can be the same as defined with respect to the R group as defined for O-carboxy. An N-sulfonamido may be substituted.

[0089] A “trihalomethanesulfonamido” group refers to an “X₃CSO₂N(R)-” group with X as halogen and R can be the same as defined with respect to O-carboxy. A trihalomethanesulfonamido may be substituted.

[0090] A “C-amido” group refers to a “-C(=O)NR_AR_B” group in which R_A and R_B independently of each other can be the same as defined with respect to the R group as defined for O-carboxy, or combined to form a ring system selected from the group consisting of substituted or unsubstituted C₃₋₈ cycloalkyl, substituted or unsubstituted C₃₋₈ cycloalkenyl, substituted or unsubstituted heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A C-amido may be substituted.

[0091] An “N-amido” group refers to a “RC(=O)NR_A-” group in which R and R_A independently of each other can be the same as defined with respect to the R group as defined for O-carboxy. An N-amido may be substituted.

[0092] An “ester” refers to a “-C(=O)OR” group in which R can be the same as defined with respect to O-carboxy. An ester may be substituted.

[0093] A lower alkoxyalkyl refers to an alkoxy group connected via a lower alkylene group. A lower alkoxyalkyl may be substituted.

[0094] An “amine” or “amino” refers to “RNH₂” (a primary amine), “R₂NH” (a secondary amine), “R₃N” (a tertiary amine). An amino group may be substituted.

[0095] An aminoalkyl refers to an amino group connected via a lower alkylene group. An aminoalkyl may be substituted.

[0096] As used herein “0” (zero), for example in connection with a subscript means that it’s absent. For example -(CH₂)_S-C₂₋₆ alkyl, wherein S can be “0” means that the -(CH₂)- is absent and the remaining group is -C₂₋₆ alkyl

[0097] Any unsubstituted or monosubstituted amine group on a compound herein can be converted to an amide, any hydroxyl group can be converted to an ester and any carboxyl group can be converted to either an amide or ester using techniques well-known to those skilled in the art (see, for example, Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999).

[0098] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (See, Biochem. 11:942-944 (1972)).

[0099] As employed herein, the following terms have their accepted meaning in the chemical literature.

EtOAc	Ethylacetate
DIEA	N,N-Diisopropylethylamine
HCl	Hydrochloric acid
DMF	N,N-dimethylformamide
THF	Tetrahydrofuran
CDCl ₃	Chloroform-d
DMSO-D ₆	Dimethylsulfoxide-d ₆
MgSO ₄	Magnesium Sulfate
POCl ₃	Phosphorus(V) oxychloride
KOH	Potassium hydroxide
NaOH	Sodium hydroxide
Na ₂ SO ₄	Sodium Sulfate
K ₂ CO ₃	Potassium carbonate
Na ₂ CO ₃	Sodium carbonate
TFA	Trifluoroacetic acid
Boc	<i>t</i> -butoxycarbonyl
FMOC	Fluorenylmethyloxycarbonyl
FMOC-Cl	9-Fluorenylmethoxycarbonyl chloride
TEOC	2-(trimethylsilyl)ethoxycarbonyl
equiv.	equivalents
min	minutes
cat	catalytical
HCl	hydrochloric acid

HPLC high performance liquid chromatography

[00100] It is understood that, in any compound disclosed herein having one or more stereocenters or chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure or be stereoisomeric mixtures. Further, compounds provided herein may be scalemic mixtures. In addition, it is understood that in any compound having one or more double bond(s) generating geometrical isomers that can be defined as E or Z each double bond may independently be E or Z or a mixture thereof. Likewise, all tautomeric forms are also intended to be included.

[00101] As used herein, "tautomer" and "tautomeric" refer to alternate forms of a compound disclosed herein that differ in the position of a proton. Non-limiting examples include enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- moiety and a ring =N- moiety such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

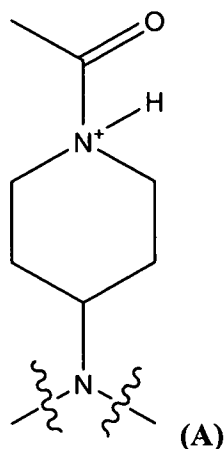
[00102] It is understood that isotopes may be present in the compounds described herein. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound described herein a hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise. For example the term "methyl" includes -CH₃, -CD₃, -CH₂D etc.

[00103] As used herein, "pharmaceutically acceptable salt" refers to a salt of a compound that does not abrogate the biological activity and properties of the compound. Pharmaceutical salts can be obtained by reaction of a compound disclosed herein with an acid or base. Base-formed salts include, without limitation, ammonium salt (NH₄⁺); alkali metal, such as, without limitation, sodium or potassium, salts; alkaline earth, such as, without limitation, calcium or magnesium, salts; salts of organic bases such as, without limitation, dicyclohexylamine, piperidine, piperazine, methylpiperazine, N-methyl-D-glucamine, diethylamine, ethylenediamine, tris(hydroxymethyl)methylamine; and salts with the amino group of amino acids such as, without limitation, arginine and lysine. Useful acid-based salts include, without limitation, acetates, adipates, aspartates, ascorbates, benzoates, butyrates, caprate, caproate, caprylate, camsylates, citrates, decanoates, formates, fumarates, gluconates, glutarate, glycolates, hexanoates, laurates, lactates, maleates, nitrates, oleates, oxalates, octanoates, propanoates, palmitates, phosphates, sebacates, succinates, stearates, sulfates,

sulfonates, such as methanesulfonates, ethanesulfonates, p-toluenesulfonates, salicylates, tartrates, and tosylates.

[00104] Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent of water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

[00105] As used herein, a “prodrug” refers to a compound that may not be pharmaceutically active but that is converted into an active drug upon *in vivo* administration. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. Prodrugs are often useful because they may be easier to administer than the parent drug. They may, for example, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have better solubility than the active parent drug in pharmaceutical compositions. An example, without limitation, of a prodrug would be a compound disclosed herein, which is administered as an ester (the “prodrug”) to facilitate absorption through a cell membrane where water solubility is detrimental to mobility but which then is metabolically hydrolyzed to a carboxylic acid (the active entity) once inside the cell where water-solubility is beneficial. A further example of a prodrug might be a short peptide (polyaminoacid) bonded to an acid group where the peptide is metabolized *in vivo* to release the active parent compound. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those skilled in the art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.* Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392). A specific example of prodrugs relates to formation of a basic nitrogen comprising the piperidyl group of Formula (I), wherein the basic nitrogen may be formed by the metabolic cleavage of a group attached to the nitrogen of the piperidyl group, forming a basic nitrogen, *e.g.* as shown in Formula A. Particular examples are acyl and tosyl groups attached to the nitrogen.



[00106] “Anti-drug” refers to a compound or composition acting against or opposing illicit drugs or their use. Compounds of the present application may act as anti-drugs.

[00107] As used herein, to “modulate” the activity of a receptor means either to activate it, i.e., to increase its cellular function over the base level measured in the particular environment in which it is found, or deactivate it, i.e., decrease its cellular function to less than the measured base level in the environment in which it is found and/or render it unable to perform its cellular function at all, even in the presence of a natural binding partner. A natural binding partner is an endogenous molecule that is an agonist for the receptor.

[00108] An “agonist” is defined as a compound that increases the basal activity of a receptor (i.e. signal transduction mediated by the receptor).

[00109] As used herein, “partial agonist” refers to a compound that has an affinity for a receptor but, unlike an agonist, when bound to the receptor it elicits only a fractional degree of the pharmacological response normally associated with the receptor even if a large number of receptors are occupied by the compound.

[00110] An “inverse agonist” is defined as a compound, which reduces, or suppresses the basal activity of a receptor, such that the compound is not technically an antagonist but, rather, is an agonist with negative intrinsic activity.

[00111] As used herein, “antagonist” refers to a compound that binds to a receptor to form a complex that does not give rise to any response, as if the receptor was unoccupied. An antagonist attenuates the action of an agonist on a receptor. An antagonist may bind reversibly or irreversibly, effectively eliminating the activity of the receptor permanently or at least until the antagonist is metabolized or dissociates or is otherwise removed by a physical or biological process.

[00112] As used herein, a “subject” refers to an animal that is the object of treatment, observation or experiment. “Animal” includes cold- and warm-blooded vertebrates and

invertebrates such as birds, fish, shellfish, reptiles and, in particular, mammals. "Mammal" includes, without limitation, mice; rats; rabbits; guinea pigs; dogs; cats; sheep; goats; cows; horses; primates, such as monkeys, chimpanzees, and apes, and, in particular, humans.

[00113] As used herein, a "patient" refers to a subject that is being treated by a medical professional such as an M.D. or a D.V.M. to attempt to cure, or at least ameliorate the effects of, a particular disease or disorder or to prevent the disease or disorder from occurring in the first place.

[00114] As used herein, a "carrier" refers to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject.

[00115] As used herein, a "diluent" refers to an ingredient in a pharmaceutical composition that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the composition of human blood.

[00116] As used herein, an "excipient" refers to an inert substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A "diluent" is a type of excipient.

[00117] A "receptor" is intended to include any molecule present inside or on the surface of a cell that may affect cellular physiology when it is inhibited or stimulated by a ligand. Typically, a receptor comprises an extracellular domain with ligand-binding properties, a transmembrane domain that anchors the receptor in the cell membrane, and a cytoplasmic domain that generates a cellular signal in response to ligand binding ("signal transduction"). A receptor also includes any intracellular molecule that in response to ligation generates a signal. A receptor also includes any molecule having the characteristic structure of a receptor, but with no identifiable ligand. In addition, a receptor includes a truncated, modified, mutated receptor, or any molecule comprising partial or all of the sequences of a receptor.

[00118] "Ligand" is intended to include any substance that interacts with a receptor.

[00119] "Selective" or "selectivity" is defined as a compound's ability to generate a desired response from a particular receptor type, subtype, class or subclass while generating less or

little response from other receptor types. "Selective" or "selectivity" of one or more particular subtypes of a compound means a compound's ability to increase the activity of the subtypes while causing less, little or no increase in the activity of other subtypes. Selectivity of a compound between receptor targets may for example be determined by the ratio of potencies or affinities for those targets. For example, a compound is said to be 10-fold selectivity for Target 1 over Target 2 if said compound has a pKi of 10 nM for Target 1 and 100 nM for Target 2. Said compound is therefore 10-fold more potent at Target 1, i.e. it is 10-fold selective for Target 1.

[00120] As used herein, "IC₅₀" refers to an amount, concentration, or dosage of a particular test compound that achieves a 50% inhibition of a maximal response. The IC₅₀ can be determined using an assay. The assay may be an R-SAT® assay as described herein but is not limited to an RSAT assay.

[00121] As used herein, "EC₅₀" refers to an amount, concentration or dosage of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound, in an assay that measures such response such as but not limited to R-SAT® assay described herein.

[00122] As used herein, "pKi" refers to the negative logarithm of the Ki, the equilibrium dissociation constant of an antagonist-receptor complex measured in a functional antagonist or radioligand binding assay, e.g. R-SAT® assay as described herein.

[00123] As used herein, "coadministration" of pharmacologically active compounds refers to the delivery of two or more separate chemical entities, whether in vitro or in vivo. Coadministration means the simultaneous delivery of separate agents; the simultaneous delivery of a mixture of agents; as well as the delivery of one agent followed by delivery of a second agent or additional agents. Agents that are coadministered are typically intended to work in conjunction with each other.

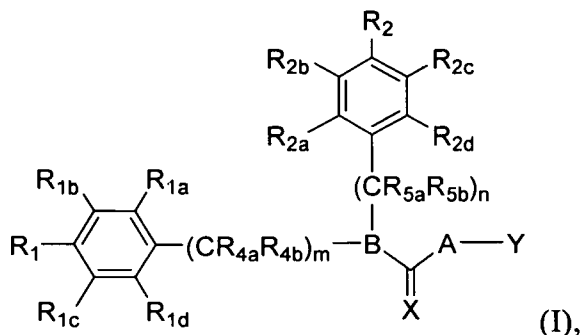
[00124] The term "an effective amount" as used herein means an amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation or palliation of the symptoms of the disease being treated.

[00125] When used herein, "prevent/preventing" should not be construed to mean that a condition and/or a disease never might occur again after use of a compound or

pharmaceutical composition according to embodiments disclosed herein to achieve prevention. Further, the term should neither be construed to mean that a condition not might occur, at least to some extent, after such use to prevent said condition. Rather, “prevent/preventing” is intended to mean that the condition to be prevented, if occurring despite such use, will be less severe than without such use.

Compounds

[00126] Provided herein are compounds according to Formula (I)



[00127] or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof, wherein:

[00128] m, and n are independently an integer selected from the group consisting of 0, 1, 2, and 3;

[00129] t is an integer selected from the group consisting of 0, 1, 2 and 3;

[00130] R₁, R_{1a}, R_{1b}, R_{1c} and R_{1d} are independently selected from the group consisting of hydrogen, deuterium, hydroxyl, -OD, halogen, cyano, amino, -SO₂R₁₀, -OC(=O)R₁₁, -C(=O)OR₁₁, unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₁₋₆ haloalkyl, unsubstituted or substituted C₁₋₆ hydroxyalkyl, unsubstituted or substituted C₁₋₆ aminoalkyl, unsubstituted or substituted C₂₋₆ alkenyl, unsubstituted or substituted C₁₋₆ alkoxy, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted C₃₋₆ heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein at least one of R₁, R_{1a}, R_{1b}, R_{1c} and R_{1d} is not hydrogen;

[00131] R₂, R_{2a}, R_{2b}, R_{2c} and R_{2d} are independently selected from the group consisting of hydrogen, deuterium, amino, hydroxyl, -OD, halogen, cyano, unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₁₋₆ haloalkyl, , unsubstituted or substituted C₁₋₆ hydroxyalkyl, unsubstituted or substituted C₂₋₆ alkenyl, unsubstituted or substituted C₁₋₆ alkoxy, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted C₃₋₆ heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein at least one of R₂, R_{2a}, R_{2b}, R_{2c} and R_{2d} is not selected from hydrogen;

[00132] R_{4a} , R_{4b} , R_{5a} , R_{5b} , R_{5c} , R_{5d} , R_{9a} , and R_{9b} , are independently selected from the group consisting of hydrogen, deuterium, and unsubstituted or substituted C_{1-6} alkyl;

[00133] A is selected from the group consisting of a bond, $-CR_{5c}R_{5d}-$, $-CR_{5c}R_{5d}O-$, $-S-$, $-O-$ and $-NH-$;

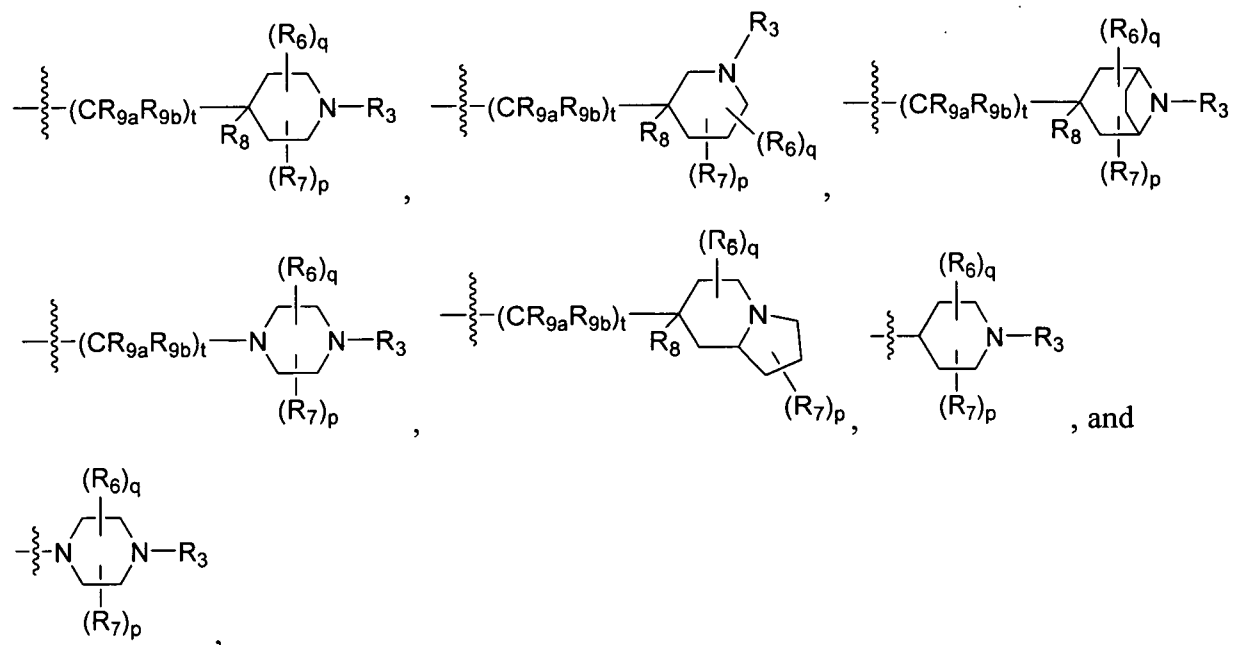
[00134] B is selected from the group consisting of $-N-$, $-NCH_2-$, $-CHNH-$, and $-CH-$;

[00135] R_{10} and R_{11} , independently are selected from the group consisting of hydrogen, amino, unsubstituted or substituted C_{1-6} alkyl;

[00136] X is O or S;

[00137] Y is $-(CR_{9a}R_{9b})_t-(\text{unsubstituted or substituted } C_{3-8} \text{ heteroalicycyl})$.

[00138] The following are also disclosed herein, compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer wherein Y is selected from the group consisting of



[00139] wherein t is an integer selected from the group consisting of 0, 1 and 2; p and q, are integers, independently selected from the group consisting of 0, 1, and 2;

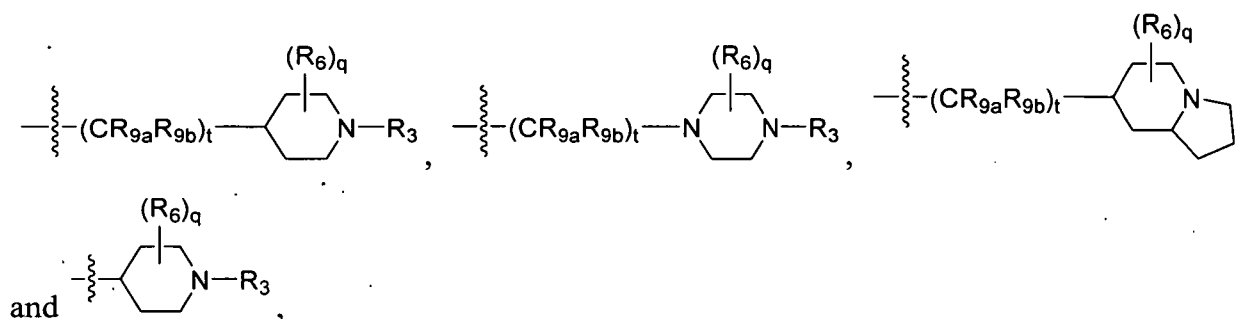
[00140] R_3 is selected from hydrogen, deuterium, hydroxyl, $-OD$, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

[00141] R_6 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy, substituted or unsubstituted aryl;

[00142] R_7 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

[00143] R_8 is absent, or selected from the group consisting of hydrogen, deuterium, cyano, hydroxyl, -OD, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{2-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy, or R_8 taken together with R_{9a} or R_{9b} is forming a ring system.

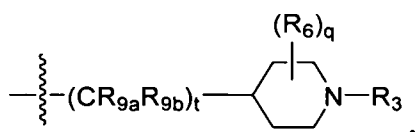
[00144] In some embodiments Y is selected from



[00145] wherein t is 0 or 1, and q is 0 or 1;

[00146] R_6 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy, substituted or unsubstituted aryl.

[00147] In some embodiments Y is selected from



[00148] wherein t is 0 or 1, and q is 0 or 1;

[00149] R_6 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy, substituted or unsubstituted aryl.

[00150] In some embodiments A is selected from the group consisting of a bond, $-CH_2-$, $-O-$, and $-NH-$, such as selected from the group consisting of $-O-$ and $-NH-$.

[00151] In some embodiments B is $-N-$ or $-CHNH-$.

[00152] In some embodiments R_1 , R_{1a} , R_{1b} , R_{1c} and R_{1d} independently are selected from the group consisting of hydrogen, deuterium, halogen, amino, $-SO_2NH_2$, $-SO_2N(C_{1-4} \text{ alkyl})_2$, -

SO₂-C₁₋₄ alkyl, -OC(=O)-C₁₋₄ alkyl, -N(C₁₋₄ alkyl)₂, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₄ cycloalkyl, C₃₋₄ cycloalkyl-C₁₋₃ alkyl and deuterated analogues thereof, e.g. R_{1a}, R_{1b}, R_{1c} and R_{1d} are independently selected from the group consisting of hydrogen, deuterium, halogen, amino, SO₂NH₂, -SO₂CH₃, -OC(=O)CH₃, methyl, -CD₃, methoxy, -OCD₃, -OCF₃ and -CF₃; and R₁ is selected from halogen, amino, SO₂NH₂, -SO₂CH₃, -OC(=O)CH₃, methyl, -CD₃, ethyl, -CD₂CD₃, optionally deuterated n-propyl, optionally deuterated iso-propyl, optionally deuterated n-butyl, optionally deuterated iso-butyl, optionally deuterated n-pentyl, optionally deuterated 2-methyl-butyl, optionally deuterated n-hexyl, optionally deuterated 2-methyl-pentyl, methoxy, -OCD₃, optionally deuterated ethoxy, optionally deuterated n-propoxy, optionally deuterated isopropoxy, optionally deuterated n-butoxy, optionally deuterated isobutoxy, optionally deuterated pentyl-oxy, optionally deuterated 4-methyl-butoxy, optionally deuterated hexyl-oxy, optionally deuterated 4-methylpentoxy, -OCF₃, -OCF₂CF₃, -OCHF₂, -OCDF₂, -CF₃, -CF₂CF₃, -CHF₂, CDF₂-CH₂CF₃, -CD₂CF₃, -CF₂, 1,1,2,2-tetrafluorobutyl and 1,1,1,2,2-pentafluorobutyl.

[00153] In some embodiments R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is deuterium, halogen, amino, SO₂NH₂, -SO₂CH₃, -OC(=O)CH₃, methyl, -CD₃, methoxy, -OCD₃, -OCF₃ and -CF₃; and R₁ is selected from halogen, methyl, methoxy, -OCF₃ and -CF₃, such as fluoro, chloro and -CF₃.

[00154] In some embodiments R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is hydrogen or fluoro; and R₁ is selected from fluoro, chloro, methyl, methoxy, -OCF₃ and -CF₃, such as fluoro, and -CF₃.

[00155] In some embodiments R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is hydrogen or fluoro; and R₁ is selected from fluoro, chloro, methoxy, -OCF₃ and -CF₃, such as fluoro, and -CF₃.

[00156] In some embodiments R_{1a}, R_{1b}, and R_{1c} are hydrogen, R_{1d} is halogen, such as fluoro, and R₁ is halogen, such as fluoro.

[00157] In some embodiments R₂, R_{2a}, R_{2b}, R_{2c} and R_{2d} independently are selected from the group consisting of hydrogen, hydroxyl, halogen, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₃₋₄ cycloalkyl, C₃₋₄ cycloalkyl-C₁₋₃ alkyl and deuterated analogues thereof, e.g. R_{2a}, R_{2b}, R_{2c} and R_{2d} independently are selected from the group consisting of hydrogen, deuterium, hydroxyl, halogen, methyl, -CD₃, methoxy, -OCD₃, -OCF₃ and -CF₃; and R₂ is selected from halogen, methyl, -CD₃, ethyl, -CD₂CD₃, optionally deuterated n-propyl, optionally deuterated iso-propyl, optionally deuterated n-butyl, optionally deuterated isobutyl, optionally deuterated n-pentyl, optionally deuterated 2-methyl-butyl, optionally

deuterated n-hexyl, optionally deuterated 2-methyl-pentyl, methoxy, -OCD₃, optionally deuterated ethoxy, optionally deuterated n-propoxy, optionally deuterated isopropoxy, optionally deuterated n-butoxy, optionally deuterated iso-butoxy, optionally deuterated pentyl-oxy, optionally deuterated 4-methyl-butoxy, optionally deuterated hexyl-oxy, optionally deuterated 4-methylpentoxy, -OCF₃, -OCF₂CF₃, -OCHF₂, -OCDF₂, -CF₃, -CF₂CF₃, -CHF₂, CDF₂-CH₂CF₃, -CD₂CF₃, -CF₂, 1,1,2,2-tetrafluorobutyl and 1,1,1,2,2-pentafluorobutyl. R₂ is not a nitro group.

[00158] In some embodiments R_{2a}, R_{2b}, R_{2c} are hydrogen, R_{2d} is hydrogen or hydroxyl, and R₂ is selected from methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, pentyl-oxy, 4-methyl-butoxy, hexyl-oxy and 4-methylpentoxy.

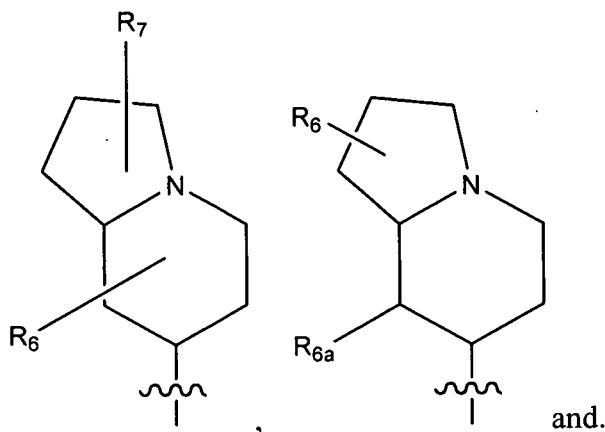
[00159] In some embodiments R₁ and R_{1d} independently are selected from the group consisting of deuterium, halogen, methyl, -CD₃, methoxy, -OCD₃, -OCF₃ and -CF₃; or R₂ and R_{2d} independently are selected from the group consisting of deuterium, halogen, methyl, -CD₃, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, pentyl-oxy, 4-methyl-butoxy, hexyl-oxy and 4-methylpentoxy, -OCD₃, -OCF₃ and -CF₃.

[00160] In some embodiments R₁ and R_{1d} are fluoro, and R₂ is C₁₋₆ alkoxy, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, pentyl-oxy, 4-methyl-butoxy, hexyl-oxy and 4-methylpentoxy. In some embodiments R₁ and R_{1d} are fluoro, and R₂ is n-propoxy, isopropoxy, n-butoxy, or iso-butoxy.

[00161] In some embodiments R₃ is selected from hydrogen, deuterium, hydroxyl, -OD, substituted or unsubstituted C₁₋₆ alkyl, substituted or unsubstituted C₁₋₆ alkoxy, substituted or unsubstituted -(CH₂)_s-C₃₋₆ cycloalkyl, substituted or unsubstituted -(CH₂)_s-C₂₋₅ heteroalicycyl, substituted or unsubstituted -(CH₂)_s-C₂₋₅ heteroaryl, and substituted or unsubstituted -(CH₂)_s-C₅₋₆ aryl, wherein each s is selected from 0, 1, 2 and 3. R₃ could for example be hydrogen, methyl, -CD₃, ethyl, -CD₂CD₃, n-propyl, -CD₂CD₂CD₃, iso-propyl, -CD₂CD₃CD₃, and -(CR_{9a}R_{9b})_tC(=O)OR_{9c} and -(CH₂)_tC(=O)NR_{9a}R_{9b}, wherein R_{9a}, R_{9b}, and R_{9c} independently are selected from hydrogen and C₁₋₄-alkyl, wherein each t is selected from the group consisting of 0, 1, 2, and 3.

[00162] In some embodiments R₃ is hydrogen or methyl.

[00163] In some embodiments R₃ is taken together with one R₆ or R₇, which is attached to a carbon atom adjacent the nitrogen atom, to form a heteroalicyclic ring system according to the following formulas:



[00164] Optionally the formed heteroalicyclic ring systems may comprise additional R_6 and/or R_7 substituents, as shown above.

[00165] In some embodiments R_{4a} , R_{4b} , R_{5a} and R_{5b} are independently selected from the group consisting of hydrogen, methyl and $-\text{CF}_3$, for example R_{4a} , R_{4b} and R_{5a} are hydrogen and R_{5b} is methyl or hydrogen; or R_{4a} , R_{5a} and R_{5b} are hydrogen and R_{4b} is methyl or hydrogen.

[00166] In some embodiments R_{4a} , R_{4b} , R_{5a} and R_{5b} are hydrogen.

[00167] In some embodiments R_6 is absent (e.g. when an unsaturation is present or when q is 0) or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, $-\text{OD}$, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy, for example deuterium, halogen, methyl and methoxy.

[00168] In some embodiments R_6 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, $-\text{OD}$, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy, for example deuterium, halogen, methyl and methoxy.

[00169] In some embodiments R_6 is fluoro and q is 1.

[00170] In some embodiments R_7 is absent (e.g. when p is 0, or when an unsaturation is present) or selected from hydrogen, deuterium, halogen, and substituted or unsubstituted C_{1-4} alkyl, for example hydrogen, fluoro and methyl. Hence in some embodiments p is 0.

[00171] In some embodiments R_8 is selected from the group consisting of hydrogen, halogen, methyl, ethyl, propyl, methoxy, ethoxy, C_{1-2} haloalkyl, and C_{1-2} haloalkoxy, e.g. hydrogen, $-\text{CF}_3$, $-\text{CHF}_2$, $-\text{CF}_2\text{CF}_3$, $-\text{OCF}_3$, $-\text{OCF}_2\text{CF}_3$ and $-\text{OCHF}_2$.

[00172] In some embodiments X is O.

[00173] In some embodiments m , and n independently are selected from the group consisting of 0 and 1, for example m is 1 and n is 0 or 1.

[00174] In some embodiments A is $-\text{N}-$.

[00175] In some embodiments A is $-N-$ and m and n are 1.

[00176] In some embodiments A is $-CH_2-$.

[00177] In some embodiments A is $-CH_2-$ and m is 1 and n is 0.

[00178] In some embodiments A is $-O-$.

[00179] In some embodiments A is $-O-$ and m and n are 1.

[00180] Some embodiments disclosed herein relate to a method for treating a disease in a patient comprising administering to the patient an effective amount of a compound, pharmaceutically acceptable salt, polymorph or stereoisomer of a compound according to Formula (I), wherein the disease is selected from the group consisting of Abnormal hormonal activity, Alzheimer's disease, Addiction (alcohol, nicotine and opioid), Addison's disease, ADHD, Alzheimer's disease psychosis, Affective disorders, Aggressiveness, Agitation, Akathisia, Alcohol addiction, Alcohol withdrawal, Amenorrhea, Amyotrophic lateral sclerosis, Anorexia, Anxiety, Appetite disorders, Asthma, Autism, Behavioral disorders, Behavioral disturbances associated with dementia, Binge eating disorder associated with impulse control disorder (ICD), Bipolar disorder, Blindness, Borderline disorder, Borderline personality disorder, Bradykinesia, Bulimia, Buying associated with ICD, Cardiac arrhythmia, Cerebral vascular accidents, Charles Bonnet disease, Chemotherapy-induced emesis, Childhood autism, Chronic pain, Chronic insomnia, Cognitive disorders, Cushing's disease, Delusion, Depression, Diabetes mellitus (non-insulin dependent), Diabetic peripheral neuropathy, Drug addiction, Double vision, Down's syndrome, Dyskinesia, Dysthymia, Dystonia, Ejaculatory problem, Emphysema, Epilepsy, Extrapyrmidal disorder, Fibromyalgia, Frailty, Friedrich's Ataxia, Frontotemporal Dementia, Gambling associated with ICD, Galactorrhea, General anxiety disorder, Glaucoma, Hair loss or thinning, Hallucination, Headache, Hemorrhoids, Huntington's disease, Hyperprolactinemia, Hypertension, Hypersexuality associated with ICD, Hypotension, Hypoglutamateriga disorders, Impulse control disorder, Idiopathic thrombocytopenic purpura, Impotence, Incontinence, Increased intraocular pressure, Infertility, Inflammatory pain, Insomnia, Ischemia, Ischemic stroke, Lewy body disease (LBD), Learning disorders, Libido (decreased), Loss of libido, Low male fertility, Low sperm mobility, Lupus, Machado-Joseph disease, Major depression, Mania, Menopausal symptoms, Metabolic syndrome, Migraine, Motor tics, Multiple sclerosis, Multiplex development disorder, Myocardial infarction, Myoclonus, Neuropathic pain, Neurodegenerative disorder, Neuropsychiatric disease, Nicotine addiction, Non motor symptoms of Parkinson's disease selected from dementia, depression, apathy, hallucinations, dribbling saliva, constipation, pain, genitourinary

problems and sleep disorders, Obsessive compulsive disorder, On/off phenomena, Opioid addiction, Osteoporosis, Pancreatitis, Panic attacks, Parkinson's disease, Parkinson's disease psychosis, Periodic limb movement during sleep (PLMS), Peripheral vascular disease, Pituitary tumor, Postherpetic neuralgia, Progressive Supranuclear Palsy, Prolactinoma, Psychomotor slowing, Psychosis, Psychoses secondary to neurodegenerative disorders, Psychosomatic disorders, Psychotic depression, post-traumatic stress disorder (PTSD), Raynaud's disease, Reflex sympathetic dystrophy, Restless legs syndrome, Retinal disease, Schizoaffective disorders, Schizophrenia, Sepsis, Serotonin syndrome, Sexual dysfunction, Sleep apnea, Sleep disorders, Sleep maintenance insomnia, social anxiety disorder, Spinal injury, Spinocerebellar Atrophy, Suicidal tendency, Thrombosis, Thrombotic stroke, Thrombotic thrombocytopenic purpura, Tinnitus, Tiredness, Tourette's syndrome, Transient insomnia, Traumatic brain injury, Treatment-resistant depression, Tremor, Vaginal dryness, Vasospasm Wakefulness, Hallucinations associated with Parkinson's disease, Delusions associated with Parkinson's disease; cancer, Pancreatic cancer, Hypoactive sexual desire disorder, and Liver fibrosis.

[00181] Suitable routes of administration of compounds of Formula (I) may, for example, include oral, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intranasal, or intraocular injections. The compounds can also be administered in sustained or controlled release dosage forms, including depot injections, osmotic pumps, pills, transdermal (including electrotransport) patches, and the like, for prolonged and/or timed, pulsed administration at a predetermined rate.

[00182] The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tableting processes.

[00183] Pharmaceutical compositions for use as described herein thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; *e.g.*, in Remington's Pharmaceutical Sciences, above.

[00184] For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

EXAMPLES

[00185] Nuclear Magnetic Resonance (NMR) spectra were recorded on Varian instrument at 400 MHz, at 25 °C. Chemical shifts are reported in ppm (δ) using the residual solvent as internal standard. Peak multiplicities are expressed as follow: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; h, heptet; m, multiplet; br s, broad singlet or combinations thereof, including but not limited to dd, doublet of doublets and dt, doublet of triplet.

[00186] LC-MS were acquired on an Agilent 1100 HPLC coupled with an Agilent MSD mass spectrometer operating in ES (+) ionization mode. Column: Waters symmetry 2.1 x 30 mm C18 or Chromolith RP-18 2 x 50 mm. Solvent A water + 0.1% TFA and solvent B Acetonitrile + 0.1% TFA. Wavelength: 254 nM

[00187] Preparative HPLC were acquired on a Gilson system. Flow: 10 ml/min Column: kromasil 100-5-C18 column. Wavelength: 220 nM. Solvent A water + 0.1% TFA and solvent B Acetonitrile + 0.1% TFA. Gradient: 40 % to 95% B in 15 min

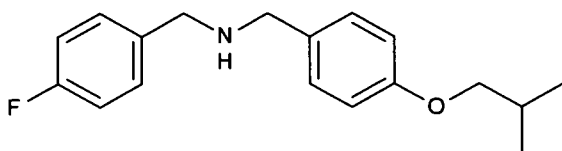
[00188] The following abbreviations are used

EtOAc	Ethylacetate
DIPEA	N,N-Diisopropylethylamine
HCl	Hydrochloric acid
DMF	N,N-dimethylformamide
THF	Tetrahydrofuran
CDCl ₃	Chloroform-d
DMSO-D ₆	Dimethylsulfoxide-d ₆
MgSO ₄	Magnesium Sulfate
POCl ₃	Phosphorus(V) oxychloride
KOH	Potassium hydroxide
NaOH	Sodium hydroxide
Na ₂ SO ₄	Sodium Sulfate
K ₂ CO ₃	Potassium carbonate
Na ₂ CO ₃	Sodium carbonate
TFA	Trifluoroacetic acid
Boc	<i>t</i> -butoxycarbonyl
FMOC	Fluorenylmethyloxycarbonyl
FMOC-Cl	9-Fluorenylmethoxycarbonyl chloride

TEOC 2-(trimethylsilyl)ethoxycarbonyl
 equiv. equivalents
 min minutes
 cat catalytical
 HCl hydrochloric acid
 HPLC high performance liquid chromatography

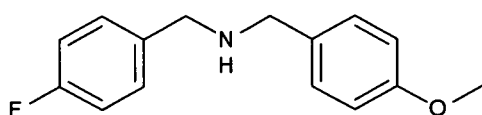
[00189] Preparation of starting materials and intermediate compounds

[00190] Intermediate 1: [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine



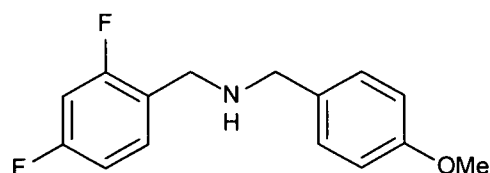
[00191] [4-(2-methylpropoxy)phenyl]methanamine (12.2 mmol, 2.20 g) was dissolved in ethanol (150 ml) and 4-fluorobenzaldehyde (12.9 mmol, 1.60 g) was added. The mixture was stirred for 30 minutes then sodium triacetoxyborohydride (161.6 mmol, 35.4 g) was added and the mixture was stirred at room temperature for 4 hours. 1 M Sodium hydroxide (100 ml) was added and the mixture was extracted with ethyl acetate (3 x 25 ml). The combined organic phases were collected, dried and evaporated to give the desired intermediate as a yellow oil (2.7 g, 84 %).

[00192] Intermediate 2: [(4-fluorophenyl)methyl][(4-methoxyphenyl)methyl]amine



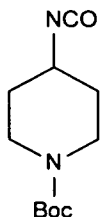
[00193] The compound was prepared in analogy with intermediate 1 using (4-fluorophenyl)methanamine and 4-methoxybenzaldehyde to yield the desired intermediate. Yield 72 %.

[00194] Intermediate 3: [(2,4-difluorophenyl)methyl][(4-methoxyphenyl)methyl]amine



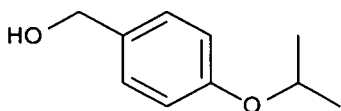
[00195] The compound was prepared in analogy with intermediate 1 using 2,4-difluorobenzylamine and 4-methoxybenzaldehyde.

[00196] Intermediate 4: Tert-butyl 4-isocyanatopiperidine-1-carboxylate



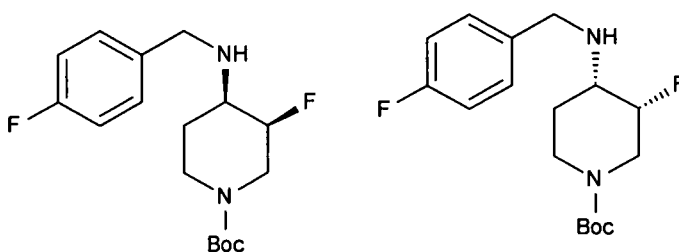
[00197] To a stirred solution of trichloromethyl chloroformate (494 μ L, 2.5 mmol) in dichloromethane (5 ml) at room temperature was added a solution of tert-butyl 4-aminopiperidine-1-carboxylate (500 mg, 2.5 mmol) and triethylamine (505 mg, 4.99 mmol) in dichloromethane (5 ml) dropwise over 45 minutes. After 1 hour, the reaction mixture was washed with hydrochloric acid (3 x 30 ml, 1 M aqueous) and sodium hydrogen carbonate (30 ml, saturated aqueous). The organic phase was separated, dried using a phase separator, and concentrated to yield the desired intermediate (424 mg, 75 %).

[00198] Intermediate 5: [4-(propan-2-yloxy)phenyl]methanol

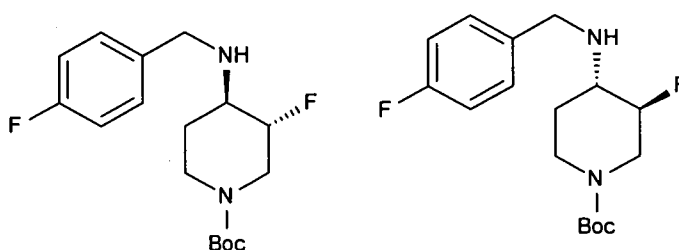


[00199] Ethyl 4-hydroxybenzoate (10.0 g, 60 mmol), potassium carbonate (180 mmol, 25 g) and 2-iodopropane (14.9 ml, 150 mmol) were stirred at 65 °C in dimethylformamide (40 ml) for 24 hours. The mixture was partitioned between diethyl ether and water. The organic phase was separated, washed with water and brine and evaporated to give ethyl 4-isopropoxybenzoate (12.59 g, 100 %). This ester (10.0 g, 48 mmol) was dissolved in diethyl ether (50 ml) and added dropwise to a suspension of lithium aluminum hydride (48 mmol, 95 %, 2.17 g) in diethyl ether (100 ml). The mixture was refluxed for 2 hours, then cooled to ambient temperature and quenched with dropwise addition of methanol (10.0 ml) in diethyl ether (40 ml). The quenched mixture was partitioned between sodium hydroxide (aqueous, 5M) and diethyl ether. The organic phase was separated, washed with brine, dried and evaporated to give the intermediate alcohol (7.85 g, 98 %).

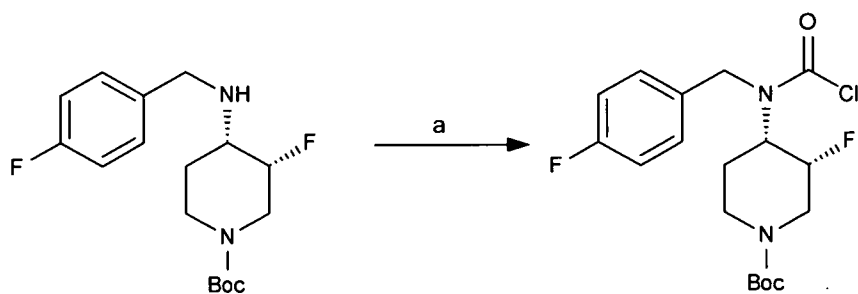
[00200] Intermediate 6: Tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}-piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}-piperidine-1-carboxylate



[00201] Intermediate 7: Tert-butyl (3R,4R)-3-fluoro-4-[[4-(4-fluorophenyl)methyl]amino]piperidine-1-carboxylate and tert-butyl (3S,4S)-3-fluoro-4-[[4-(4-fluorophenyl)methyl]amino]piperidine-1-carboxylate

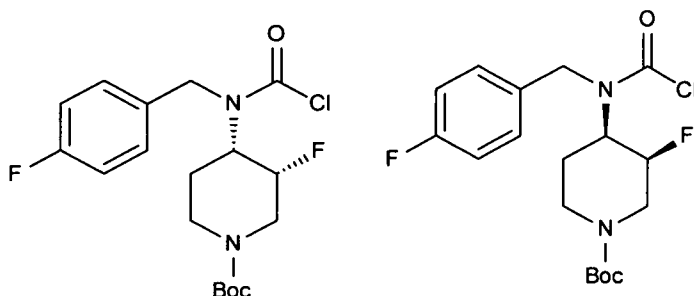


[00202] The compounds were prepared in analogy with intermediate 1 using (4-fluorophenyl)methanamine and 3-fluoro-1-methylpiperidin-4-one to yield the desired intermediates tert-butyl (3S,4R)-3-fluoro-4-[[4-(4-fluorophenyl)methyl]amino]piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-[[4-(4-fluorophenyl)methyl]amino]piperidine-1-carboxylate (2.2 g, 78 %) as the racemic mixture and tert-butyl (3R,4R)-3-fluoro-4-[[4-(4-fluorophenyl)methyl]amino]piperidine-1-carboxylate and tert-butyl (3S,4S)-3-fluoro-4-[[4-(4-fluorophenyl)methyl]amino]piperidine-1-carboxylate (0.25g, 9 %) as the racemic mixture.



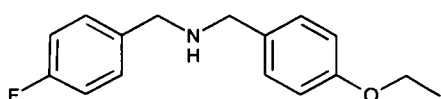
Scheme 1. Reagents: a) diphosgene, pyridine

[00203] Intermediate 8: Tert-butyl (3R,4S)-4-[(chlorocarbonyl)[(4-fluorophenyl)methyl]amino]-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-[(chlorocarbonyl)[(4-fluorophenyl)methyl]amino]-3-fluoropiperidine-1-carboxylate



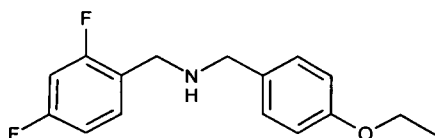
[00204] Tert-butyl (3S,4R)-3-fluoro-4-{{(4-fluorophenyl)methyl}amino}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{{(4-fluorophenyl)methyl}amino}piperidine-1-carboxylate (1:1, 660 mg, 2.0 mmol) was dissolved in dichloromethane (5 ml) and pyridine (6.0 mmol, 489 μ l) was added. This solution was added dropwise to diphosgene (187 μ l, 1.5 mmol, corresponding to 3.0 mmol phosgene) in dichloromethane (2 ml), at 0 °C. The mixture was stirred for 30 minutes, then concentrated and the residue was purified by column chromatography using silicon dioxide gel, eluting with 25% ethyl acetate in petroleum ether to afford the desired intermediates as a racemic mixture (718 mg, 91 %).

[00205] Intermediate 9: [(4-ethoxyphenyl)methyl][(4-fluorophenyl)methyl]amine



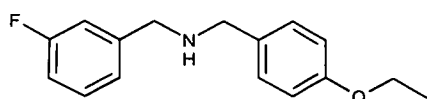
[00206] The compound was prepared in analogy with intermediate 1 using (4-fluorophenyl)methanamine and 4-ethoxybenzaldehyde to yield the desired intermediate. Yield 88 %.

[00207] Intermediate 10: [(2,4-difluorophenyl)methyl][(4-ethoxyphenyl)methyl]amine



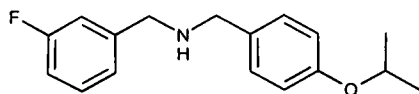
[00208] The compound was prepared in analogy with intermediate 1 using (2,4-difluorophenyl)methanamine and 4-ethoxybenzaldehyde to yield the desired intermediate. Yield 93 %.

[00209] Intermediate 11: [(4-ethoxyphenyl)methyl][(3-fluorophenyl)methyl]amine



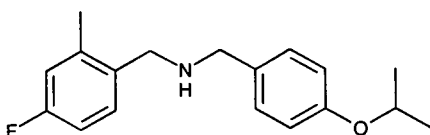
[00210] The compound was prepared in analogy with intermediate 1 using (3-fluorophenyl)methanamine and 4-ethoxybenzaldehyde to yield the desired intermediate. Yield 90 %.

[00211] Intermediate 12: [(3-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl})-amine



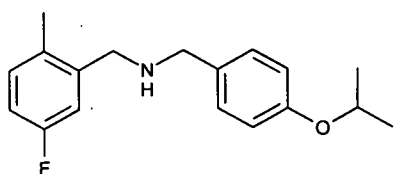
[00212] The compound was prepared in analogy with intermediate 1 using (3-fluorophenyl)methanamine and 4-(propan-2-yloxy)benzaldehyde to yield the desired intermediate. Yield 88 %.

[00213] Intermediate 13: [(4-fluoro-2-methylphenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl})amine



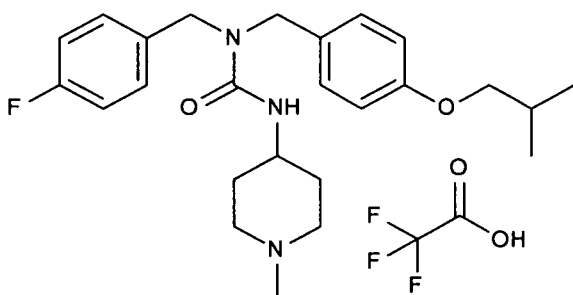
[00214] The compound was prepared in analogy with intermediate 1 using (4-fluoro-2-methylphenyl)methanamine and 4-(propan-2-yloxy)benzaldehyde to yield the desired intermediate. Yield 60 %.

[00215] Intermediate 14: [(5-fluoro-2-methylphenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl})amine

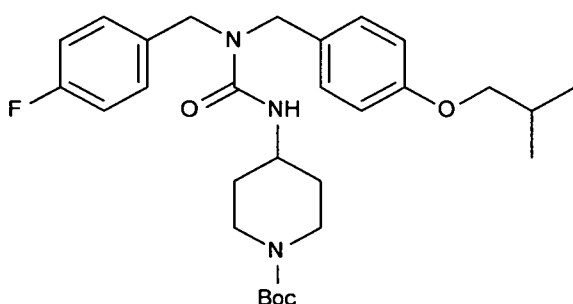


[00216] The compound was prepared in analogy with intermediate 1 using (5-fluoro-2-methylphenyl)methanamine and 4-(propan-2-yloxy)benzaldehyde to yield the desired intermediate. Yield 58 %.

[00217] Example 1: 1-[(4-fluorophenyl)methyl]-3-(1-methylpiperidin-4-yl)-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (1)

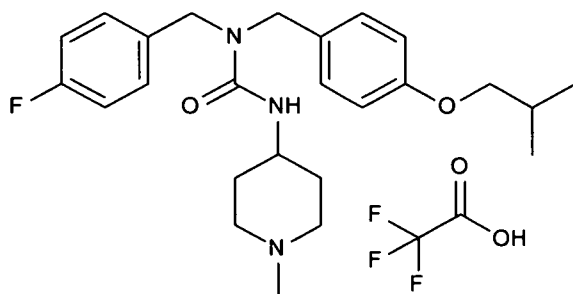


[00218] Intermediate 15: Tert-butyl 4-({[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})carbamoyl}amino)piperidine-1-carboxylate



[00219] Tert-butyl 4-isocyanatopiperidine-1-carboxylate (424 mg, 1.88 mmol) in dichloromethane (6 ml) was added to [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine (431 mg, 1.5 mmol). After 18 hours of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 33 % ethyl acetate in petroleum ether to afford the desired urea (255 mg, 16.5 %).

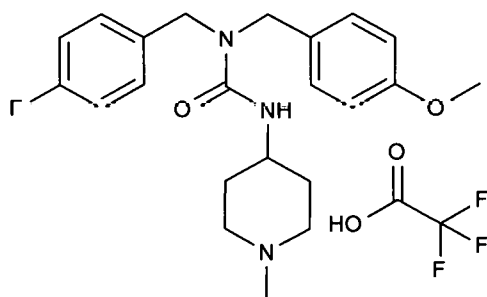
[00220] 1-[(4-fluorophenyl)methyl]-3-(1-methylpiperidin-4-yl)-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid



[00221] Tert-butyl 4-({[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})carbamoyl}amino)piperidine-1-carboxylate (255 mg, 248 μ mol) was dissolved in dichloromethane (5 ml) and trifluoroacetic acid (1 ml) was added.

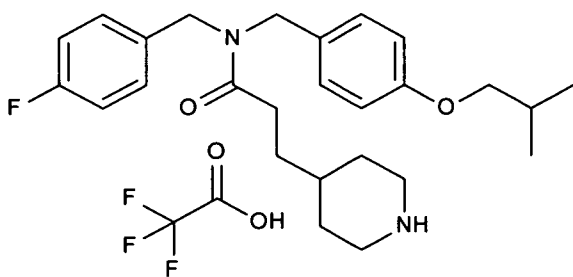
After 20 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofuran (5 ml). Formaldehyde (37 % aqueous, 228 μ l, 2.48 mmol) and sodium triacetoxyborohydride (108 mg, 496 μ mol) were added. After 48 hours, the mixture was quenched with sodium hydrogen carbonate (0.2 ml, saturated, aqueous). The mixture was concentrated, diluted with sodium hydrogen carbonate (15 ml, saturated aqueous) and extracted with dichloromethane (3 x 15 ml). The combined organic phases were washed with water (25 ml) and brine (25 ml), dried over sodium sulfate, filtered, and concentrated. The crude material was purified by HPLC, eluting with 40-75 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound. Yield: 1 %. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.20 (t, 4H), 7.02 (t, 2H), 6.84 (d, 2H), 5.76 (bs, 1H), 4.60 – 4.37 (m, 2H), 4.31 (dd, 2H), 3.95 (s, 1H), 3.71 (d, 2H), 3.55 (d, 1H), 3.42 (d, 1H), 3.07 (m, 1H), 2.74 (s, 3H), 2.55 (m, 1H), 2.08 (dd, 1H), 1.89 (m, 4H), 1.02 (d, 6H); LC-MS: 428.3 $[\text{M}+\text{H}]^+$.

[00222] Example 2: 1-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-(1-methylpiperidin-4-yl)urea; trifluoroacetic acid (2)

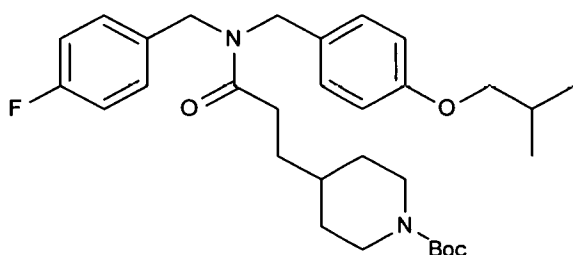


[00223] The compound was prepared in analogy with example 1 using [(4-fluorophenyl)methyl][(4-methoxyphenyl)methyl]amine and tert-butyl 4-isocyanatopiperidine-1-carboxylate. Yield: 1 %. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.20 (t, 4H), 7.02 (t, 2H), 6.85 (d, 2H), 5.82 (bs, 1H), 4.55 (d, 1H), 4.48 – 4.24 (m, 3H), 4.03 – 3.92 (m, 1H), 3.80 (s, 3H), 3.55 (d, 1H), 3.48 – 3.37 (m, 1H), 3.06 – 2.96 (m, 1H), 2.74 (s, 3H), 2.60 – 2.51 (m, 1H), 1.99 – 1.86 (m, 4H); LC-MS: 386.3 $[\text{M}+\text{H}]^+$.

[00224] Example 3: N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}-3-(piperidin-4-yl)propanamide; trifluoroacetic acid (3)

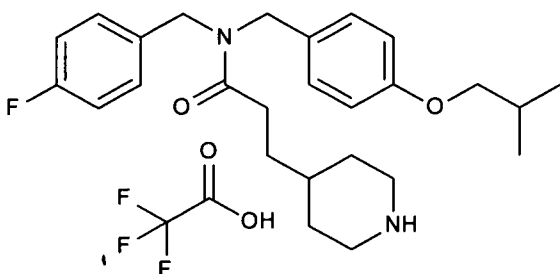


[00225] Intermediate 16: Tert-butyl 4-(2-([(4-fluorophenyl)methyl]([4-(2-methylpropoxy)phenyl)methyl])carbamoyl)ethyl)piperidine-1-carboxylate



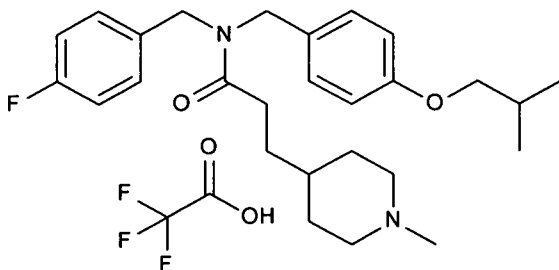
[00226] To a stirred solution of 3-{1-[(tert-butoxy)carbonyl]piperidin-4-yl}propanoic acid (102 mg, 0.384 mmol), diisopropylethylamine (149 mg, 1.15 mmol) and *N*-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (152 mg, 0.423 mmol) in dimethylformamide (1.5 ml) at room temperature was added a solution of [(4-fluorophenyl)methyl]([4-(2-methylpropoxy)phenyl)methyl]amine (115 mg, 0.384 mmol) in dimethylformamide (0.5 ml). The mixture was stirred overnight, diluted with brine (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic phases were washed with brine (40 ml), dried over sodium sulfate and concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 40-66 % ethyl acetate in petroleum ether to yield the desired intermediate (174 mg, 86 %).

[00227] *N*-[(4-fluorophenyl)methyl]-*N*-{[4-(2-methylpropoxy)phenyl)methyl]-3-(piperidin-4-yl)propanamide; trifluoroacetic acid



[00228] To a stirred solution of tert-butyl 4-(2-[[[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})carbamoyl]ethyl]piperidine-1-carboxylate (174 mg, 0.33 mmol) in dichloromethane (5 ml) at room temperature was added trifluoroacetic acid (1 ml). After 20 minutes the reaction mixture was concentrated. The crude material was purified by HPLC, eluting with 37-75 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (72 mg, 40 %). ¹H NMR (400 MHz, Chloroform-*d*) δ 9.18 (bs, 1H), 8.65 (bs, 1H), 7.18 (m, 2H), 7.04 (m, 4H), 6.87 (dd, 2H), 4.60 – 4.48 (m, 2H), 4.44 – 4.33 (m, 2H), 3.76 – 3.67 (m, 2H), 3.44 – 3.32 (m, 2H), 2.91 – 2.76 (m, 2H), 2.50 – 2.35 (m, 2H), 2.15 – 2.03 (m, 1H), 1.82 (d, 2H), 1.70 (d, 2H), 1.58 (m, 1H), 1.54 – 1.40 (m, 2H), 1.07 – 0.98 (m, 6H); LC-MS: 427.3 [M+H]⁺.

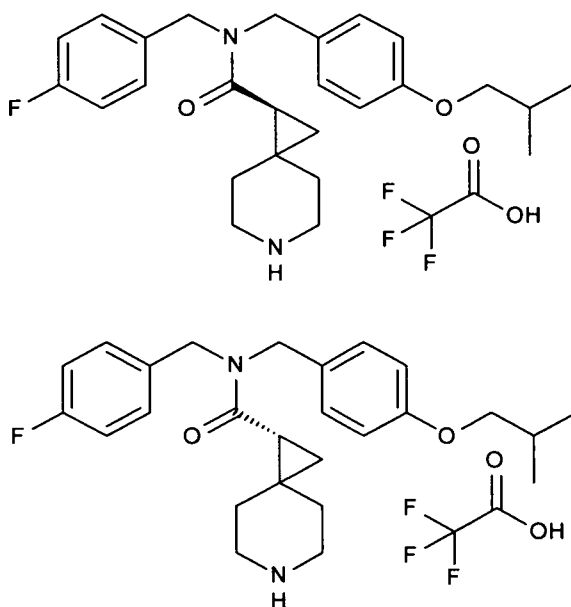
[00229] Example 4: N-[(4-fluorophenyl)methyl]-3-(1-methylpiperidin-4-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide; trifluoroacetic acid (4)



[00230] To a stirred solution of N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}-3-(piperidin-4-yl)propanamide (89.2 mg, 0.165 mmol) in tetrahydrofuran (3 ml) at room temperature was added formaldehyde (75.7 μl, 30 % in water, 0.825 mmol). The mixture was stirred for 5 minutes, then sodium triacetoxyborohydride (71.8 mg, 0.33 mmol) was added. The mixture was stirred for 3 hours, then additional formaldehyde (75 μl, 30 % in water, 0.82 mmol) and sodium triacetoxyborohydride (71 mg, 0.33 mmol) were added. The reaction was stirred overnight then sodium hydrogen carbonate (0.2 ml, saturated, aqueous) was added. The mixture was concentrated, diluted with sodium hydrogen carbonate (15 ml, saturated aqueous) and extracted with dichloromethane (3 x 15 ml). The combined organic

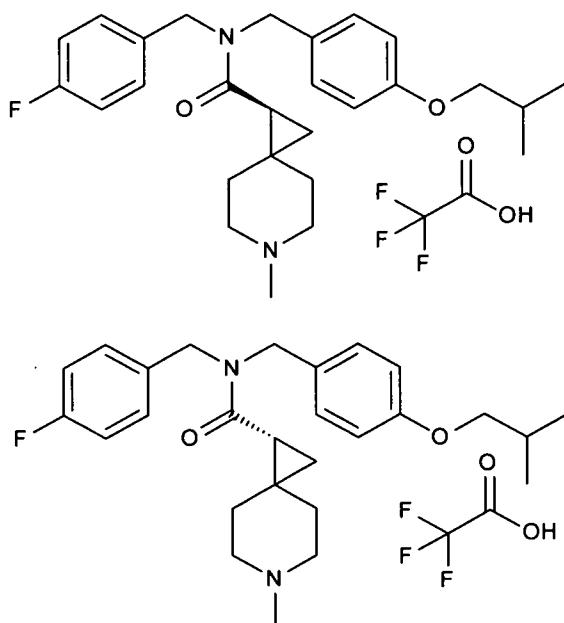
phases were washed with water (25 ml) and brine (25 ml), dried over sodium sulfate, filtered, and concentrated. The crude material was purified by HPLC, eluting with 40-75 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (78 mg, 84 %). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.21 – 7.10 (m, 2H), 7.09 – 6.97 (m, 4H), 6.86 (dd, 2H), 4.53 (d, 2H), 4.44 – 4.35 (m, 2H), 3.75 – 3.69 (m, 2H), 3.64 – 3.56 (m, 2H), 2.84 – 2.75 (m, 3H), 2.61 (m, 2H), 2.43 (m, 2H), 2.09 (m, 1H), 1.81 (m, 2H), 1.67 (m, 5H), 1.09 – 0.99 (m, 6H); LC-MS: 441.3 $[\text{M}+\text{H}]^+$.

[00231] Example 5: (1R)-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]-6-azaspiro[2.5]octane-1-carboxamide; trifluoroacetic acid (5a) and (1S)-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]-6-azaspiro[2.5]octane-1-carboxamide; trifluoroacetic acid (5b)



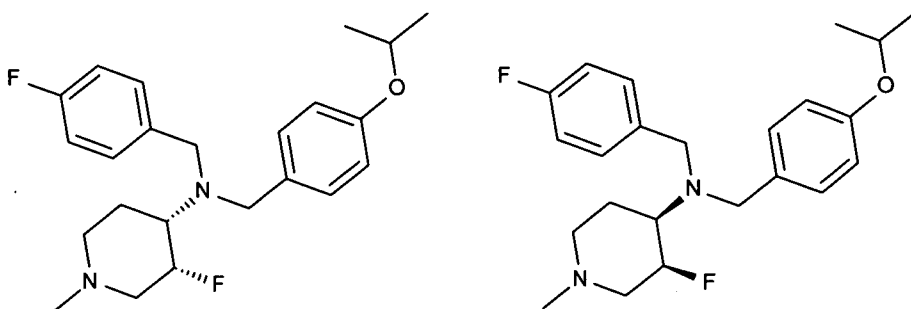
[00232] The compounds were prepared in analogy with example 3 using 6-[(tert-butoxy)carbonyl]-6-azaspiro[2.5]octane-1-carboxylic acid. Isolated as a racemic mixture. Yield: 28 %. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.27 (s, 1H), 9.05 (s, 1H), 7.20 – 6.96 (m, 6H), 6.88 (dd, 2H), 4.91 (d, 1H), 4.68 (d, 1H), 4.42 (t, 1H), 4.21 (dd, 1H), 3.72 (dd, 2H), 3.11 (m, 4H), 2.05 (m, 1H), 1.97 – 1.69 (m, 3H), 1.45 (m, 2H), 1.06 – 0.98 (m, 6H), 0.88 (dt, 1H); LC-MS: 425.3 $[\text{M}+\text{H}]^+$.

[00233] Example 6: (1R)-N-[(4-fluorophenyl)methyl]-6-methyl-N-[[4-(2-methylpropoxy)phenyl]methyl]-6-azaspiro[2.5]octane-1-carboxamide; trifluoroacetic acid (6a) and (1S)-N-[(4-fluorophenyl)methyl]-6-methyl-N-[[4-(2-methylpropoxy)phenyl]methyl]-6-azaspiro[2.5]octane-1-carboxamide; trifluoroacetic acid (6b)



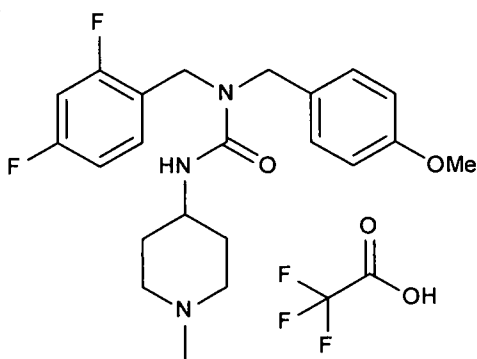
[00234] The compounds were prepared in analogy with example 4 using (1R)-N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}-6-azaspiro[2.5]octane-1-carboxamide; trifluoroacetic acid and (1S)-N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}-6-azaspiro[2.5]octane-1-carboxamide; trifluoroacetic acid. Isolated as a racemic mixture. Yield: 67 %. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.84 (s, 1H), 7.26 – 6.96 (m, 6H), 6.95 – 6.81 (m, 2H), 4.99 – 4.78 (m, 1H), 4.66 – 4.43 (m, 2H), 4.26 (m, 1H), 3.72 (m, 2H), 3.64 (m, 2H), 2.82 (m, 4H), 2.65 (m, 1H), 2.47 – 2.19 (m, 2H), 2.09 (m, 2H), 1.96 – 1.78 (m, 2H), 1.43 (m, 1H), 1.03 (m, 6H), 0.97 – 0.77 (m, 1H); LC-MS: 439.3 [M+H]⁺

[00235] Example 7: (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methyl-N-{[4-(propan-2-yloxy)phenyl]methyl}piperidin-4-amine (7a) and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methyl-N-{[4-(propan-2-yloxy)phenyl]methyl}piperidin-4-amine (7b)



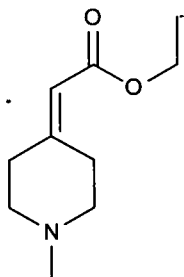
[00236] Tert-Butyl (3R,4S)-4-[(chlorocarbonyl)[(4-fluorophenyl)methyl]amino]-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-[(chlorocarbonyl)[(4-fluorophenyl)methyl]amino]-3-fluoropiperidine-1-carboxylate (1:1, 0.9 mmol, 350 mg) in tetrahydrofuran (2 ml) were added to a mixture of [4-(propan-2-yloxy)phenyl]methanol (1.2 mmol, 200 mg) and sodium hydride (1.8 mmol, 75 mg) in tetrahydrofuran (2 ml). The mixture was stirred for 3 hours and then partitioned between dichloromethane and water. The organic phase was dried and evaporated. The crude was purified by column chromatography using silicon dioxide gel, eluting with 30% ethyl acetate in heptane to afford the intermediate carbamate (387 mg, 83 %). This material (349 mg, 0.67 mmol) was dissolved in diethyl ether (3 ml) and hydrochloric acid (2 M in diethyl ether, 6.7 mmol, 3.4 ml) was added. After 3 hours, the mixture was partitioned between diethyl ether and sodium hydroxide (aqueous, 0.5 M) and the organic phase was dried and evaporated. The residue was dissolved in tetrahydrofuran (3 ml) and formaldehyde (37 % solution, 2.01 mmol, 150 μ l) followed by sodium triacetoxyborohydride (2.01 mmol, 439 mg) were added. The mixture was stirred for 2 hours before more formaldehyde (37 % solution, 2.01 mmol, 150 μ l) and sodium triacetoxyborohydride (2.01 mmol, 439 mg) were added. The mixture was stirred for 2 hours, then concentrated and partitioned between sodium hydroxide (aqueous, 0.5 M) and dichloromethane. The organic phase was dried and concentrated. The residue was purified by column chromatography using silicon dioxide gel, eluting with 5% to 20% methanol in ethyl acetate to afford impure material. This material was purified by column chromatography using silicon dioxide gel, eluting with 30% to 50% ethyl acetate in petroleum ether to afford the title compound (20 mg, 6 %), as a racemic mixture: ^1H NMR (400 MHz, Chloroform- d) δ 7.28 (dd, 2H), 7.20 (d, 2H), 6.98 (t, 2H), 6.83 (d, 2H), 4.94 (d, 1H), 4.53 (m, 1H), 3.68 (dd, 2H), 3.51 (dd, 2H), 3.18 (t, 1H), 3.03 (d, 1H), 2.46 (dd, 1H), 2.31 (s, 3H), 2.23-2.00 (m, 3H), 1.69 (d, 1H), 1.33 (d, 6H); LC-MS: 389.3 $[\text{M}+\text{H}]^+$.

[00237] Example 8: 1-[(2,4-difluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-(1-methylpiperidin-4-yl)urea; trifluoroacetic acid (8),



[00238] [(2,4-difluorophenyl)methyl][(4-methoxyphenyl)methyl]amine (100 mg, 380 μmol) in dichloromethane (1 ml) was added to diphosgene (91.1 μl , 760 μmol) in dichloromethane (1 ml). The mixture was stirred for 30 minutes at ambient temperature before it was concentrated. The crude was suspended in dichloromethane (1 ml) and 1-methylpiperidin-4-amine (143 μl , 1.14 mmol) in dichloromethane (1 ml) was added. After 15 hours, the mixture was heated to 40 $^{\circ}\text{C}$ and stirred for additionally 6 hours before it was cooled to ambient temperature. The mixture was washed with sodium hydroxide (1M, 1 ml). The aqueous phase was extracted with dichloromethane (2 x 1 ml). The combined organic phase was dried (phase separator) and concentrated. The crude material was purified by silica gel chromatography, eluting with 2.5-5 % diethylamine in ethyl acetate. Fractions containing product were pooled and concentrated to give 70.1 mg impure material. 50 mg of the impure material was purified by HPLC, eluting with 20-50 % acetonitrile in water (0.1 % trifluoroacetic acid), to afford the title compound (20 mg). ^1H NMR (400 MHz, Chloroform- d) δ 12.77 (bs, 1H), 7.28 – 7.21 (m, 1H), 7.10 (d, 2H), 6.91 – 6.77 (m, 4H), 4.51 (s, 2H), 4.38 (s, 2H), 4.02 – 3.85 (m, 1H), 3.81 (s, 3H), 3.56 (d, 2H), 2.87 – 2.68 (m, 5H), 2.07 (d, 2H), 1.95 – 1.78 (m, 2H). MS: 404.2.

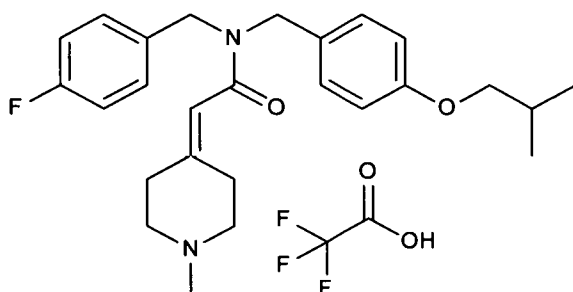
[00239] Intermediate 17: Ethyl 2-(1-methylpiperidin-4-ylidene)acetate



[00240] Triethyl phosphonoacetate (893 μl , 4.5 mmol) in tetrahydrofuran (2.5 ml) was added dropwise to sodium hydride (60% on mineral oil, 200 mg, 5 mmol) in tetrahydrofuran

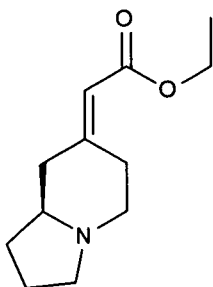
(2.5 ml) at 0 °C. The mixture was heated to ambient temperature and then cooled back to 0 °C. 1-methylpiperidin-4-one (615 µl, 5 mmol) in tetrahydrofuran (2.5 ml) was added and the mixture was heated to ambient temperature. After 1 hour, the mixture was diluted with ethyl acetate (100 ml), washed with sodium hydroxide (1M, 100 ml) and brine (100 ml), dried (phase separator) and concentrated to yield the desired intermediate (865 mg, 94%).

[00241] Example 9: N-[(4-fluorophenyl)methyl]-2-(1-methylpiperidin-4-ylidene)-N-{{[4-(2-methylpropoxy)phenyl]methyl}acetamide; trifluoroacetic acid (9)



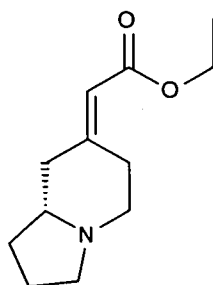
[00242] Sodium hydroxide (2M, 200 µl, 400 µmol) was added to ethyl 2-(1-methylpiperidin-4-ylidene)acetate (18.3 mg, 100 µmol) in methanol (200 µl). The mixture was stirred for 3 hours at ambient temperature before it was quenched with hydrochloric acid (concentrated, 58.3 µl), concentrated and suspended in dimethylformamide (1 ml). N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (23.0 mg, 120 µmol), 1-hydroxybenzotriazole hydrate (18.4 mg, 120 µmol), triethylamine (41.8 µl, 300 µmol) and [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine (43.1 mg, 150 µmol) were added. After 16 hours, the mixture was diluted with ethyl acetate (10 ml), washed with water (5 x 10 ml), dried (phase separator) and concentrated. The crude was purified by HPLC, eluting with 20-80 % acetonitrile in water (0.1 % trifluoroacetic acid), to give the title compound (20.7 mg, 38%). ¹H NMR (400 MHz, Chloroform-d) δ 13.02 (bs, 1H), 7.18 (dd, 1H), 7.14 – 6.97 (m, 5H), 6.87 (dd, 2H), 6.10 (d, 1H), 4.72 (dd, 1H), 4.51 – 4.22 (m, 3H), 3.80 – 3.61 (m, 4H), 3.47 (d, 1H), 3.01 – 2.51 (m, 7H), 2.36 (d, 1H), 2.18 – 1.99 (m, 1H), 1.03 (dd, 6H). MS: 425.3.

[00243] Intermediate 18: Ethyl 2-[(8aS)-octahydroindolizin-7-ylidene]acetate



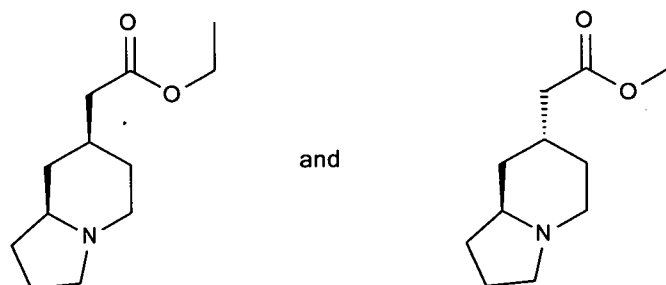
[00244] The compound was prepared in analogy with intermediate 17 using (8aS)-octahydroindolizin-7-one.

[00245] Intermediate 19: Ethyl 2-[(8aR)-octahydroindolizin-7-ylidene]acetate



[00246] The compound was prepared in analogy with intermediate 17 using (8aR)-octahydroindolizin-7-one.

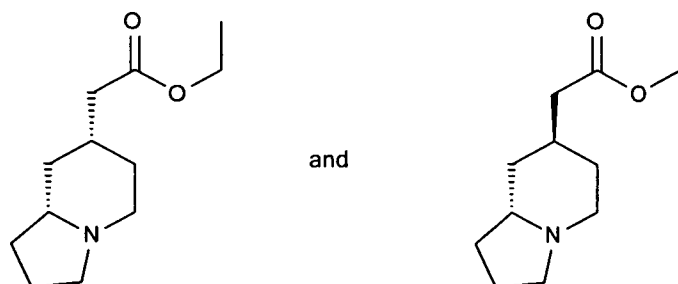
[00247] Intermediates 20 and 21: Ethyl 2-[(7S,8aS)-octahydroindolizin-7-yl]acetate and ethyl 2-[(7R,8aS)-octahydroindolizin-7-yl]acetate



[00248] Palladium (10% on carbon, 35 mg) was added to ethyl 2-[(8aS)-octahydroindolizin-7-ylidene]acetate (179 mg, 588 μ mol) in methanol (2 ml). The atmosphere was exchanged for hydrogen (3 x vacuum/hydrogen) and the resulting mixture was stirred at ambient temperature for 4 hours before it was filtered through a plug of celite and concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting with 50-100% dichloromethane:methanol:ammonia (100:10:1) in

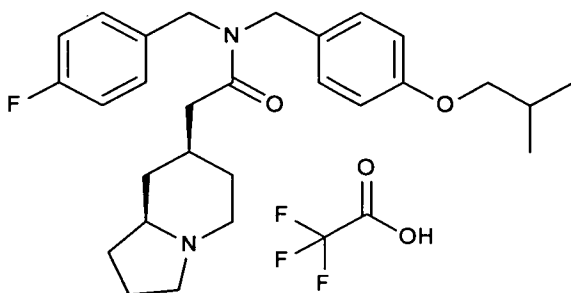
dichloromethane to afford ethyl 2-[(7S,8aS)-octahydroindolizin-7-yl]acetate (118.6 mg, 66%) and ethyl 2-[(7R,8aS)-octahydroindolizin-7-yl]acetate (26 mg, 14%).

[00249] Intermediates 22 and 23: Ethyl 2-[(7R,8aR)-octahydroindolizin-7-yl]acetate and ethyl 2-[(7S,8aR)-octahydroindolizin-7-yl]acetate



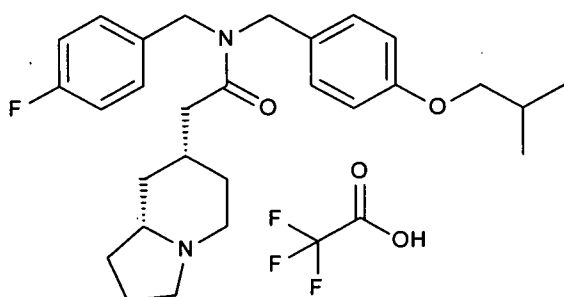
[00250] The compounds were prepared in analogy with intermediates 20 and 21 using ethyl 2-[(8aR)-octahydroindolizin-7-ylidene]acetate.

[00251] Example 10: 2-[(7S,8aS)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide; trifluoroacetic acid (10)



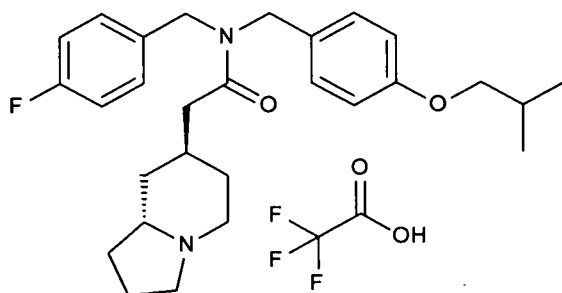
[00252] The compound was prepared in analogy with example 9 using ethyl 2-[(7S,8aS)-octahydroindolizin-7-yl]acetate and [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine. ¹H NMR (400 MHz, Chloroform-d) δ 11.37 (bs, 1H), 7.21 – 7.12 (m, 1H), 7.12 – 6.96 (m, 5H), 6.92 – 6.80 (m, 2H), 4.52 (d, 2H), 4.39 (d, 2H), 3.89 – 3.74 (m, 2H), 3.71 (t, 2H), 2.95 – 2.80 (m, 1H), 2.78 – 2.61 (m, 2H), 2.49 – 2.27 (m, 3H), 2.27 – 2.11 (m, 3H), 2.11 – 1.85 (m, 4H), 1.80 – 1.56 (m, 2H), 1.08 – 0.95 (m, 6H). MS: 453.3.

[00253] Example 11: 2-[(7R,8aR)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide; trifluoroacetic acid (11)



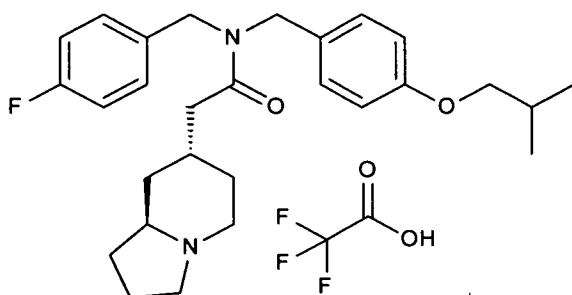
[00254] The compound was prepared in analogy with example 9 using ethyl 2-[(7R,8aR)-octahydroindolizin-7-yl]acetate and [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine. ^1H NMR (400 MHz, Chloroform- d) δ 11.53 (bs, 1H), 7.16 (dd, 1H), 7.13 – 6.96 (m, 5H), 6.86 (dd, 2H), 4.53 (d, 2H), 4.39 (d, 2H), 3.90 – 3.73 (m, 2H), 3.71 (t, 2H), 2.96 – 2.79 (m, 1H), 2.78 – 2.59 (m, 2H), 2.50 – 2.38 (m, 2H), 2.38 – 2.27 (m, 1H), 2.27 – 2.12 (m, 3H), 2.12 – 1.85 (m, 4H), 1.81 – 1.69 (m, 1H), 1.64 (q, 1H), 1.03 (dd, 6H). MS: 453.3.

[00255] Example 12 : 2-[(7S,8aR)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}acetamide; trifluoroacetic acid (12),



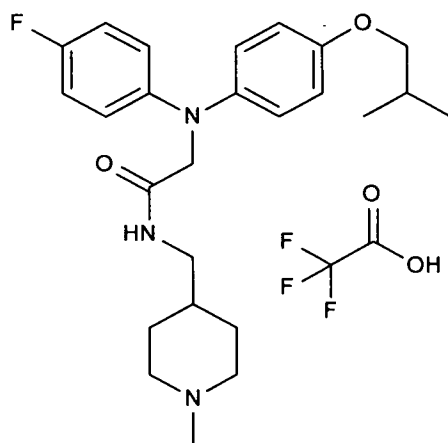
[00256] The compound was prepared in analogy with example 9 using ethyl 2-[(7S,8aR)-octahydroindolizin-7-yl]acetate and [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine. ^1H NMR (400 MHz, Chloroform- d) δ 11.97 (bs, 1H), 7.16 (dd, 1H), 7.13 – 7.03 (m, 3H), 7.02 – 6.98 (m, 2H), 6.89 (d, 1H), 6.84 (d, 1H), 4.56 – 4.49 (m, 2H), 4.38 (d, 2H), 3.97 – 3.84 (m, 1H), 3.71 (t, 2H), 3.64 – 3.50 (m, 1H), 3.39 (d, 1H), 3.17 – 3.05 (m, 1H), 2.83 (q, 1H), 2.44 – 2.31 (m, 3H), 2.17 – 2.06 (m, 5H), 2.04 – 1.93 (m, 2H), 1.87 – 1.71 (m, 1H), 1.67 – 1.53 (m, 1H), 1.03 (dd, 6H). MS: 453.3.

[00257] Example 13: 2-[(7R,8aS)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}acetamide; trifluoroacetic acid (13)

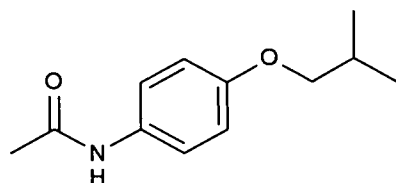


[00258] The compound was prepared in analogy with example 9 using ethyl 2-[(7R,8aS)-octahydroindolizin-7-yl]acetate and [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine. ¹H NMR (400 MHz, Chloroform-d) δ 11.94 (bs, 1H), 7.16 (dd, 1H), 7.12 – 7.05 (m, 3H), 7.04 – 6.96 (m, 2H), 6.89 (d, 1H), 6.84 (d, 1H), 4.56 – 4.50 (m, 2H), 4.39 (d, 2H), 3.89 (s, 1H), 3.72 (t, 2H), 3.63 – 3.51 (m, 1H), 3.39 (d, 1H), 3.17 – 3.05 (m, 1H), 2.84 (q, 1H), 2.43 – 2.33 (m, 3H), 2.17 – 2.06 (m, 5H), 2.01 – 1.94 (m, 2H), 1.88 – 1.77 (m, 1H), 1.68 – 1.53 (m, 1H), 1.03 (dd, 6H). MS: 453.3.

[00259] Example 14: 2-[(4-fluorophenyl)[4-(2-methylpropoxy)phenyl]amino]-N-[(1-methylpiperidin-4-yl)methyl]acetamide; trifluoroacetic acid (14)



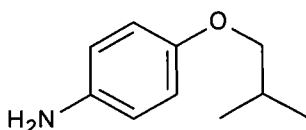
[00260] Intermediate 24. N-[4-(2-methylpropoxy)phenyl]acetamide



[00261] N-(4-hydroxyphenyl)acetamide (4.5 g, 29.8 mmol), isobutyl bromide (8.09 ml, 74.4 mmol), tetrabutylammonium iodide (1.1 g, 2.98 mmol) and potassium carbonate (16.5 g,

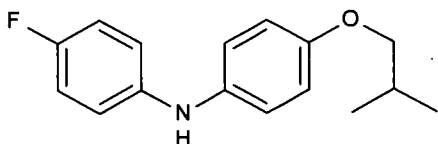
119 mmol) were suspended in dimethylformamide (35 ml). The mixture was stirred at 70 °C overnight. Water (80 ml) was added and the mixture was extracted with diethyl ether (2 x 200 ml). The combined organic phase was washed with water (2 x 200 ml) and brine (200 ml), dried (sodium sulfate), filtered and concentrated to give the desired ether (5.3 g, 86%).

[00262] Intermediate 25. 4-(2-methylpropoxy)aniline



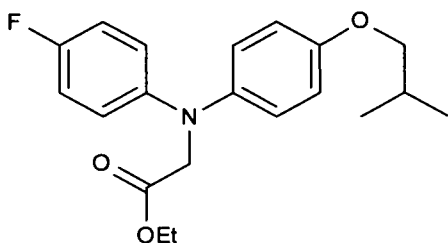
[00263] Hydrochloric acid (concentrated, 1 ml) was added to N-[4-(2-methylpropoxy)-phenyl]acetamide (500 mg, 2.41 mmol) in methanol (5 ml). The mixture was heated by microwave irradiation to 100 °C for 1 hour before it was cooled to ambient temperature and concentrated. Sodium hydroxide (1M, 10 ml) was added and the resulting mixture was extracted with dichloromethane (2 x 10 ml). The organic phase was dried (phase separator) and concentrated to give the desired aniline (397 mg, quantitative).

[00264] Intermediate 26. 4-fluoro-N-[4-(2-methylpropoxy)phenyl]aniline



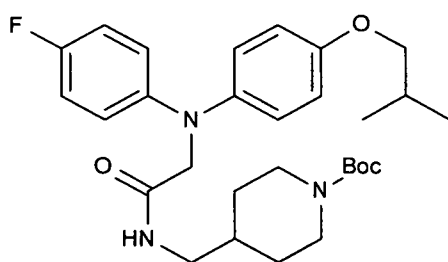
[00265] 4-(2-methylpropoxy)aniline (223 mg, 1.35 mmol) and 1-bromo-4-fluorobenzene (222 µl, 2.02 mmol) in toluene (3.4 ml) were added to [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (98.7 mg, 135 µmol) and potassium tert-butoxide (303 mg, 2.70 mmol) under a nitrogen atmosphere. The mixture was heated by microwave irradiation to 110 °C for 15 minutes before it was cooled to ambient temperature. More 1-bromo-4-fluorobenzene (666 µl, 6.06 mmol) was added and the resulting mixture was heated once more by microwave irradiation to 110 °C for 75 minutes before it was cooled to ambient temperature, diluted by water (20 ml) and extracted with dichloromethane (20 ml). The organic phase was dried (phase separator) and concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting with 0-5% ethyl acetate in petroleum ether to afford the desired intermediate (23.8 mg, 7 %).

[00266] Intermediate 27. Ethyl 2-[(4-fluorophenyl)[4-(2-methylpropoxy)phenyl]amino]acetate



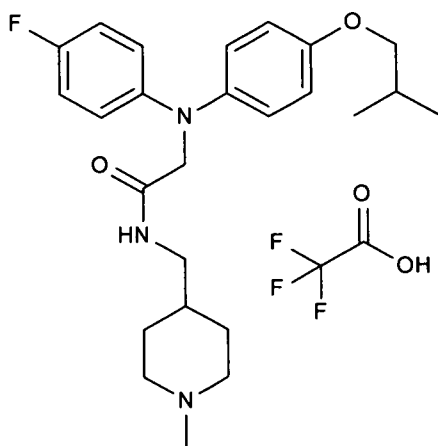
[00267] Ethyl chloroacetate (49.1 μ l, 459 μ mol) was added to sodium iodide (68.8 mg, 459 μ mol) in acetone (500 μ l). After 1 hour, the mixture was filtered and concentrated. The crude was dissolved in dimethylformamide (250 μ l) and added to 4-fluoro-N-[4-(2-methylpropoxy)phenyl]aniline (23.8 mg, 91.8 μ mol) and potassium carbonate (14.0 mg, 101 μ mol) in dimethylformamide (250 μ l). The mixture was heated to 50 °C and stirred for 4 days before more potassium carbonate (14.0 mg, 101 μ mol) was added. After additionally 2 days of stirring, the mixture was diluted with ethyl acetate (10 ml), washed with water (5 x 10 ml), dried (phase separator) and concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting with 0-5% ethyl acetate in petroleum ether to afford a 1:1 mixture of the desired amide and starting material. The mixture (18 mg, 28 %) was used without further purification.

[00268] Intermediate 28: Tert-butyl 4-({2-[(4-fluorophenyl)[4-(2-methylpropoxy)phenyl]amino}acetamido)methyl)piperidine-1-carboxylate



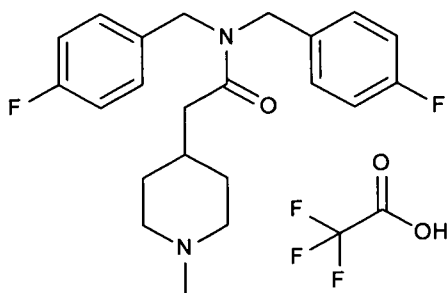
[00269] The compound was prepared in analogy with example 9 using ethyl 2-[(4-fluorophenyl)[4-(2-methylpropoxy)phenyl]amino]acetate and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate. Yield: 77%.

[00270] 2-[(4-fluorophenyl)[4-(2-methylpropoxy)phenyl]amino]-N-[(1-methylpiperidin-4-yl)methyl]acetamide; trifluoroacetic acid



[00271] The compound was prepared in analogy with example 4 using tert-butyl 4-({2-[(4-fluorophenyl)[4-(2-methylpropoxy)phenyl]amino]acetamido}methyl)piperidine-1-carboxylate. ¹H NMR (400 MHz, Chloroform-d) δ 12.75 (bs, 1H), 7.00 – 6.84 (m, 6H), 6.78 (dd, 2H), 4.21 (s, 2H), 3.71 (d, 2H), 3.50 (d, 2H), 3.18 (t, 2H), 2.74 (s, 3H), 2.58 – 2.43 (m, 2H), 2.15 – 2.02 (m, 1H), 1.86 – 1.39 (m, 5H), 1.04 (d, 6H). MS: 428.3.

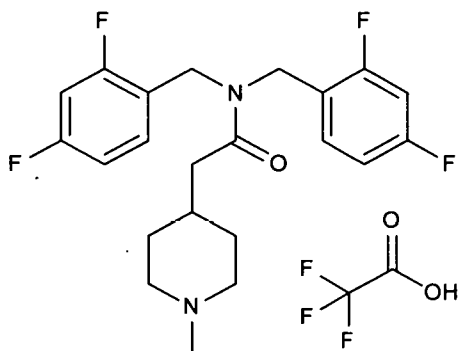
[00272] Example 15: N,N-bis[(4-fluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide; trifluoroacetic acid (15)



[00273] 4-Fluorobenzylamine (114 μ l, 1 mmol) was added to 4-fluorobenzaldehyde (107 μ l, 1 mmol) in dichloromethane (2 ml). After 10 minutes, sodium triacetoxyborohydride (318 mg, 1.5 mmol) was added and the mixture was stirred for 1 hour before it was washed with sodium hydroxide (1M, 2 ml) and dried (phase separator). One fourth of the mixture was concentrated and redissolved in dimethylformamide. N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (57.5 mg, 300 μ mol), 1-hydroxybenzotriazole hydrate (45.9 mg, 300 μ mol), triethylamine (83.6 μ l, 600 μ mol) and 2-(1-methylpiperidin-4-yl)acetic acid (47.2 mg, 300 μ mol) were added. After 18 hours, the mixture was diluted with ethyl acetate (10 ml), washed with water (5 x 10 ml), dried (phase separator) and concentrated. The crude material was purified by HPLC, eluting with 40-40% acetonitrile in water (containing 0.1%

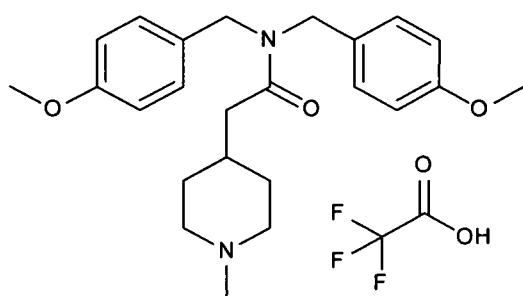
trifluoroacetic acid) to afford the title compound (44.7 mg). ^1H NMR (400 MHz, Chloroform-d) δ 12.47 (bs, 1H), 7.14 (dd, 2H), 7.05 (d, 4H), 6.99 (t, 2H), 4.53 (s, 2H), 4.40 (s, 2H), 3.57 (d, 2H), 2.82 – 2.65 (m, 5H), 2.37 (d, 2H), 2.30 – 2.14 (m, 1H), 1.99 (d, 2H), 1.80 – 1.63 (m, 2H). MS: 373.2.

[00274] Example 16: N,N-bis[(2,4-difluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide; trifluoroacetic acid (16)



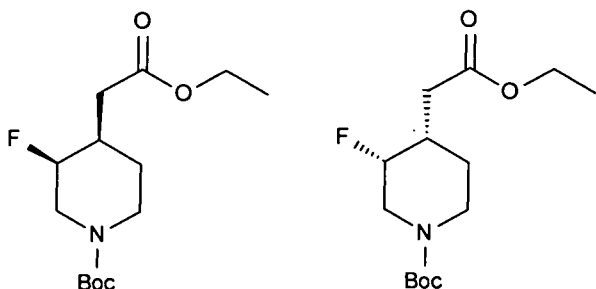
[00275] The compound was prepared in analogy with example 15 using 2,4-difluorobenzylamine and 2,4-difluorobenzaldehyde. ^1H NMR (400 MHz, Chloroform-d) δ 12.61 (bs, 1H), 7.32 – 7.20 (m, 1H), 7.03 (q, 1H), 6.92 – 6.69 (m, 4H), 4.55 (s, 2H), 4.49 (s, 2H), 3.58 (d, 2H), 2.85 – 2.61 (m, 5H), 2.41 (d, 2H), 2.30 – 2.12 (m, 1H), 1.99 (d, 2H), 1.80 – 1.62 (m, 2H). MS: 409.2

[00276] Example 17: N,N-bis[(4-methoxyphenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide; trifluoroacetic acid (17)



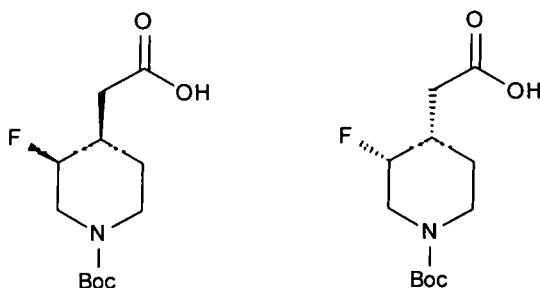
[00277] The compound was prepared in analogy with example 15 using 4-methoxybenzylamine and 4-methoxybenzaldehyde. ^1H NMR (400 MHz, Chloroform-d) δ 12.56 (bs, 1H), 7.11 (d, 2H), 7.01 (d, 2H), 6.89 (d, 2H), 6.84 (d, 2H), 4.51 (s, 2H), 4.35 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.57 (d, 2H), 2.81 – 2.64 (m, 5H), 2.37 (d, 2H), 2.28 – 2.16 (m, 1H), 1.99 (d, 2H), 1.78 – 1.61 (m, 2H). MS: 397.3.

[00278] Intermediate 29: Tert-butyl (3R,4S)-4-(2-ethoxy-2-oxoethyl)-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-(2-ethoxy-2-oxoethyl)-3-fluoropiperidine-1-carboxylate



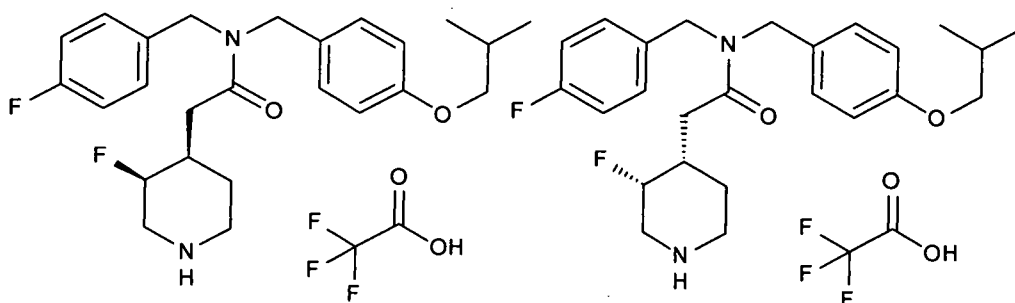
[00279] The compounds were prepared in analogy with intermediates 20 and 21 using tert-butyl 3-fluoro-4-oxopiperidine-1-carboxylate. Isolated as a racemic mixture. Yield: 28 %.

[00280] Intermediate 30: 2-[(3R,4S)-1-[(tert-butoxy)carbonyl]-3-fluoropiperidin-4-yl]acetic acid and 2-[(3S,4R)-1-[(tert-butoxy)carbonyl]-3-fluoropiperidin-4-yl]acetic acid



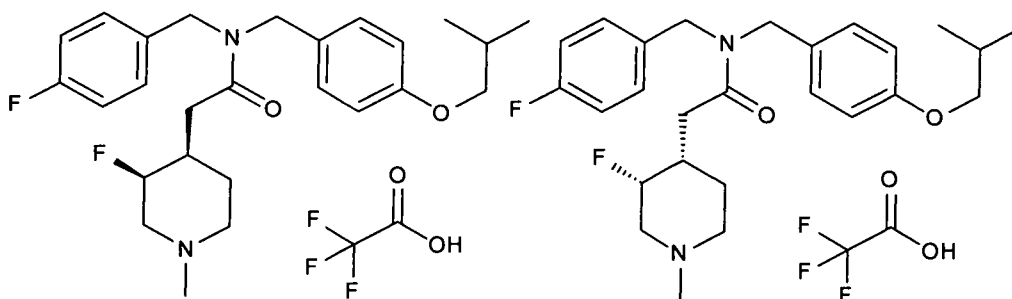
[00281] Sodium hydroxide (aqueous, 2M, 691 μ mol) was added to tert-butyl (3R,4S)-4-(2-ethoxy-2-oxoethyl)-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-(2-ethoxy-2-oxoethyl)-3-fluoropiperidine-1-carboxylate (1:1, 100 mg, 246 μ mol) in ethanol (0.5 ml). After 30 minutes, the mixture was concentrated, diluted with hydrochloric acid (aqueous, 1M, 1 ml) and extracted with dichloromethane (3 x 1 ml). The combined organic phase was dried (phase-separator) and concentrated to give the desired intermediate (93 mg, quantitative), as a racemic mixture.

[00282] Intermediate 31: N-[(4-fluorophenyl)methyl]-2-[(3R,4S)-3-fluoropiperidin-4-yl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-2-[(3S,4R)-3-fluoropiperidin-4-yl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide; trifluoroacetic acid



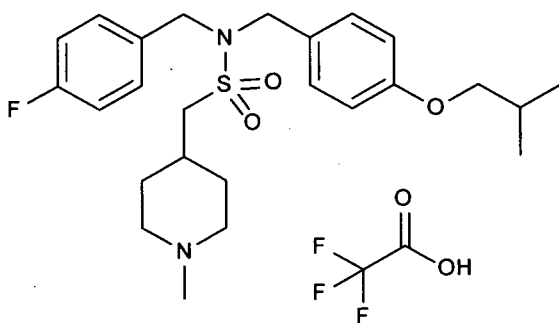
[00283] The compounds were prepared in analogy with example 3 using 2-[(3R,4S)-1-[(tert-butoxy)carbonyl]-3-fluoropiperidin-4-yl]acetic acid and 2-[(3S,4R)-1-[(tert-butoxy)carbonyl]-3-fluoropiperidin-4-yl]acetic acid (1:1). *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride and 1-Hydroxybenzotriazole hydrate (1:1) was used instead of *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide. Isolated as a racemic mixture. Yield: 57 %.

[00284] Example 18: 2-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-*N*-[(4-fluorophenyl)methyl]-*N*-{[4-(2-methylpropoxy)phenyl]methyl}acetamide; trifluoroacetic acid (18a) and 2-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-*N*-[(4-fluorophenyl)methyl]-*N*-{[4-(2-methylpropoxy)phenyl]methyl}acetamide; trifluoroacetic acid (18b)



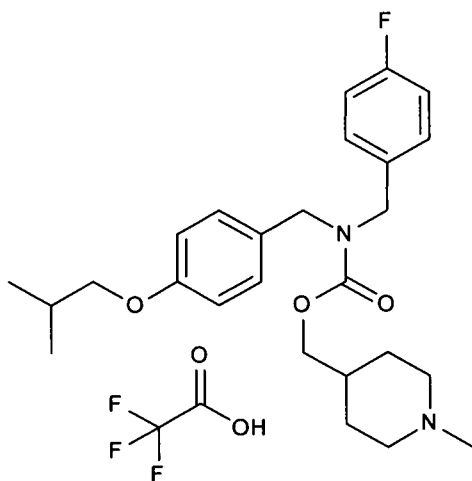
[00285] The compounds were prepared in analogy with example 4 using *N*-[(4-fluorophenyl)methyl]-2-[(3R,4S)-3-fluoropiperidin-4-yl]-*N*-{[4-(2-methylpropoxy)phenyl]methyl}acetamide; trifluoroacetic acid and *N*-[(4-fluorophenyl)methyl]-2-[(3S,4R)-3-fluoropiperidin-4-yl]-*N*-{[4-(2-methylpropoxy)phenyl]methyl}acetamide; trifluoroacetic acid. Yield: 84 %. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.03 (m, 4H), 7.03 – 6.96 (m, 2H), 6.92 – 6.80 (m, 2H), 5.01 (d, 1H), 4.59 – 4.43 (m, 2H), 4.43 – 4.32 (m, 2H), 3.96 – 3.64 (m, 4H), 3.09 – 2.60 (m, 6H), 2.58 – 2.29 (m, 2H), 2.24 – 1.99 (m, 2H), 1.81 (d, 1H), 1.02 (dd, 6H); LC-MS: 445.3 [M+H]⁺.

[00286] Example 19: N-[(4-fluorophenyl)methyl]-1-(1-methylpiperidin-4-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}methanesulfonamide; trifluoroacetic acid (19)



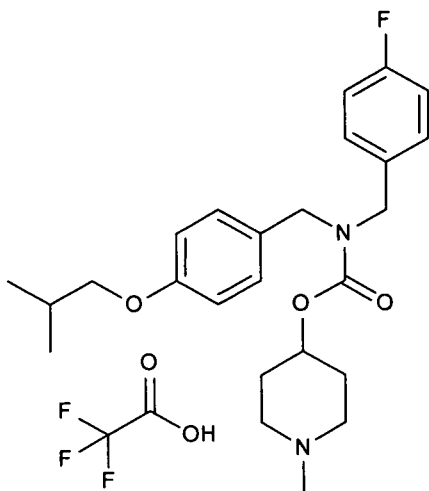
[00287] To a solution of [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine (81 mg, 282 μmol) and diisopropylethylamine (80 μL , 458 μmol) in dichloromethane (2 ml) was added tert-butyl 4-[(chlorosulfonyl)methyl]piperidine-1-carboxylate (92.3 mg, 310 μmol). The mixture was stirred for 4 hours before it was concentrated and purified by column chromatography using silicone dioxide gel, eluting with 25% ethyl acetate in petroleum ether to afford the desired intermediate. The intermediate was dissolved in dichloromethane (5 ml) at room temperature and trifluoroacetic acid (1 ml) was added. After 20 minutes the reaction mixture was concentrated. The crude material was purified by HPLC, eluting with 37-75 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (66mg, 51 %): ^1H NMR (400 MHz, Chloroform-*d*) δ 7.25 (d, 2H), 7.15 (d, 2H), 7.05 (t, 2H), 6.87 (d, 2H), 4.26 (d, 4H), 3.72 (d, 2H), 3.60 (d, 2H), 2.86 – 2.58 (m, 4H), 2.30 – 2.00 (m, 4H), 1.88 (dd, 5H), 1.04 (d, 6H); LC-MS: 463.6 $[\text{M}+\text{H}]^+$

[00288] Example 20:(1-methylpiperidin-4-yl)methyl N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}carbamate; trifluoroacetic acid (20)



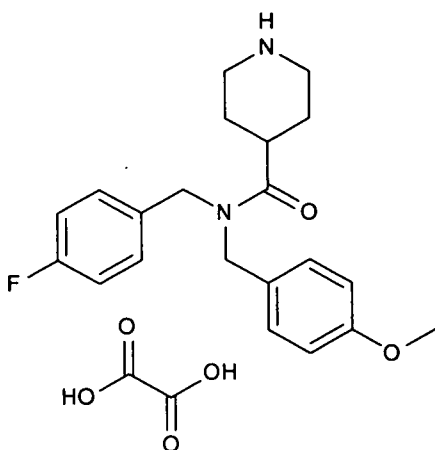
[00289] [(4-Fluorophenyl)methyl]([4-(2-methylpropoxy)phenyl]methyl)amine (150 mg, 0.522 mmol) and pyridine (253 μ l, 3.1 mmol) in dichloromethane (1.3 ml) was added dropwise to trichloromethyl chloroformate (94 μ l, 0.783 mmol in dichloromethane (1.0 ml) at 0 °C. After 7 hours, the mixture was concentrated. The crude was purified by column chromatography using silicon dioxide gel, eluting with ethyl acetate in petroleum ether to afford N-[(4-fluorophenyl)methyl]-N-{[4-(2 methylpropoxy)phenyl]methyl} carbamoyl chloride (159 mg). Tert-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (75 mg, 0.35 mmol) was dissolved in dry tetrahydrofuran (1.5 ml). Sodium hydride (60% in mineral oil, 22 mg, 0.91 mmol) was added and the mixture was stirred for 30 minutes at room temperature. The resulting suspension was added dropwise to a solution of N-[(4-fluorophenyl)methyl]-N-{[4-(2 methylpropoxy)phenyl]methyl} carbamoyl chloride (79 mg, 0.23 mmol) in dry tetrahydrofuran (1.0 ml). The mixture was stirred overnight at ambient temperature. The mixture was concentrated. The residue was dissolved in diethyl ether and water. The organic layer was collected. The water phase was extracted twice with ether and the collected organic layers were dried over sodium sulfate. The product was purified by column chromatography using silicon dioxide gel, eluting with ethyl acetate in petroleum ether to afford tert-butyl 4-[(4-[(4-fluorophenyl)methyl]([4-(2-methylpropoxy)phenyl] methyl))carbamoyl]oxy)methyl]piperidine-1-carboxylate (96 mg). This intermediate was dissolved in dichloromethane (2 ml) and the solution was cooled to 0 °C. Trifluoroacetic acid (1 ml) was added. The cooling bath was removed and the reaction was stirred at room temperature for 1 h. The reaction mixture was concentrated. The crude material was dissolved in tetrahydrofuran (1.0 ml) and formaldehyde, 37 wt% in water (68 μ l, 0.912 mmol) was added followed by sodium triacetoxyborohydride (193 mg, 0.912 mmol). The reaction mixture was stirred for 2 h, concentrated and the residue was dissolved in dichloromethane and sodium hydroxide (1 M, aqueous). The organic layer was collected. The water phase was extracted twice with dichloromethane and the collected organic layers were dried over sodium sulfate. The solid was filtered of and the reaction mixture was concentrated. The crude material was purified by HPLC, eluting with 35-60 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (9 mg). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.02 (m, 4H), 7.01 (t, 2H), 6.85 (d, 2H), 4.47 – 4.25 (m, 4H), 4.08 (d, 2H), 3.71 (d, 2H), 3.60 (d, 2H), 2.77 (s, 3H), 2.67 – 2.53 (m, 2H), 2.08 (dp, 1H), 1.94 – 1.68 (m, 5H), 1.03 (d, 6H). LC-MS: 443.3 [M+H]⁺.

[00290] Example 21: 1-methylpiperidin-4-yl N-[(4-fluorophenyl)methyl]-N-{{[4-(2-methylpropoxy)phenyl]methyl}} carbamate; trifluoroacetic acid (21)

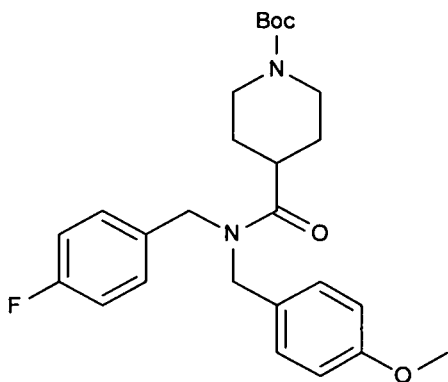


[00291] The title compound was prepared in analogy with example 20, using tert-butyl 4-hydroxypiperidine-1-carboxylate and [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amine. Yield: 23 %. Major conformer: ^1H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 6.97 (m, 6H), 6.94 – 6.78 (m, 2H), 5.07 (s, 1H), 4.67 – 4.24 (m, 4H), 3.71 (d, 2H), 3.34 – 3.17 (m, 2H), 2.52 (s, 3H), 2.39 – 1.94 (m, 7H), 1.02 (d, 6H). Minor conformer: ^1H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 6.97 (m, 6H), 6.94 – 6.78 (m, 2H), 4.93 – 4.82 (m, 1H), 4.67 – 4.24 (m, 4H), 3.77 – 3.61 (m, 4H), 2.90 – 2.76 (m, 5H), 2.39 – 1.94 (m, 5H), 1.02 (d, 6H). LC-MS: 429.3 $[\text{M}+\text{H}]^+$

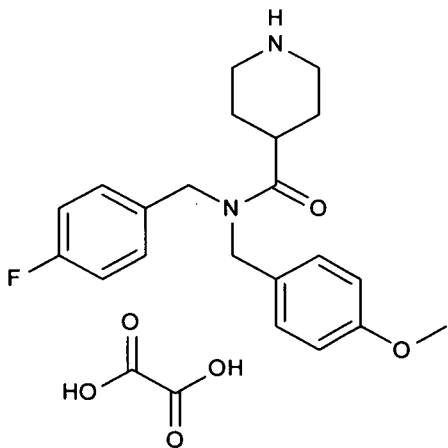
[00292] Example 22: N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]piperidine-4-carboxamide; oxalic acid (22)



[00293] Intermediate 32: Tert-butyl 4-{{[(4-fluorophenyl)methyl][(4-methoxyphenyl)methyl]carbonyl}piperidine-1-carboxylate



[00294] To a solution of [(4-fluorophenyl)methyl][(4-methoxyphenyl)methyl]amine (100 mg, 0.41 mmol) in dichloromethane (3 ml) were added 1-[(tert-butoxy)carbonyl]piperidine-4-carboxylic acid (103 mg, 0.45 mmol), diisopropylethylamine (132 mg, 1.02 mmol), (3-[[[(ethylimino)methylidene]amino}propyl]dimethylamine hydrochloride (93.8 mg, 0.49 mmol) and 1H-1,2,3-benzotriazol-1-ol (74.9 mg, 0.49 mmol). After 12 hours of stirring at ambient temperature water (5 ml) was added. The phases were separated and the water phase was extracted with dichloromethane (2 x 5 ml). The combined organic phases were dried with sodium sulfate, filtered and concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting with 20-50% ethyl acetate in petroleum ether to afford the amide (171 mg, 92 %).

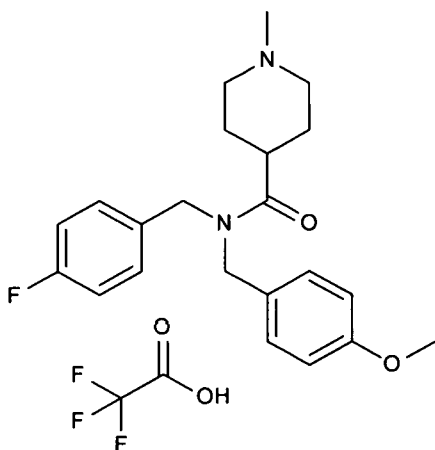


[00295] N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]piperidine-4-carboxamide; oxalic acid

[00296] Tert-butyl 4-[[[(4-fluorophenyl)methyl][(4-methoxyphenyl)methyl]carbamoyl]-piperidine-1-carboxylate (150 mg, 0.33 mmol) was dissolved in hydrochloric acid (4M in dioxane). After 3 hours of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting

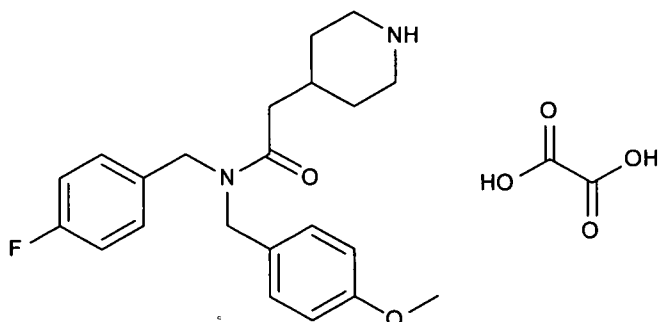
with 0-10% methanol in ethyl acetate to afford N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]piperidine-4-carboxamide (117 mg, 100%). N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]piperidine-4-carboxamide (15 mg, 42 μ mol) was dissolved in acetone (0.5 ml) and oxalic acid (4.3 mg, 46 μ mol) was added. The resulting precipitate was washed with acetone and dried to afford the title compound (18 mg, 96 %). ^1H NMR (400 MHz, methanol- d_4) δ 7.21 (dt, 2H), 7.12 (dd, 3H), 7.04 (t, 1H), 6.90 (dd, 2H), 4.63 – 4.49 (m, 4H), 3.78 (d, 3H), 3.42 (d, 2H), 3.16 – 2.93 (m, 3H), 2.00 – 1.81 (m, 4H); LC-MS: 357.2 $[\text{M}+\text{H}]^+$.

[00297] Example 23: N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-1-methylpiperidine-4-carboxamide; trifluoroacetic acid (23)



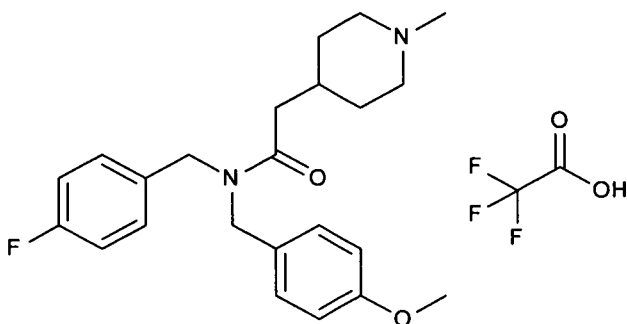
[00298] The compound was prepared in analogy example 4, using N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]piperidine-4-carboxamide. Yield 78 %. ^1H NMR (400 MHz, Chloroform- d) δ 7.18 – 7.02 (m, 5H), 6.97 (t, 1H), 6.86 (dd, 2H), 4.51 (d, 2H), 4.39 (d, 2H), 3.80 (d, 3H), 2.91 (d, 2H), 2.57 – 2.39 (m, 1H), 2.25 (s, 3H), 2.06 – 1.95 (m, 2H), 1.95 – 1.85 (m, 2H), 1.70 (t, 2H); LC-MS: 371.3 $[\text{M}+\text{H}]^+$.

[00299] Example 24: N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-(piperidin-4-yl)acetamide; oxalic acid (24)



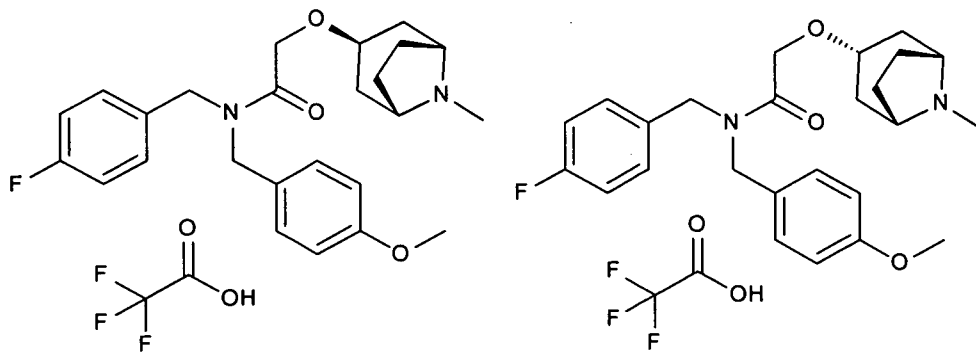
[00300] The compound was prepared in analogy with example 22, using [(4-fluorophenyl)methyl][(4-methoxyphenyl)methyl]amine and 2-{1-[(tert-butoxy)carbonyl]-piperidin-4-yl}acetic acid. Yield 89 %. ¹H NMR (400 MHz, methanol-d₄) δ 7.27 – 7.21 (m, 1H), 7.21 – 7.16 (m, 1H), 7.14 (d, 1H), 7.10 (dd, 2H), 7.03 (t, 1H), 6.89 (dd, 2H), 4.53 (dd, 4H), 3.78 (d, 3H), 3.37 (d, 2H), 2.97 (t, 2H), 2.47 (dd, 2H), 2.24 – 2.10 (m, 1H), 1.96 (d, 2H), 1.43 (q, 2H). LC-MS: 371.3 [M+H]⁺.

[00301] Example 25: N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide; trifluoroacetic acid (25)

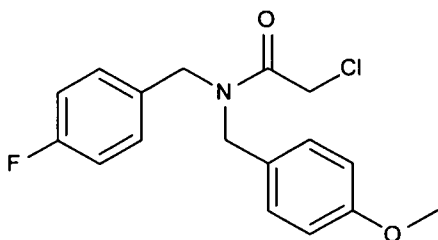


[00302] The compound was prepared in analogy example 4, using N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-(piperidin-4-yl)acetamide. Yield 78 %. ¹H NMR (400 MHz, Chloroform-d) δ 7.19 – 7.12 (m, 1H), 7.10 (d, 1H), 7.06 (d, 2H), 7.00 (t, 2H), 6.87 (dd, 2H), 4.52 (d, 2H), 4.38 (d, 2H), 3.80 (d, 3H), 3.59 (d, 2H), 2.79 (s, 3H), 2.77 – 2.68 (m, 2H), 2.38 (dd, 2H), 2.24 (s, 1H), 2.01 (d, 2H), 1.69 (q, 2H); LC-MS: 385.3 [M+H]⁺.

[00303] Example 26: N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-[[[(1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}acetamide; trifluoroacetic acid (26a) and N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-[[[(1R,3S,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}acetamide; trifluoroacetic acid (26b)

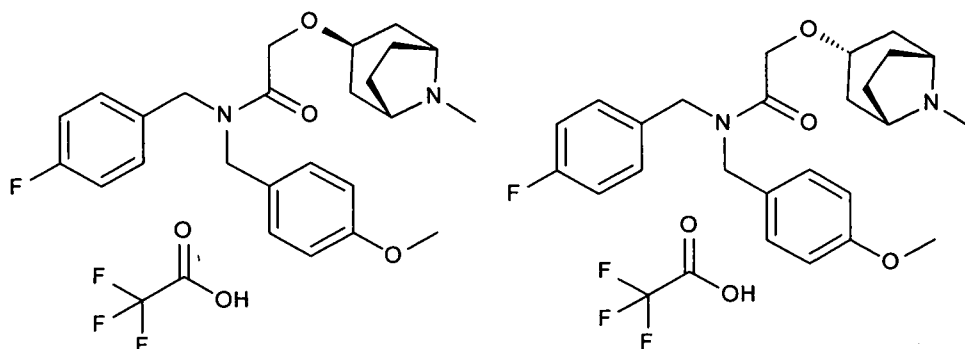


[00304] Intermediate 33: 2-chloro-N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]acetamide



[00305] To a mixture of [(4-fluorophenyl)methyl][(4-methoxyphenyl)methyl]amine (183 μ l, 0.82 mmol) in tetrahydrofuran (12 ml) under nitrogen atmosphere was added triethylamine (124 μ l, 1.22 mmol). After 10 minutes of stirring at ambient temperature 2-chloroacetyl chloride (64.9 μ l, 0.82 mmol) was added. After 1 hour of stirring at ambient temperature the mixture was partitioned between ethyl acetate (20 ml) and water (20 ml). The organic phase was separated, washed with water (2 x 20 ml) and brine (20 ml), dried with sodium sulfate, filtered and concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting with 20% ethyl acetate in petroleum ether to afford the amide (157 mg, 60 %).

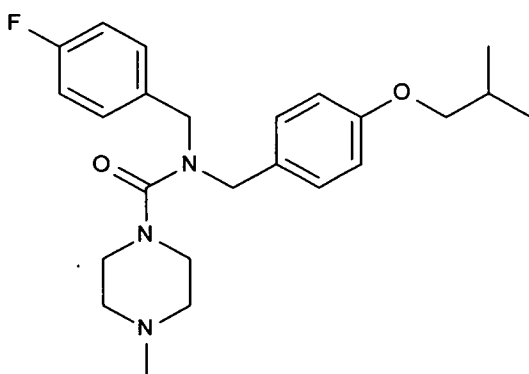
[00306] N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-{[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}acetamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-{[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}acetamide; trifluoroacetic acid



[00307] 2-chloro-N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]acetamide (100 mg, 0.31 mmol) and (1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol and (1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (52.7 mg, 0.37 mmol) were dissolved in tetrahydrofuran (3 ml) and cooled to 0 °C. Sodium hydride (24.9 mg, 0.62 mmol) was added

and the mixture was warmed to ambient temperature. After 3 hours of stirring at ambient temperature the mixture was quenched with ammonium chloride (aqueous, saturated, 10 ml) and extracted with ethyl acetate (3 x 20 ml). The organic phases were washed with water and brine, dried using sodium sulfate, filtered and concentrated. The crude material was purified by HPLC, eluting with 20-55 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-[[[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}acetamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-[[[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}acetamide; trifluoroacetic acid (ratio: 89:11, 147 mg, 88%). ¹H NMR (400 MHz, Chloroform-d) δ 7.18 (d, 1H), 7.14 (d, 2H), 7.06 (d, 2H), 7.00 (t, 1H), 6.87 (dd, 2H), 4.48 (d, 2H), 4.42 (d, 2H), 4.24 (d, 2H), 3.89 (s, 1H), 3.81 (s, 3H), 3.77 (s, 2H), 2.73 (d, 3H), 2.30 (s, 4H), 2.06 (s, 2H), 1.88 (d, 2H); LC-MS: 427.2 [M+H]⁺.

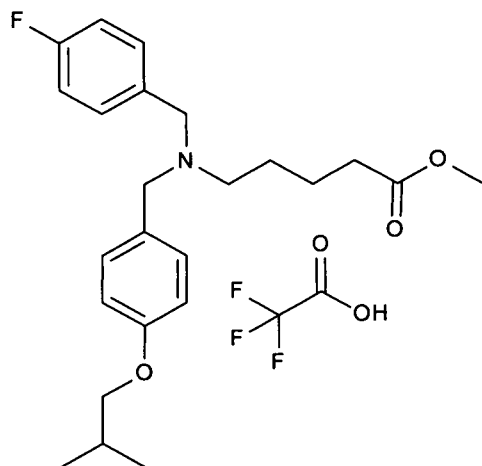
[00308] Example 27: N-[(4-fluorophenyl)methyl]-4-methyl-N-[[4-(2-methylpropoxy)phenyl]methyl] piperazine-1-carboxamide (27)



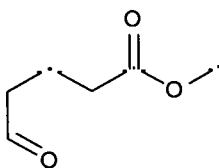
[00309] To the solution of [(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl})amine (96.0 mg, 0.334 mmol) in dichloromethane (4 ml), N,N-diisopropylethylamine (0.233 ml, 1.34 mmol) and followed by 4-methyl-1-piperazinecarbonyl chloride hydrochloride (83.1 mg, 0.418 mmol) were added portion wise. Reaction was stirred overnight at room temperature. Volatiles were evaporated in vacuo. Brine (5.0 ml) was added and the compound was extracted with dichloromethane (4 x 7 ml). The combined organic layers were dried over sodium sulfate and the solvent was removed by rotary evaporation. Crude product was purified by preparative HPLC using acetonitrile : water : NH₃ mixture as eluent. Yield: 70.0 mg (48%) of colorless gum. ¹H NMR (400 MHz, Chloroform-d) δ 7.17 – 7.09 (m, 2H), 7.08 – 6.96 (m, 4H), 6.89 – 6.82 (m, 2H), 4.23 (d, 4H),

3.72 (d, 2H), 3.50 – 3.31 (m, 4H), 2.56 (s, 4H), 2.39 (s, 3H), 2.09 (m, 1H), 1.04 (d, J = 6.7 Hz, 6H). LC-MS: 414.3 [M+H]⁺.

[00310] Example 28: Methyl 5-[[[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amino}pentanoate; trifluoroacetic acid (28)

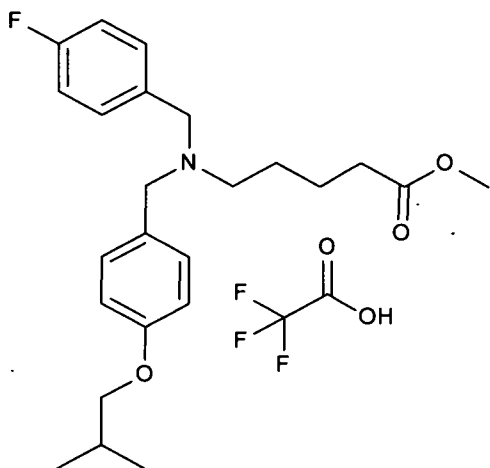


[00311] Intermediate 34: methyl 5-oxopentanoate



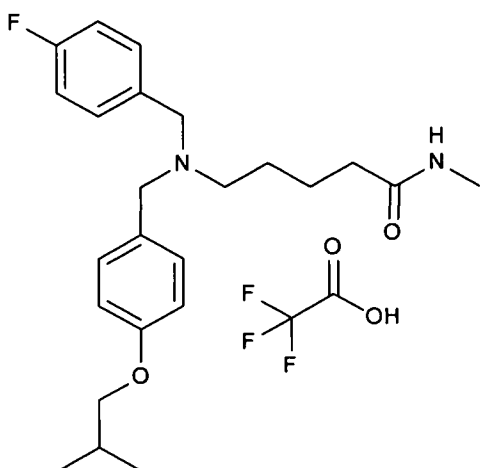
[00312] Oxan-2-one (1,0 g, 9,99 mmol) was dissolved in methanol (9,5 ml). Triethylamine (0,46 ml, 3,30 mmol) was added. The solution was stirred for 18 hours at room temperature. Toluene was added and the solvent was removed under reduced pressure. The toluene treatment was repeated one more time. The crude residue and triethylamine (4,11 ml, 29,5 mmol) were dissolved under argon in dry dimethylsulfoxide (20,0 ml). Sulfur trioxide-pyridine (4,69 g, 29,5 mmol) was dissolved in dimethylsulfoxide (15,0 ml) and was added drop-wise to the alcohol. The mixture was stirred for 14 hours at room temperature. The reaction was poured into a mixture of brine, (300 ml) and ice, (75 ml). Dichloromethane was added. The mixture was shaken and the organic layer was collected. The water phase was extracted once more with dichloromethane and once with ethyl acetate. The collected organic phases were dried over sodium sulfate. The solid was filtered of and the solvent was evaporated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with a gradient of ethyl acetate in petroleum ether, to give the desired intermediate (0,84 g, 65 %).

[00313] Methyl 5-{{[(4-fluorophenyl)methyl]}([4-(2-methylpropoxy)phenyl)methyl]}-amino}pentanoate; trifluoroacetic acid



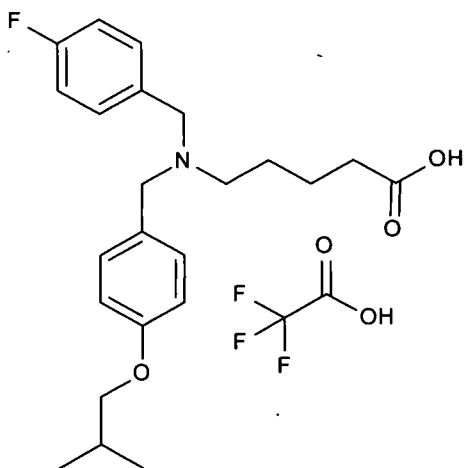
[00314] [(4-fluorophenyl)methyl]([4-(2-methylpropoxy)phenyl)methyl]amine (100 mg, 0.35 mmol) was dissolved in ethanol (1,4 ml). Methyl 5-oxopentanoate (45 mg, 0,36 mmol) was added. The mixture was stirred for 10 minutes. Sodium triacetoxymethylborohydride (111 mg, 0,522 mmol) was added and the mixture was stirred overnight. The solvent was evaporated and the residue was dissolved in dichloromethane and a 1:1 mixture of water and saturated sodium carbonate. The mixture was shaken and the phases separated. The water phase was extracted two more times with dichloromethane. The combined organic phase was dried over sodium sulfate. The solid was filtered off and the solvent was evaporated. The crude material was purified by HPLC, eluting with 35-55% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (69 mg, 38 %): ¹H NMR (400 MHz, Chloroform-d) δ 7.41 (dd, 2H), 7.29 (d, 2H), 7.08 (t, 2H), 6.89 (d, 2H), 4.44 – 3.87 (m, 4H), 3.69 (d, 2H), 3.62 (s, 3H), 2.83 – 2.74 (m, 2H), 2.26 (t, 2H), 2.04 (hept, 1H), 1.85 – 1.73 (m, 2H), 1.46 (q, 2H), 0.98 (d, 6H); LC-MS: 402.3 [M+H]⁺

[00315] Example 29: 5-{{[(4-fluorophenyl)methyl]}([4-(2-methylpropoxy)phenyl)methyl]}amino}-N-methylpentanamide; trifluoroacetic acid (29)



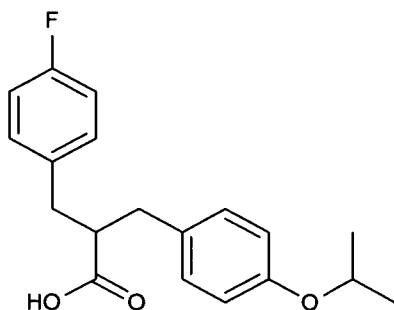
[00316] Methyl 5-[[[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amino}pentanoate (33 mg, 0,082 mmol) was dissolved in ethanol (100 μ L). Methylamine, 33 wt% in ethanol (97 μ L, 0,74 mmol) was added. The mixture was stirred at room temperature overnight. Methylamine (97.5 μ L, 0,74 mmol) was added and the reaction was warmed to 50 $^{\circ}$ C and stirred overnight. The solvent was evaporated. The crude material was purified by HPLC, eluting with 35-55% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (27 mg, 64 %): ^1H NMR (400 MHz, Chloroform- d) δ 7.41 (dd, 2H), 7.28 (d, 2H), 7.09 (t, 2H), 6.90 (d, 2H), 6.38 (s, 1H), 4.39 – 3.80 (m, 4H), 3.70 (d, 2H), 2.89 – 2.80 (m, 2H), 2.73 (d, 3H), 2.12 (t, 2H), 2.05 (dt, 1H), 1.85 – 1.73 (m, 2H), 1.55 (p, 2H), 1.00 (d, 6H); LC-MS: 401.3 $[\text{M}+\text{H}]^+$.

[00317] Example 30: 5-[[[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})amino}pentanoic acid; trifluoroacetic acid (30)



[00318] Methyl 5-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl})-amino}pentanoate (33 mg, 0,082 mmol) was dissolved in ethanol (100 μ l). Sodium hydroxide, 2 M in water, (123 μ l, 0,247 mmol) was added. The mixture was stirred at room temperature overnight. The crude material was purified by HPLC, eluting with 35-50% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (21 mg, 51 %): ^1H NMR (400 MHz, Chloroform- d) δ 7.41 (dd, 2H), 7.28 (d, 2H), 7.07 (t, 2H), 6.89 (d, 2H), 4.16 (s, 4H), 3.69 (d, 2H), 2.90 – 2.81 (m, 2H), 2.29 (t, 2H), 2.05 (m, 1H), 1.82 (s, 2H), 1.48 (p, 2H), 0.99 (d, 6H); LC-MS: 388.3 $[\text{M}+\text{H}]^+$.

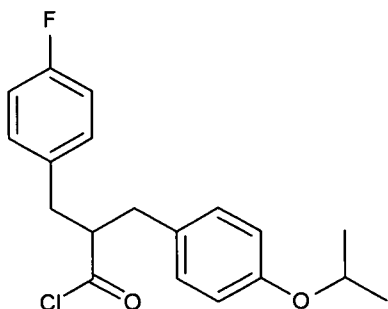
[00319] Intermediate 35: 3-(4-fluorophenyl)-2-{[4-(propan-2-yloxy)phenyl]methyl}propanoic acid



[00320] Sodium hydride (2.45 g, 61.2 mmol) was added cautiously to methanol (100 ml) followed by diethylmalonate (10 g, 61.2 mmol). To the solution was added slowly p-fluorobenzylbromide (41 mmol, 5.1 ml) and the mixture was stirred 1 hour and then concentrated. The residue was partitioned between ethyl acetate and 0.5 M aqueous hydrochloric acid, the organic phase was concentrated and the resulting oil was purified by distillation. Sodium hydride (10 mmol, 400 mg, 60 % in oil) was added portionwise to ethanol (20 ml) under nitrogen. To the solution of sodium ethoxide in ethanol was added the distilled 1,3-diethyl 2-[(4-fluorophenyl)methyl]propanedioate (1.48 g, 5.52 mmol) and then p-isopropoxybenzyl chloride (1 g, 6.07 mmol). The mixture was stirred for 72 hours, then partitioned between ethyl acetate and 0.5 M hydrochloric acid. The organic phase was collected, dried, and evaporated. The crude was purified by column chromatography using silicon dioxide gel, eluting with 20% ethyl acetate in petroleum ether to afford the desired intermediate (2.195g). This material (2.17 g, 4.48 mmol) was refluxed for 18 hours in a mixture of 2 M sodium hydroxide (10 ml) and ethanol (10 ml). The mixture was partitioned between ethyl acetate and 0.5 M hydrochloric acid. The organic phase was collected, dried, and evaporated. The crude was purified by column chromatography using silicon dioxide gel, eluting with 0-10% methanol in ethyl acetate to afford the desired intermediate (1.45 g, 4.02

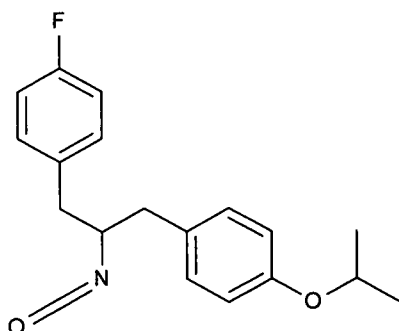
mmol). This material was refluxed in acetic acid for 8 hours, the solvent was evaporated and the residue was purified by column chromatography using silicon dioxide gel, eluting with 33-50% ethyl acetate in hexane to afford the desired intermediate (1.105 g, 87 %).

[00321] Intermediate 36: 3-(4-fluorophenyl)-2-{{4-(propan-2-yloxy)phenyl}methyl}propanoyl chloride



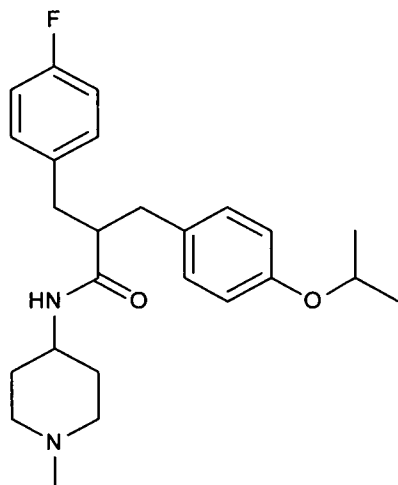
[00322] 3-(4-fluorophenyl)-2-{{4-(propan-2-yloxy)phenyl}methyl}propanoic acid (782 mg, 2.47 mmol) was dissolved in dichloromethane (5 ml) and oxalyl chloride (365 ul, 4.2 mmol) was added followed by N,N-dimethylformamide (10 ul). The mixture was stirred 4 hours and was then evaporated to give the title compound (827 mg, 100%).

[00323] Intermediate 37: 1-[3-(4-fluorophenyl)-2-isocyanatopropyl]-4-(propan-2-yloxy)benzene



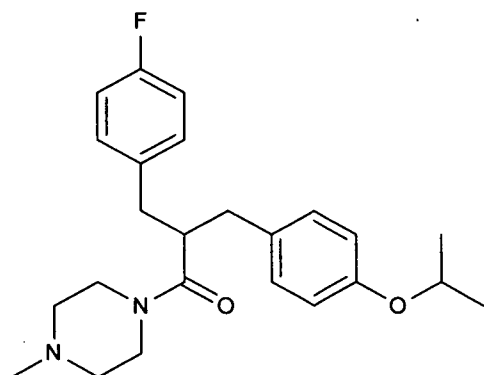
[00324] 3-(4-fluorophenyl)-2-{{4-(propan-2-yloxy)phenyl}methyl}propanoyl chloride (627 mg, 1.87 mmol) was dissolved in acetone (2 ml) and added dropwise at 0 °C to a solution of sodium azide (172 mg, 2.62 mmol) in acetone (2 ml). The mixture was stirred for 1 hour at 0 °C, then partitioned between toluene (30 ml) and water, the organic phase was concentrated to approximately 25 ml volume and was then heated at 65 °C until the gas evolution ceased. Evaporation of the volatiles gave the title compound (505 mg, 86 %).

[00325] Example 31: 2-[(4-fluorophenyl)methyl]-N-(1-methylpiperidin-4-yl)-3-[4-(propan-2-yloxy)phenyl]propanamide (31)



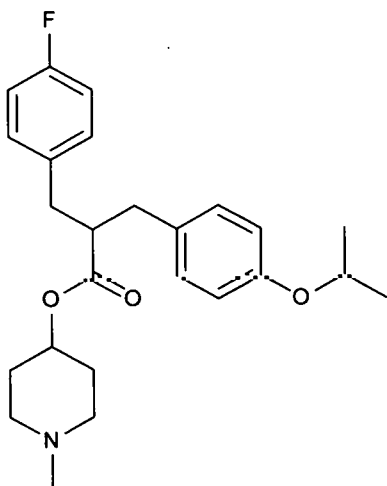
[00326] 3-(4-fluorophenyl)-2-([4-(propan-2-yloxy)phenyl]methyl)propanoic acid (168 mg, 0.53 mmol), 1H-1,2,3-benzotriazol-1-ol hydrate (106 mg, 0.69 mmol), and (3-[[[(ethylimino)methylidene]amino]propyl]dimethylamine hydrochloride (137 mg, 0.69 mmol) were dissolved in N,N- dimethylformamide (1.0 ml) and N-methyl-4-aminopiperidine (88 μ l, 0.69 mmol) followed by triethylamine (114 μ l, 0.80 mmol) were added. The mixture was stirred 3 hours and then partitioned between diethyl ether and 0.5 M sodium hydroxide. The organic phase was dried and evaporated. The crude was purified by column chromatography using silicon dioxide gel, eluting with 15% methanol in ethyl acetate to afford the title compound (74 mg, 34% yield): ^1H NMR (400 MHz, Chloroform-d) δ 7.12 (dd, 2H), 7.05 (d, 2H), 6.93 (t, 2H), 6.78 (d, 2H), 4.74 (d, 1H), 4.48 (m, 1H), 3.67 – 3.51 (m, 1H), 3.00-2.85 (m, 2H), 2.78-2.66 (m, 2H), 2.58 (bs, 2H), 2.35 (m, 1H), 2.21 (s, 3H), 2.00 (t, 2H), 1.55 (d, 2H), 1.30 (d, 6H), 1.09 (q, 2H); LC-MS: 413.3 $[\text{M}+\text{H}]^+$.

[00327] Example 32: 2-[(4-fluorophenyl)methyl]-1-(4-methylpiperazin-1-yl)-3-[4-(propan-2-yloxy)phenyl]propan-1-one (32)



[00328] 3-(4-fluorophenyl)-2-{{[4-(propan-2-yloxy)phenyl]methyl}propanoic acid (168 mg, 0.53 mmol), 1H-1,2,3-benzotriazol-1-ol hydrate (106 mg, 0.69 mmol), and (3-{{[(ethylimino)methylidene]amino}propyl)dimethylamine hydrochloride (137 mg, 0.69 mmol) were dissolved in N,N- dimethylformamide (1.0 ml) and N-methylpiperazine (71 mg, 0.69 mmol) followed by triethylamine (114 μ l, 0.80 mmol) were added. The mixture was stirred 18 hours and then partitioned between diethyl ether and 0.5 M sodium hydroxide. The organic phase was dried and evaporated. The crude was purified by column chromatography using silicon dioxide gel, eluting with 0-10% methanol in ethyl acetate to afford the title compound (186 mg, 88%). LC-MS: 399.3 [M+H]⁺.

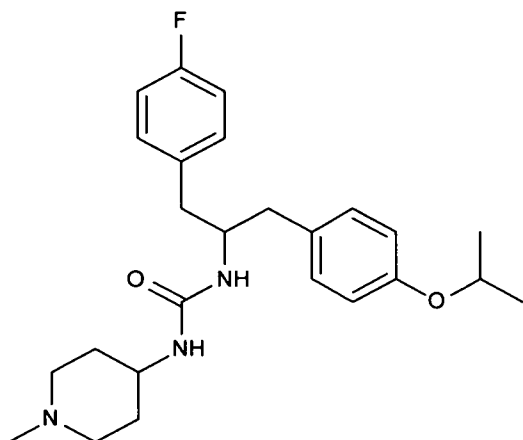
[00329] Example 33: 1-methylpiperidin-4-yl 2-[(4-fluorophenyl)methyl]-3-[4-(propan-2-yloxy)phenyl]propanoate (33)



[00330] 3-(4-fluorophenyl)-2-{{[4-(propan-2-yloxy)phenyl]methyl}propanoyl chloride (200 mg, 0.59 mmol) was dissolved in dichloromethane (1 ml) and added dropwise to a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (155 mg, 0.767 mmol) and pyridine (98 μ l, 1.2 mmol) in dichloromethane (1 ml). After 1 hour the mixture was applied directly onto a silicon dioxide gel column and eluting with 33% ethyl acetate in hexane. This material was dissolved in a mixture of dichloromethane (2 ml) and trifluoroacetic acid (1 ml) for 15 minutes and then concentrated. To this was added sodium triacetoxyborohydride (375 mg, 1.73 mmol), tetrahydrofuran (2 ml) and formaldehyde (129 μ l, 1.73 mmol). The mixture was stirred for 1 hour, then partitioned between ether and saturated sodium hydrogen carbonate. The organic phase was dried and evaporated. The crude was purified by column chromatography using silicon dioxide gel, eluting with 15-20% methanol in ethyl acetate to afford the title compound (0.271 mmol, 112 mg, 46 % yield): ¹H NMR (400 MHz,

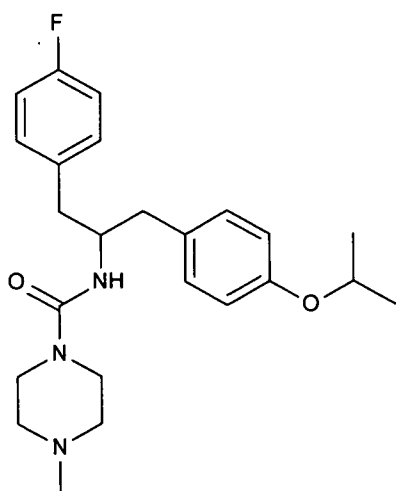
Chloroform-d) δ 7.14 (dd, 2H), 7.07 (d, 2H), 6.96 (t, 2H), 6.79 (d, 2H), 4.76 (bs, 1H), 4.48 (hept, 1H), 2.99-2.62 (m, 7H), 2.62-2.04 (m, 2H) 2.52 (s, 3H), 1.92 (m, 2H), 1.57 (m, 2H), 1.31 (d, 6H); LC-MS: 414.3 $[M+H]^+$.

[00331] Example 34: 3-[1-(4-fluorophenyl)-3-[4-(propan-2-yloxy)phenyl]propan-2-yl]-1-(1-methylpiperidin-4-yl)urea (34)



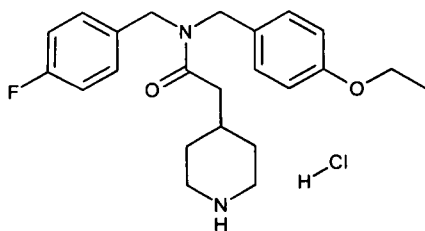
[00332] 1-[3-(4-fluorophenyl)-2-isocyanatopropyl]-4-(propan-2-yloxy)benzene (150 mg, 0.47 mmol) was stirred in dichloromethane (1 ml) and N-methyl-4-aminopiperidine (91 μ l, 0.705 mmol) dissolved in dichloromethane (1 ml) was added. After stirring 1 hour at room temperature the mixture was partitioned between dichloromethane and 0.5 M sodium hydroxide, the organic phase was dried, evaporated and purified by column chromatography using silicon dioxide gel, eluting with 20-33% methanol in ethyl acetate to give (141 mg). The material was further purified by column chromatography using a Waters C18 column, eluting with 20-100% acetonitrile in water to give the title compound (79 mg, 39 %): ^1H NMR (400 MHz, Chloroform-d) δ 7.14 (dd, 2H), 7.07 (d, 2H), 6.96 (t, 2H), 6.81 (d, 2H), 4.50 (h, 1H), 4.19 (d, 1H), 4.16 – 4.00 (m, 2H), 3.43 (m, 1H), 2.72 (m, 6H), 2.26 (s, 3H), 2.06 (t, 2H), 1.81 (m, 2H), 1.39-1.26 (m, 8H); LC-MS: 428.3 $[M+H]^+$.

[00333] Example 35: N-[1-(4-fluorophenyl)-3-[4-(propan-2-yloxy)phenyl]propan-2-yl]-4-methylpiperazine-1-carboxamide (35)



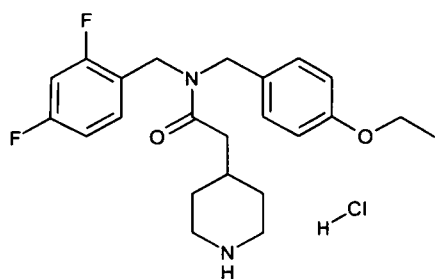
[00334] 1-[3-(4-fluorophenyl)-2-isocyanatopropyl]-4-(propan-2-yloxy)benzene (159 mg, 0.507 mmol) was dissolved in dichloromethane (1.5 ml) and N-methylpiperazine (85 μ l, 0.96 mmol) was added. The mixture was stirred for 20 hours and then applied directly onto a silicon dioxide gel column and eluting with 0-20% methanol in ethyl acetate to give the title compound. (109 mg, 52 % yield): ^1H NMR (400 MHz, Chloroform-*d*) δ 7.15 (dd, 2H), 7.07 (d, 2H), 6.98 (t, 2H), 6.82 (d, 2H), 4.51 (hept, 1H), 4.27 (h, 1H), 4.17 (d, 1H), 3.27 (dd, 4H), 2.85 – 2.64 (m, 4H), 2.30 (dd, 4H), 2.28 (s, 3H), 1.33 (d, 6H); LC-MS: 414.3 $[\text{M}+\text{H}]^+$.

[00335] Example 36: N-[(4-ethoxyphenyl)methyl]-N-[(4-fluorophenyl)methyl]-2-(piperidin-4-yl)acetamide hydrochloride



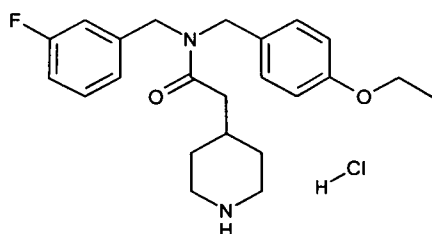
[00336] The compounds were prepared in analogy with example 3 using [(4-ethoxyphenyl)methyl][(4-fluorophenyl)methyl]amine and 2-{1-[(tert-butoxy)carbonyl]piperidin-4-yl}acetic acid. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.42 (s, 1H), 9.18 (s, 1H), 7.17 – 7.10 (m, 1H), 7.06 (t, 2H), 6.98 (t, 2H), 6.84 (dd, 3H), 4.50 (d, 2H), 4.37 (d, 2H), 4.01 (p, 2H), 3.47 (d, 2H), 2.92 (q, 2H), 2.39 (dd, 2H), 2.26 (s, 1H), 1.98 (d, 2H), 1.66 (q, 2H), 1.40 (q, 3H); LC-MS: 385.3 $[\text{M}+\text{H}]^+$.

[00337] Example 37: N-[(2,4-difluorophenyl)methyl]-N-[(4-ethoxyphenyl)methyl]-2-(piperidin-4-yl)acetamide hydrochloride



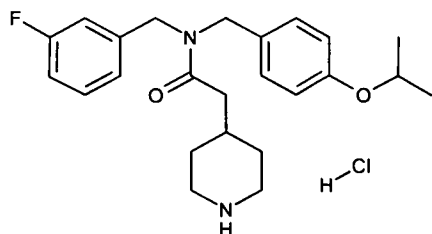
[00338] The compounds were prepared in analogy with example 3 using [(2,4-difluorophenyl)methyl][(4-ethoxyphenyl)methyl]amine and 2-{1-[(tert-butoxy)carbonyl]piperidin-4-yl}acetic acid. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.61 (s, 1H), 9.30 (s, 1H), 7.33 – 7.24 (m, 1H), 7.05 (dd, 2H), 6.91 – 6.73 (m, 4H), 4.60 – 4.37 (m, 4H), 4.03 (p, 2H), 3.48 (q, 2H), 2.90 (s, 2H), 2.37 (d, 2H), 2.23 (s, 1H), 1.99 (t, 2H), 1.63 (d, 2H), 1.45 – 1.37 (m, 3H); LC-MS: 403.3 $[\text{M}+\text{H}]^+$.

[00339] Example 38: N-[(4-ethoxyphenyl)methyl]-N-[(3-fluorophenyl)methyl]-2-(piperidin-4-yl)acetamide hydrochloride



[00340] The compounds were prepared in analogy with example 3 using [(4-ethoxyphenyl)methyl][(3-fluorophenyl)methyl]amine and 2-{1-[(tert-butoxy)carbonyl]piperidin-4-yl}acetic acid. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.21 (d, 2H), 7.37 – 6.74 (m, 8H), 4.53 (d, 2H), 4.42 (d, 2H), 4.01 (p, 2H), 3.47 (d, 2H), 2.94 (d, 2H), 2.45 (dd, 2H), 2.28 (s, 1H), 1.97 (s, 2H), 1.67 (p, 2H), 1.41 (t, 3H); LC-MS: 385.3 $[\text{M}+\text{H}]^+$.

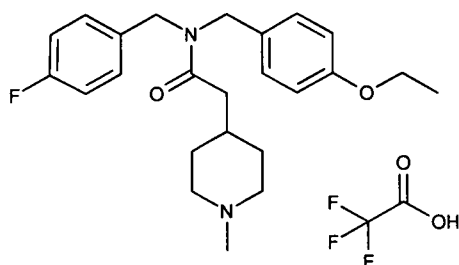
[00341] Example 39: N-[(3-fluorophenyl)methyl]-2-(piperidin-4-yl)-N-{[4-(propan-2-yloxy)phenyl]methyl}acetamide hydrochloride



[00342] The compounds were prepared in analogy with example 3 using [(3-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl})amine and 2-{1-[(tert-

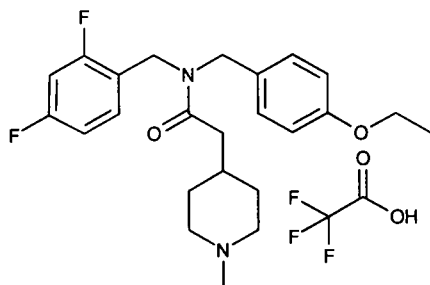
butoxy)carbonyl]piperidin-4-yl}acetic acid. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.33 (d, 2H), 7.41 – 6.74 (m, 8H), 4.52 (d, 3H), 4.39 (d, 2H), 3.46 (d, 2H), 2.92 (s, 2H), 2.39 (d, 2H), 2.27 (s, 1H), 1.98 (s, 2H), 1.63 (d, 2H), 1.32 (t, 6H); LC-MS: 398.5 $[\text{M}+\text{H}]^+$.

[00343] Example 40: N-[(4-ethoxyphenyl)methyl]-N-[(4-fluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide; trifluoroacetic acid



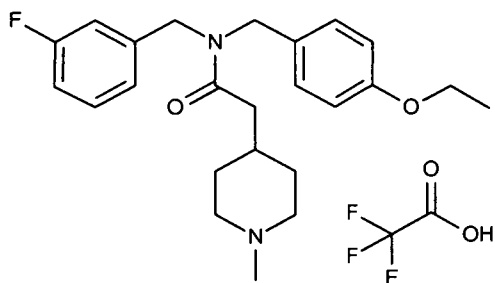
[00344] The compounds were prepared in analogy with example 4 using N-[(4-ethoxyphenyl)methyl]-N-[(4-fluorophenyl)methyl]-2-(piperidin-4-yl)acetamide hydrochloride. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.94 (s, 1H), 7.16 (dd, 1H), 7.11 – 6.96 (m, 5H), 6.86 (dd, 2H), 4.52 (d, 2H), 4.38 (d, 2H), 4.03 (p, 2H), 3.60 (d, 2H), 2.79 (s, 3H), 2.77 – 2.68 (m, 2H), 2.39 (dd, 2H), 2.24 (s, 1H), 2.01 (d, 2H), 1.70 (q, 2H), 1.42 (td, 3H); LC-MS: 399.3 $[\text{M}+\text{H}]^+$.

[00345] Example 41: N-[(2,4-difluorophenyl)methyl]-N-[(4-ethoxyphenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide; trifluoroacetic acid



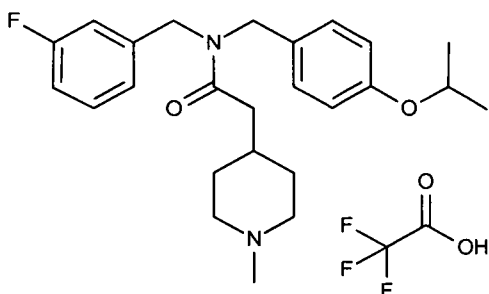
[00346] The compounds were prepared in analogy with example 4 using N-[(2,4-difluorophenyl)methyl]-N-[(4-ethoxyphenyl)methyl]-2-(piperidin-4-yl)acetamide hydrochloride. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.46 (s, 1H), 7.27 (d, 1H), 7.05 (dd, 2H), 6.92 – 6.73 (m, 4H), 4.63 – 4.38 (m, 4H), 4.03 (p, 2H), 3.61 (d, 2H), 2.80 (s, 3H), 2.74 (d, 2H), 2.41 (t, 2H), 2.23 (s, 1H), 2.01 (t, 2H), 1.67 (q, 2H), 1.41 (td, 3H); LC-MS: 417.3 $[\text{M}+\text{H}]^+$.

[00347] Example 42: N-[(4-ethoxyphenyl)methyl]-N-[(3-fluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide; trifluoroacetic acid



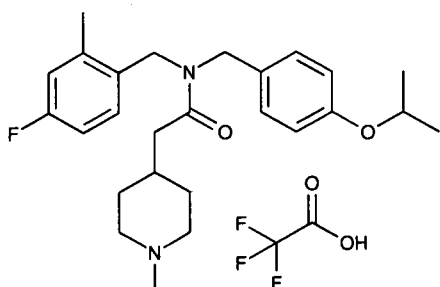
[00348] The compounds were prepared in analogy with example 4 using N-[(4-ethoxyphenyl)methyl]-N-[(3-fluorophenyl)methyl]-2-(piperidin-4-yl)acetamide hydrochloride. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.78 (s, 1H), 7.39 – 7.24 (m, 1H), 7.10 (d, 1H), 7.06 – 6.76 (m, 6H), 4.55 (d, 2H), 4.41 (d, 2H), 4.03 (p, 2H), 3.62 (d, 2H), 2.80 (s, 3H), 2.78 – 2.69 (m, 2H), 2.44 (d, 1H), 2.35 (d, 1H), 2.26 (s, 1H), 2.03 (d, 2H), 1.69 (p, 2H), 1.42 (td, 3H); LC-MS: 399.3 $[\text{M}+\text{H}]^+$.

[00349] Example 43: N-[(3-fluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)-N-{[4-(propan-2-yloxy)phenyl]methyl}acetamide; trifluoroacetic acid



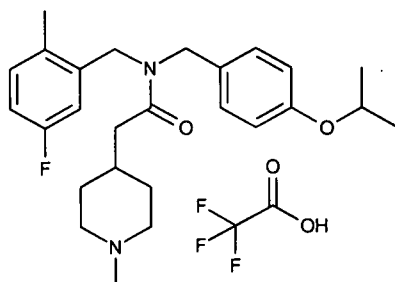
[00350] The compounds were prepared in analogy with example 4 using N-[(3-fluorophenyl)methyl]-2-(piperidin-4-yl)-N-{[4-(propan-2-yloxy)phenyl]methyl}acetamide hydrochloride. ^1H NMR (400 MHz, Chloroform-*d*) δ 11.87 (s, 1H), 7.38 – 7.24 (m, 1H), 7.09 (d, 1H), 7.05 – 6.76 (m, 6H), 4.59 – 4.49 (m, 3H), 4.41 (d, 2H), 3.62 (d, 2H), 2.80 (s, 3H), 2.74 (d, 2H), 2.44 (d, 1H), 2.34 (d, 1H), 2.26 (s, 1H), 2.04 (d, 2H), 1.70 (p, 2H), 1.37 – 1.31 (m, 6H); LC-MS: 413.3 $[\text{M}+\text{H}]^+$.

[00351] Example 44: N-[(4-fluoro-2-methylphenyl)methyl]-2-(1-methylpiperidin-4-yl)-N-{[4-(propan-2-yloxy)phenyl]methyl}acetamide; trifluoroacetic acid



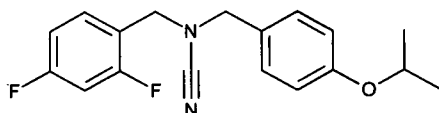
[00352] The compound was prepared in analogy with example 15 using (4-fluoro-2-methylphenyl)methanamine and 4-(propan-2-yloxy)benzaldehyde. Yield 77 %. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (bs, 1H), 7.14 – 6.86 (m, 6H), 6.83 (d, 1H), 4.57 (dq, 1H), 4.48 – 4.37 (m, 4H), 3.37 (d, 2H), 3.00 – 2.86 (m, 2H), 2.73 (s, 3H), 2.41 (d, 1H), 2.25 (d, 1H), 2.17 (d, 3H), 2.09 – 1.95 (m, 1H), 1.93 – 1.83 (m, 2H), 1.36 – 1.16 (m, 8H).; LCMS: 427.3 [M+H]⁺.

[00353] Example 45: N-[(5-fluoro-2-methylphenyl)methyl]-2-(1-methylpiperidin-4-yl)-N-[[4-(propan-2-yloxy)phenyl]methyl]acetamide; trifluoroacetic acid



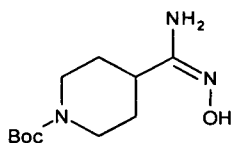
[00354] The compound was prepared in analogy with example 15 using (5-fluoro-2-methylphenyl)methanamine and 4-(propan-2-yloxy)benzaldehyde. Yield 32%. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (bs, 1H), 7.27 – 7.06 (m, 3H), 7.05 – 6.94 (m, 1H), 6.90 (d, 1H), 6.83 (d, 1H), 6.68 (dd, 1H), 4.62 – 4.52 (m, 1H), 4.51 – 4.39 (m, 4H), 3.54 – 3.31 (m, 2H), 3.00 – 2.86 (m, 2H), 2.73 (d, 3H), 2.46 (d, 1H), 2.23 (d, 1H), 2.13 (d, 3H), 2.09 – 1.95 (m, 1H), 1.93 – 1.81 (m, 2H), 1.39 – 1.15 (m, 8H).; LCMS: 427.3 [M+H]⁺.

[00355] Intermediate 38: Cyano[(2,4-difluorophenyl)methyl]{{[4-(propan-2-yloxy)phenyl]methyl}amine



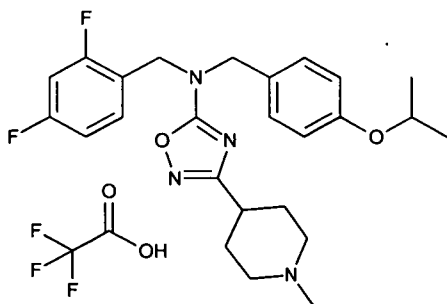
[00356] [4-(propan-2-yloxy)phenyl]methanamine (1.66 ml, 10 mmol) was added to 2,4-difluorobenzaldehyde (1.09 ml, 10 mmol) in ethanol (20 ml). After 1 hour of stirring at ambient temperature sodium borohydride (378 mg, 10 mmol) was added. The mixture was stirred for 15 hours before it was diluted with ethyl acetate (50 ml), washed with water (50 ml) and brine (50 ml), dried using a phase separator and concentrated to give the secondary amine (2.93 g, quantitative). The secondary amine (1.46 g, 5 mmol) was dissolved in dichloromethane (15 ml) and sodium hydrogen carbonate (aqueous, 2M, 5 ml) was added. The mixture was cooled to 0 °C and cyanogen bromide (556 mg, 5.25 mmol) in dichloromethane (5 ml) was added. The mixture was stirred at 0 °C for 30 minutes before it was heated to ambient temperature. After additionally 1 hour the organic phase was separated, dried using a phase separator and concentrated. The crude material was purified by silica gel chromatography, eluting with 10-20 % ethyl acetate in petroleum ether to afford the desired intermediate (1.32 g, 84%).

[00357] Intermediate 39: Tert-butyl 4-(N'-hydroxycarbamimidoyl)piperidine-1-carboxylate



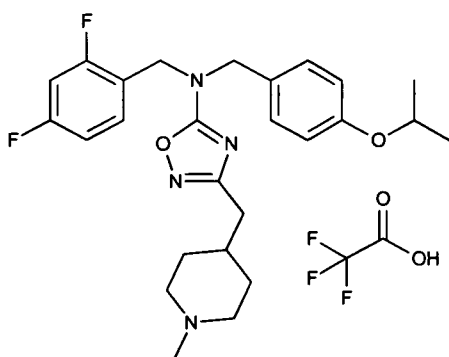
[00358] Hydroxylamine (50% aqueous, 307 µl, 5 mmol) was added to tert-butyl 4-cyanopiperidine-1-carboxylate (526 mg, 2.5 mmol) in ethanol (10 ml). The mixture was heated to 80 °C and stirred for 22 hours before it was cooled to ambient temperature and concentrated. The crude material was purified by silica gel chromatography, eluting with ethyl acetate to afford the desired intermediate (554 mg, 91%).

[00359] Example 46: N-[(2,4-difluorophenyl)methyl]-3-(1-methylpiperidin-4-yl)-N-{[4-(propan-2-yloxy)phenyl]methyl}-1,2,4-oxadiazol-5-amine; trifluoroacetic acid¹



[00360] Zinc chloride in diethyl ether (1M, 750 μ l, 750 μ mol) was added to tert-butyl 4-(N'-hydroxycarbamimidoyl)piperidine-1-carboxylate (122 mg, 500 μ mol) and cyano[(2,4-difluorophenyl)methyl]{[4-(propan-2-yloxy)phenyl]methyl}amine (158 mg, 500 μ mol) in tetrahydrofuran (750 μ l). The mixture was heated to 50 °C and stirred for 90 minutes before it was cooled to ambient temperature and concentrated. The crude was dissolved in ethyl acetate (2 ml) and acetic acid (1 ml) was added. The mixture was heated to 100 °C and stirred for 30 minutes before it was cooled to ambient temperature, concentrated and re-dissolved in tetrahydrofuran (2 ml). Formaldehyde (37% aqueous, 74.5 μ l, 1 mmol) and sodium triacetoxyborohydride (212 mg, 1 mmol) were added. After 1 hour of stirring at ambient temperature more sodium triacetoxyborohydride (212 mg, 1 mmol) was added. The mixture was stirred for additionally 1 hour before more sodium triacetoxyborohydride (212 mg, 1 mmol) was added. After 2 hours, the mixture was concentrated and re-dissolved in dichloromethane (10 ml). The mixture was washed with sodium hydroxide (5M aqueous, 10 ml), dried using a phase separator and concentrated. The crude was dissolved in tetrahydrofuran (2 ml). Formaldehyde (37% aqueous, 74.5 μ l, 1 mmol) and sodium triacetoxyborohydride (212 mg, 1 mmol) were added. After 1 hour, the mixture was concentrated and sodium hydroxide (1M aqueous, 2 ml) was added. The aqueous phase was extracted with dichloromethane (3 x 2 ml). The organic phase was dried using a phase separator and concentrated. The 1/3 of the crude material was purified by HPLC, eluting with 30-70 % acetonitrile in water (0.1 % trifluoroacetic acid), to afford the title compound (78 mg, 82 %). ¹H NMR (400 MHz, Chloroform-d) δ 12.95 – 12.23 (m, 1H), 7.35 – 7.23 (m, 1H), 7.16 (d, 2H), 6.91 – 6.77 (m, 4H), 4.62 – 4.48 (m, 5H), 3.74 (d, 1H), 3.47 (d, 1H), 3.22 (s, 1H), 3.09 (q, 1H), 2.87 – 2.76 (m, 4H), 2.52 – 2.36 (m, 1H), 2.35 – 2.21 (m, 3H), 1.34 (d, 6H). MS: 457.3 [M+H]⁺.

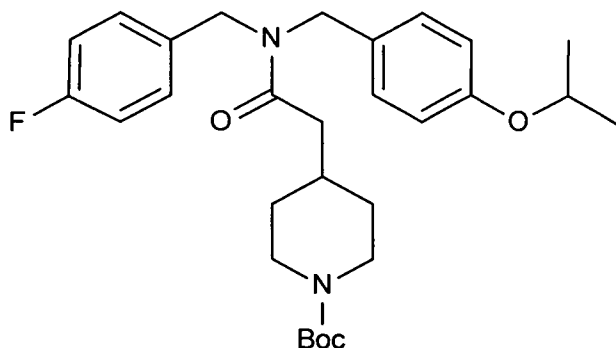
[00361] Example 47: N-[(2,4-difluorophenyl)methyl]-3-[(1-methylpiperidin-4-yl)methyl]-N-{[4-(propan-2-yloxy)phenyl]methyl}-1,2,4-oxadiazol-5-amine; trifluoroacetic acid



[00362] The compound was prepared in analogy with Example 46 using tert-butyl 4-(cyanomethyl)piperidine-1-carboxylate instead of tert-butyl 4-cyanopiperidine-1-carboxylate. Yield: 77 mg, 79 %. ¹H NMR (400 MHz, Chloroform-d) δ 12.74 – 12.38 (m, 1H), 7.33 – 7.21 (m, 1H), 7.15 (d, 2H), 6.91 – 6.75 (m, 4H), 4.63 – 4.44 (m, 5H), 3.63 (d, 2H), 2.79 (s, 3H), 2.74 – 2.62 (m, 2H), 2.59 (d, 2H), 2.07 – 1.93 (m, 3H), 1.93 – 1.79 (m, 2H), 1.33 (d, 6H). MS: 471.3 [M+H]⁺

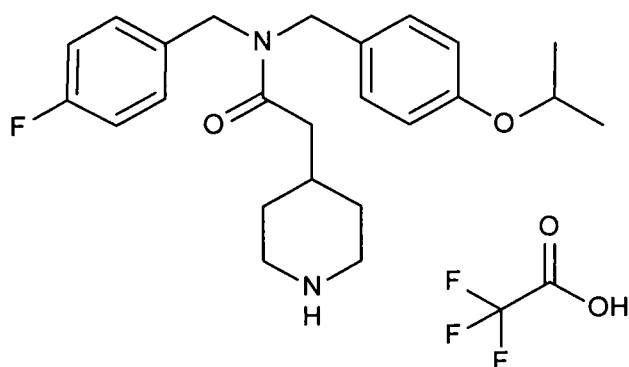
[00363] Example 48: N-[(4-fluorophenyl)methyl]-2-(piperidin-4-yl)-N-{[4-(propan-2-yloxy)phenyl]methyl}acetamide; trifluoroacetic acid

[00364] tert-butyl 4-({[(4-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl})carbamoyl}methyl)piperidine-1-carboxylate



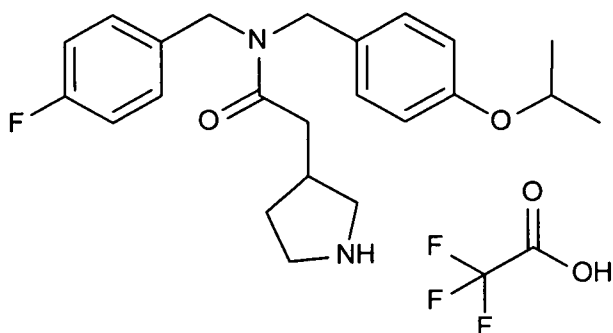
[00365] The compound was prepared in analogy with example 15 using 4-fluorobenzaldehyde, [4-(propan-2-yloxy)phenyl]methanamine, and 2-{1-[(tert-butoxy)carbonyl]piperidin-4-yl}acetic acid. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 0-50% ethyl acetate in petroleum ether to afford the desired intermediate (434 mg, 72%).

[00366] N-[(4-fluorophenyl)methyl]-2-(piperidin-4-yl)-N-{[4-(propan-2-yloxy)phenyl]methyl}acetamide; trifluoroacetic acid



[00367] tert-butyl 4-((4-fluorophenyl)methyl)-N-([4-(propan-2-yloxy)phenyl]methyl)carbamoylmethylpiperidine-1-carboxylate (434 mg, 0.87 mmol) was dissolved in HCl (3 ml, 2 M in diethyl ether). After 1 hour of stirring at room temperature the mixture was concentrated. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (16.5 mg, 4 %): ^1H NMR (400 MHz, Chloroform-*d*) δ 8.98 (m, 1H), 8.58 (m, 1H), 7.16 (dd, 1H), 7.08 (t, 3H), 7.00 (dt, 2H), 6.86 (dd, 2H), 4.54 (m, 3H), 4.40 (d, 2H), 3.43 (d, 2H), 2.94 (q, 2H), 2.40 (dd, 2H), 2.27 (s, 1H), 1.99 (d, 2H), 1.55 (m, 2H), 1.34 (t, 6H).; LCMS: 399.3 $[\text{M}+\text{H}]^+$.

[00368] Example 49: N-[(4-fluorophenyl)methyl]-N-([4-(propan-2-yloxy)phenyl]methyl)-2-(pyrrolidin-3-yl)acetamide; trifluoroacetic acid



[00369] The compound was prepared in analogy with N-[(4-fluorophenyl)methyl]-2-(piperidin-4-yl)-N-([4-(propan-2-yloxy)phenyl]methyl)acetamide using 4-fluorobenzaldehyde, [4-(propan-2-yloxy)phenyl]methanamine, and 2-{1-[(tert-butoxy)carbonyl]pyrrolidin-3-yl}acetic acid. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (14.2 mg, 3 %): ^1H NMR (400 MHz, Chloroform-*d*) δ 9.45 (m, 2H), 7.06 (m, 6H), 6.85 (dd, 2H), 4.49 (m, 5H), 3.61 (s, 1H), 3.43 (s, 1H), 3.23 (s, 1H), 3.04 (s, 1H), 2.87 (s, 1H), 2.64 (m, 2H), 2.28 (s, 1H), 1.71 (m, 1H), 1.34 (t, 6H).; LCMS: 385.3 $[\text{M}+\text{H}]^+$.

[00370] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein.

Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.

[00371] In vitro determination of receptor activity

[00372] Receptor Selection and Amplification (R-SAT) Assays. The functional receptor assay, Receptor Selection and Amplification Technology (R-SAT®), was used (with minor modifications from the procedure described previously (Brann, M. R. US Patent 5,707,798, 1998; Chem. Abstr. 1998,128, 111548) to screen compounds for activity at the 5-HT_{2A} receptor. Briefly, NIH3T3 cells were grown in 96 well tissue culture plates to 70-80% confluence. Cells were transfected for 12-16 h with plasmid DNAs using superfect (Qiagen Inc.) as per manufacturer's protocols. R-SAT's were generally performed with 50 ng/well of receptor and 20 ng/well of β -galactosidase plasmid DNA. All receptor constructs used were in the pSI mammalian expression vector (Promega Inc) as described previously. The 5-HT_{2A} receptor gene was amplified by nested PCR (polymerase chain reaction) from brain cDNA using the oligodeoxynucleotides based on the published sequence (Saltzman et. al, Biochem. Biophys. Res. Comm. 1991,181, 1469). For large-scale transfections, cells were transfected for 12-16 h, then trypsinized and frozen in DMSO. Frozen cells were later thawed, plated at 10,000-40,000 cells per well of a 96 well plate that contained a compound according to Formula(I). To run functional antagonist assays, cells and compounds were additionally combined with a fixed concentration (approximately 3 x the previously determined EC₅₀) of an agonist (usually 5-CT) at 5-HT_{2A} or other appropriate agonists for other receptors. With both methods, cells were then grown in a humidified atmosphere with 5% ambient CO₂ for five days. Media was then removed from the plates and marker gene activity was measured by the addition of the β -galactosidase substrate o-nitrophenyl β -D-galactopyranoside (ONPG, in PBS with 5% NP-40). The resulting colorimetric reaction was measured in a spectrophotometric plate reader (Titertek Inc.) at 420 nM. All data were analyzed using the computer program XLFit (IDBSm). Efficacy is the percent maximal repression compared to repression by a control compound (ritanserin in the case of 5-HT_{2A}). pIC₅₀ is the negative of

the $\log(\text{IC}_{50})$, where IC_{50} is the calculated concentration in molar that produces 50% maximal repression. The compounds as provided herein were assayed as described herein.

[00373] Compounds disclosed herein demonstrated high inhibition of the 5-HT_{2a} receptor activity as shown in the table below. This data below indicates that compounds as provide herein may be useful as pharmaceutical agents.

The data in table one may for example be interpreted using the following guidance

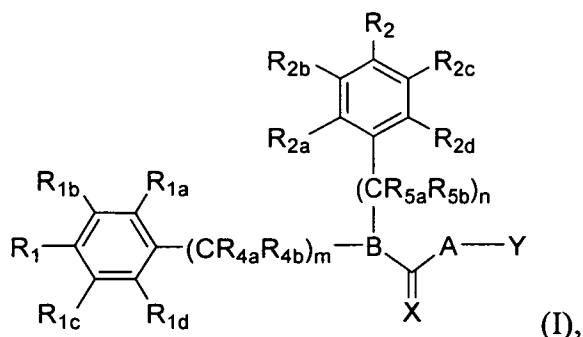
High affinity	$\text{pK}_i \geq 8.4$
Moderate affinity	$\text{pK}_i \geq 7.7$

Table 1 – pK_i values of exemplified compounds

Compound	5-HT _{2a} (pK_i)	Compound	5-HT _{2a} (pK_i)	Compound	5-HT _{2a} (pK_i)
1	6.8	18a/18b	8.9	35	8.8
2	7.1	19	6.6	36	8.5
3	7.4	20	7.7	37	7.9
4	7.6	21	9.3	38	7.2
5a/5b	6.5	22	7.1	39	7.4
6a/6b	6.7	23	6.9	40	8.9
7a/7b	7.4	24	8.6	41	8.5
8	8.3	25	8.9	42	7.8
9	8.3	26	7.0	43	7.6
10	10.3	27	7.8	44	7.2
11	9.8	28	1	45	1.0
12	9.6	29	1	46	7.5
13	9.4	30	1	47	1
14	6.8	31	6.7	48	8.7
15	8.2	32	1	49	8.3
16	7.0	33	7.5		
17	7.8	34	6.6		

WHAT IS CLAIMED IS:

1. A compound according to Formula (I)



or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof, wherein:

m, and n are independently an integer selected from the group consisting of 0, 1, 2, and 3;

t is an integer selected from the group consisting of 0, 1, 2 and 3;

R₁, R_{1a}, R_{1b}, R_{1c} and R_{1d} are independently selected from the group consisting of hydrogen, deuterium, hydroxyl, -OD, halogen, cyano, amino, -SO₂R₁₀, -OC(=O)R₁₁, -C(=O)OR₁₁, unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₁₋₆ haloalkyl, unsubstituted or substituted C₁₋₆ hydroxyalkyl, unsubstituted or substituted C₁₋₆ aminoalkyl, unsubstituted or substituted C₂₋₆ alkenyl, unsubstituted or substituted C₁₋₆ alkoxy, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted C₃₋₆ heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein at least one of R₁, R_{1a}, R_{1b}, R_{1c} and R_{1d} is not hydrogen;

R₂, R_{2a}, R_{2b}, R_{2c} and R_{2d} are independently selected from the group consisting of hydrogen, deuterium, amino, hydroxyl, -OD, halogen, cyano, unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₁₋₆ haloalkyl, unsubstituted or substituted C₁₋₆ hydroxyalkyl, unsubstituted or substituted C₂₋₆ alkenyl, unsubstituted or substituted C₁₋₆ alkoxy, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted C₃₋₆ heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, wherein at least one of R₂, R_{2a}, R_{2b}, R_{2c} and R_{2d} is not selected from hydrogen;

R_{4a}, R_{4b}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, R_{9a}, and R_{9b}, are independently absent or selected from the group consisting of hydrogen, deuterium, and unsubstituted or substituted C₁₋₆ alkyl;

A is selected from the group consisting of a bond, -CR_{5c}R_{5d}-, -CR_{5c}R_{5d}O-, -S-, -O- and -NH-;

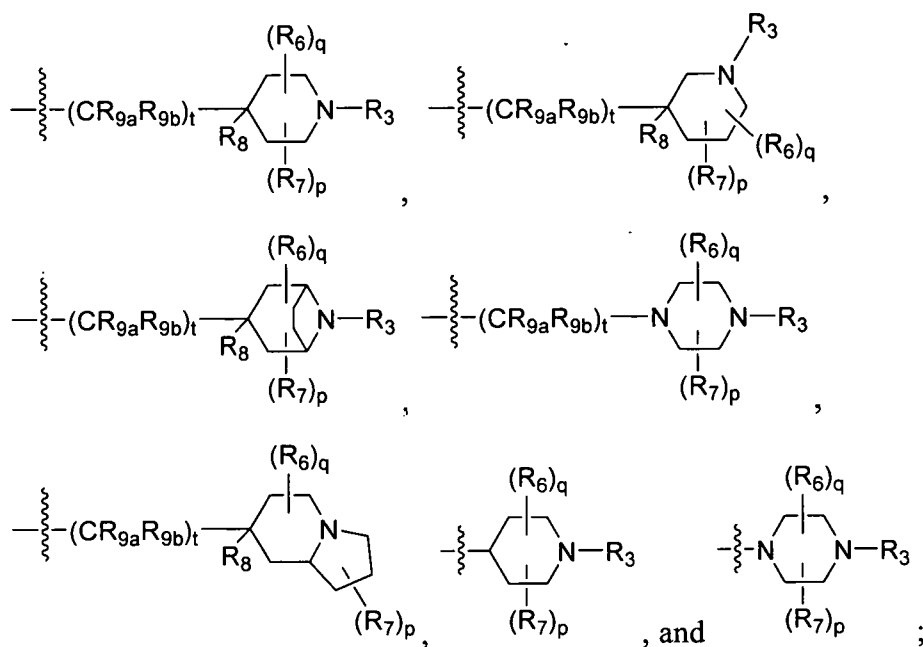
B is selected from the group consisting of $-N-$, $-NCH_2-$, $-CHNH-$, and $-CH-$;

R_{10} and R_{11} , independently are selected from the group consisting of hydrogen, amino, and unsubstituted or substituted C_{1-6} alkyl;

X is O or S; and

Y is $-(CR_{9a}R_{9b})_t$ -(unsubstituted or substituted C_{3-8} heteroalicycyl).

2. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 1, wherein Y is selected from the group consisting of



wherein t is an integer selected from the group consisting of 0, 1 and 2; p and q, are integers, independently selected from the group consisting of 0, 1, and 2;

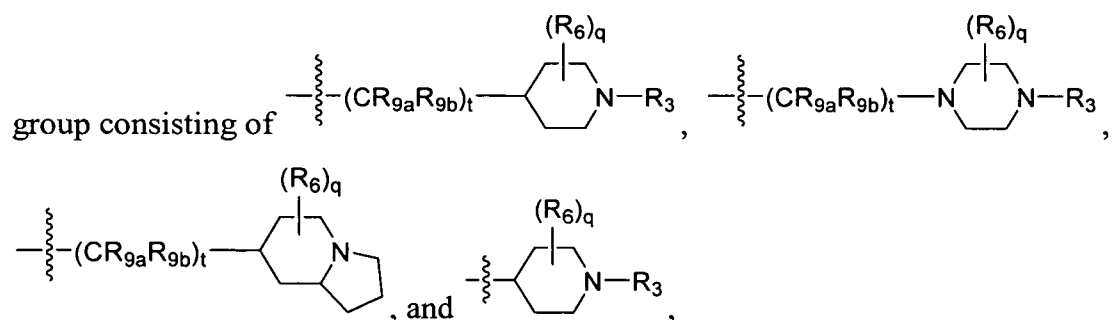
R_3 is selected from hydrogen, deuterium, hydroxyl, $-OD$, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

R_6 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, $-OD$, cyano, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkoxy, and substituted or unsubstituted aryl;

R₇ is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C₁₋₄ alkyl, and substituted or unsubstituted C₁₋₄ alkoxy; and

R₈ is absent, or selected from the group consisting of hydrogen, deuterium, cyano, hydroxyl, -OD, substituted or unsubstituted C₁₋₄ alkyl, substituted or unsubstituted C₂₋₄ alkenyl, substituted or unsubstituted C₃₋₆ cycloalkyl, and substituted or unsubstituted C₁₋₄ alkoxy; or R₈ taken together with R_{9a} or R_{9b} is forming a ring system.

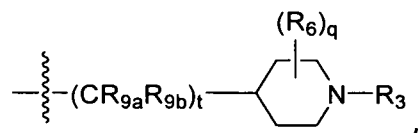
3. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claims 1 or 2, wherein Y is selected from the



wherein t is 0 or 1, and q is 0 or 1;

R₆ is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C₁₋₄ alkyl, substituted or unsubstituted C₁₋₄ alkoxy, and substituted or unsubstituted aryl.

4. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-3, wherein Y is



wherein t is 0 or 1, and q is 0 or 1;

R₆ is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C₁₋₄ alkyl, substituted or unsubstituted C₁₋₄ alkoxy, and substituted or unsubstituted aryl.

5. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-4, wherein A is selected from the group consisting of a bond, $-\text{CH}_2-$, $-\text{O}-$, and $-\text{NH}-$.
6. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-5, wherein A is a bond.
7. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-6, wherein B is $-\text{N}-$ or $-\text{CHNH}-$.
8. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 1, wherein R_1 is selected from the group consisting of deuterium, hydroxyl, $-\text{OD}$, halogen, cyano, amino, $-\text{SO}_2\text{R}_{10}$, $-\text{OC}(=\text{O})\text{R}_{11}$, $-\text{C}(=\text{O})\text{OR}_{11}$, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} aminoalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;
 R_{1d} is selected from the group consisting of hydrogen, deuterium, hydroxyl, $-\text{OD}$, halogen, cyano, amino, $-\text{SO}_2\text{R}_{10}$, $-\text{OC}(=\text{O})\text{R}_{11}$, $-\text{C}(=\text{O})\text{OR}_{11}$, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} aminoalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,;
 R_2 is selected from the group consisting of deuterium, amino, hydroxyl, $-\text{OD}$, halogen, cyano, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; and

R_{2d} is selected from the group consisting of hydrogen, deuterium, amino, hydroxyl, -OD, halogen, cyano, unsubstituted or substituted C₁₋₆ alkyl, unsubstituted or substituted C₁₋₆ haloalkyl, unsubstituted or substituted C₁₋₆ hydroxyalkyl, unsubstituted or substituted C₂₋₆ alkenyl, unsubstituted or substituted C₁₋₆ alkoxy, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted C₃₋₆ heteroalicycyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

9. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 1-8, wherein R_{1a}, R_{1b}, R_{1c}, R_{2a}, R_{2b}, and R_{2c} are hydrogen, and at least one of R_{1d} and R_{2d} is not hydrogen.
10. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-8, wherein R₁, R_{1a}, R_{1b}, R_{1c} and R_{1d} independently are selected from the group consisting of hydrogen, halogen, hydroxyl, amino, -SO₂NH₂, -SO₂N(C₁₋₄ alkyl)₂, -SO₂-C₁₋₄ alkyl, -OC(=O)-C₁₋₄ alkyl, -S(C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, C₁₋₆ alkoxy, C₃₋₄ cycloalkyl, and C₃₋₄ cycloalkyl-C₁₋₃ alkyl and deuterated analogues thereof.
11. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-10, wherein R_{1a}, R_{1b}, R_{1c} and R_{1d} independently are selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, -SO₂NH₂, -SO₂CH₃, -OC(=O)CH₃, methyl, -CD₃, methoxy, -OCD₃, -OCF₃ and -CF₃.
12. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-11, wherein R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is selected from the group consisting of deuterium, halogen, hydroxyl, methyl, -CD₃, methoxy, -OCD₃, -OCF₃ and -CF₃.
13. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-12, wherein R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is selected from the group consisting of hydrogen, hydroxyl and fluoro.

14. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-13, wherein R_1 is selected from the group consisting of halogen, methyl, $-CD_3$, ethyl, $-CD_2CD_3$, optionally deuterated n-propyl, optionally deuterated iso-propyl, optionally deuterated n-butyl, optionally deuterated iso-butyl, optionally deuterated n-pentyl, optionally deuterated 2-methyl-butyl, optionally deuterated n-hexyl, optionally deuterated 2-methyl-pentyl, methoxy, $-OCD_3$, optionally deuterated ethoxy, optionally deuterated n-propoxy, optionally deuterated isopropoxy, optionally deuterated n-butoxy, optionally deuterated iso-butoxy, optionally deuterated pentyl-oxy, optionally deuterated 4-methyl-butoxy, optionally deuterated hexyl-oxy, optionally deuterated 4-methylpentoxy, $-OCF_3$, $-OCF_2CF_3$, $-OCHF_2$, $-OCDF_2$, $-CF_3$, $-CF_2CF_3$, $-CHF_2$, $CDF_2 - CH_2CF_3$, $-CD_2CF_3$, $-CF_2$, 1,1,2,2-tetrafluorobutyl and 1,1,1,2,2-pentafluorobutyl.
15. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-14, wherein R_1 is selected from the group consisting of fluoro, chloro, methoxy, $-OCF_3$ and $-CF_3$.
16. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 15, wherein R_1 is selected from the group consisting of fluoro, and $-CF_3$.
17. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-16, wherein R_2 , R_{2a} , R_{2b} , R_{2c} and R_{2d} independently are selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-4} cycloalkyl, and C_{3-4} cycloalkyl- C_{1-3} alkyl and deuterated analogues thereof.
18. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-17, wherein R_{2a} , R_{2b} , R_{2c} and R_{2d} independently are selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, methyl, $-CD_3$, methoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$.

19. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-18, wherein R_{2a} , R_{2b} , and R_{2c} are hydrogen, and R_{2d} is hydrogen or hydroxyl.
20. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-19, wherein R_2 is selected from the group consisting of halogen, cyano, methyl, $-CD_3$, ethyl, $-CD_2CD_3$, optionally deuterated n-propyl, optionally deuterated iso-propyl, optionally deuterated n-butyl, optionally deuterated iso-butyl, optionally deuterated n-pentyl, optionally deuterated 2-methyl-butyl, optionally deuterated n-hexyl, optionally deuterated 2-methyl-pentyl, methoxy, $-OCD_3$, optionally deuterated ethoxy, optionally deuterated n-propoxy, optionally deuterated isopropoxy, optionally deuterated n-butoxy, optionally deuterated iso-butoxy, optionally deuterated pentyl-oxy, optionally deuterated 4-methyl-butoxy, optionally deuterated hexyl-oxy, optionally deuterated 4-methylpentoxy, $-OCF_3$, $-OCF_2CF_3$, $-OCHF_2$, $-OCDF_2$, $-CF_3$, $-CF_2CF_3$, $-CHF_2$, $CDF_2-CH_2CF_3$, $-CD_2CF_3$, $-CF_2$, 1,1,2,2-tetrafluorobutyl and 1,1,1,2,2-pentafluorobutyl.
21. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-20, wherein R_2 is selected from the group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, pentyl-oxy, 4-methyl-butoxy, hexyl-oxy and 4-methylpentoxy.
22. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-21, wherein R_1 and R_{1d} independently are selected from the group consisting of deuterium, hydroxyl, halogen, methyl, $-CD_3$, methoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$; or
- R_2 and R_{2d} independently are selected from the group consisting of deuterium, halogen, hydroxyl methyl, $-CD_3$, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, pentyl-oxy, 4-methyl-butoxy, hexyl-oxy and 4-methylpentoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$.

23. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-22, wherein halogen is fluoro.
24. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-23, wherein R_3 is selected from the group consisting of hydrogen, deuterium, hydroxyl, -OD, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted $-(CH_2)_s-C_{3-6}$ cycloalkyl, substituted or unsubstituted $-(CH_2)_s-C_{2-5}$ heteroalicycyl, substituted or unsubstituted $-(CH_2)_s-C_{2-5}$ heteroaryl, and substituted or unsubstituted $-(CH_2)_s-C_{5-6}$ aryl, wherein each s is selected from the group consisting of 0, 1, 2 and 3.
25. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-24, wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CD_3$, ethyl, $-CD_2CD_3$, n-propyl, $-CD_2CD_2CD_3$, iso-propyl, cyclopropyl, $CD_2CD_3CD_3$, $-(CR_{9a}R_{9b})_tC(-O)OR_{9c}$ and $-(CH_2)_tC(=O)NR_{9a}R_{9b}$, wherein R_{9a} , R_{9b} , and R_{9c} independently are hydrogen or C_{1-4} -alkyl, wherein each t is selected from the group consisting of 0, 1, 2 and 3.
26. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-25, wherein R_3 is hydrogen or methyl.
27. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-26, wherein R_{4a} , R_{4b} , R_{5a} and R_{5b} are independently hydrogen or methyl.
28. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-27, wherein R_{4a} , R_{4b} and R_{5a} are hydrogen and R_{5b} is methyl or hydrogen.

29. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-29, wherein R_{4a}, R_{5a} and R_{5b} are hydrogen and R_{4b} is methyl or hydrogen.
30. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-30, wherein R_{4a}, R_{4b}, R_{5a} and R_{5b} are hydrogen.
31. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-23, wherein q is 0 or 1, and whenever q is 1 then R₆ is halogen or C₁₋₄ alkyl.
32. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 31, wherein R₆ is fluoro.
33. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-33, wherein R₈ is selected from the group consisting of hydrogen, halogen, methyl, ethyl, propyl, methoxy, ethoxy, C₁₋₂- haloalkyl, and C₁₋₂- haloalkoxy.
34. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-34, wherein R₈ is selected from the group consisting of hydrogen, -CF₃, -CHF₂, -CF₂CF₃, -OCF₃, -OCF₂CF₃ and -OCHF₂.
35. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-35, wherein R₈ is hydrogen.
36. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-35, wherein X is O.
37. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-36, wherein m, and n independently are selected from the group consisting of 0 and 1.

38. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-36, wherein m is 1 and n is 0 or 1.

39. The compound, pharmaceutically acceptable salt, polymorph or stereoisomer according to claim 1, selected from the group consisting of:

- 1-[(4-fluorophenyl)methyl]-3-(1-methylpiperidin-4-yl)-1-[[4-(2-methylpropoxy)phenyl]methyl]urea;
- 1-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-(1-methylpiperidin-4-yl)urea;
- N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]-3-(piperidin-4-yl)propanamide;
- N-[(4-fluorophenyl)methyl]-3-(1-methylpiperidin-4-yl)-N-[[4-(2-methylpropoxy)phenyl]methyl]propanamide;
- 1R)-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]-6-azaspiro[2.5]octane-1-carboxamide;
- (1S)-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]-6-azaspiro[2.5]octane-1-carboxamide;
- (1R)-N-[(4-fluorophenyl)methyl]-6-methyl-N-[[4-(2-methylpropoxy)phenyl]methyl]-6-azaspiro[2.5]octane-1-carboxamide;
- (1S)-N-[(4-fluorophenyl)methyl]-6-methyl-N-[[4-(2-methylpropoxy)phenyl]methyl]-6-azaspiro[2.5]octane-1-carboxamide;
- 1-[(2,4-difluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-(1-methylpiperidin-4-yl)urea;
- N-[(4-fluorophenyl)methyl]-2-(1-methylpiperidin-4-ylidene)-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide;
- 2-[(7S,8aS)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide;
- 2-[(7R,8aR)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide;
- 2-[(7S,8aR)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide;
- 2-[(7R,8aS)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide;
- 2-[(4-fluorophenyl)[4-(2-methylpropoxy)phenyl]amino]-N-[(1-methylpiperidin-4-yl)methyl]acetamide;
- N,N-bis[(4-fluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide;
- N,N-bis[(2,4-difluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide;
- N,N-bis[(4-methoxyphenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide;
- 2-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-N-[[4-(2-methylpropoxy)phenyl]methyl]acetamide;

2-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}acetamide;
(1-methylpiperidin-4-yl)methyl N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl}carbamate;
1-methylpiperidin-4-yl N-[(4-fluorophenyl)methyl]-N-{[4-(2-methylpropoxy)phenyl]methyl} carbamate;
N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]piperidine-4-carboxamide;
N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-1-methylpiperidine-4-carboxamide;
N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-(piperidin-4-yl)acetamide;
N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide;
N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-[[1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}acetamide;
N-[(4-fluorophenyl)methyl]-N-[(4-methoxyphenyl)methyl]-2-[[1R,3S,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]oxy}acetamide;
N-[(4-fluorophenyl)methyl]-4-methyl-N-{[4-(2-methylpropoxy)phenyl]methyl}piperazine-1-carboxamide;
2-[(4-fluorophenyl)methyl]-N-(1-methylpiperidin-4-yl)-3-[4-(propan-2-yloxy)phenyl]-propanamide;
2-[(4-fluorophenyl)methyl]-1-(4-methylpiperazin-1-yl)-3-[4-(propan-2-yloxy)phenyl]propan-1-one;
1-methylpiperidin-4-yl 2-[(4-fluorophenyl)methyl]-3-[4-(propan-2-yloxy)phenyl]-propanoate;
3-[1-(4-fluorophenyl)-3-[4-(propan-2-yloxy)phenyl]propan-2-yl]-1-(1-methylpiperidin-4-yl)urea;
N-[1-(4-fluorophenyl)-3-[4-(propan-2-yloxy)phenyl]propan-2-yl]-4-methylpiperazine-1-carboxamide;
N-[(4-ethoxyphenyl)methyl]-N-[(4-fluorophenyl)methyl]-2-(piperidin-4-yl)acetamide;
N-[(2,4-difluorophenyl)methyl]-N-[(4-ethoxyphenyl)methyl]-2-(piperidin-4-yl)-acetamide;
N-[(4-ethoxyphenyl)methyl]-N-[(3-fluorophenyl)methyl]-2-(piperidin-4-yl)acetamide;
N-[(3-fluorophenyl)methyl]-2-(piperidin-4-yl)-N-{[4-(propan-2-yloxy)phenyl]methyl}acetamide;
N-[(4-ethoxyphenyl)methyl]-N-[(4-fluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)-acetamide;
N-[(2,4-difluorophenyl)methyl]-N-[(4-ethoxyphenyl)methyl]-2-(1-methylpiperidin-4-yl)acetamide;
N-[(4-ethoxyphenyl)methyl]-N-[(3-fluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)-acetamide;

N-[(3-fluorophenyl)methyl]-2-(1-methylpiperidin-4-yl)-N-{{[4-(propan-2-yloxy)phenyl]methyl}acetamide;
 N-[(4-fluoro-2-methylphenyl)methyl]-2-(1-methylpiperidin-4-yl)-N-{{[4-(propan-2-yloxy)phenyl]methyl}acetamide; and
 N-[(5-fluoro-2-methylphenyl)methyl]-2-(1-methylpiperidin-4-yl)-N-{{[4-(propan-2-yloxy)phenyl]methyl}acetamide.

40. A method for treating a disease in a patient comprising administering to the patient an effective amount of a compound, pharmaceutically acceptable salt, polymorph or stereoisomer of a compound according to any one of claims 1-39, wherein the disease is selected from the group consisting of Abnormal hormonal activity, Alzheimer's disease, Alzheimer's disease dementia, Alzheimer's disease psychosis, Addiction (alcohol, cocaine, methamphetamine, nicotine and opioid), Addison's disease, ADHD, Alzheimer's disease psychosis, Affective disorders, Aggressiveness, Agitation, Akathisia, Alcohol addiction, Alcohol withdrawal, Amenorrhea, Amyotrophic lateral sclerosis, Anhedonia, Anorexia, Anti-NMDAR encephalitis, Anxiety, Appetite disorders, Asthma, Autism, Behavioral disorders, Behavioral disturbances associated with dementia, Binge eating disorder associated with impulse control disorder (ICD), Bipolar disorder, Blindness, Borderline disorder, Borderline personality disorder, Bradykinesia, Bulimia, Buying associated with ICD, Cardiac arrhythmia, Cerebral vascular accidents, Charles Bonnet disease, Chemotherapy-induced emesis, Childhood autism, Chronic pain, Chronic insomnia, cocaine addiction, Cognitive disorders, craniofacial pain, temporomandibular joint (TMJ) / temporomandibular disorder (TMD), Cushing's disease, Delusion, Dementia, Dementia with Lewy Body or Lewy Body dementia, dementia and psychosis associated with Creutzfeld-Jakob disease (CJD), Gerstmann-Strausser-Schenker disease (GSSD) and fatal familial insomnia (FFI), Depression, Diabetes mellitus (non-insulin dependent), Diabetic peripheral neuropathy, Drug addiction, Double vision, Down's syndrome, Dyskinesia, Dysthymia, Dystonia, Ejaculatory problem, Emphysema, Epilepsy, Extrapyrimal disorder, Fibromyalgia, Frailty, Friedrich's Ataxia, Frontotemporal Dementia, Gambling associated with ICD, Galactorrhea, General anxiety disorder, Glaucoma, Hair loss or thinning, Hallucination, Headache, Hemorrhoids, Huntington's disease, Hyperprolactinemia, Hypertension, Hypersexuality associated with ICD, Hypotension, Hypoglutamateriga disorders, Impulse control disorder, Idiopathic thrombocytopenic purpura, Impotence,

Incontinence, Increased intraocular pressure, Infertility, Inflammatory pain, Insomnia, Ischemia, Ischemic stroke, Lewy body disease (LBD), Learning disorders, Libido (decreased), Loss of libido, Low male fertility, Low sperm mobility, Lupus, Machado-Joseph disease, Major depression, Mania, Menopausal symptoms, Metabolic syndrome, methamphetamine addiction, Migraine, mild cognitive impairment (MCI), Motor tics, Multi-infarct dementia, Multiple sclerosis, Multiplex development disorder, Myocardial infarction, Myoclonus, Neuropathic pain, Neurodegenerative disorder, Neuropsychiatric disease, Nicotine addiction, Non motor symptoms of Parkinson's disease selected from dementia, depression, apathy, hallucinations, dribbling saliva (sialorrhea), constipation, pain, genitourinary problems and sleep disorders, Obsessive compulsive disorder, On/off phenomena, Opioid addiction, Osteoporosis, Pancreatitis, Panic attacks, Parkinson's disease, Parkinson's disease dementia, Parkinson's disease psychosis, Periodic limb movement during sleep (PLMS), Peripheral vascular disease, Pituitary tumor, Postherpetic neuralgia, Progressive Supranuclear Palsy, Prion disease including Creutzfeld-Jakob disease (CJD), Gerstmann-Straussler-Schenker disease (GSSD) and fatal familial insomnia (FFI), Prolactinoma, Pseudobulbar affect (PBA), Psychomotor slowing, Psychosis, Psychoses secondary to neurodegenerative disorders, Psychosomatic disorders, Psychotic depression, post-traumatic stress disorder (PTSD), Raynaud's disease, Reflex sympathetic dystrophy, Restless legs syndrome, Retinal disease, Schizoaffective disorders, Schizophrenia, negative symptoms of schizophrenia, cognitive impairment associated with schizophrenia, Sepsis, Serotonin syndrome, Sexual dysfunction, Sexual dysfunction associated with antidepressant use, Sleep apnea, Sleep disorders, Sleep maintenance insomnia, social anxiety disorder, Spinal injury, Spinocerebellar Atrophy, Suicidal tendency, Thrombosis, Thrombotic stroke, Thrombotic thrombocytopenic purpura, Tinnitus, Tiredness, Tourette's syndrome, Transient insomnia, Traumatic brain injury, Treatment-resistant depression, Treatment-resistant schizophrenia, Tremor, Vaginal dryness, Vasospasm, Wakefulness, vascular dementia, Hallucinations associated with Parkinson's disease, Delusions associated with Parkinson's disease; cancer, brain cancer, glioma, Pancreatic cancer, Hypoactive sexual desire disorder, adult type 2 diabetes mellitus with Parkinson's disease or dementia and Liver fibrosis.

41. The compound, pharmaceutically acceptable salt, polymorph or stereoisomer according to any one of claims 1-39, for use in treating a disease selected from the group consisting of Abnormal hormonal activity, Alzheimer's disease, Alzheimer's disease dementia, Alzheimer's disease psychosis, Addiction (alcohol, cocaine, methamphetamine, nicotine and opioid), Addison's disease, ADHD, Alzheimer's disease psychosis, Affective disorders, Aggressiveness, Agitation, Akathisia, Alcohol addiction, Alcohol withdrawal, Amenorrhea, Amyotrophic lateral sclerosis, Anhedonia, Anorexia, Anti-NMDAR encephalitis, Anxiety, Appetite disorders, Asthma, Autism, Behavioral disorders, Behavioral disturbances associated with dementia, Binge eating disorder associated with impulse control disorder (ICD), Bipolar disorder, Blindness, Borderline disorder, Borderline personality disorder, Bradykinesia, Bulimia, Buying associated with ICD, Cardiac arrhythmia, Cerebral vascular accidents, Charles Bonnet disease, Chemotherapy-induced emesis, Childhood autism, Chronic pain, Chronic insomnia, cocaine addiction, Cognitive disorders, craniofacial pain, temporomandibular joint (TMJ) / temporomandibular disorder (TMD), Cushing's disease, Delusion, Dementia, Dementia with Lewy Body or Lewy Body dementia, dementia and psychosis associated with Creutzfeld-Jakob disease (CJD), Gerstmann-Strausser-Schenker disease (GSSD) and fatal familial insomnia (FFI), Depression, Diabetes mellitus (non-insulin dependent), Diabetic peripheral neuropathy, Drug addiction, Double vision, Down's syndrome, Dyskinesia, Dysthymia, Dystonia, Ejaculatory problem, Emphysema, Epilepsy, Extrapyrarnidal disorder, Fibromyalgia, Frailty, Friedrich's Ataxia, Frontotemporal Dementia, Gambling associated with ICD, Galactorrhea, General anxiety disorder, Glaucoma, Hair loss or thinning, Hallucination, Headache, Hemorrhoids, Huntington's disease, Hyperprolactinemia, Hypertension, Hypersexuality associated with ICD, Hypotension, Hypoglutamateriga disorders, Impulse control disorder, Idiopathic thrombocytopenic purpura, Impotence, Incontinence, Increased intraocular pressure, Infertility, Inflammatory pain, Insomnia, Ischemia, Ischemic stroke, Lewy body disease (LBD), Learning disorders, Libido (decreased), Loss of libido, Low male fertility, Low sperm mobility, Lupus, Machado-Joseph disease, Major depression, Mania, Menopausal symptoms, Metabolic syndrome, methamphetamine addiction, Migraine, mild cognitive impairment (MCI), Motor tics, Multi-infarct dementia, Multiple sclerosis, Multiplex development disorder, Myocardial infarction, Myoclonus, Neuropathic pain, Neurodegenerative disorder, Neuropsychiatric disease,

Nicotine addiction, Non motor symptoms of Parkinson's disease selected from dementia, depression, apathy, hallucinations, dribbling saliva (sialorrhea), constipation, pain, genitourinary problems and sleep disorders, Obsessive compulsive disorder, On/off phenomena, Opioid addiction, Osteoporosis, Pancreatitis, Panic attacks, Parkinson's disease, Parkinson's disease dementia, Parkinson's disease psychosis, Periodic limb movement during sleep (PLMS), Peripheral vascular disease, Pituitary tumor, Postherpetic neuralgia, Progressive Supranuclear Palsy, Prion disease including Creutzfeld-Jakob disease (CJD), Gerstmann-Strausser-Schenker disease (GSSD) and fatal familial insomnia (FFI), Prolactinoma, Pseudobulbar affect (PBA), Psychomotor slowing, Psychosis, Psychoses secondary to neurodegenerative disorders, Psychosomatic disorders, Psychotic depression, post-traumatic stress disorder (PTSD), Raynaud's disease, Reflex sympathetic dystrophy, Restless legs syndrome, Retinal disease, Schizoaffective disorders, Schizophrenia, negative symptoms of schizophrenia, cognitive impairment associated with schizophrenia, Sepsis, Serotonin syndrome, Sexual dysfunction, Sexual dysfunction associated with antidepressant use, Sleep apnea, Sleep disorders, Sleep maintenance insomnia, social anxiety disorder, Spinal injury, Spinocerebellar Atrophy, Suicidal tendency, Thrombosis, Thrombotic stroke, Thrombotic thrombocytopenic purpura, Tinnitus, Tiredness, Tourette's syndrome, Transient insomnia, Traumatic brain injury, Treatment-resistant depression, Treatment-resistant schizophrenia, Tremor, Vaginal dryness, Vasospasm Wakefulness, vascular dementia, Hallucinations associated with Parkinson's disease, Delusions associated with Parkinson's disease; cancer, brain cancer, glioma, Pancreatic cancer, Hypoactive sexual desire disorder, adult type 2 diabetes mellitus with Parkinson's disease or dementia and Liver fibrosis.