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

(57) Abstract: The present disclosure relates to compounds according to Formulae disclosed herein, useful for treating diseases.

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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 (Moulignier, *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-HT2A 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-HT2A 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-HT2A 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-HT2A 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-HT2A receptors is an alternate molecular mechanism for drugs with antipsychotic efficacy, possibly through antagonism of heightened or exaggerated signal transduction through serotonergic systems. 5-HT2A antagonists are therefore good candidates for treating psychosis without extrapyramidal side effects or other undesired effects associated with blockade of dopamine D_2 receptors.

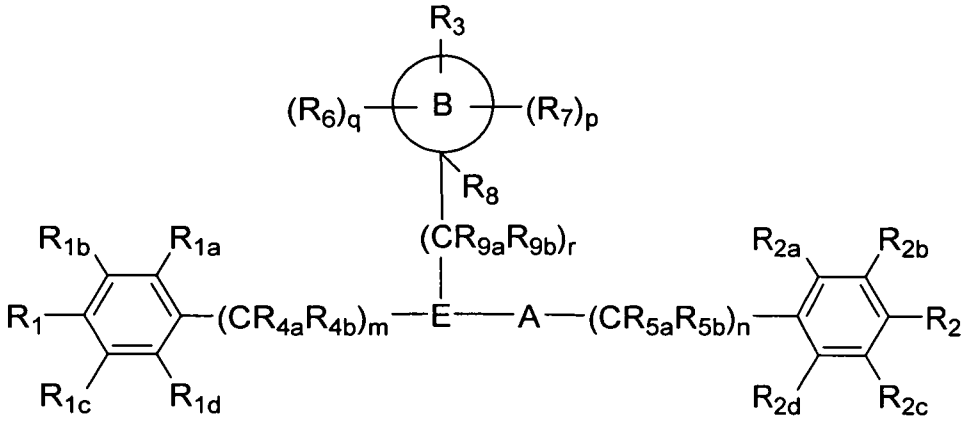
[0011] Traditionally, GPCRs such as the 5-HT2A receptor have been assumed to exist in a quiescent state unless activated by the binding of an agonist (a drug that activates a receptor). It is now appreciated that many, if not most, of the GPCR monoamine receptors, including serotonin receptors, can exist 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),



(I),

[0014] or a pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof, wherein:

[0015] m, and n are independently an integer selected from the group consisting of 0, 1, 2, and 3;

[0016] p is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6;

[0017] q is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

[0018] r is an integer selected from the group consisting of 0, 1, 2, and 3;

[0019] R_1, R_{1a}, R_{1b}, R_{1c} and R_{1d} are independently selected from the group consisting of hydrogen, deuterium, hydroxyl, -OD, halogen, cyano, amino, $-SO_2R_{10}$, $-OC(=O)R_{11}$, $-C(=O)OR_{11}$, 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_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

[0020] R_2, 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 C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6}

alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or R_2 and R_{2b} or R_{2c}, taken together with the atoms to which they are attached form a ring system;

[0021] 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_{1-6} alkenyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

[0022] 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;

[0023] 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;

[0024] 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;

[0025] 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_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy;

[0026] R_{10} and R_{11}, independently are selected from the group consisting of hydrogen, amino, unsubstituted or substituted C_{1-6} alkyl;

[0027] A is selected from the group consisting of -C(=X)–$CR_{5c}R_{5d}$-, – C(=S)–($CR_{5c}R_{5d}$)NH-, -C(=S)-S-, -C(=X)-O-, -C(=X)–NH-, and substituted or unsubstituted heteroaryl;

[0028] E is N or CH;

[0029] B is a ring system selected from the group consisting of substituted or unsubstituted 4-12 membered heteroalicyclic ring systems; and

[0030] X is O or S.

[0031] 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 familiar 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, Extrapyramidal 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, Pancreatis, 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,

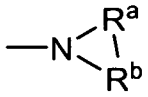
Progressive Supranucelar Palsy, Prion disease including Creutzfeld-Jakob disease (CJD), Gerstmann-Strausser-Schenker disease (GSSD) and fatal familiar insomnia (FFI), Prolactinoma, Pseudobulbar affect (PBA), Psychomotor slowing, Psychosis, Psychoses secondary to neurodegenerative disorders, Psychosomatic 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

[0032] 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.

[0033] As used herein, any "R" group(s) such as, without limitation, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, and R_{10}, 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 heteroalicyclyl. 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 heteroalicyclyl 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:



[0034] 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.

[0035] 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, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)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.

[0036] Whenever a group, such as an "unsubstituted or substituted" alkyl group, is described without the use of "unsubstituted or substituted", e.g. "alkyl" it is understood as an "unsubstituted alkyl", unless the group is separately defined herein to be able to carry substituents. For example C_{1-6} alkyl means an unsubstituted alkyl comprising 1 to 6 carbon atoms.

[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, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)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] 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 "C_1 to C_6 alkyl" group refers to all alkyl groups having from 1 to 6 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$-, $CH_3CH(CH)_3CH_2$- , $CH_3CH(CH)_3CH_2$- and $(CH_3)_3C$-. If no "m" and "n" are designated with regard to a group, the broadest range described in these definitions is to be assumed.

[0039] 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 "C_{1-6}". 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 "C_1-C_4 alkyl," "C_{1-4} alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" or "C_{1-4} 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, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)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.

[0040] 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).

[0041] 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, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)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.

[0042] 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.

[0043] As used herein, "hetero" refers to heteroatoms selected from nitrogen, oxygen, phosphorus and sulfur.

[0044] 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

[0045] 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, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)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.

[0046] As used herein, "heteroaryl" refers to a monocyclic or multicyclic 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 multicyclic "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, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)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.

[0047] 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.

[0048] 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.

[0049] 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 "C_{1-6}" The alkylene could also be a lower alkylene having 1 to 4 carbon atoms. The alkylene may be designated as "C_1-C_4 alkylene", "C_{1-4} alkylene" or similar designations. Non-limiting examples include, methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), and butylene (-$(CH_2)_4$-) groups. In the case of methylene, the two connected fragments are connected to the same carbon atom. A lower alkylene group may be substituted.

[0050] 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 -CH_2-O-, -CH_2-CH_2-O-, -CH_2-CH_2-CH_2-O-, -CH_2-NH-, -CH_2-CH_2-NH-, -CH_2-CH_2-CH_2-NH-, -CH_2-CH_2- NH-CH_2-, -O-CH_2-CH_2-O-CH_2-CH_2-O-, -O-CH_2-CH_2-O-CH_2-CH_2-, and the like.

[0051] 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, methylidene (=CH_2) and ethylidene (=$CHCH_3$). 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.

[0052] 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, iso-butoxy, sec-butoxy, tert-butoxy, amoxy, tert-amoxy and the like. An alkoxy may be substituted.

[0053] 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.

[0054] 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.

[0055] 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-pentenyloxy, tert-pentenyloxy, and the like. The alkenyloxy may be substituted.

[0056] 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.

[0057] 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 C_3 to C_{10}, such as from C_3 to C_6. 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.

[0058] 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 C_3 to C_{10}, such as from C_3 to C_8 or from C_5 to C_{10}. For example, C_{3-8} cycloalkenyl includes C_{4-8} cycloalkenyl, C_{5-8} cycloalkenyl or C_{6-8} 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.

[0059] 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 C_8 to C_{12}. A cycloalkynyl group may be unsubstituted or substituted. When

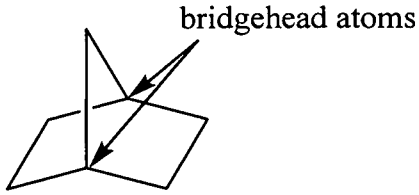
substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated. When substituted, substituents on a cycloalkynyl group may form an aromatic ring fused to the cycloalkynyl group, including an aryl and a heteroaryl.

[0060] As used herein, "heteroalicyclic" or "heteroalicyclyl" 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 heteroalicyclyl groups may range from C_2 to C_{10}, in some embodiments it may range from C_2 to C_9, and in other embodiments it may range from C_2 to C_8. The "heteroalicyclic" or "heteroalicyclyl" 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 "heteroalicyclyl" 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. Heteroalicyclyl 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, heteroalicyclyl, aralkyl, heteroaralkyl, (heteroalicyclyl)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 "heteroalicyclyl" include but are not limited to, azepinyl, dioxolanyl, imidazolinyl, morpholinyl, oxetanyl, furanyl, 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 heteroalicyclyl group may form an aromatic ring fused to the heteroalicyclyl group, including an aryl and a heteroaryl.

[0061] 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.

[0062] A "spiro bicyclic ring" refers to a bicyclic ring wherein the two rings share one atom.

[0063] 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



[0064] 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.

[0065] 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.

[0066] 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.

[0067] As used herein, "halo" or "halogen" refers to F (fluoro), Cl (chloro), Br (bromo) or I (iodo).

[0068] 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.

[0069] 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-1-fluoromethoxy, 2-fluoroisobutyoxy. A haloalkoxy may be substituted.

[0070] 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, heteroalicyclyl, aralkyl, or (heteroalicyclyl)alkyl, as defined herein. An O-carboxy may be substituted.

[0071] 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.

[0072] A "trihalomethanesulfonyl" group refers to an "X_3CSO_2-" group" wherein X is a halogen.

[0073] 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.

[0074] A "nitro" group refers to a "-NO_2" group.

[0075] A "cyano" group refers to a "-CN" group.

[0076] A "cyanato" group refers to an "-OCN" group.

[0077] An "isocyanato" group refers to a "-NCO" group.

[0078] A "thiocyanato" group refers to a "-SCN" group.

[0079] A "carbonyl" group refers to a "–C(=O)-" group.

[0080] A "thiocarbonyl" group refers to a "–C(=S)-" group.

[0081] An "oxo" group refers to a " =O " group.

[0082] A "hydroxy" group or "hydroxyl" group refers to an "-OH" group.

[0083] An "isothiocyanato" group refers to an " -NCS" group.

[0084] 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.

[0085] A "sulfonyl" group refers to an "SO_2R" group in which R can be the same as defined with respect to O-carboxy. A sulfonyl may be substituted.

[0086] An "S-sulfonamido" group refers to a "-$SO_2NR_AR_B$" 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 C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A S-sulfonamido may be substituted.

[0087] An "N-sulfonamido" group refers to a "$RSO_2N(R_A)$-" 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.

[0088] A "trihalomethanesulfonamido" group refers to an "$X_3CSO_2N(R)$-" group with X as halogen and R can be the same as defined with respect to O-carboxy. A trihalomethanesulfonamido may be substituted.

[0089] 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 C_{3-8} cycloalkyl, substituted or unsubstituted C_{3-8} cycloalkenyl, substituted or unsubstituted heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. A C-amido may be substituted.

[0090] 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.

[0091] 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.

[0092] A lower alkoxyalkyl refers to an alkoxy group connected via a lower alkylene group. A lower alkoxyalkyl may be substituted.

[0093] An "amine" or "amino" refers to "RNH_2" (a primary amine), "R_2NH" (a secondary amine), "R_3N" (a tertiary amine). An amino group may be substituted.

[0094] An aminoalkyl refers to an amino group connected via a lower alkylene group. An aminoalkyl may be substituted.

[0095] As used herein "0" (zero), for example in connection with a subscript means that it's absent. For example $-(CH_2)_s-C_{2-6}$ alkyl, wherein S can be "0" means that the $–(CH_2)-$ is absent and the remaining group is $-C_{2-6}$ alkyl, another illustrative example is whenever "r" is "0",then the $-(CR_{9a}R_{9b})-$ group is absent and a bond is connecting "E" to ring system "B".

[0096] 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).

[0097] 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)).

[0098] 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-D6	Dimethylsulfoxide-d6
$MgSO_4$	Magnesium Sulfate
$POCl_3$	Phosphorus(V) oxychloride
KOH	Potassium hydroxide
NaOH	Sodium hydroxide
Na_2SO_4	Sodium Sulfate
K_2CO_3	Potassium carbonate
Na_2CO_3	Sodium carbonate
TFA	Trifluoroacetic acid
Boc	*t*-butoxycarbonyl
FMOC	Fluorenylmethyloxycarbonyl
FMOC-Cl	9-Fluorenylmethoxycarbonyl chloride
TEOC	2-(trimetylsilyl)ethoxycarbonyl
equiv.	equivalents
min	minutes
cat	catalytical
HCl	hydrochloric acid
HPLC	high performance liquid chromatography

[0099] 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 enatiomerically 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.

[00100] 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.

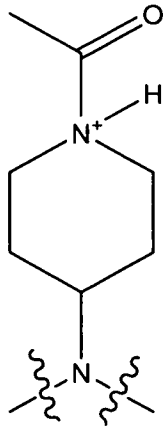
[00101] It is understood that isotopes may be present in the compounds described herein. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound described herein a hydrogen atom can be any isotope of hydrogen, including but not 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 $-CH_3$, $-CD_3$, $-CH_2D$ etc.

[00102] 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 (NH_4^+); 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.

[00103] 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.

[00104] 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.



(A)

[00105] "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.

[00106] 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.

[00107] An "agonist" is defined as a compound that increases the basal activity of a receptor (i.e. signal transduction mediated by the receptor).

[00108] 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.

[00109] 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.

[00110] 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.

[00111] 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.

[00112] 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.

[00113] 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.

[00114] 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.

[00115] 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.

[00116] 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.

[00117] "Ligand" is intended to include any substance that interacts with a receptor.

[00118] "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.

[00119] 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.

[00120] 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.

[00121] 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.

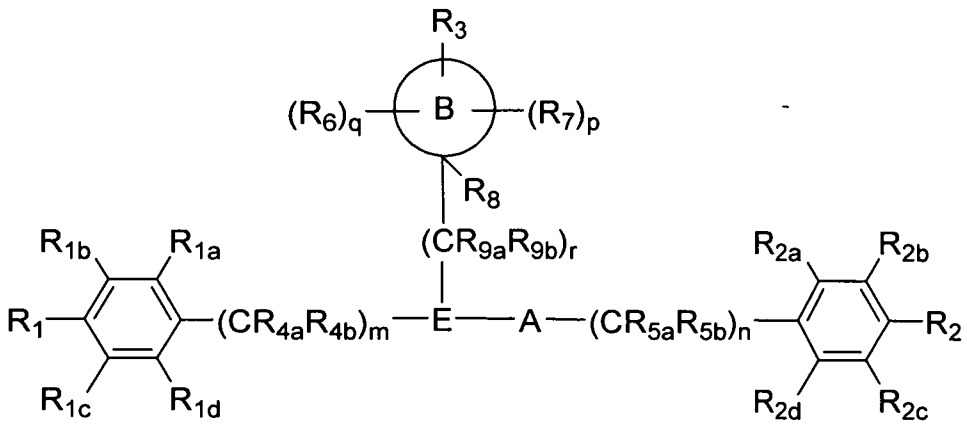
[00122] As used herein, "coadministration" of pharmacologically active compounds refers to the delivery of two or more separate chemical entities, whether in vitro or in vivo. Coadministration means the simultaneous delivery of separate agents; the simultaneous delivery of a mixture of agents; as well 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.

[00123] 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.

[00124] 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

[00125] Embodiments disclosed herein relate to a compound according to Formula (I)



(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;

p is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6;

q is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

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

R_1, R_{1a}, R_{1b}, R_{1c} and R_{1d} are independently selected from the group consisting of hydrogen, deuterium, hydroxyl, -OD, halogen, cyano, amino, $-SO_2R_{10}$, $-OC(=O)R_{11}$, $-C(=O)OR_{11}$, 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_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

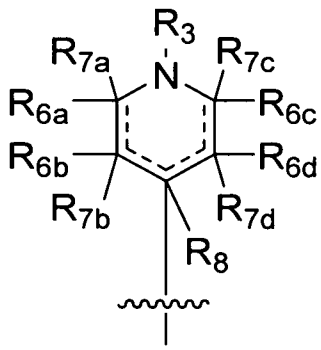
R_2, R_{2a}, R_{2b}, R_{2c} and R_{2d} are independently selected from the group consisting of hydrogen, deuterium, amino, hydroxyl, -OD, halogen, cyano, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or R_2 and R_{2b} or R_{2c}, taken together with the atoms to which they are attached form a ring system;

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_{1-6} alkenyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

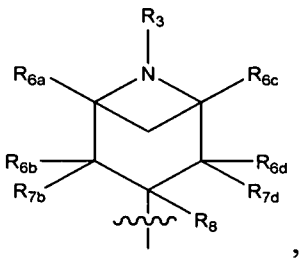
R_{4a}, R_{4b}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, R_{9a} and R_{9b} are independently selected from the group consisting of hydrogen, deuterium, and unsubstituted or substituted C_{1-6} alkyl;
R_6 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy, substituted or unsubstituted aryl;
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;
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_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy;
R_{10} and R_{11}, independently are selected from the group consisting of hydrogen, amino, unsubstituted or substituted C_{1-6} alkyl;
A is selected from the group consisting of -C(=X)–$CR_{5c}R_{5d}$-, – C(=S)–$(CR_{5c}R_{5d})$NH-, -C(=S)-S-, -C(=X)-O-, -C(=X)–NH-, and substituted or unsubstituted heteroaryl;
E is N or CH;
B is a ring system selected from the group consisting of substituted or unsubstituted 4-12 membered heteroalicyclic ring systems; and
X is O or S.

[00126] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein A is substituted or unsubstituted 5 or 6 membered heteroaryl, e.g. substituted or unsubstituted oxadiazolyl or substituted or unsubstituted triazolyl, such as substituted or unsubstituted 1,2,4-oxadiazol-5-yl, substituted or unsubstituted 1,2,4-oxadiazol-3-yl or substituted or unsubstituted triazolyl.

[00127] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein ring system B has the formula:



, or R_{6a}, R_{6b}, R_{6c} and R_{6d} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and R_{7a}, R_{7b}, R_{7c} and R_{7d} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; R_8 is absent, or selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy; or R_{7a}, and R_{7c}; or R_{7b} and R_{7d}; or R_{7a} and R_{7d}; or R_{7a} and R_{7d}; or R_3 and R_8 are combined and taken together with ring system B and to form: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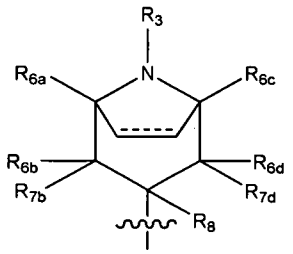
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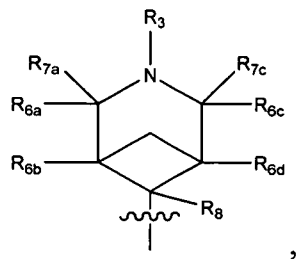
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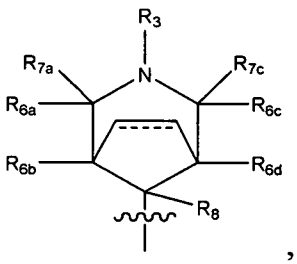
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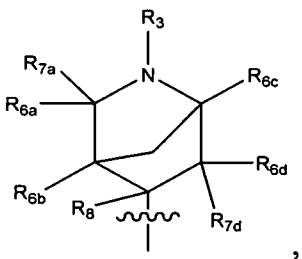
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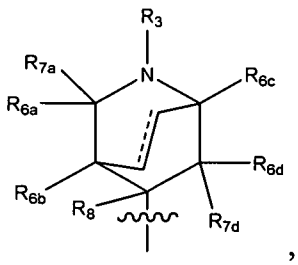
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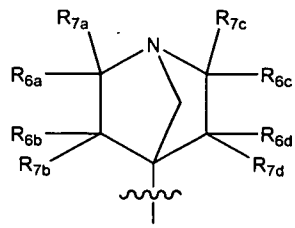
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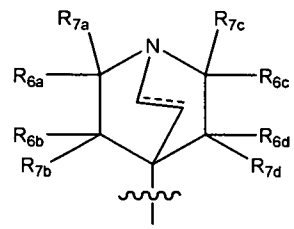
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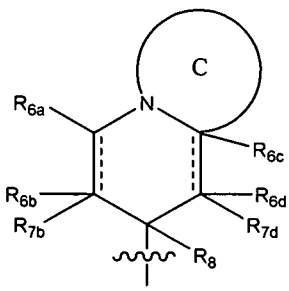
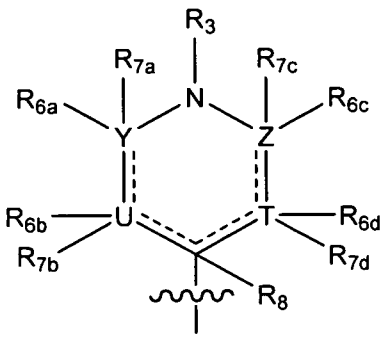


and , wherein ring system C combined with the nitrogen and carbon atoms to which they are attached form a 5 or 6 membered heteroalicyclic ring.

[00128] In some embodiments r is 0 or 1, e.g. when the ring system B is selected from the group consisting of 4, 5, 6 or 7 membered ring comprising at least one nitrogen atom, as described hereinabove. In some embodiments r is 0.

[00129] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the ring system B is selected from the group consisting of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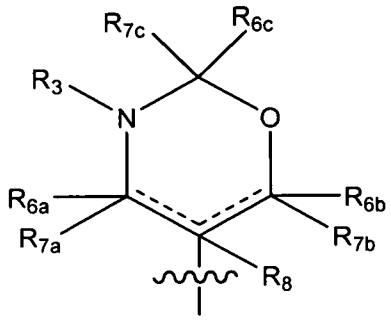
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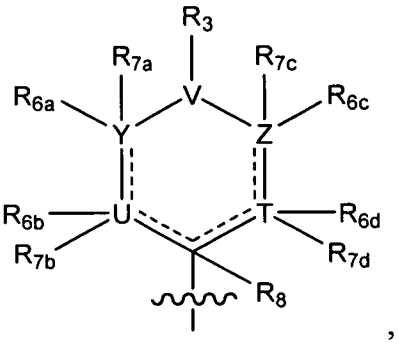
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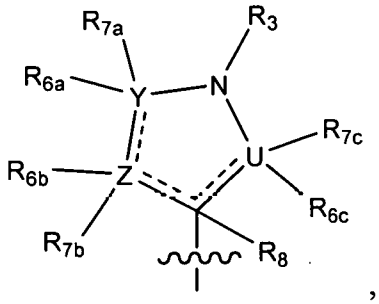
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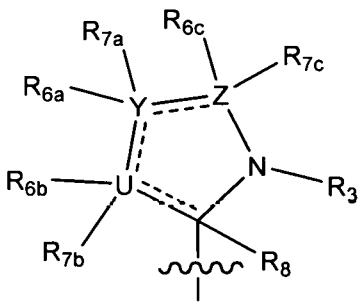
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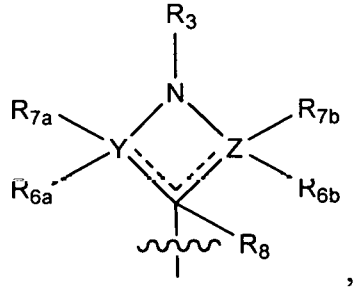
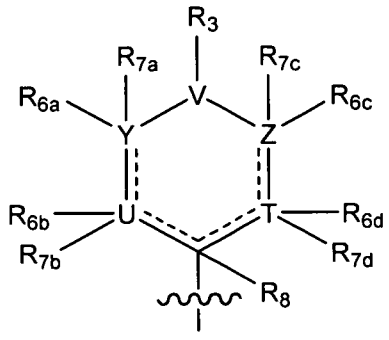

,

wherein

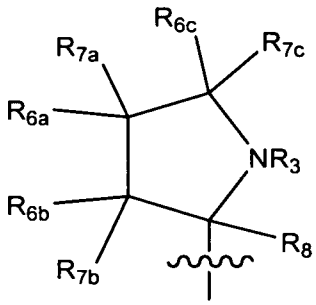
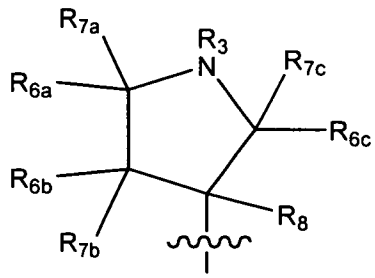
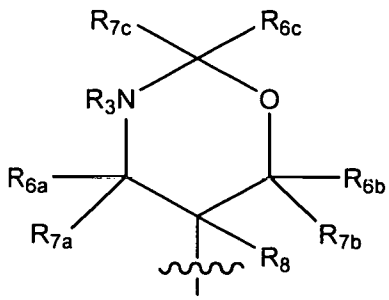
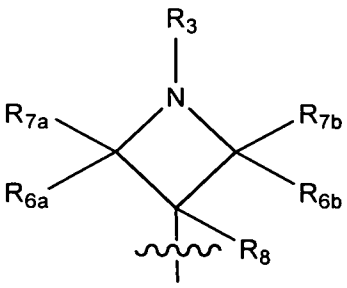
T, U, V, Y, Z are independently selected from the group consisting of –O-, -C-, and -N-; wherein when B is selected from



then at least one of T,U,V,Y,Z are –O- or –N-; R_{6a}, R_{6b}, R_{6c} and R_{6d} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and R_{7a}, R_{7b}, R_{7c} and R_{7d} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and

substituted or unsubstituted C_{1-4} alkoxy; and R_8 is absent, or selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy. In some these embodiments r is 0 or 1. In some embodiments r is 1.

[00130] In some embodiments T, U, Y, and Z are –C- (carbon atom).

[00131] In some embodiments the ring system B is selected from the group consisting of  ,  ,  and  ,wherein R_{6a}, R_{6b}, and R_{6c} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and R_{7a}, R_{7b}, and R_{7c} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; R_8 is selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy; and r is 1; R_{9a} and R_{9b} are hydrogen.

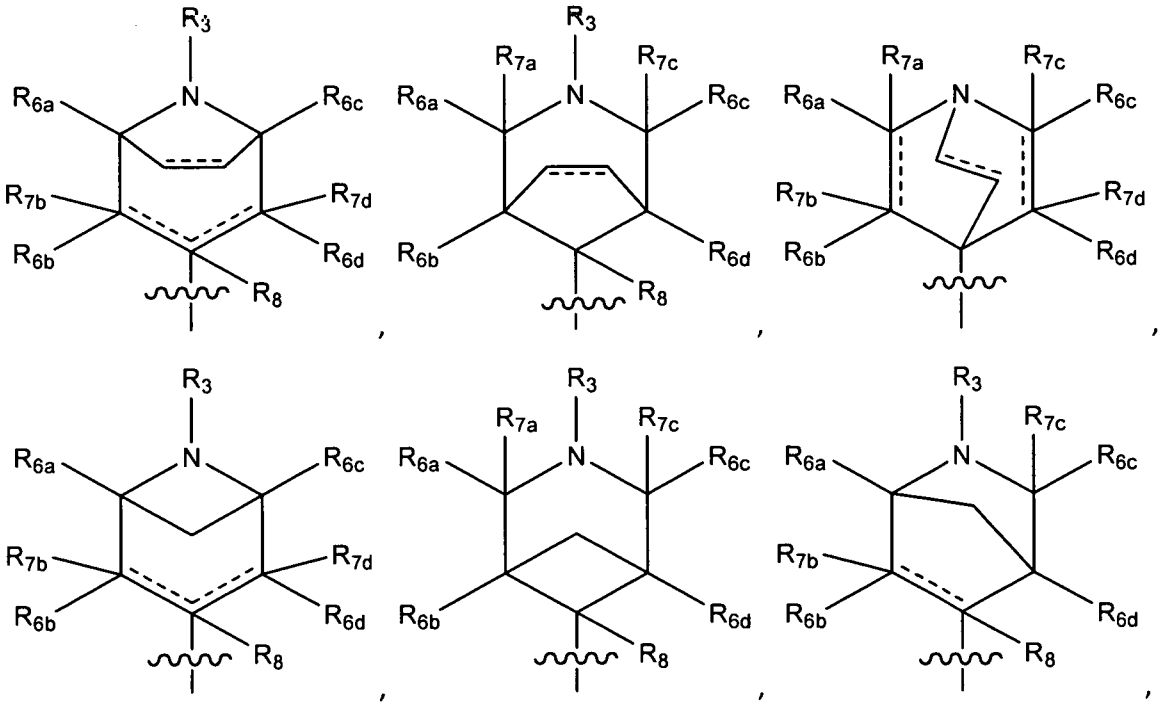
[00132] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the ring system B is selected from the group consisting of a bridged bicyclic ring system, wherein the two rings of the bridged bicyclic ring system share three or more atoms; a fused bicyclic ring system, wherein the two rings share two adjacent atoms; and a spiro bicyclic ring system, wherein the two rings share one atom and ring system, and wherein ring system B is heteroalicyclic. In some embodiments the bicyclic ring

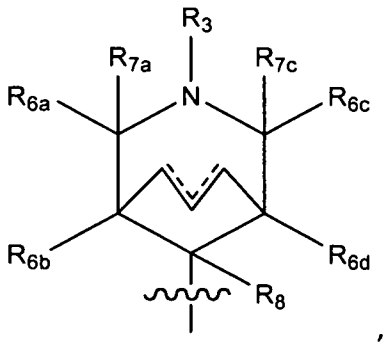
system comprises at least one nitrogen atom. In some embodiments the bicyclic ring system consist of one nitrogen atom as the only heteroatom.

[00133] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the bicyclic ring system is a ring system wherein at least one of the rings in ring system B is selected from the group consisting of a 4-membered ring, 5-membered ring or a 6-membered ring system, such as a 4-membered ring, 5-membered ring or a 6-membered ring system comprising carbon atoms and one nitrogen atom.

[00134] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the bridged bicyclic ring system is a 6-12 membered bicyclic ring system comprising at least one nitrogen atom, such as a ring system consisting of carbon atoms and one nitrogen atom only.

[00135] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the ring system B is selected from the group consisting of





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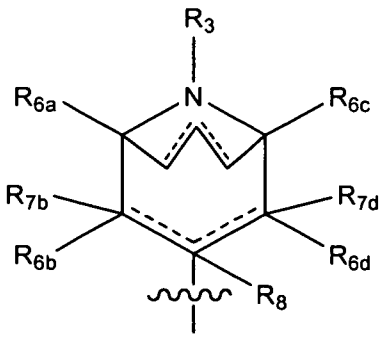

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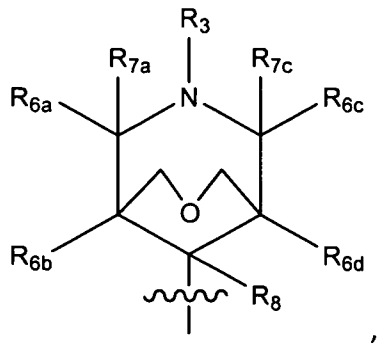

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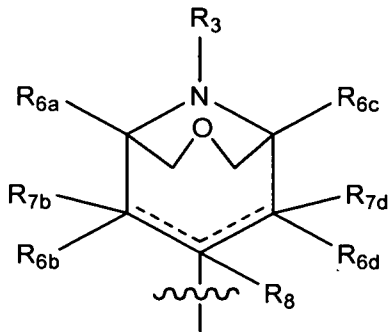

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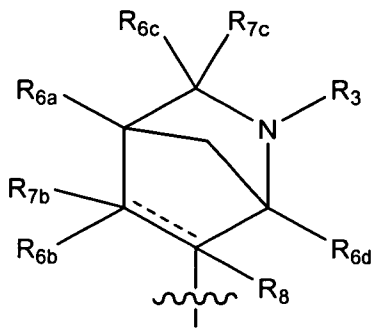

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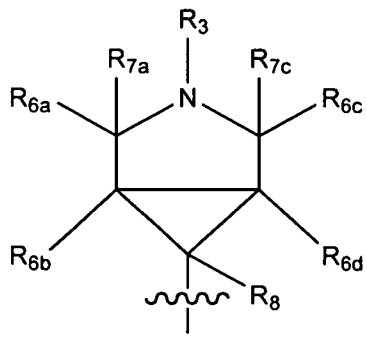
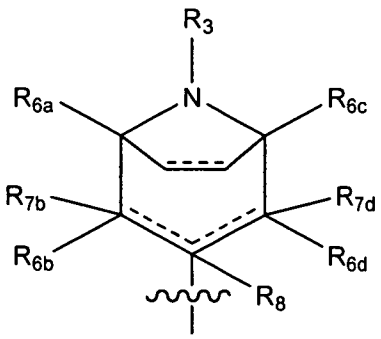


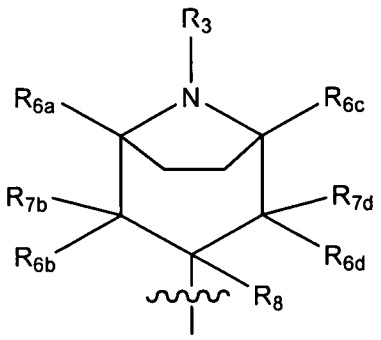
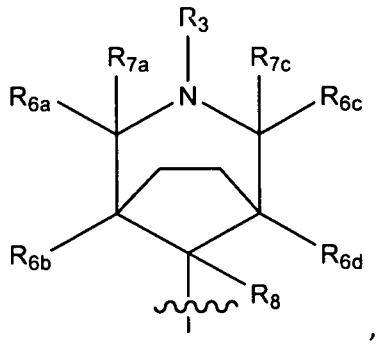
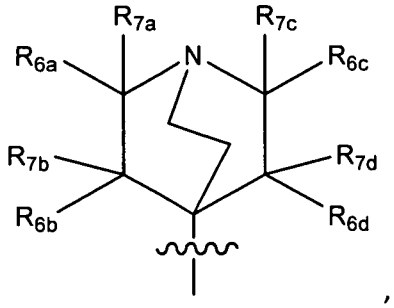
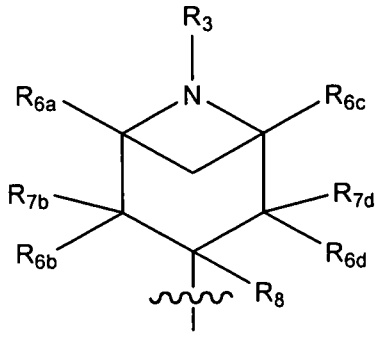
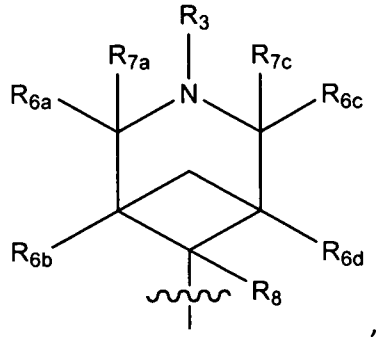
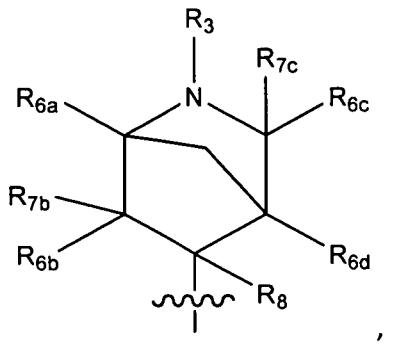
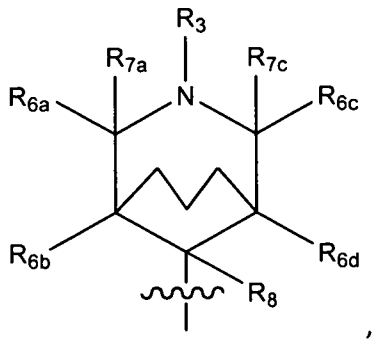
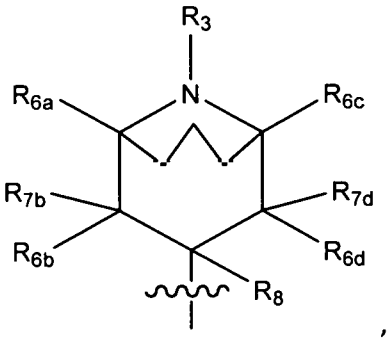
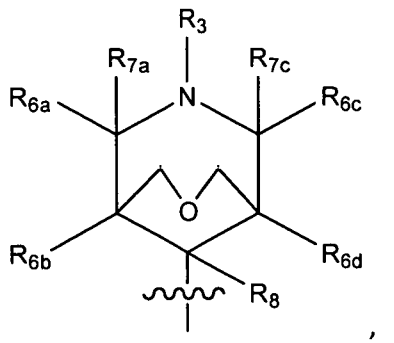
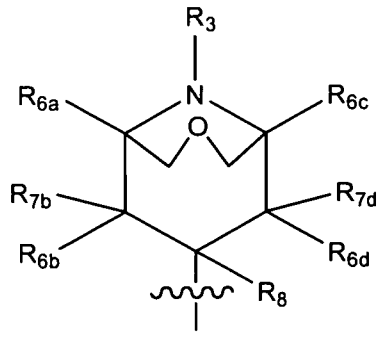
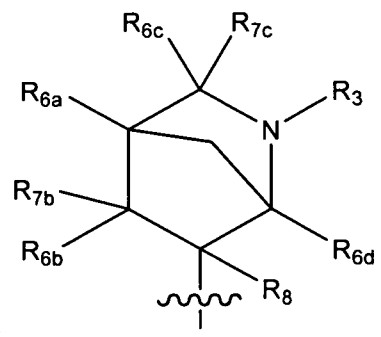
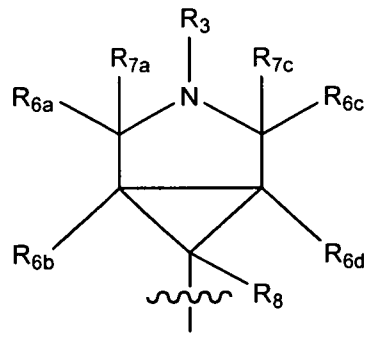
,

wherein R_{6a}, R_{6b}, R_{6c} and R_{6d} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; R_{7a}, R_{7b}, R_{7c} and R_{7d} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; R_8 is absent, or selected from the group consisting of hydrogen, cyano, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy; provided that whenever A is –



(CH_2)- and B is selected from , then R_1 cannot be methyl.

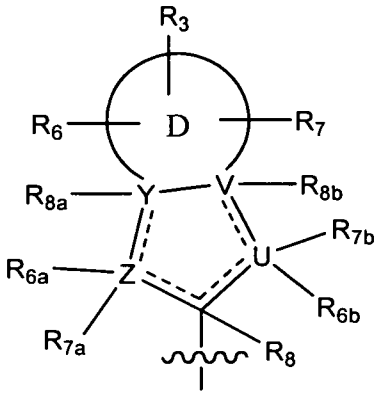
[00136] In some embodiments the ring system B is selected from the group consisting of

Wherein R_{6a}, R_{6b}, R_{6c} and R_{6d} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; R_{7a}, R_{7b}, R_{7c} and R_{7d} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; R_8 is absent, or selected from the group consisting of hydrogen, cyano, -OH, substituted or

unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy.

[00137] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the ring system B is selected from the group consisting of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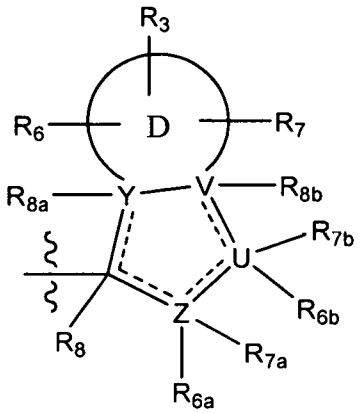
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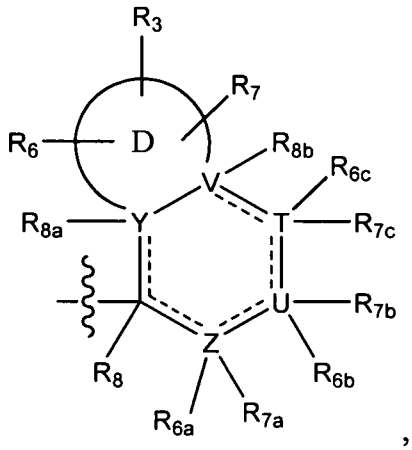
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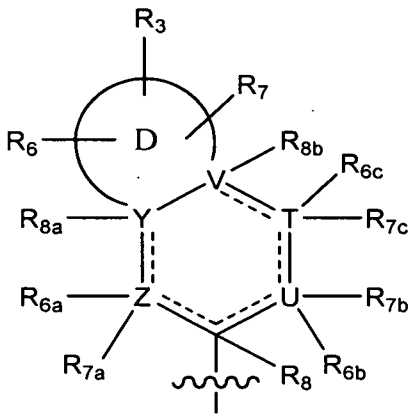
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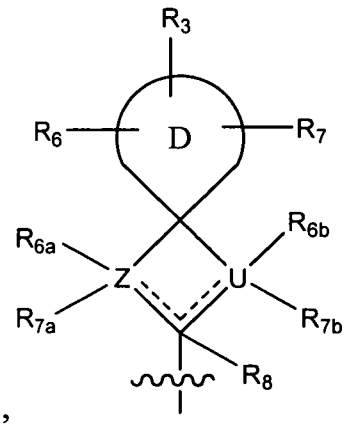
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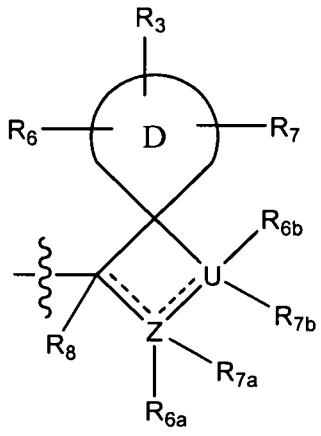
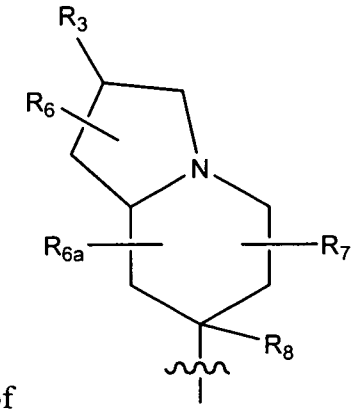
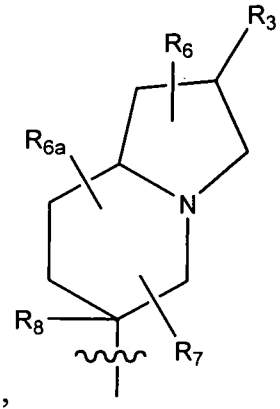
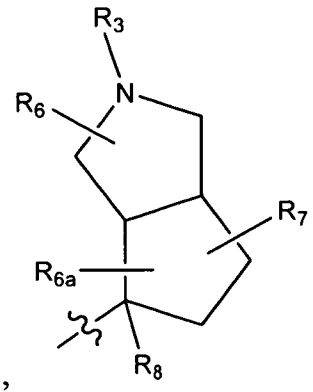
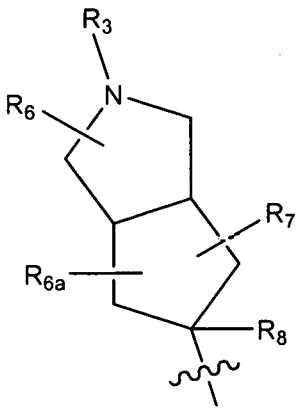
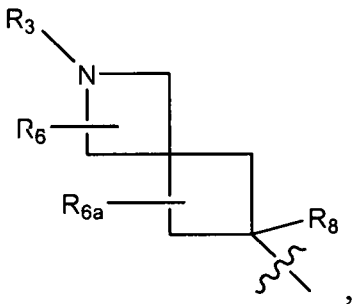
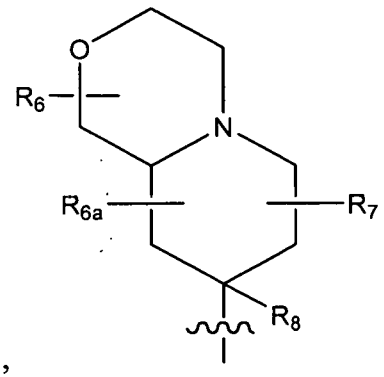
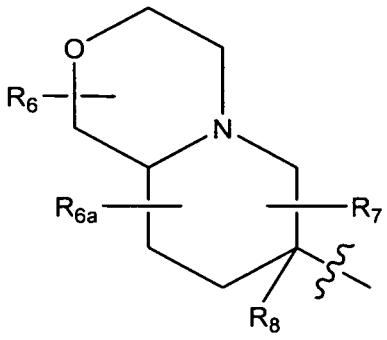


,wherein T, U, V, Y, and Z are independently selected from the group consisting of –O-, -C-, and -N-; R_6, R_{6a}, R_{6b}, R_{6c} and R_6 independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and R_7, R_{7a}, R_{7b}, R_{7c} and R_7 independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and R_{8a}, R_{8b} and R_8 is absent, or selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy; and ring system D is a 4-7 membered heteroalicyclic or heteroaryl ring system comprising at least one nitrogen atom. For example in some embodiments T, U,

V, Y, and Z are independently selected from the group consisting of -C- and -N-; or T, U, and Z are -C-; and V and Y are independently selected from the group consisting of -C- and -N-; or T, U, V, Y, and Z are -C-.

[00138] Some embodiments relate to the ring system B selected from the group consisting of  ,  ,  ,  ,  ,  ,



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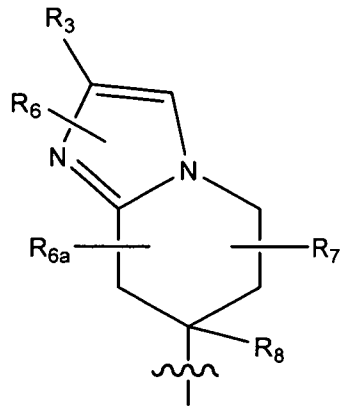
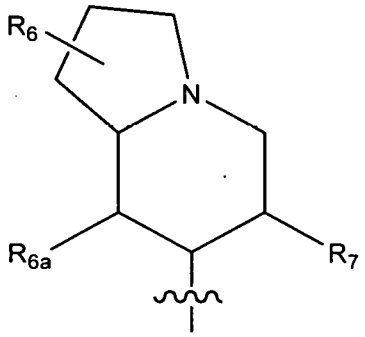


, such as



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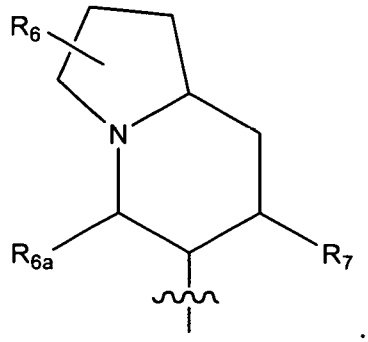
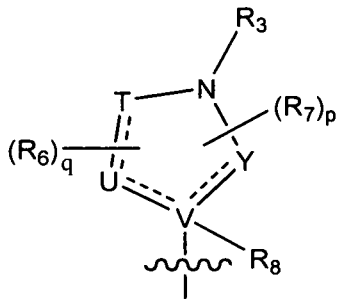


.

[00139] Some embodiments disclosed herein relate to the ring system B being a bicyclic ring system comprising one or more heteroatoms, and it is readily understood by those skilled in the art that the ring systems disclosed herein, such as hereinabove could be combined with other embodiments not explicitly disclosed in combination.

[00140] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the ring system B is selected from the group consisting of



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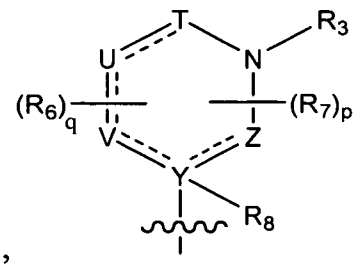

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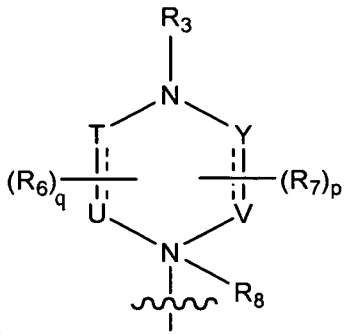
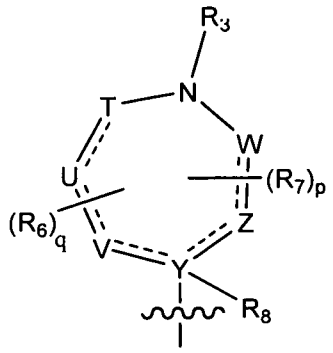
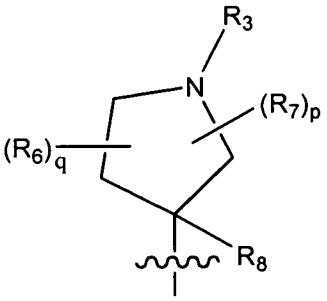


, and



,wherein T, U, V, W, Y, and Z are independently selected from the group consisting of –O-, -C-, and -N-; R_6 is absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; R_7 is absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and R_8 is absent, or selected from the group consisting of hydrogen, cyano, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy. For example T, U, V, W, Y, and Z may independently selected from the group consisting of -C- and -N-.

[00141] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the ring system B



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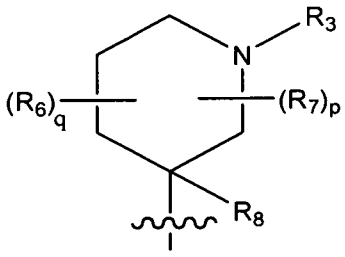

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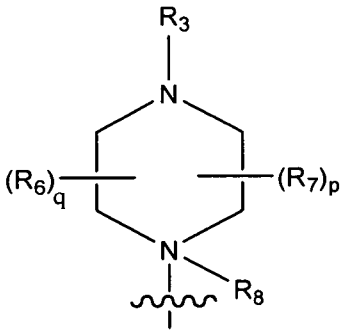
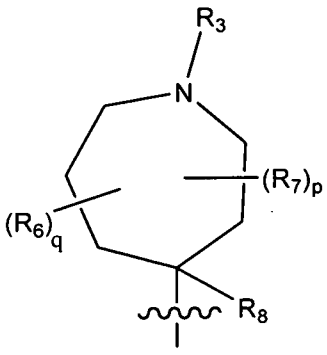
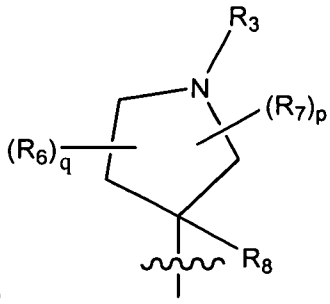
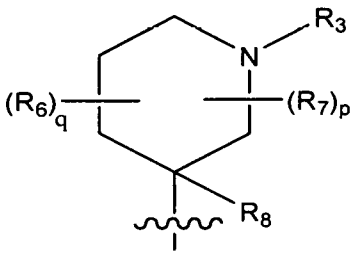
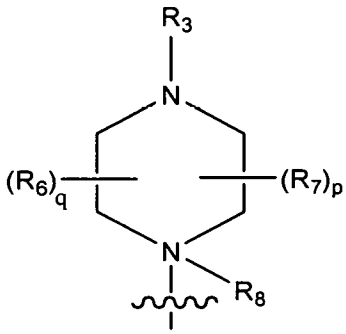
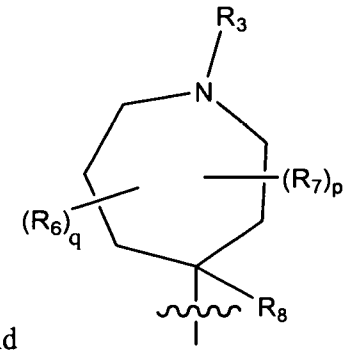


,and

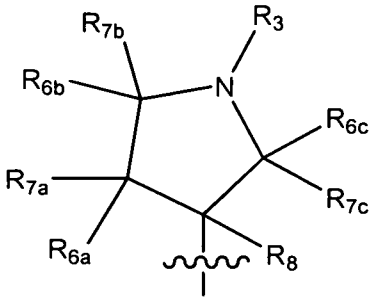
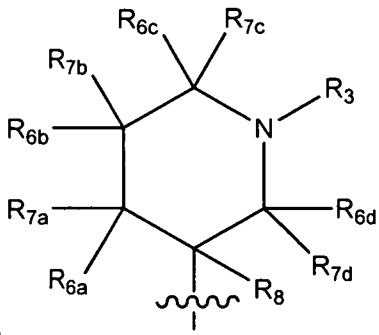
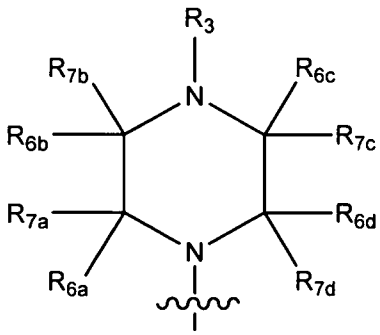
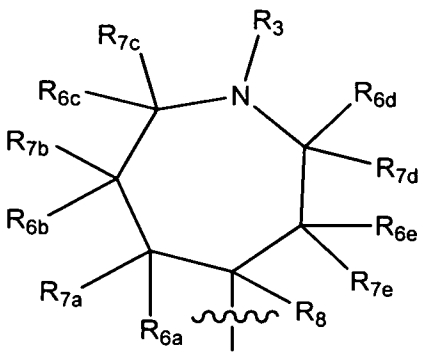


, wherein q and p, independently are 0 or 1.

[00142] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the ring system B  ,

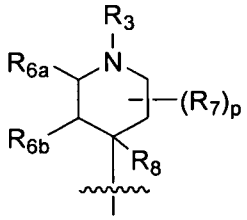
 ,  ,and  , wherein q and p, independently are 0 or 1.

[00143] For example ring system B may be selected from the group consisting of

 ,  ,  , and  , wherein R_{6a}, R_{6b}, R_{6c}, R_{6d}, and R_{6e}, R_{7a}, R_{7b}, R_{7c}, R_{7d} and R_{7e} are independently selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and R_{7a}, R_{7b}, R_{7c}, R_{7d} and R_{7e} are independently selected from the group

consisting of hydrogen, deuterium, halogen, hydroxyl, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and R_8, is selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy.

[00144] Some embodiments relate to compounds of Formula (I), or pharmaceutically acceptable salts, hydrates, solvates, polymorphs, prodrugs, stereoisomers, and deuterated analogues thereof, wherein the ring system B has the following formula

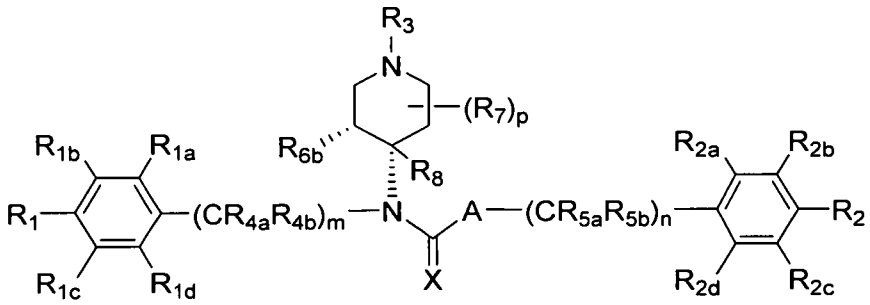


, wherein R_{6a}, and R_{6b} are independently selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy, substituted or unsubstituted aryl; R_7 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, cyano, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; when p is 0 then at least one of R_{6a} and R_{6b} is not hydrogen.

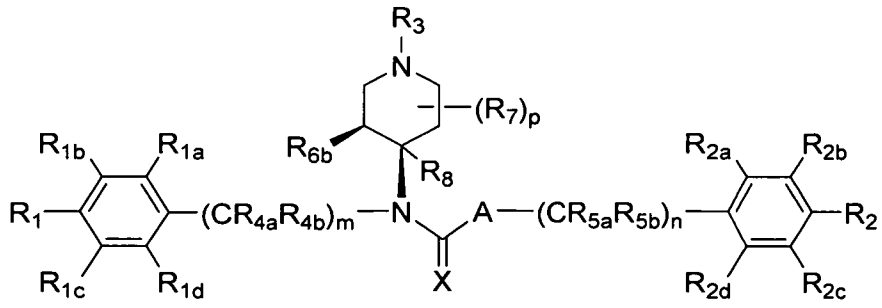
[00145] For example at least one of R_{6a} and R_{6b} is not hydrogen or deuterium; or one of R_{6a} and R_{6b} is selected from halogen, C_{1-4} alkyl and aryl, such as R_{6b} is halogen and R_{6a} is hydrogen, or R_{6b} is fluoro and R_{6a} is hydrogen

[00146] Some embodiments relate to the compound is a compound according to the following Formulae

[00147]



or

[00148]  , wherein R_{6b} is halogen.

[00149] In some of the herein disclosed embodiments R_{8a}, R_{8b} and R_8 (when present in a formula) independently are absent, or selected from the group consisting hydrogen, $-CF_3$, $-CHF_2$, $-CF_2CF_3$, $-OCF_3$, $-OCF_2CF_3$ and $-OCHF_2$. In some embodiments R_{8a}, R_{8b} and R_8 independently are absent or hydrogen,

[00150] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof R_1, R_{1a}, R_{1b}, R_{1c} and R_{1d} independently are selected from the group consisting of hydrogen, halogen, hydroxyl, amino, $-SO_2NH_2$, $-SO_2N(C_{1-4}\text{ alkyl})_2$, $-SO_2-C_{1-4}$ alkyl, $-OC(=O)-C_{1-4}$ alkyl, $-S(C_{1-6}$ alkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-3} alkyl and deuterated analogues thereof.

[00151] In some embodiments R_{1a}, R_{1b}, R_{1c} and R_{1d} independently may be selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, $-SO_2NH_2$, $-SO_2CH_3$, $-OC(=O)CH_3$, methyl, $-CD_3$, methoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$, such as hydrogen, deuterium, halogen, hydroxyl, methyl, $-CD_3$, methoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$.

[00152] In some embodiments wherein R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, methyl, $-CD_3$, methoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$, such as hydrogen or fluoro.

[00153] In some embodiments R_1 is selected from the group consisting of halogen, amino, 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, for example R_1 may be selected from fluoro, chloro, methoxy, $-OCF_3$, $-CF_3$ and methyl.

[00154] In many embodiments R_1 is fluoro, and R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, methyl, $-CD_3$, methoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$, such as hydrogen or fluoro. For example R_1 is fluoro; R_{1d} is hydrogen or fluoro and R_{1a}, R_{1b}, and R_{1c} are hydrogen.

[00155] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof 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_{1-6} haloalkoxy, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-3} alkyl and deuterated analogues thereof; or R_2 and R_{2b}, taken together with the phenyl ring they attach to and the atoms to which they are attached form a bicyclic fused ring system.

[00156] In some embodiments R_{2a}, R_{2c}, R_{2d}, and R_{2b} independently are selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, methyl, $-CD_3$, methoxy, $-OCD_3$,$-OCF_3$ and $-CF_3$.

[00157] In some embodiments R_{2a}, R_{2c} and R_{2b} are hydrogen, and R_{2d} is hydrogen, fluoro or hydroxyl, for example R_{2a}, R_{2c}, R_{2b} and R_{2d} are hydrogen.

[00158] In some embodiments 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, optionally deuterated methoxy, optionally deuterated ethoxy, optionally deuterated n-propoxy, optionally deuterated isopropoxy, optionally deuterated allyloxy, optionally deuterated prop-2-yn-1-yloxy, optionally deuterated n-butoxy, optionally deuterated iso-butoxy, optionally deuterated tert-butoxy, optionally deuterated pentyl-oxy, optionally deuterated 4-methyl-butoxy, optionally deuterated hexyl-oxy, optionally deuterated 4-methylpentoxy, optionally deuterated cyclopropyloxy, optionally deuterated cyclopropylmethoxy, optionally deuterated cyclopropylethoxy, optionally deuterated cyclobutyloxy, optionally deuterated cyclobutyloxy, optionally deuterated cyclobutylmethoxy, optionally deuterated cyclobutylethoxy, optionally deuterated C_{1-6} haloalkoxy, $-OCF_3$, $-OCF_2CF_3$, $-OCHF_2$, $-OCDF_2$, $-CF_3$, $-CF_2CF_3$, $-CHF_2$, CDF_2 $-CH_2CF_3$, $-CD_2CF_3$, $-CF_2$, 1,1,2,2-tetrafluorobutyl and 1,1,1,2,2-pentafluorobutyl. For example R_2 may be selected from methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, prop-2-yn-1-yloxy, n-

butoxy, iso-butoxy, tert-butoxy, pentyl-oxy, 4-methyl-butoxy, hexyl-oxy, 4-methylpentoxy, cyclopropyloxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutyloxy, cyclobutylmethoxy, cyclobutylethoxy, 2-fluoroethoxy, 3-fluoropropoxy, 4-fluoroethoxy, -OCF_3 and (1,3-difluoropropan-2-yl)oxy.

[00159] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof 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 $-(CH_2)_s-C_{2-5}$ heteroalicyclyl, 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. R_3 may for example be selected from hydrogen, methyl, $-CD_3$. ethyl, $-CD_2CD_3$, n-propyl, $-CD_2CD_2CD_3$, iso-propyl, cyclopropyl, cyclobutyl, $-CDCD_3CD_3$, $-CH_2CH_3OH$, $-(CR_{9c}R_{9d})_tC(=O)OR_{9e}$ and $-(CH_2)_tC(=O)NR_{9c}R_{9d}$, wherein R_{9c} ,R_{9d}, and R_{9e} independently are hydrogen or C_{1-4}-alkyl, wherein each t is selected from the group consisting of 0, 1, 2 and 3. Many embodiments disclosed herein relates to R_3 being hydrogen or methyl.

[00160] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof R_{4a}, R_{4b}, R_{5a}, R_{5b}, R_{5c} and R_{5d}, when present, are independently hydrogen or methyl. For example all of R_{4a}, R_{4b}, R_{5a}, R_{5b}, R_{5c} and R_{5d} are hydrogen when said R-group is present.

[00161] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof R_6, R_{6a}, R_{6b}, R_{6c}, R_{6d}, and R_{6e} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, and substituted or unsubstituted C_{1-4} alkyl. For example R_6 is hydrogen or fluoro, or R_{6a}, R_{6b}, R_{6c}, R_{6d}, and R_{6e} independently are absent or selected from the group consisting of hydrogen, fluoro, methyl and methoxy. Additional examples are R_{6a}, R_{6b}, R_{6c}, R_{6d}, and R_{6e} are independently selected from the group consisting of from fluoro, methyl and methoxy, and the others are hydrogen or absent.

[00162] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof R_7, R_{7a}, R_{7b}, R_{7c}, R_{7d} and R_{7e}, independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, methyl and methoxy. In many embodiments R_7, R_{7a}, R_{7b}, R_{7c}, R_{7d} and R_{7e} are absent.

[00163] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof one R_6 (e.g. R_{6b}) is fluoro or hydrogen and any other R_6 are absent or hydrogen, and p is zero, i.e. no R_7 group is present.

[00164] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof R_8 R_{8a}, and R_{8b} independently are absent or selected from the group consisting of hydrogen, halogen, methyl, ethyl, propyl, methoxy, ethoxy, C_{1-2}- haloalkyl, and C_{1-2}- haloalkoxy; such as hydrogen, $-CF_3$, $-CHF_2$, $-CF_2CF_3$ $-OCF_3$, $-OCF_2CF_3$ and $-OCHF_2$. In many embodiments R_8 is hydrogen.

[00165] In some embodiments R_8 (when present) is hydrogen, R_6 hydrogen or fluoro, and no R_7 group is present irrespectively of which heteroalicyclic ring system B disclosed herein is selected. Examples are ring system B selected from 4, 5, 6 or 7 membered rings comprising at least one nitrogen atom (e.g. monocyclic nitrogen containing heteroalicyclic ring system, such as a 4-7 membered ring system, and provided that when B is a substituted or unsubstituted piperidyl-4-yl or unsubstituted 1-phenylmethyl pyrrolidin-3-yl R_{6b} is not hydrogen); bridged heteroalicyclic bicyclic ring system, wherein the two rings share three or more atoms, comprising at least one nitrogen atom; fused heteroalicyclic bicyclic ring system, wherein the two rings share two adjacent atoms, a spiro heteroalicyclic bicyclic ring system, wherein the two rings share one atom, comprising at least one nitrogen atom.

[00166] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof E is N (i.e. a nitrogen atom).

[00167] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof A is "-C(=O)–NH-" or "-C(=O)-O-"., in many embodiments A is "–C(=O)-NH-".

[00168] In some of the herein disclosed formulae or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof r is 0 or 1, and/or m and n independently are selected from 0 and 1, such as m is 1 and n is 0 or 1; and/or p and q independently are selected from 0 and 1.

[00169] The embodiments presented herein are considered exemplifying embodiments and each embodiment could be combined with any other embodiments as long as the compound is a compounds Formula (I) or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof. For example, ring

system B may be selected from any of the option presented herein, and q is 0 or 1 and p is 0; R_3 is hydrogen or methyl; E is N; A is "–C(=O)-NH-"; R_{4a}, R_{4b}, R_{5a}, R_{5b} are hydrogen and m and n are 1; r is 0 (i.e. a bond); R_{1a}, R_{1b}, and R_{1c} are hydrogen R_{1d} is hydrogen or fluoro; R_1 is fluoro; R_{2a}, R_{2b}, R_{2c} are and R_{2d} are hydrogen; and R_2 is selected from the group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, prop-2-yn-1-yloxy, n-butoxy, iso-butoxy, tert-butoxy, pentyl-oxy, 4-methyl-butoxy, hexyl-oxy, 4-methylpentoxy, cyclopropyloxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutyloxy, cyclobutylmethoxy, cyclobutylethoxy, 2-fluoroethoxy, 3-fluoropropoxy, 4-fluoroethoxy, -OCF_3 and (1,3-difluoropropan-2-yl)oxy.

[00170] 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 Formulas (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, Extrapyramidal 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, 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, Pancreatis, Panic attacks, Parkinson's disease, Parkinson's disease psychosis, Periodic limb movement during sleep (PLMS), Peripheral vascular disease, Pituitary tumor, Postherpetic neuralgia, Progressive Supranucelar 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.

[00171] 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.

[00172] 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.

[00173] 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.

[00174] 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

[00175] 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; b s, broad singlet or combinations thereof, including but not limited to dd, doublet of doublets and dt, doublet of triplet.

[00176] 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

[00177] 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

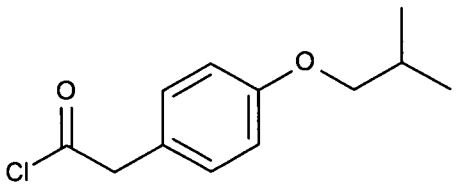
[00178] The following abbreviations are used

EtOAc	Ethylacetate
DIEA	N,N-Diisopropylethylamine
HCl	Hydrochloric acid
DMF	N,N-dimethylformamide
THF	Tetrahydrofuran
$CDCl_3$	Chloroform-d
DMSO-D6	Dimethylsulfoxide-d6
$MgSO_4$	Magnesium Sulfate
$POCl_3$	Phosphorus(V) oxychloride
KOH	Potassium hydroxide
NaOH	Sodium hydroxide
Na_2SO_4	Sodium Sulfate

K_2CO_3	Potassium carbonate
Na_2CO_3	Sodium carbonate
TFA	Trifluoroacetic acid
Boc	*t*-butoxycarbonyl
FMOC	Fluorenylmethyloxycarbonyl
FMOC-Cl	9-Fluorenylmethoxycarbonyl chloride
TEOC	2-(trimetylsilyl)ethoxycarbonyl
equiv.	equivalents
min	minutes
cat	catalytical
HCl	hydrochloric acid
HPLC	high performance liquid chromatography

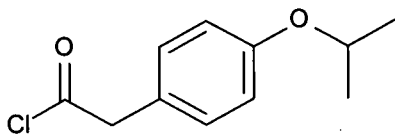
[00179] Preparation of starting materials and intermediate compounds

[00180] Intermediate 1: 2-[4-(2-methylpropoxy)phenyl]acetyl chloride

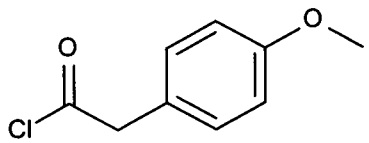


[00181] Thionyl chloride (21.6 ml, 298 mmol) was added to 2-[4-(2-methylpropoxy)phenyl]acetic acid (6.21 g, 29.8 mmol) in dichloromethane (29.8 ml). The mixture was stirred at ambient temperature for 18 hours before it was concentrated to afford the title compound (6.77 g, 100%).

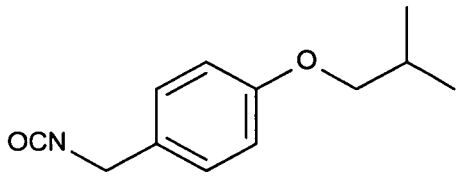
[00182] Intermediate 2: 2-[4-(propan-2-yloxy)phenyl]acetyl chloride was prepared in analogy with intermediate 1 using 2-[4-(propan-2-yloxy)phenyl]acetic acid.



[00183] Intermediate 3: 2-(4-methoxyphenyl)acetyl chloride was prepared in analogy with intermediate 1 using 2-(4-methoxyphenyl)acetic acid

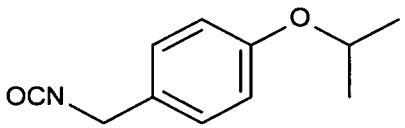


[00184] Intermediate 4: 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene

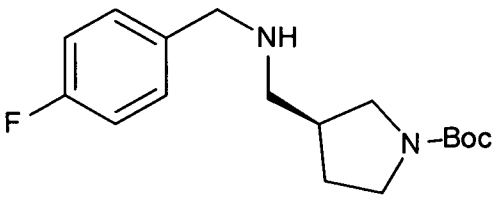


[00185] 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (6.12 g, 27 mmol) was dissolved in acetone (8 ml) and the resulting solution was added over 10 minutes to sodium azide (2.46 g, 37.8 mmol) in water (8 ml). After stirring for additionally 1 hour the mixture was diluted with water and extracted with toluene (3 x 25 ml). The organic phase was dried using sodium sulfate and filtered. The filtrate was gently concentrated to about 25 ml. The mixture was stirred at 65 °C for 20 minutes before it was concentrated to afford the title compound (5.41 g, 98%).

[00186] Intermediate 5: 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene was prepared in analogy with intermediate 4 using 2-[4-(propan-2-yloxy)phenyl]acetyl chloride.



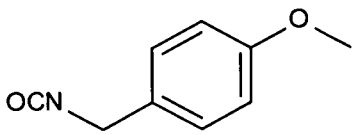
[00187] Intermediate 6: tert-butyl (3S)-3-({[(4-fluorophenyl)methyl]amino}methyl)-pyrrolidine-1-carboxylate



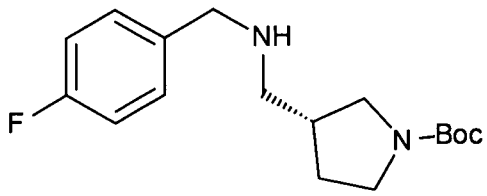
[00188] 4-fluorobenzaldehyde (268 µl, 2.5 mmol) was added to a solution of tert-butyl (3S)-3-(aminomethyl)pyrrolidine-1-carboxylate (501 mg, 2.5 mmol) in ethanol (5 ml). After 1 hour of stirring at ambient temperature sodium triacetoxyborohydride (795 mg, 3.75 mmol) was added. After additionally 18 hours of stirring the mixture was 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 using a phase separator and

concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting with 5-10% methanol in dichloromethane to afford the title compound (619 mg, 80%).

[00189] Intermediate 7: 1-(isocyanatomethyl)-4-methoxybenzene was prepared in analogy with intermediate 4 using 2-(4-methoxyphenyl)acetyl chloride

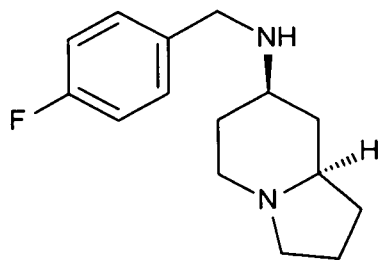


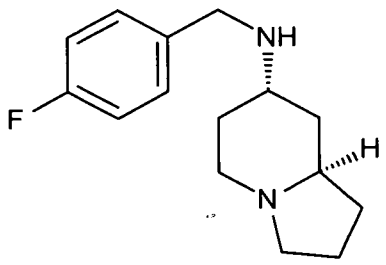
[00190] Intermediate 8: tert-butyl (3R)-3-({[(4-fluorophenyl)methyl]amino}methyl)-pyrrolidine-1-carboxylate



[00191] The compound was prepared in analogy with intermediate 6 using tert-butyl (3R)-3-(aminomethyl)pyrrolidine-1-carboxylate.

[00192] Intermediate 9: (7R,8aR)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine and (7S,8aR)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine

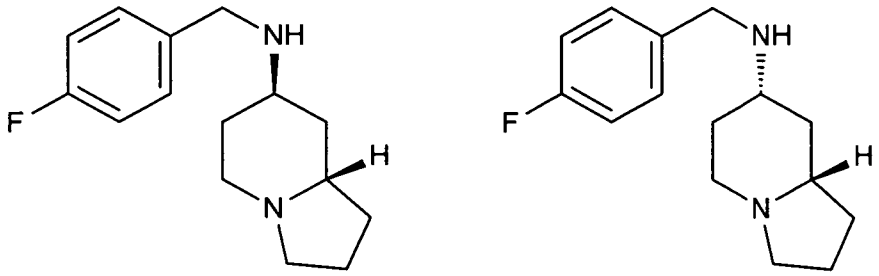




[00193] To a mixture of 4-fluorobenzylamine (438 mg, 3.5 mmol) and (8aR)-octahydroindolizin-7-one (0.5 g, 3.5 mmol) in ethanol (50 ml) sodium triacetoxyborohydride (1.48 g, 7 mmol) was added at ambient temperature under nitrogen atmosphere. After stirring for 1 hour the mixture was evaporated to a solid and redissolved in ethyl acetate and water. The water phase was separated and washed with ethyl acetate. To the water phase was added sodium hydroxide (aqueous, 2M) and mixture was extracted with ethyl acetate. The organic

phase was dried with magnesium sulfate and concentrated. The crude material was purified by HPLC, eluting with 5-25% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford (7R,8aR)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine (50 mg, faster eluting compound) and (7S,8aR)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine (30 mg, slower eluting compound).

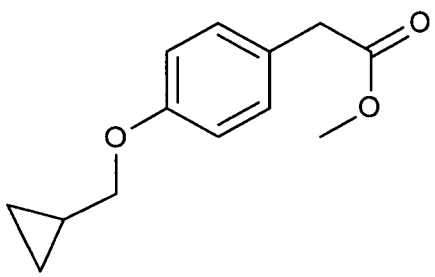
[00194] Intermediate 10: (7R,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine and (7S,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine



[00195] To a mixture of 4-fluorobenzylamine (438 mg, 3.5 mmol) and (8aS)-octahydro-indolizin-7-one (0.5 g, 3.5 mmol) in ethanol (50 ml) sodium triacetoxyborohydride (1.48 g, 7 mmol) was added at ambient temperature under nitrogen atmosphere. After stirring for 1 hour the mixture was evaporated to a solid and redissolved in ethyl acetate and water. The water phase was separated and washed with ethyl acetate. To the water phase was added sodium hydroxide (aqueous, 2M) and mixture was extracted with ethyl acetate. The organic phase was dried with magnesium sulfate and concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 4% methanol in dichloromethane with 3% triethylamine to afford (7R,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine (47 mg, faster eluting compound) and (7S,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine (35 mg, slower eluting compound).

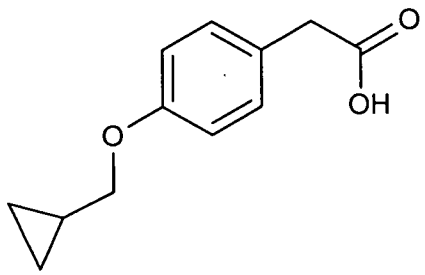
[00196] Intermediate 11: 2-[4-(Cyclopropylmethoxy)phenyl]acetic acid

[00197] Methyl 2-[4-(cyclopropylmethoxy)phenyl]acetate



[00198] Methyl 2-(4-hydroxyphenyl)acetate (1.05 g, 6.33 mmol), (chloromethyl)cyclopropane (1.33 ml, 13.9 mmol) and tetrabutylammonium iodide (350 mg, 945 μmol) were added to potassium carbonate (1.75 g, 12.6 mmol) in dimethylformamide (10 ml). The mixture was heated to 80 °C for 4 days before it was diluted with water (40 ml) and extracted with diethyl ether (3 x 50 ml). The organic phase was washed with water (2 x 100 ml), dried (sodium sulfate), filtered and concentrated to yield the desired ether (1.32 g).

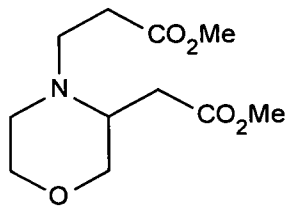
[00199] 2-[4-(Cyclopropylmethoxy)phenyl]acetic acid



[00200] Sodium hydroxide (5M, aqueous, 4.76 ml, 23.8 mmol) was added dropwise to methyl 2-[4-(cyclopropylmethoxy)phenyl]acetate (1.31 g, 5.95 mmol) in methanol (30 ml). After 4 hours of stirring at ambient temperature the mixture was acidified with hydrochloric acid (5M, aqueous, 4.85 ml, 24.3 mmol) and extracted with diethyl ether (3 x 50 ml). The organic phase was washed with water (4 x 50 ml), dried (sodium sulfate), filtered and concentrated to yield the desired acid (1.16 g).

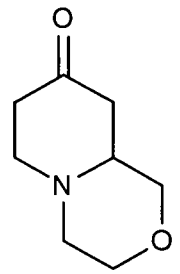
[00201] Intermediate 12: Octahydropyrido[2,1-c]morpholin-8-one

[00202] Methyl 3-[3-(2-methoxy-2-oxoethyl)morpholin-4-yl]propanoate



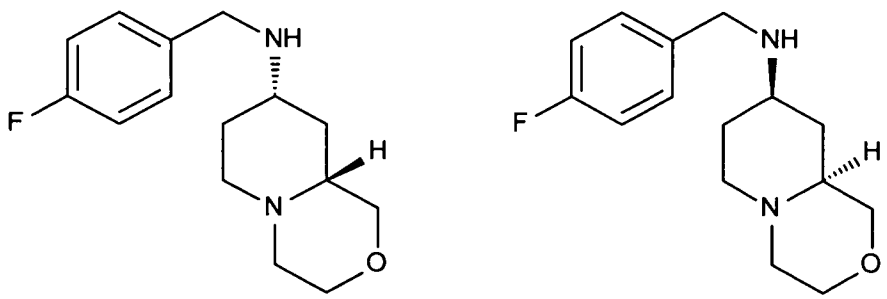
[00203] A mixture of methyl 2-(morpholin-3-yl)acetate hydrochloride (2 g, 10.2 mmol), methyl prop-2-enoate (1.389 ml, 15.31 mmol) and triethylamine (2.85 ml, 20.4 mmol) in methanol (50 ml) was stirred for 24 hours at ambient temperature. Solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (10 ml), washed with brine, dried and concentrated to yield the diester (1.72 g, 68.6%), which was used directly in the next step without further purification.

[00204] Octahydropyrido[2,1-c]morpholin-8-one



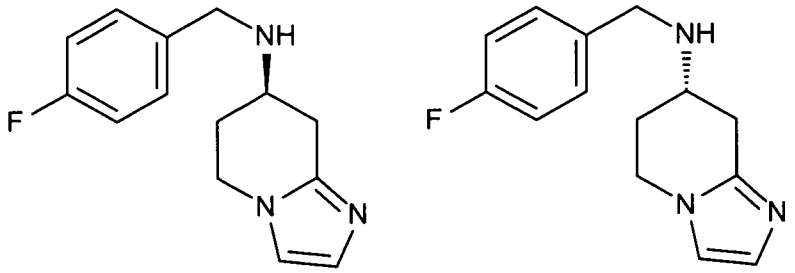
[00205] A solution of methyl 3-[3-(2-methoxy-2-oxoethyl)morpholin-4-yl]propanoate (1.72 g, 6.93 mmol) in tetrahydrofuran (30 mL) was cooled to -78 °C and treated with lithium bis(trimethylsilyl)amide in tetrahydrofuran (1M, 13.9 mL, 13.9 mmol). After stirring for 4 hours the mixture was allowed to warm to ambient temperature, quenched with sodium bicarbonate (aqueous, saturated, 5 ml), extracted with ethyl acetate (3 x 20 ml), washed with brine, dried and concentrated. Hydrochloric acid (concentrated, 15 ml) was added and the mixture was heated to 50 °C. After 12 hours the mixture was allowed to cool to ambient temperature, treated with sodium hydroxide (5M, aqueous, 50 ml) and extracted with ethyl acetate (3 x 15 ml). The organic phase was dried and concentrated to yield the desired ketone (750 mg, 70%).

[00206] Intermediate 13: (8R,9aS)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine and (8S,9aR)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine



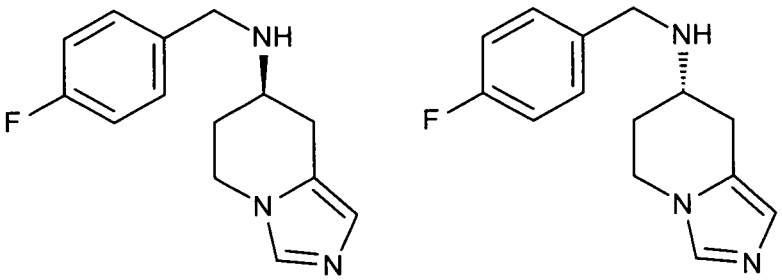
[00207] The compounds were prepared in analogy with tert-butyl (3S)-3-({[(4-fluorophenyl)methyl]amino}methyl)pyrrolidine-1-carboxylate using octahydropyrido[2,1-c]morpholin-8-one and 4-fluorobenzylamine. Isolated as a racemic mixture. Yield: 680 mg, 65%.

[00208] Intermediate 14: (7R)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-amine and (7S)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-amine



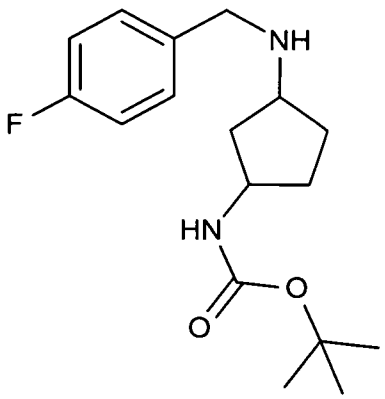
[00209] To 5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-amine (1 equivalent) and 4-fluorobenzaldehyde (1 equivalent) in dichloromethane at room temperature was added sodium triacetoxyborohydride (2 equivalents) in portions. The mixture was stirred for 4 hours, then sodium hydroxide (aqueous, 5 M) was added. The resulting mixture was stirred for 1 hour and then partitioned between diethyl ether and water. The organic phase was collected, the aqueous phase was extracted once again with diethyl ether. The combined organic phases were dried and evaporated to give the desired intermediate as an oil.

[00210] Intermediate 15: (7R)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-amine; (7S)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-amine



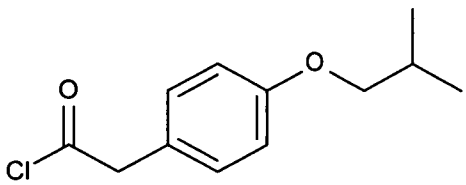
[00211] To 5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-amine (1 equivalent) and 4-fluorobenzaldehyde (1 equivalent) in dichloromethane at room temperature was added sodium triacetoxyborohydride (2 equivalents) in portions. The mixture was stirred for 4 hours, then sodium hydroxide (aqueous, 5 M) was added. The resulting mixture was stirred for 1 hour and then partitioned between diethyl ether and water. The organic phase was collected, the aqueous phase was extracted once again with diethyl ether. The combined organic phases were dried and evaporated to give the desired intermediate as an oil.

[00212] Intermediate 16: tert-butyl N-(3-{[(4-fluorophenyl)methyl]amino}-cyclopentyl)carbamate



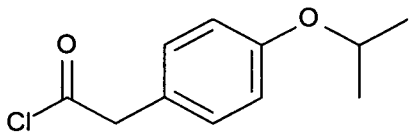
[00213] To (4-fluorophenyl)methanamine (1 equivalent) and tert-butyl N-(3-oxocyclopentyl)carbamate (1 equivalent) in ethanol at room temperature was added sodium triacetoxyborohydride (2 equivalents) in portions. The mixture was stirred for 4 hours, then sodium hydroxide (aqueous, 5 M) was added. The resulting mixture was stirred for 1 hour and then partitioned between diethyl ether and water. The organic phase was collected, the aqueous phase was extracted once again with diethyl ether. The combined organic phases were dried and evaporated to give the desired intermediate as an oil. Yield 57 %.

[00214] Intermediate 17: 2-[4-(2-methylpropoxy)phenyl]acetyl chloride

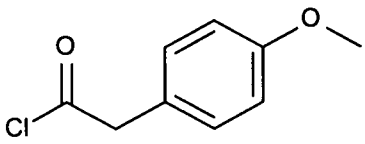


[00215] Thionyl chloride (21.6 ml, 298 mmol) was added to 2-[4-(2-methylpropoxy)phenyl]acetic acid (6.21 g, 29.8 mmol) in dichloromethane (29.8 ml). The mixture was stirred at ambient temperature for 18 hours before it was concentrated to afford the title compound (6.77 g, 100%).

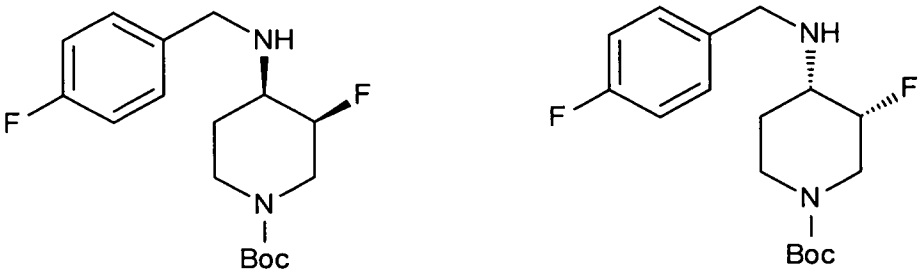
[00216] Intermediate 18: 2-[4-(propan-2-yloxy)phenyl]acetyl chloride was prepared in analogy with intermediate 17 using 2-[4-(propan-2-yloxy)phenyl]acetic acid



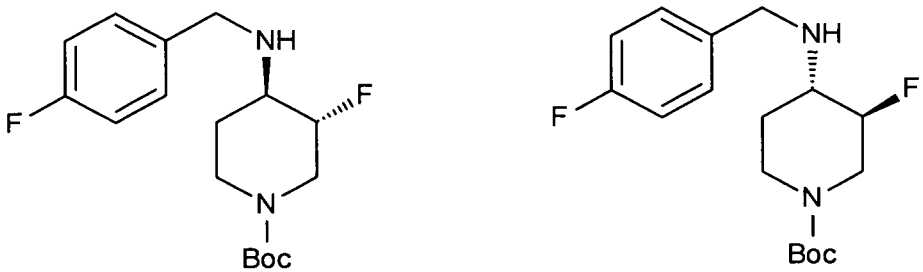
[00217] Intermediate 19: 2-(4-methoxyphenyl)acetyl chloride was prepared in analogy with intermediate 17 using 2-(4-methoxyphenyl)acetic acid



[00218] Intermediate 20: 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



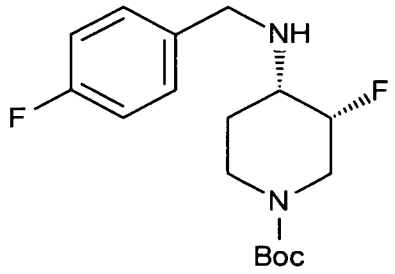
[00219] Intermediate 21: tert-butyl (3R,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}-piperidine-1-carboxylate and tert-butyl (3S,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}-piperidine-1-carboxylate



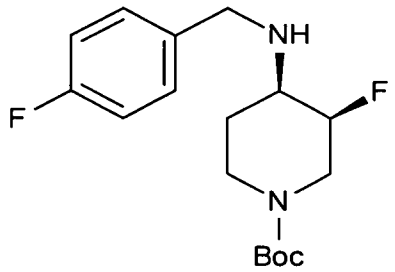
[00220] To a mixture of (4-fluorophenyl)methanamine (1.07 mL, 9.44 mmol) and tert-butyl 3-fluoro-4-oxopiperidine-1-carboxylate (1.87 g, 8.58 mmol) in dichloromethane (35 ml) sodium triacetoxyborohydride (2.73 g, 12.9 mmol) was added in portions over 20 minutes and stirring was continued for 1 hour at room temperature. The reaction was diluted with sodium hydrogen carbonate (saturated, aqueous, 100 ml) and extracted with dichloromethane (3 x 50 ml). The organic phase was dried (phase-separator) and concentrated. The crude (3 g) was purified by column chromatography using silicon dioxide gel, eluting with 30% ethyl acetate in petroleum ether to afford (2.2 g, 78%) of 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 as the racemic mixture and (0.25g, 9%) of tert-butyl (3R,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate

and tert-butyl (3S,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate as the racemic mixture.

[00221] Intermediate 22: tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}-piperidine-1-carboxylate

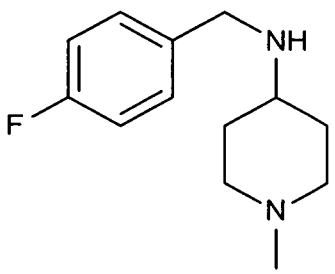


[00222] Intermediate 23: tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}-piperidine-1-carboxylate



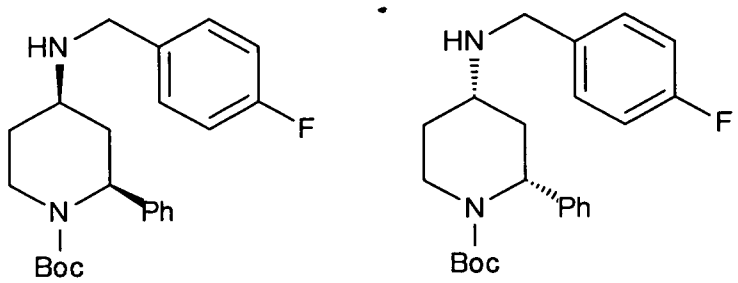
[00223] Intermediate 22 and intermediate 23 were purified from intermediate 21 by chiral chromatography using a Daicel IA column eluting with petroleum-ether (boiling point 40-65 °C): ethanol: methanol with ratio 95: 2.5: 2.5 modified with diethylamine 0,1% to give tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate as the faster eluting enantiomer and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate as the slower eluting enantiomer.

[00224] Intermediate 24: N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine



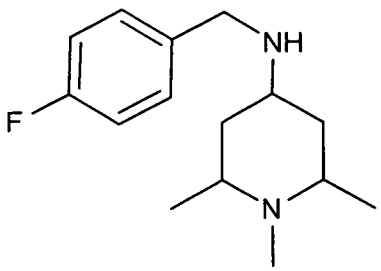
[00225] 4-fluorobenzylamine (80.8 mmol, 10.4 g) was dissolved in ethanol (80 ml) and N-methyl-4-piperidone (80.8 mmol, 9.43 g) was added. Sodium triacetoxyborohydride (161.6 mmol, 35.4 g) was added in portions and the mixture was stirred at room temperature for 4 hours. Sodium hydroxide (aqueous, 5M) was added until pH> 13 and the resulting mixture was stirred for 1 hour and then partitioned between diethyl ether and water. The organic phase was collected and the aqueous phase was extracted once again with diethyl ether. The combined organic phases were dried and evaporated to give the desired intermediate as a yellow oil (17.48 g, 97 %).

Intermediate 25: tert-butyl (2R,4S)-4-{[(4-fluorophenyl)methyl]amino}-2-phenylpiperidine-1-carboxylate and tert-butyl (2S,4R)-4-{[(4-fluorophenyl)methyl]amino}-2-phenylpiperidine-1-carboxylate



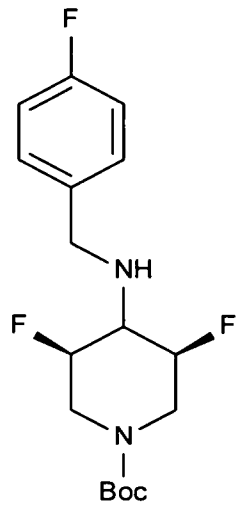
[00226] The compounds were prepared in analogy with intermediate 24, using tert-butyl 4-oxo-2-phenylpiperidine-1-carboxylate and 4-fluorobenzylamine to yield the desired intermediate. Dichloromethane was used instead of ethanol. Isolated as a racemic mixture.

[00227] Intermediate 26: N-[(4-fluorophenyl)methyl]-1,2,6-trimethylpiperidin-4-amine



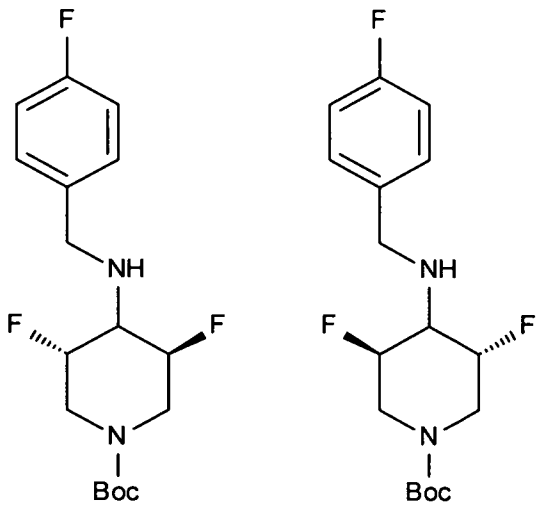
[00228] The compound was prepared in analogy with intermediate 24 using 1,2,6-trimethylpiperidin-4-one and 4-fluorobenzylamine to yield the desired intermediate.

[00229] Intermediate 27: tert-butyl (3R,5S)-3,5-difluoro-4-{[(4-fluorophenyl)methyl]-amino}piperidine-1-carboxylate



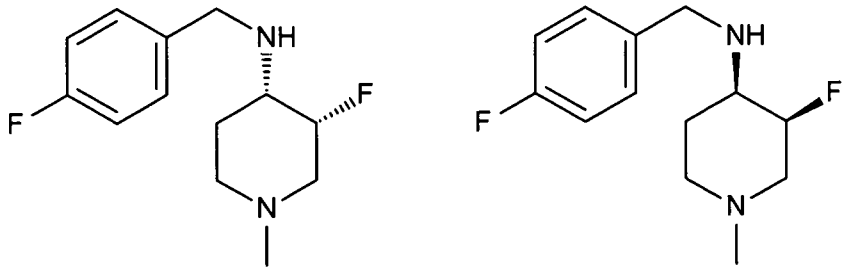
[00230] The compound was prepared in analogy with intermediate 24 using tert-butyl (3R,5S)-3,5-difluoro-4,4-dihydroxypiperidine-1-carboxylate and 4-fluorobenzylamine to yield the desired intermediate. 1 equivalent of acetic acid was added to the reaction. Yield: 33 %.

[00231] Intermediate 28: tert-butyl (3R,5R)-3,5-difluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,5S)-3,5-difluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate



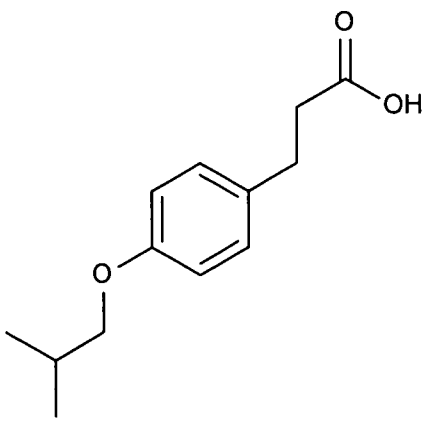
[00232] The compounds were prepared in analogy with intermediate 24 using tert-butyl (3R,5R)-3,5-difluoro-4,4-dihydroxypiperidine-1-carboxylate and tert-butyl (3S,5S)-3,5-difluoro-4,4-dihydroxypiperidine-1-carboxylate (1:1) and 4-fluorobenzylamine to yield the desired intermediate. 1 equivalent of acetic acid was added to the reaction. Yield: 5 %. The compounds were isolated as a racemic mixture.

[00233] Intermediate 29: (3R,4S)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine; (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine



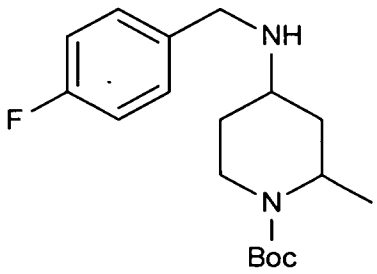
[00234] Trifluoroacetic acid (5 ml) was added to tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1, 1.73 g, 5.31 mmol) in dichloromethane (15 ml). The mixture was stirred at ambient temperature for 50 minutes before it was concentrated and re-dissolved in ethanol (53 ml). Formaldehyde (37% aqueous, 198 µl, 2.66 mmol) and sodium triacetoxyborohydride (1.13 g, 5.31 mmol) were added. After 30 minutes, additional formaldehyde (37% aqueous, 99 µl, 1.33 mmol) and sodium triacetoxyborohydride (563 mg, 2.66 mmol) were added. The mixture was stirred for 45 minutes before it was concentrated. Sodium hydrogen carbonate (aqueous, saturated, 100 ml) was added and the resulting mixture was extracted with dichloromethane (3 x 100 ml). The organic phase was dried (phase-separator) and concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 5-15% methanol in dichloromethane to afford the desired amines (545 mg, 43%), as a racemic mixture.

[00235] Intermediate 29: 3-[4-(2-methylpropoxy)phenyl]propanoic acid



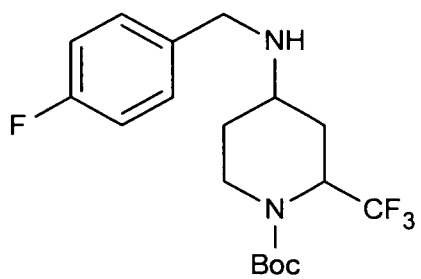
[00236] Methyl 3-(4-hydroxyphenyl)propanoate (3.5 g, 19.39 mmol) was added to potassium carbonate (5.36 g 38.8 mmol) suspended in dry dimethylformamide (20 ml). Tetrabutylammonium iodide (0.71 g 1.94 mmol) and 1-bromo-2-methylpropane (4.21 ml, 38.8 mmol) were added and the reaction was heated to 75 °C for 72 hours. More tetrabutylammonium iodide and 1-bromo-2-methylpropane were added and the reaction was heated overnight. The reaction mixture was diluted with water (100 ml) and the aqueous phase was extracted with diethyl ether (3 x 200 ml). The combined organic phases were evaporated and the crude material was purified by column chromatography using silicon dioxide gel, eluting with 25% ethyl acetate in petroleum ether to afford the intermediate ester (4.31 g). A portion of the ester (2.32 g, 9.8 mmol) was dissolved in methanol (40 ml) before sodium hydroxide (8 ml, 5M) was added. After stirring at ambient temperature for 19 hours the methanol was removed under reduced pressure and the mixture was neutralized using hydrochloric acid. The suspension was extracted with diethyl ether (2 x 250 ml), dried (sodium sulfate), filtered and concentrated to give the desired intermediate (2.03g, 93%).

[00237] Intermediate 30: tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-2-methylpiperidine-1-carboxylate



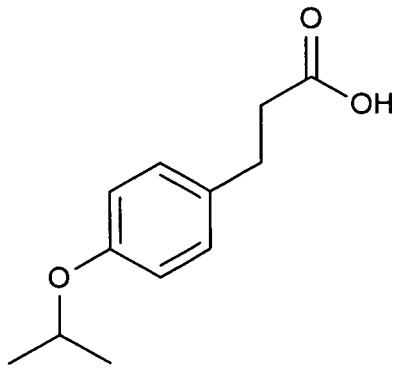
[00238] The compound was prepared in analogy with intermediate 20 using tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate and 4-fluorobenzylamine. Methanol was used as solvent. Yield: 75%.

[00239] Intermediate 31: tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-2-(trifluoromethyl)piperidine-1-carboxylate



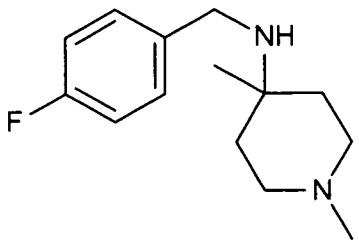
[00240] The compound was prepared in analogy with intermediate 20 using tert-butyl 4-oxo-2-(trifluoromethyl)piperidine-1-carboxylate and 4-fluorobenzylamine. Methanol was used as solvent.

[00241] Intermediate 32: 3-[4-(propan-2-yloxy)phenyl]propanoic acid



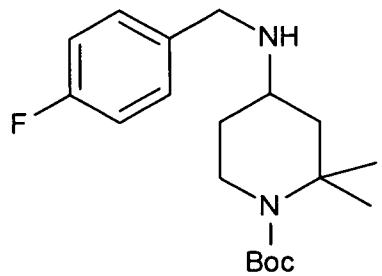
[00242] The compound was prepared in analogy with intermediate 29 using methyl 3-(4-hydroxyphenyl)propanoate and 2-bromopropane.

[00243] Intermediate 33: tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-4-methylpiperidine-1-carboxylate



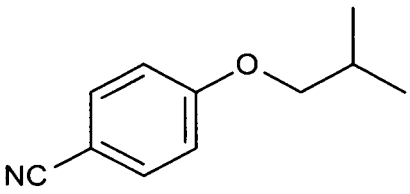
[00244] The compound was prepared in analogy with intermediate 20 using 1,4-dimethylpiperidin-4-amine and 4-fluorobenzaldehyde.

[00245] Intermediate 34: tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-2,2-dimethylpiperidine-1-carboxylate



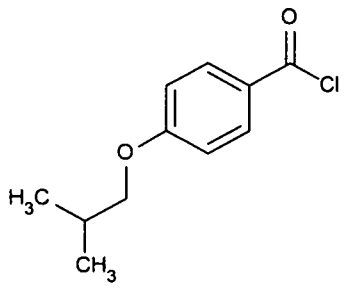
[00246] The compound was prepared in analogy with intermediate 20 using (4-fluorophenyl)methanamine and tert-butyl 2,2-dimethyl-4-oxopiperidine-1-carboxylate.

[00247] Intermediate 35: 4-(2-methylpropoxy)benzonitrile



[00248] Tetrabutylammonium iodide (3.7 g, 10 mmol), potassium carbonate (55.2 g, 400 mmol) and isobutyl bromide (27 ml, 250 mmol) were added to 4-hydroxybenzonitrile (11.9 g, 100 mmol) in dimethylformamide (100 ml). The mixture was heated to 70 °C. After 18 hours, the mixture was cooled to ambient temperature, diluted with water (150 ml) and extracted with diethyl ether (2 x 400 ml). The organic phase was washed with water (3 x 200 ml), dried (sodium sulfate), filtered and concentrated to give the desired intermediate (17.2 g, 98 %).

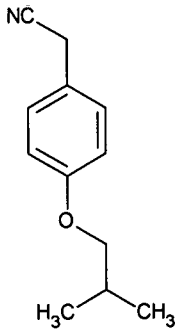
[00249] Intermediate 36: 4-(2-Methylpropoxy)benzoyl chloride



[00250] Thionyl chloride (6.02 ml, 82.92 mmol) was added to a suspension of 4-(2-methylpropoxy)-benzoic acid (1.62 g, 8.29 mmol) in dry dichloromethane (6 ml). The reaction was stirred 20 hours before it was evaporated and the residue was re-evaporated with toluene to get 4-(2-methylpropoxy)benzoyl chloride (1.75 g, quantitative yield) as light yellow oil.

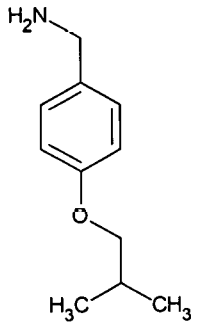
[00251] Example 1: (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine; trifluoroacetic acid and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine; trifluoroacetic acid

[00252] 2-[4-(2-methylpropoxy)phenyl]acetonitrile



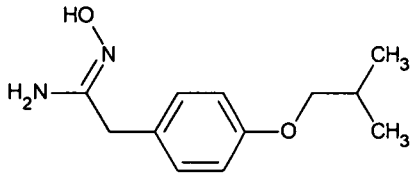
[00253] The compound was prepared in analogy with 4-(2-methylpropoxy)benzonitrile. Yield: 90 % (3.40 g). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 (d, 2H), 6.93 – 6.85 (m, 2H), 3.71 (d, 2H), 3.67 (s, 2H), 2.08 (dt, 1H), 1.03 (d, 6H).

[00254] [4-(2-methylpropoxy)phenyl]methanamine



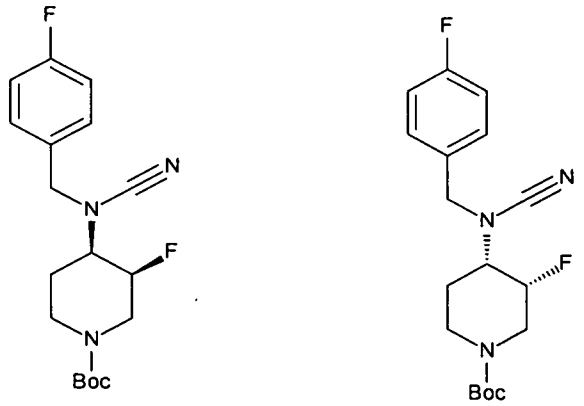
[00255] Lithium aluminiumhydride (7.6 g, 200 mmol) is suspended in diethylether (dry, 150 ml) and a solution of 2-[4-(2-methylpropoxy)phenyl]acetonitrile (17.0 g, 97 mmol) in diethyl ether (dry, 100 ml), is added dropwise under nitrogen. The reaction mixture is then refluxed for 18 h. The reaction mixture is quenched by very slow addition of water (8 ml), aqueous sodium hydroxide solution (15%, 8 ml) and water (24 ml). The suspension is filtered and the residue is rinsed with diethylether (100 ml). The filtrate is washed with brine (200 ml), dried (Na_2SO_4) and evaporated to give the product. 15.0 g, 86%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 (d, 2H), 6.86 (d, 2H), 3.79 (s, 2H), 3.71 (d, 2H), 2.07 (h, 1H), 1.02 (d, 6H).

[00256] N'-hydroxy-2-[4-(2-methylpropoxy)phenyl]ethenimidamide



[00257] 2-[4-(2-methylpropoxy)phenyl]acetonitrile (3.4 g, 18 mmol) is dissolved in ethanol (100 ml). Hydroxylamine (50 % aqueous solution, 2.2 ml, 36 mmol) is added. After having refluxed the solution for 3 h under nitrogen, the reaction mixture is evaporated to dryness. Water (50 ml) is added and the aqueous phase is extracted with dichloromethane (400 ml). The organic phase is washed with brine (200 ml), dried (Na_2SO_4) and evaporated to dryness. The off-white crude product is chromatographed on silica gel (dichloromethane:methanol 100:5) to give the product as an off-white solid (2.65 g, 60%). 1H NMR (400 MHz, Chloroform-d) δ 7.19 (d, 2H), 6.91 – 6.83 (m, 2H), 4.48 (s, 1H), 3.71 (d, 2H), 3.41 (s, 2H), 2.08 (h, 1H), 1.03 (d, 6H).

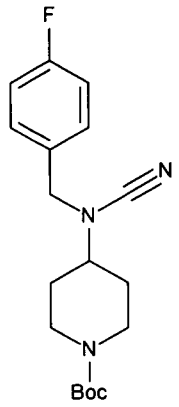
[00258] tert-butyl (3R,4S)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate



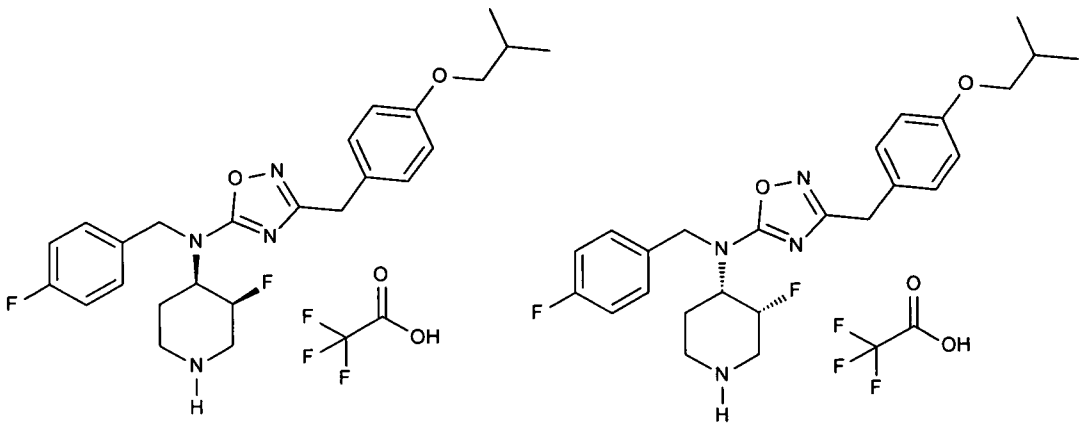
[00259] Tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (700 mg, 2.1 mmol), Sodium carbonate (455 mg, 4.3 mmol) and carbononitridic bromide (341 mg, 3.2 mmol) are mixed in methanol (dry, 8 ml) and stirred at ambient temperature overnight. The solvent is evaporated, the residue suspended in water (25 ml) and extracted with diethyl ether (2 x 200 ml). The combined organic phases are washed with brine (120 ml), dried (Na_2SO_4) and evaporated to give the crude product as a yellowish oil

(630 mg). Chromatography on silica gel (dichloromethane: methanol 100:2) furnishes the pure product (225 mg, 28 %). LC-MS: 374.15 $[M+Na]^+$.

[00260] tert-butyl 4-{cyano[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate



[00261] The compound was prepared in analogy with tert-butyl (3R,4S)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate. Yield 87% 670 mg. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 2H), 7.13 – 7.05 (m, 2H), 4.22 (s, 2H), 4.12 (d, 2H), 2.88 (tt, 1H), 2.70 (t, 2H), 1.87 (d, 2H), 1.72 – 1.56 (m, 2H), 1.46 (s, 9H). (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine; trifluoroacetic acid ; and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine; trifluoroacetic acid.

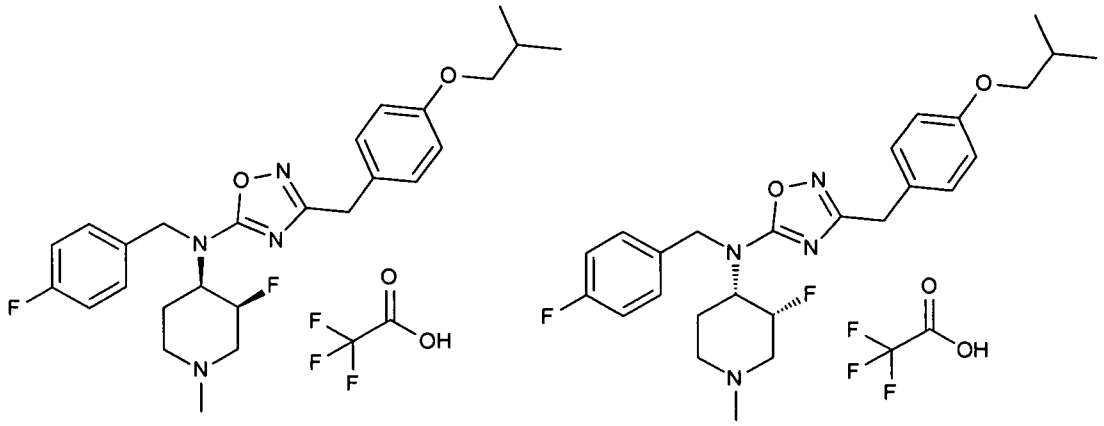


tert-butyl (3R,4S)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-

fluoropiperidine-1-carboxylate (225 mg, 0.64 mmol), N'-hydroxy-2-[4-(2-methylpropoxy)phenyl]ethenimidamide (142 mg, 0.64 mmol) and Zinc chloride (1M in diethyl ether, 1 ml) are mixed in THF (dry, 1 ml) and stirred at 50^0 C for 5h. The solvent is evaporated and the residue is heated for 1h at 100 ^{0}C in a mixture of Ethyl acetate (3 ml) and Acetic acid (1.5 ml). After evaporation of the solvents Sodium bicarbonate solution (sat., 10 ml) is added and the reaction mixture is extracted with diethyl ether (2x 200 ml). The organic phase is washed with brine (50 ml), dried (Na_2SO_4) and evaporated. Purification by HPLC affords 140 mg (38%) of the product. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.26 – 7.16 (m, 4H), 7.04 – 6.97 (m, 2H), 6.90 – 6.83 (m, 2H), 5.13 (d, 1H), 4.88 (d, 1H), 4.61 (d, 1H), 4.40 (dd, 1H), 3.83 (s, 2H), 3.70 (m, 3H), 3.50 (d, 1H), 3.23 (dd, 1H), 3.01 (t, 1H), 2.57 – 2.39 (m, 1H), 2.08 (h, 1H), 1.76 (d, 1H), 1.02 (d, 6H). LC-MS: 457.3 $[M+H]^+$.

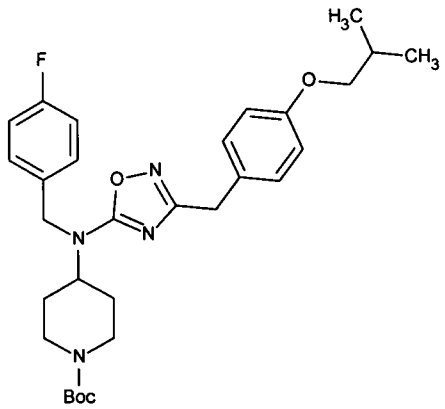
[00262] Tert-butyl (3R,4S)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate (225 mg, 0.64 mmol), N'-hydroxy-2-[4-(2-methylpropoxy)phenyl]ethenimidamide (142 mg, 0.64 mmol) and Zinc chloride (1M in diethyl ether, 1 ml) are mixed in THF (dry, 1 ml) and stirred at 50^0 C for 5h. The solvent is evaporated and the residue is heated for 1h at 100 ^{0}C in a mixture of Ethyl acetate (3 ml) and Acetic acid (1.5 ml). After evaporation of the solvents Sodium bicarbonate solution (sat., 10 ml) is added and the reaction mixture is extracted with diethyl ether (2x 200 ml). The organic phase is washed with brine (50 ml), dried (Na_2SO_4) and evaporated. Purification by HPLC affords 140 mg (38%) of the product. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.26 – 7.16 (m, 4H), 7.04 – 6.97 (m, 2H), 6.90 – 6.83 (m, 2H), 5.13 (d, 1H), 4.88 (d, 1H), 4.61 (d, 1H), 4.40 (dd, 1H), 3.83 (s, 2H), 3.70 (m, 3H), 3.50 (d, 1H), 3.23 (dd, 1H), 3.01 (t, 1H), 2.57 – 2.39 (m, 1H), 2.08 (h, 1H), 1.76 (d, 1H), 1.02 (d, 6H). LC-MS: 457.3 $[M+H]^+$.

[00263] (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine; trifluoroacetic acid and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine; trifluoroacetic acid



[00264] The compound was prepared in analogy with N-[(4-fluorophenyl)methyl]-1-methyl-N-{1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine (4d). Yield: 10 mg (9%) of the title compound. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.26 – 7.19 (m, 4H), 7.00 (t, 2H), 6.86 (d, 2H), 5.11 (d, 1H), 4.88 (d, 1H), 4.62(d, 1H), 4.37 (dd, 1H), 3.82 (s, 3H), 3.70 (d, 3H), 2.79 (d, 5H), 2.08 (h, 1H), 1.76 (d, 1H), 1.02 (d, 6H). LC-MS: 471.4 $[M+H]^+$

[00265] Example 2: tert-butyl 4-{[(4-fluorophenyl)methyl](3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)amino}piperidine-1-carboxylate (2a); N-[(4-fluorophenyl)methyl]-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine (2b); and N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine (2c)

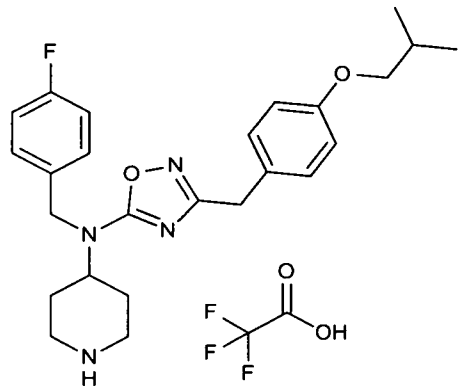


(2a)

[00266] Tert-butyl 4-{cyano[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (650 mg, 1.95 mmol) and N'-hydroxy-2-[4-(2-methylpropoxy)phenyl]ethenimidamide (433 mg, 1.95 mmol) are dissolved in ethyl acetate (5 ml)/ THF (3 ml). Zinc chloride (1M solution in

ether, 3 ml) is slowly added dropwise at ambient temperature. The solution is stirred at 50^0 C for 4h, the resulting suspension filtered, the white precipitate air dried (760 mg) and then heated in ethanol (3 ml) /acetic acid (1.5 ml) for 1.5h. After evaporating the solvents the residue is distributed between dichloromethane (250 ml) and Sodium hydroxide solution (1M in water, 25 ml). The organic phase is washed with water (50 ml), dried (Na_2SO_4) and evaporated to give the title compound (690 mg, 66 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.19 (m, 4H), 7.05 – 6.94 (m, 2H), 6.90 – 6.81 (m, 2H), 5.31 (s, 2H), 4.58 (s, 2H), 4.23 – 3.97 (m, 2H), 3.83 (s, 2H), 3.71 (d, 2H), 2.70 (m, 1H), 2.07 (dq, 1H), 1.64 (d, 4H), 1.45 (s, 9H), 1.02 (d, 6H).

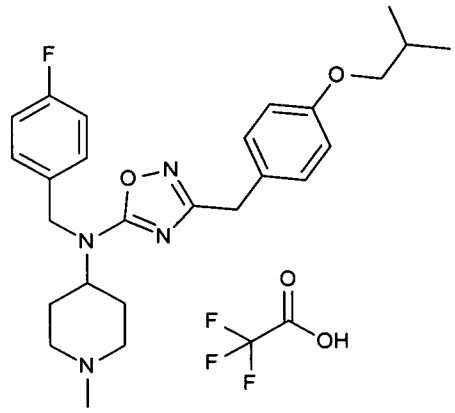
[00267] N-[(4-fluorophenyl)methyl]-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine; trifluoroacetic acid (2b)



(2b)

[00268] tert-butyl 4-{[(4-fluorophenyl)methyl](3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)amino}piperidine-1-carboxylate (690 mg, 1.28 mmol) is stirred in dichloromethane (20 ml)/ TFA (4 ml) over night. The solvent is evaporated and the residue freeze dried from acetonitrile / water. The title compound is an off-white powder as a TFA salt), 600 mg (85 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.33 (s, 1H), 9.05 (s, 1H), 7.27 – 7.21 (m, 4H), 7.00 (t, 2H), 6.88 – 6.83 (m, 2H), 4.62 (s, 2H), 4.20 (m, 1H), 3.84 (s, 2H), 3.71 (d, 2H), 3.45 (d, 2H), 2.93 (d, 2H), 2.23 – 2.13 (m, 2H), 2.08 (tt, 1H), 1.88 (d, 2H), 1.02 (d, 6H). LC-MS: 439.3 $[M+H]^+$

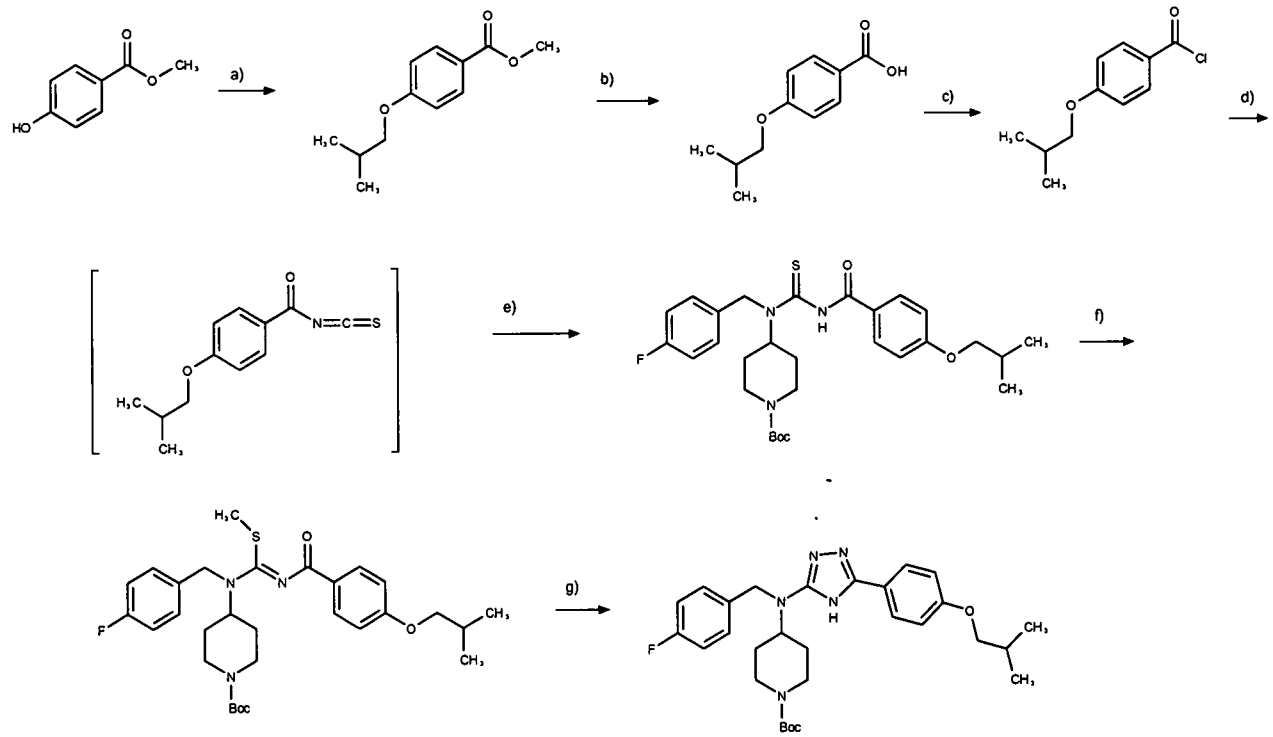
[00269] N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine; trifluoroacetic acid (2c)



(2c)

[00270] The compound was prepared in analogy with N-[(4-fluorophenyl)methyl]-1-methyl-N-{1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine (4d). Yield: 69 mg (19%) as TFA salt. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.74 (s, 1H), 7.31 – 7.21 (m, 4H), 7.00 (t, 2H), 6.86 (d, 2H), 4.63 (s, 2H), 4.26 (t, 1H), 3.84 (s, 2H), 3.71 (d, 2H), 3.60 (d, 2H), 2.86-2.71 (s+m, 5H), 2.37 (q, 2H), 2.08 (h, 1H), 1.87 (d, 2H), 1.02 (d, 6H). LC-MS: 453.4[M+H]$^+$

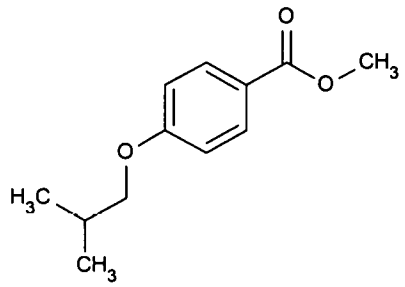
[00271] Example 3:



(3a)

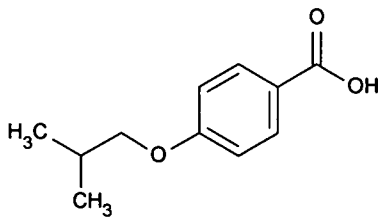
[00272] Scheme 1. Reagents: a) K_2CO_3/tetra-*n*-butylammonium iodide/DMF/2-methylpropyl bromide; b) 5N NaOH/methanol; c) thionyl chloride/dichloromethane; d) potassium thiocyanate/acetone; e) tert-butyl 4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate/THF; f) Na_2CO_3/THF/methyl iodide; g) hydrazine hydrate/dioxane

[00273] Methyl 4-(2-methylpropoxy)-benzoate



[00274] To a suspension of potassium carbonate (5.36 g, 38.76 mmol) in dry DMF (20 ml) methyl 4-hydroxybenzoate (2.95 g, 19.39 mmol) was added in one portion under nitrogen flow, followed by 2-methylpropyl bromide (5.31 g, 38.76 mmol) and tetra-n-butylammonium iodide (0.72 g, 1.940 mmol). After 10 minutes the reaction was heated to 72°C and stirred 65 hours before all the starting material was consumed. The reaction mixture was diluted with water (100 ml) and extracted by diethyl ether (3 x 100 ml). The combined organic phases were washed twice with water (250 ml) and once with brine (200 ml), dried over Na_2SO_4 and concentrated to dryness to get methyl 4-(2-methylpropoxy)-benzoate (3.81 g, yield 94.4%).

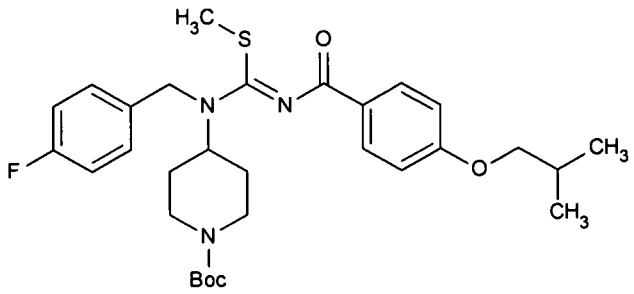
[00275] 4-(2-Methylpropoxy)benzoic acid



[00276] To a solution of methyl 4-(2-methylpropoxy)-benzoate (3.35 g, 16.09 mmol) in methanol (50 ml) 5N NaOH in water (12.87 ml, 64.34 mmol) was added in 10 minutes. The reaction was stirred for 18 hours until hydrolysis was completed. To the reaction suspension 5N HCl (12.87 ml, 64.34 mmol) was added, the reaction was concentrated to remove methanol. The residue was diluted with water (40 ml), pH was adjusted to 3 by 5N HCl and the product was extracted by diethyl ether (5 x 60 ml). Combined organic phase was washed

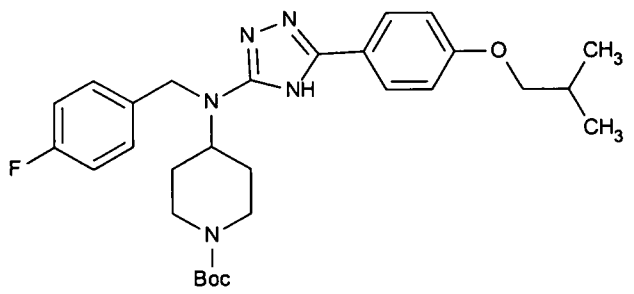
with water (70 ml), dried over Na_2SO_4 and evaporated to dryness to get 4-(2-methylpropoxy)benzoic acid as white solid (3.10 g, 99%).

[00277] tert-Butyl 4-{[(4-fluorophenyl)methyl][(1Z)-[(Z)-4-(2-methylpropoxy)-benzoyl-imino]-(methylsulfanyl)methyl]amino}piperidine-1-carboxylate



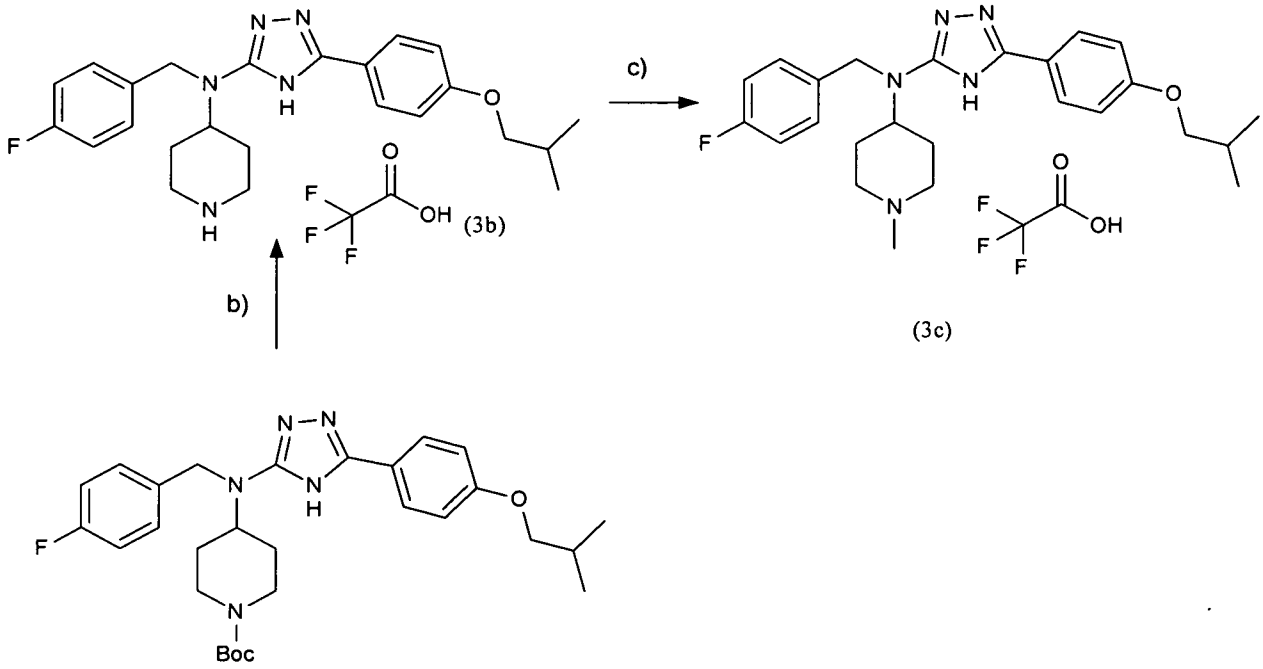
[00278] To a solution of 4-(2-methylpropoxy)benzoyl chloride (1.75 g, 8.25 mmol) in dry THF (27 ml) a solution of sodium thioisocyanate (0.96 g, 9.90 mmol) in dry acetone (27 ml) was added dropwise under nitrogen flow. After 15 min stirring at room temperature the reaction was heated to reflux. The reaction was kept at reflux for 10 min, then solid tert-butyl 4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (prepared in analogy to intermediate 20) (2.54 g, 8.25 mmol) was added to the reaction during 15 min in several portions. The reaction was kept under reflux for one hour. Potassium carbonate (1.37 g, 9.90 mmol) was added in one portion, followed by methyl iodide (1.23 ml, 19.8 mmol) (after 15 min). The reaction was kept at reflux during 18 hours before it was cooled down and diluted with ethyl acetate (20 ml). The suspension was filtered through silica gel. The solid on silica was washed with more ethyl acetate (3 x 20 ml). Combined organic solution was concentrated to get the product (4.46 g, yield 97%) as a yellow oil.

[00279] tert-Butyl 4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}-piperidine-1-carboxylate (3a)



(3a)

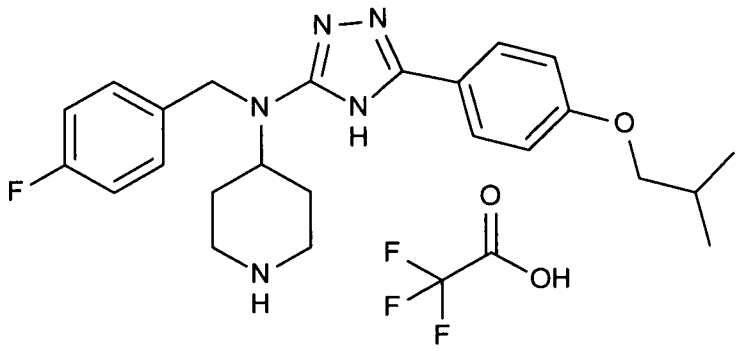
[00280] A solution of tert-butyl 4-{[(4-fluorophenyl)methyl][(1Z)-[(Z)-4-(2-methylpropoxy)benzoylimino]-(methylsulfanyl)methyl]amino}piperidine-1-carboxylate (4.45 g, 7.98 mmol) in dioxane (180 ml) was heated to reflux before hydrazine hydrate (1.164 ml 50% water solution, 23.93 mmol) was added by one equivalent portions every hour. After all hydrazine hydrate was added, the reaction was refluxed for 5 hours and the reaction was kept at room temperature for 16 hours. The reaction mixture was concentrated and the product was purified by column chromatography using silica gel, eluting with petroleum ether-ethyl acetate 2:1 to get 1.64 g (39.3%) of the product. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.79 (m, 2H), 7.35 – 7.25 (m, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.49 (s, 2H), 4.42 – 4.32 (m, 1H), 4.28 – 4.13 (m, 2H), 3.75 (d, *J* = 6.5 Hz, 2H), 2.81 (t, *J* = 14.5 Hz, 2H), 2.15 – 2.04 (m, 1H), 1.88 – 1.79 (m, 2H), 1.70 – 1.58 (m, 2H), 1.46 (s, 9H), 1.08 – 1.01 (m, 6H).

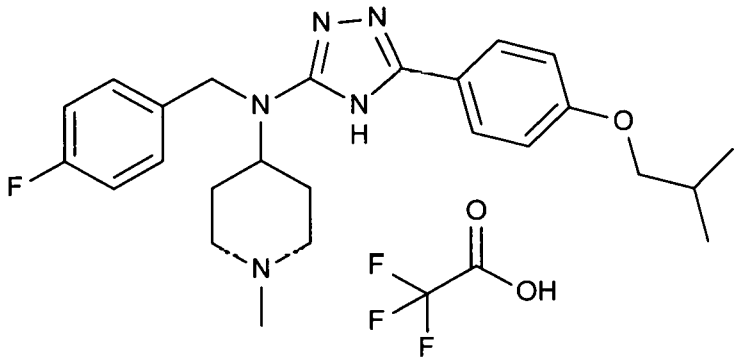


[00281] Scheme 2. Reagents: b) TFA/dichloromethane; c) formaldehyde, 30% water solution/sodium cyanoborohydride/THF

[00282] Compounds N-[(4-fluorophenyl)methyl]-N-{5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl}piperidin-4-amine; trifluoroacetic acid (3b) and N-[(4-fluorophenyl)methyl]-1-methyl-N-{5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-

yl}piperidin-4-amine; trifluoroacetic acid (3c) were prepared in analogy with Compounds (4c) and (4d) in Example 4



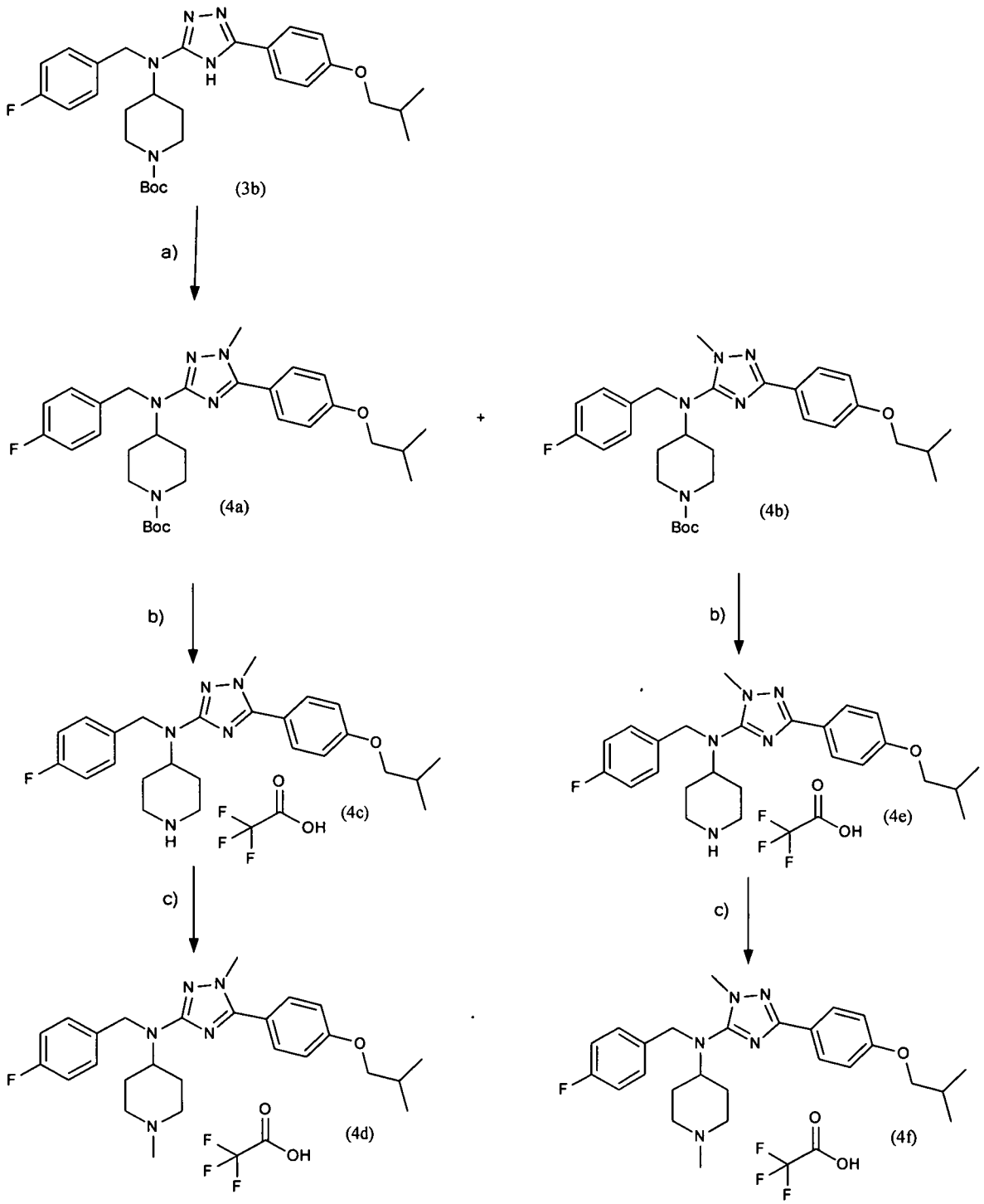


[00283] N-[(4-fluorophenyl)methyl]-1-methyl-N-{5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl}piperidin-4-amine; trifluoroacetic acid (3c)

[00284] The compound was prepared in analogy with Compound (4d) in Example 4. Yield: 28.5%, 71 mg.

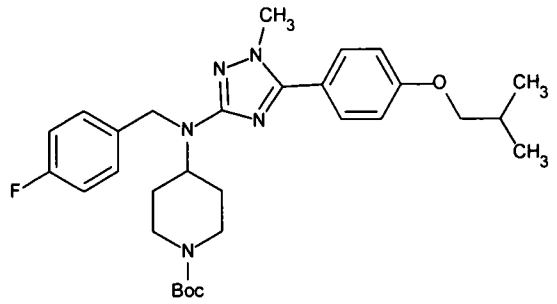
[00285] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.23 – 7.13 (m, 2H), 7.01 – 6.88 (m, 4H), 4.61 (s, 2H), 4.51 (m, 1H), 3.71 (d, *J* = 6.4 Hz, 2H), 3.43 (d, *J* = 11.2 Hz, 2H), 3.05 (t, *J* = 12.1 Hz, 2H), 2.72 (s, 3H), 2.31 (q, *J* = 13.0, 12.3 Hz, 2H), 2.14 – 1.99 (m, *J* = 6.9 Hz, 1H), 1.87 (d, *J* = 13.2 Hz, 2H), 1.02 (d, *J* = 6.7 Hz, 6H). LC-MS: 438.3 $[M+H]^+$.

[00286] Example 4:

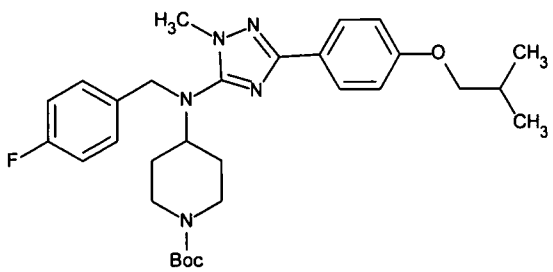


[00287] Scheme 3. Reagents: a) potassium tert-butoxide/DMF/methyl iodide; b) TFA/dichloromethane; c) formaldehyde, 30% water solution/sodium cyanoborohydride/THF.

[00288] Tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl})amino}piperidine-1-carboxylate (4a) and tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-3-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-5-yl})amino}piperidine-1-carboxylate (4b)



(4a)

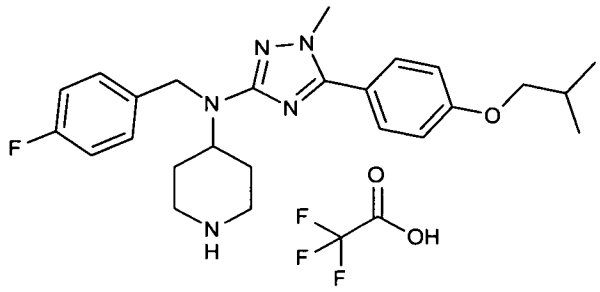


(4b)

[00289] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)-phenyl]-4H-1,2,4-triazol-3-yl})amino}-piperidine-1-carboxylate (235.0 mg, 0.45 mmol) in dry DMF (3.5 ml) under nitrogen flow potassium *t*-butylate (60.6 mg, 0.54 mmol) was added in one portion at room temperature. After addition the reaction mixture was stirred 15 min before methyl iodide (39.0 µL, 0.63 mmol) was added in one portion. The reaction was stirred at room temperature during 2.5 hours until all starting material was consumed. Brine (20 ml) was added to the reaction solution and the products were extracted by ethyl acetate (3 x 25 ml). The combined organic phase was washed with water (30 ml), dried over Na_2SO_4 and evaporated to get 3:1 mixture of products. The mixture was separated by preparative HPLC with 70 to 95% acetonitrile in water (containing 0.1 % TFA) to get 135 mg (46.1%) of the main product tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl})amino}piperidine-1-carboxylate and 55 mg (18.8%) of the minor product tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-3-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-5-yl})amino}piperidine-1-carboxylate as TFA salts.

[00290] N-[(4-fluorophenyl)methyl]-N-{1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine (4c); and N-[(4-fluorophenyl)methyl]-1-methyl-N-{1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine; trifluoroacetic acid (4d)

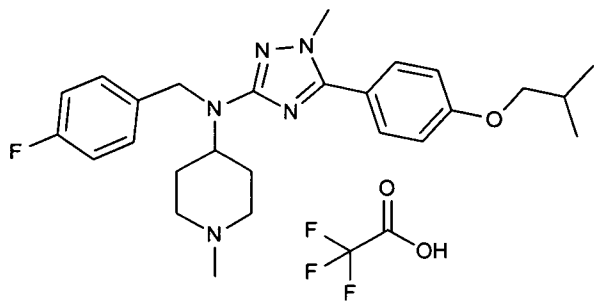
[00291] N-[(4-fluorophenyl)methyl]-N-{1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine; trifluoroacetic acid; trifluoroacetic acid (4c)



(4c)

[00292] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-5-[4-(2-methylpropoxy) phenyl]-1H-1,2,4-triazol-3-yl})amino}piperidine-1-carboxylate, TFA salt (136 mg, 0.209 mmol) in dry dichloromethane (7.5 ml), TFA (2.5 ml) was added in one minute at room temperature. After 30 min stirring the reaction was evaporated to dryness and crude product was purified by preparative HPLC with 40 to 75% acetonitrile in water (containing 0.1 % TFA) to get the product (113 mg, 98.1%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.62 (d, J = 8.4 Hz, 2H), 7.40 – 7.34 (m, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.04 (t, J = 8.6 Hz, 2H), 4.64 (s, 2H), 4.19 (t, J = 11.8 Hz, 1H), 3.83 (d, J = 6.4 Hz, 2H), 3.80 (s, 3H), 3.45 (d, J = 13.1 Hz, 2H), 3.06 (t, J = 14.1 Hz, 2H), 2.15 – 1.96 (m, 5H), 1.05 (d, J = 6.7 Hz, 6H). LC-MS: 438.3 $[M+H]^+$.

[00293] N-[(4-fluorophenyl)methyl]-1-methyl-N-{1-methyl-5-[4-(2-methylpropoxy)-phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine; trifluoroacetic acid (4d)

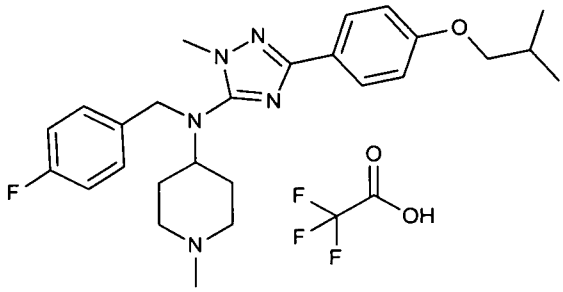


(4d)

[00294] To a solution of N-[(4-fluorophenyl)methyl]-N-{1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine, TFA salt (43.0 mg, 0.080 mmol) in dry THF (2 ml) under nitrogen flow a 30% formaldehyde solution (10.7 µL, 0.120 mmol) was added. The solution was stirred for 15 min before sodium cyanoborohydride (9.9 mg, 0.160 mmol) was added. The reaction mixture was evaporated and the residue was diluted with ether (20 ml). The organic phase was washed with water (10 ml), dried over

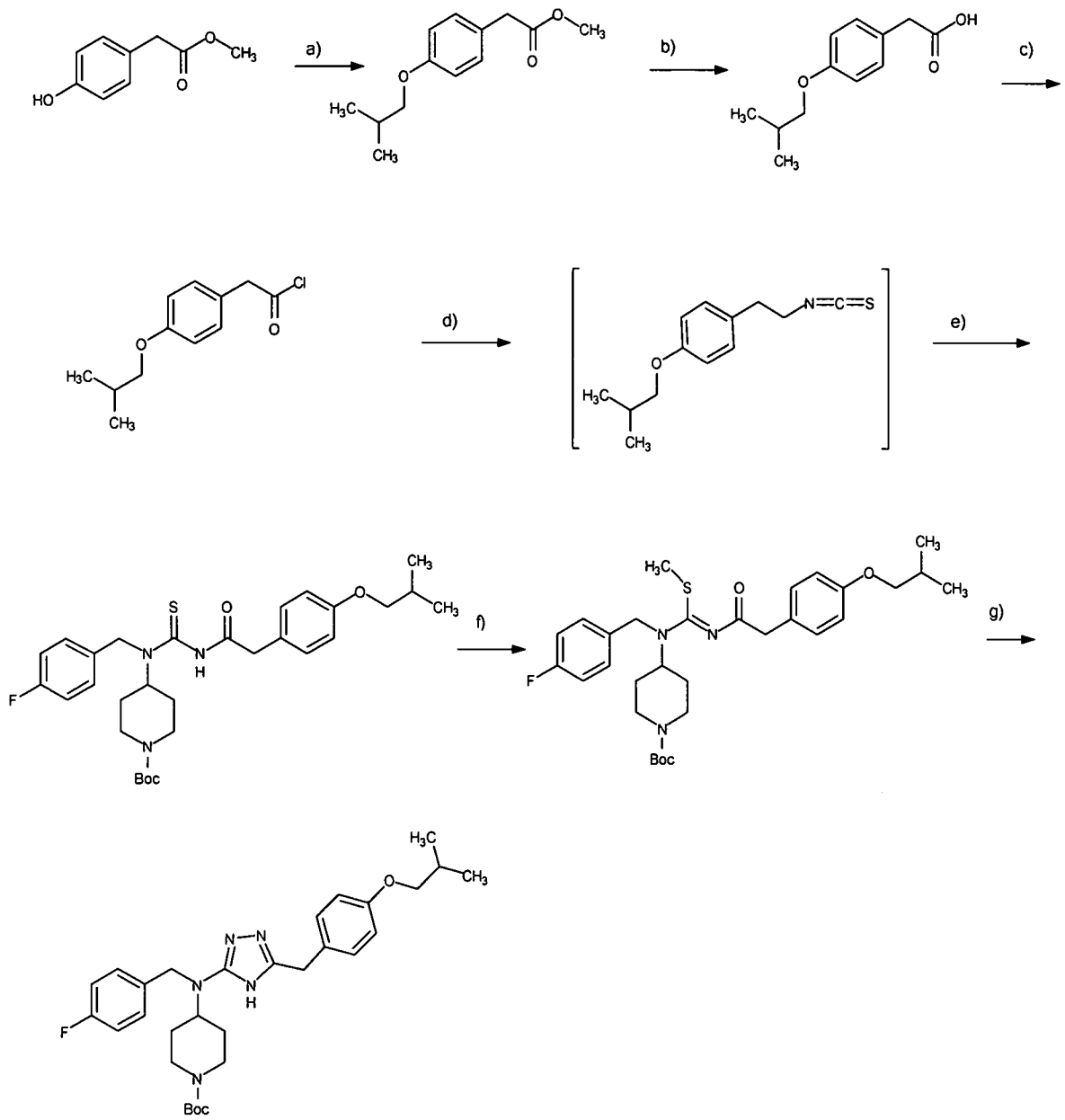
Na_2SO_4, concentrated. Crude product was purified by preparative HPLC with 43 to 90% acetonitrile in water (containing 0.1 % TFA) to get the product (20.0 mg, yield 44%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.60 (d, *J* = 8.7 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.08 – 6.96 (m, 4H), 5.38 (s, 3H), 4.63 (s, 2H), 4.51 – 4.41 (m, 1H), 3.85 (s, 3H), 3.80 (d, *J* = 6.5 Hz, 2H), 3.55 (d, *J* = 12.7 Hz, 2H), 3.01 – 2.88 (m, 2H), 2.77 (s, 3H), 2.38 (q, *J* = 12.7 Hz, 2H), 2.20 – 2.08 (m, 1H), 1.92 (d, *J* = 15.0 Hz, 2H), 1.06 (d, *J* = 6.7 Hz, 6H). LC-MS: 452.3 $[M+H]^+$.

[00295] N-[(4-fluorophenyl)methyl]-1-methyl-N-{1-methyl-3-[4-(2-methylpropoxy) phenyl]-1H-1,2,4-triazol-5-yl}piperidin-4-amine; trifluoroacetic acid (4f)



(4f)

[00296] The compound was prepared in analogy with compound 4d, utilizing compound 4b. Yield: 49.6%, 20.0 mg. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.97 – 7.90 (m, 2H), 7.22 – 7.14 (m, 2H), 7.03 – 6.91 (m, 4H), 4.28 (s, 2H), 3.78 (d, 2H), 3.66 – 3.59 (m, 2H), 3.57 – 3.50 (m, 1H), 3.47 (s, 3H), 2.86 – 2.71 (m, 5H), 2.30 – 2.05 (m, 5H), 1.05 (d, *J* = 6.7 Hz, 6H). LC-MS: 452.3 $[M+H]^+$.

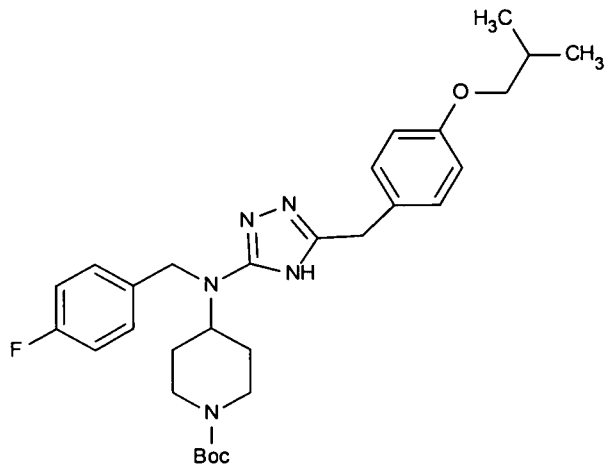


Scheme 4. Reagents: a) K_2CO_3/tetra-*n*-butylammonium iodide/DMF/2-methylpropyl bromide; b) 5N NaOH/methanol; c) thionyl chloride/dichloromethane; d) potassium thiocyanate/acetone; e) tert-butyl 4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate /THF; f) Na_2CO_3/THF/methyl iodide; g) hydrazine hydrate/dioxane

[00297] Example 5: tert-Butyl 4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)-phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidine-1-carboxylate (5a); N-[(4-fluorophenyl)methyl]-N-(5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine (5b); N-[(4-fluorophenyl)methyl]-1-methyl-N-(5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine (5c); and 3-(4-{[(4-

fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidin-1-yl)propanamide (5d)

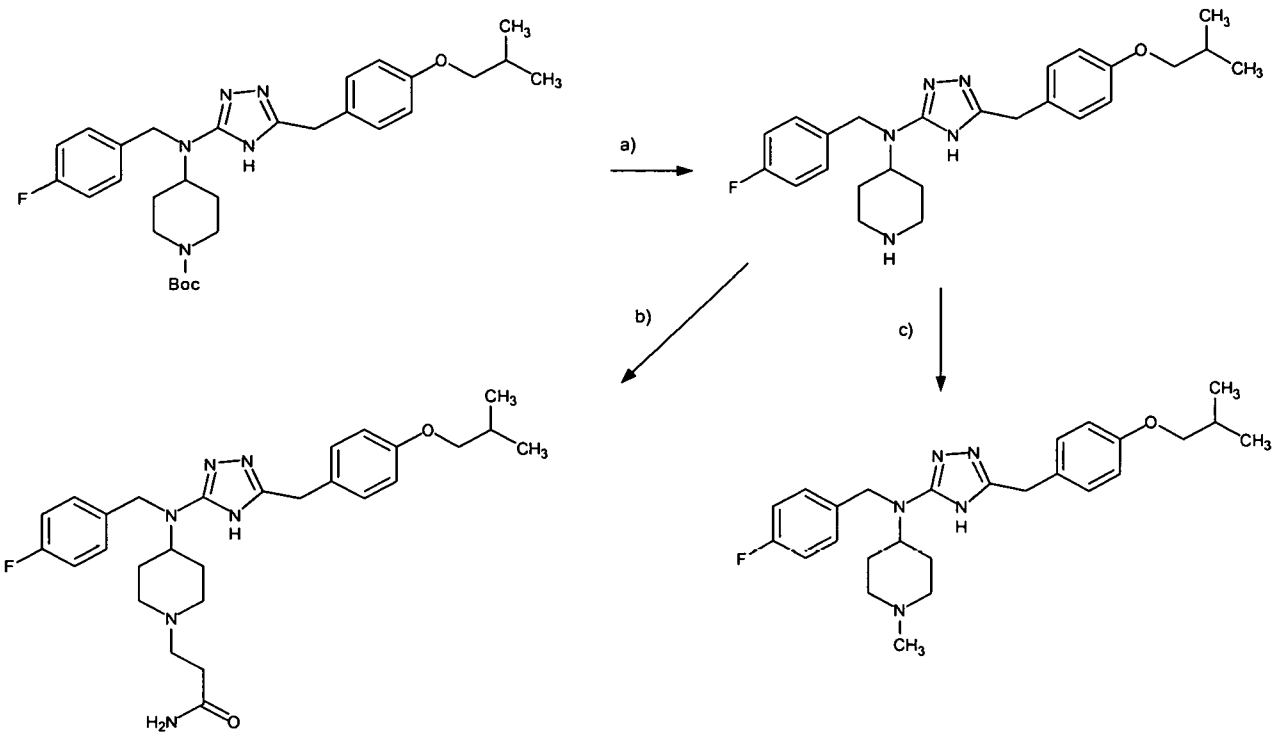
[00298] tert-Butyl 4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidine-1-carboxylate (5a)



(5a)

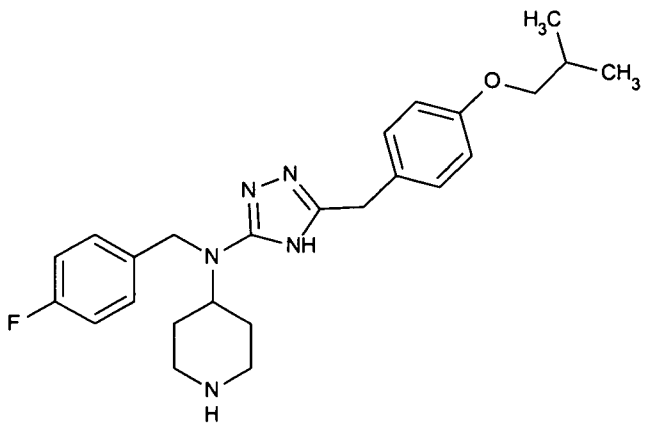
[00299] The compound was prepared using conditions as in Example 3, and as further described in scheme 4. Yield: 54.6% (from 2-[4-(2-methylpropoxy)phenyl]acetyl chloride), 890 mg. LC-MS: 538.4 $[M+H]^+$.

[00300]



[00301] Scheme 5. Reagents: a) TFA/dichloromethane, sodium hydrocarbonate; b) Acryl amide/acetonitrile/silica, reflux; c) HCOH/THF/Sodium triacetoxyborohydride

[00302] N-[(4-fluorophenyl)methyl]-N-(5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine (5b)

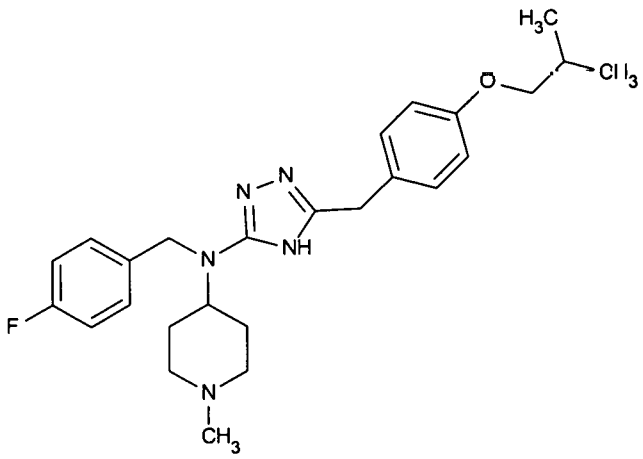


(5b)

[00303] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl](5-{[4-(2-ethylpropoxy)-phenyl] methyl}-4H-1,2,4- triazol-3-yl)amino}piperidine-1-carboxylate (715 mg, 1.33 mmol) in dry dichloromethane (12 ml), TFA (4 ml) was added dropwise at room temperature. The solution was stirred for 25 min before the TFA salt of N-[(4-fluorophenyl)-methyl]-N-(5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)-piperidin-4-

amine was evaporated and dissolved again in 20 ml dichloromethane. A saturated water solution of sodium hydrocarbonate (20 ml) was added, the two phase system was stirred intensively for 15 min before the phases were separated. The aqueous phase was washed with dichloromethane (20 ml) and the combined organic phase was washed with 20% brine (2 x 20 ml), dried over Na_2SO_4, concentrated and was purified by column chromatography using silica gel, eluting with ethylacetate:methanol 1:0.2 to ethylacetate:methanol:triethyl amine 1:0.2:0.02 to get the product as free base (321 mg, 55.2%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.21 (m, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.54 (s, 2H), 4.12 – 4.00 (m, 1H), 3.89 (s, 2H), 3.68 (d, *J* = 6.5 Hz, 2H), 3.44 (d, *J* = 12.7 Hz, 2H), 2.89 (t, *J* = 12.9 Hz, 2H), 2.25 (d, *J* = 13.2 Hz, 2H), 2.05 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.82 (d, *J* = 12.2 Hz, 2H), 1.04 – 0.97 (m, 6H). LC-MS: 438.4 $[M+H]^+$.

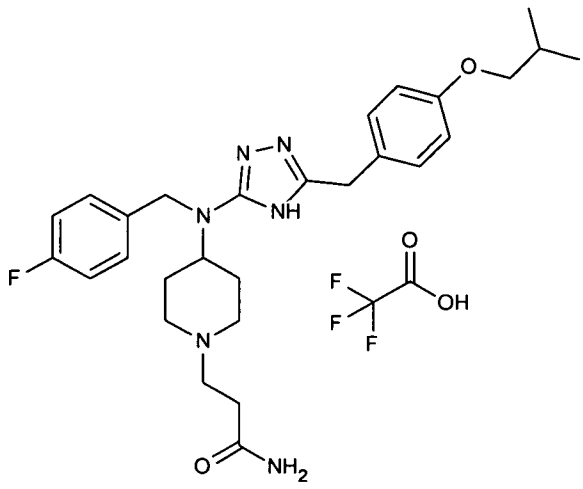
[00304] N-[(4-fluorophenyl)methyl]-1-methyl-N-(5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine (5c)



(5c)

[00305] The compound was prepared in analogy with example 3. Yield 21.0 %, 10 mg. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 (d, *J* = 8.4 Hz, 2H), 7.16 – 7.10 (m, 2H), 6.93 (t, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.52 (s, 2H), 4.42 – 4.31 (m, 1H), 4.02 (s, 2H), 3.67 (d, *J* = 6.5 Hz, 2H), 3.42 (d, *J* = 11.5 Hz, 2H), 2.95 (t, *J* = 12.1 Hz, 2H), 2.70 (s, 3H), 2.37 – 2.22 (m, 2H), 2.05 (dp, *J* = 13.6, 6.8 Hz, 1H), 1.83 (d, *J* = 13.0 Hz, 2H), 1.00 (d, *J* = 6.7 Hz, 6H). LC-MS: 452.3 $[M+H]^+$.

[00306] 3-(4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidin-1-yl)propanamide; trifluoroacetic acid (5d)

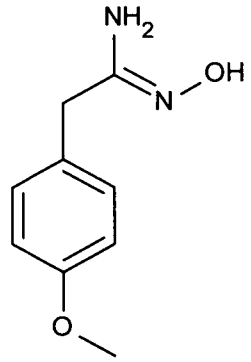


(5d)

[00307] To a solution of N-[(4-fluorophenyl)methyl]-N-(5-{[4-(2-methylpropoxy)phenyl]-methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine, free base (25.0 mg, 0.057 mmol) and acryl amide (40.8 mg, 0.570 mmol) in dry acetonitrile (2.5 ml) silica gel (35 mg) was added. The reaction mixture was heated to reflux and kept under reflux during 44 hours, additional acryl amide in 10 equivalents portions (50 equivalents) were added before the reaction was completed. The reaction suspension was filtered to remove silica and the silica gel was washed with 3 ml acetonitrile. The combined acetonitrile solution was concentrated and the product was purified by preparative HPLC with 40 to 90% acetonitrile in water (containing 0.1 % TFA) to get 24.1 mg (68%) as a TFA salt. ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.37 – 7.23 (m, 2H), 7.16 (d, J = 7.8 Hz, 2H), 7.04 (t, J = 8.2 Hz, 2H), 6.86 (d, J = 7.7 Hz, 2H), 4.61 (s, 2H), 4.14 (m, 1H), 3.94 (s, 2H), 3.78 – 3.68 (m, 2H), 3.63 (d, J = 11.6 Hz, 2H), 3.41 – 3.33 (m, 2H), 3.06 (t, J = 12.0 Hz, 2H), 2.71 (t, J = 6.2 Hz, 2H), 2.19 – 1.92 (m, 5H), 1.08 – 0.94 (m, 6H). LC-MS: 509.3 $[M+H]^+$.

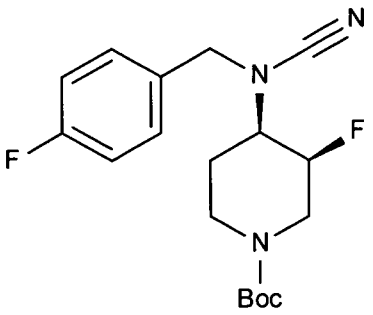
[00308] Example 6: (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}piperidin-4-amine; trifluoroacetic acid and (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}piperidin-4-amine; trifluoroacetic acid

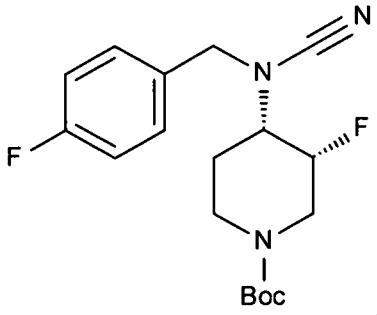
[00309] N'-hydroxy-2-(4-methoxyphenyl)ethenimidamide



[00310] 2-(4-methoxyphenyl)acetonitrile (4.415 g, 30 mmol) was dissolved in ethanol (50 ml). Hydroxylamine hydrochloride (2.18 g, 31.5 mmol) and diisopropylethylamine (5.45 ml, 31.5 mmol) were added. After having refluxed the solution for 3 hours under nitrogen, the reaction mixture was evaporated to dryness. Water (50 ml) was added and the aqueous phase was extracted with dichloromethane (400 ml). The organic phase was washed with brine (200 ml), dried (sodium sulfate), filtered and evaporated to dryness. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 15% methanol in dichloromethane to afford the title compound (1.5 g, 28 %).

[00311] tert-butyl (3R,4S)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate and tert-butyl (3S,4R)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate

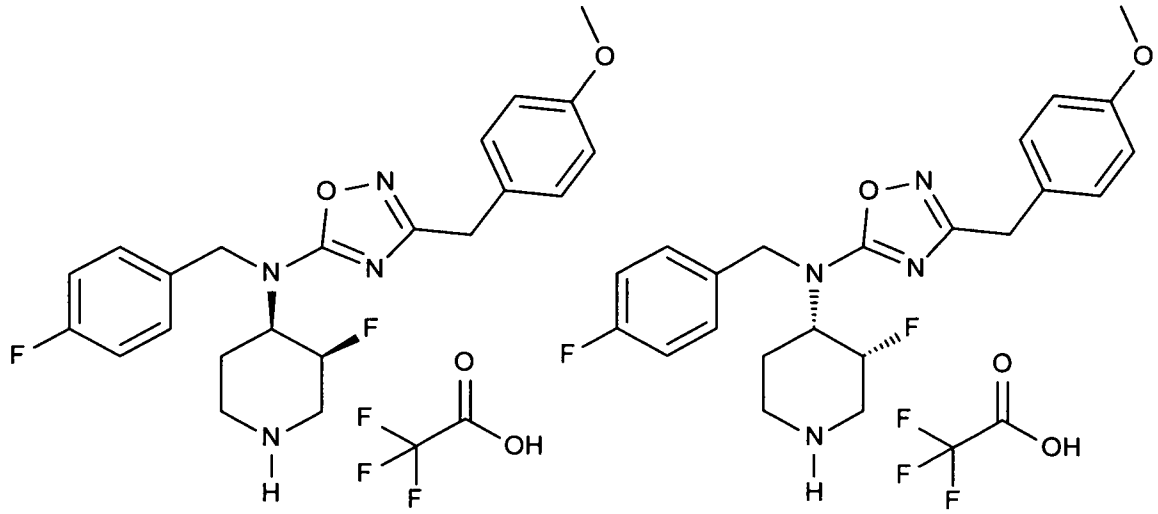




[00312] Tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1, 915 mg, 2.8 mmol), sodium carbonate (593 mg, 5.6 mmol) and carbononitridic bromide (445 mg, 4.2 mmol) were mixed in methanol (dry, 20 ml) and stirred at ambient temperature overnight. The solvent was evaporated and the residue was suspended in water (20 ml). The resulting mixture was extracted with diethyl ether (2 x 200 ml). The

combined organic phases were dried (sodium sulfate) and evaporated to give the crude product as a colorless oil (840 mg). The crude material was purified by column chromatography using silicon dioxide gel, eluting with 50% ethyl acetate in petroleum ether to afford the desired intermediate (600 mg, 61 %).

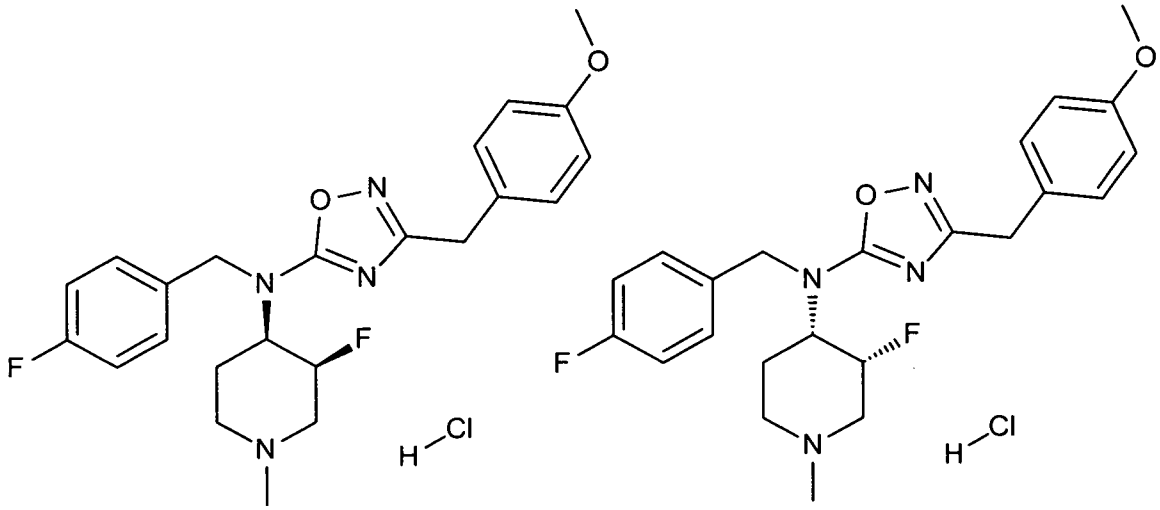
[00313] (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}piperidin-4-amine; trifluoroacetic acid and (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}piperidin-4-amine; trifluoroacetic acid



[00314] Tert-butyl (3R,4S)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate and tert-butyl (3R,4S)-4-{cyano[(4-fluorophenyl)methyl]amino}-3-fluoropiperidine-1-carboxylate (1:1, 600 mg, 1.70 mmol), N'-hydroxy-2-[4-(2-methoxyphenyl]ethenimidamide (307 mg, 1.70 mmol) and zinc chloride (1M in diethyl ether, 2.5 ml) were mixed in ethyl acetate (dry, 5 ml) and tetrahydrofuran (2 ml) and stirred at 50 °C for 3 hours. After cooling to room temperature, the white precipitate was filtered and the filtrate was evaporated to dryness. The crude was then heated in a mixture of ethanol (4 ml) and acetic acid (2 ml) for 1 hour at 100 °C. After evaporation of the solvent the crude was purified by column chromatography using silicon dioxide gel, eluting with 66% ethyl acetate in petroleum ether to give an oil (150 mg) which was stirred in a mixture of dichloromethane (4 ml) and trifluoroacetic acid (1.6 ml) overnight. The solvent was evaporated and the product was freeze dried from 1,4-dioxane to give the title compounds as a white powder (105 mg, 12%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.30 – 7.17 (m, 4H), 7.00 (t, 2H), 6.87 (d, 2H), 5.12 (d, 1H), 4.87 (d, 1H), 4.62 (d, 1H), 4.49 – 4.30 (m, 1H), 3.83 (s, 2H), 3.80 (s,

3H), 3.66 (t, 1H), 3.49 (d, 1H), 3.22 (dd, 1H), 3.00 (t, 1H), 2.47 (q, 1H), 1.75 (d, 1H), LC-MS: 415.3 $[M+H]^+$.

[00315] Example 7: (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}-1-methylpiperidin-4-amine hydrochloride and (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}-1-methylpiperidin-4-amine hydrochloride

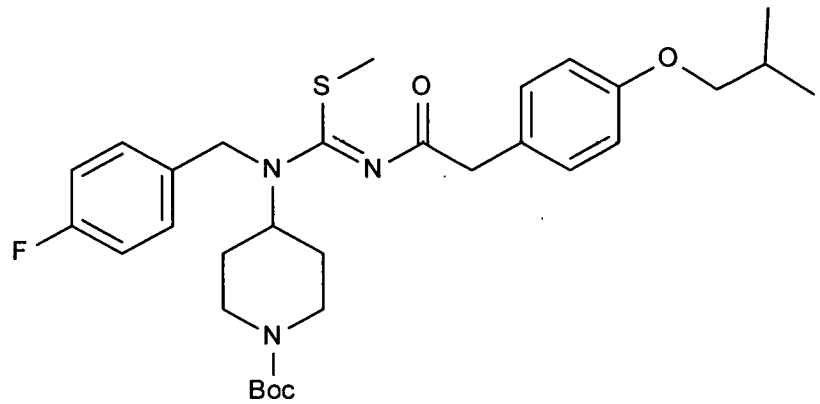


[00316] (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}piperidin-4-amine; trifluoroacetic acid and (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}piperidin-4-amine; trifluoroacetic acid (1:1, 105 mg, 0.2 mmol), were dissolved in tetrahydrofuran (2 ml) and mixed with formaldehyde (aqueous, 37%, 23 µl) and sodium cyanoborohydride (25 mg, 0.4 mmol). After stirring overnight, the reaction mixture was evaporated and the residue was dissolved in methanol (10 ml). The solution was refluxed for 2 hours. After evaporating the solvent, the residue was dissolved in ether (150 ml) and washed with sodium hydrogen carbonate solution (aqueous, saturated, 25 ml). The organic phase is dried (sodium sulfate), filtered and evaporated to dryness. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 2.5% methanol in dichloromethane to afford the corresponding free bases of the title compounds (15.5 mg, 18%). Freeze drying from a mixture of acetonitrile and aqueous hydrogen chloride solution affords the title compounds as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.31 – 7.19 (m, 4H), 7.02 – 6.93 (m, 2H), 6.90 – 6.83 (m, 2H), 4.93 – 4.61 (m, 2H), 4.22 – 4.06 (m, 1H), 3.82 (d,

5H), 3.18 (ddt, 1H), 2.97 – 2.88 (m, 1H), 2.35 – 2.28 (m, 4H), 2.28 – 2.17 (m, 1H), 2.15 – 2.04 (m, 1H), 1.58 – 1.50 (m, 1H), LC-MS: 429.2 $[M+H]^+$.

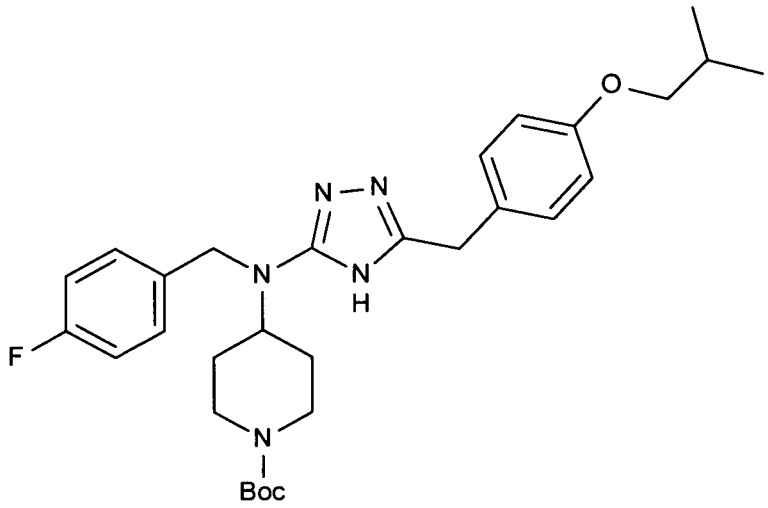
[00317] Example 8: 3-(4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidin-1-yl)propanoic acid; trifluoroacetic acid (8)

[00318] tert-butyl 4-{[(4-fluorophenyl)methyl][(1Z)-({2-[4-(2-methylpropoxy)phenyl]-acetyl}imino)(methylsulfanyl)methyl]amino}piperidine-1-carboxylate



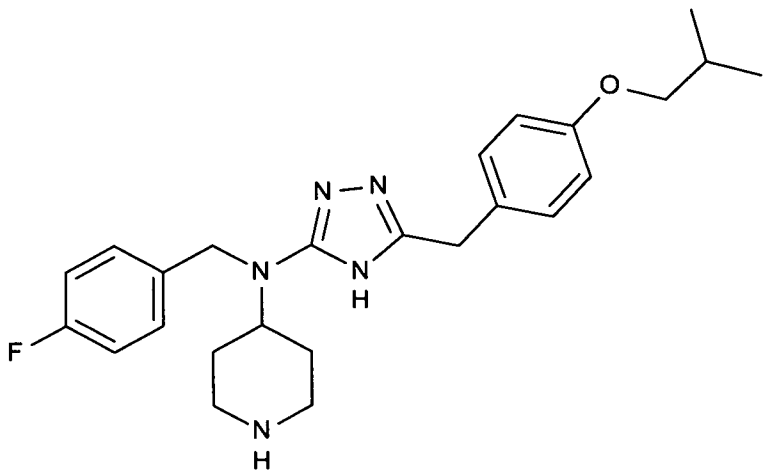
[00319] To a stirred solution of 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (650 mg, 3.03 mmol) in tetrahydrofuran (10 ml) at room temperature was added a solution of potassium thiocyanate (353 mg, 3.63 mmol) in acetone (10 ml) dropwise, followed by tert-butyl 4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (prepared in analogy to intermediate 20) (933 mg, 3.03 mmol). The mixture was heated to reflux for 2 hours, then potassium carbonate (501.3 mg, 3.632 mmol) was added in portions followed by methyl iodide (0.46 ml, 7.27 mmol) dropwise over 10 minutes. The mixture was cooled to room temperature and stirred overnight. Ethyl acetate (10 ml) was added. The solids were filtered off and washed with ethyl acetate (2 x 10 ml). The combined organic phases were concentrated to give the desired intermediate (1.75 g) that was used without further purification.

[00320] tert-butyl 4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidine-1-carboxylate



[00321] To a stirred solution of tert-butyl 4-{[(4-fluorophenyl)methyl][(1Z)-({2-[4-(2-methylpropoxy)phenyl]acetyl}imino)(methylsulfanyl)methyl]amino}piperidine-1-carboxylate (1.675 g, 2.93 mmol) in dioxane (70 ml) at room temperature was added a hydrazine hydrate (285 µl, 5.86 mmol) dropwise over 5 minutes. The mixture was heated to reflux, stirred for 1.5 hours, then additional hydrazine hydrate (285 µl, 5.86 mmol) was added and the resulting mixture was stirred overnight. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 1-3 % methanol in dichloromethane to afford the desired intermediate (716 mg, 45 %).

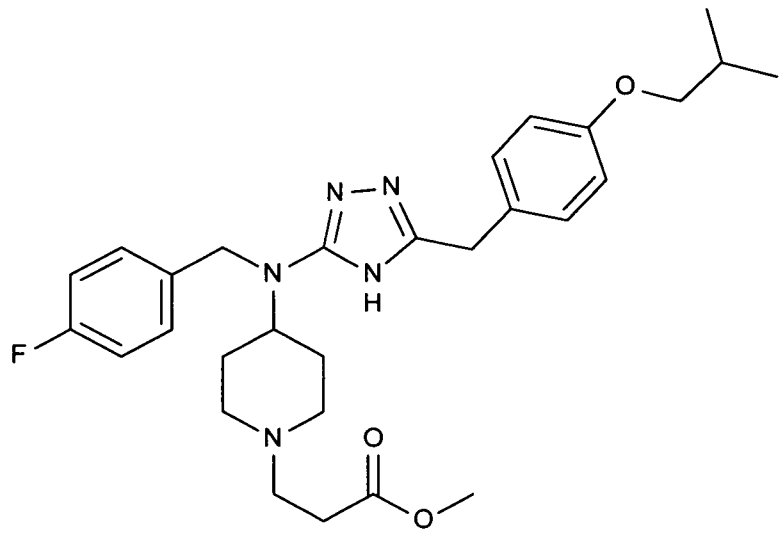
[00322] N-[(4-fluorophenyl)methyl]-N-(5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine



[00323] To a stirred solution of tert-butyl 4-{[(4-fluorophenyl)methyl](5-{[4-(2-methyl-propoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidine-1-carboxylate (715 mg, 1.33 mmol) in dichloromethane (12 ml) at room temperature was added trifluoroacetic acid (4

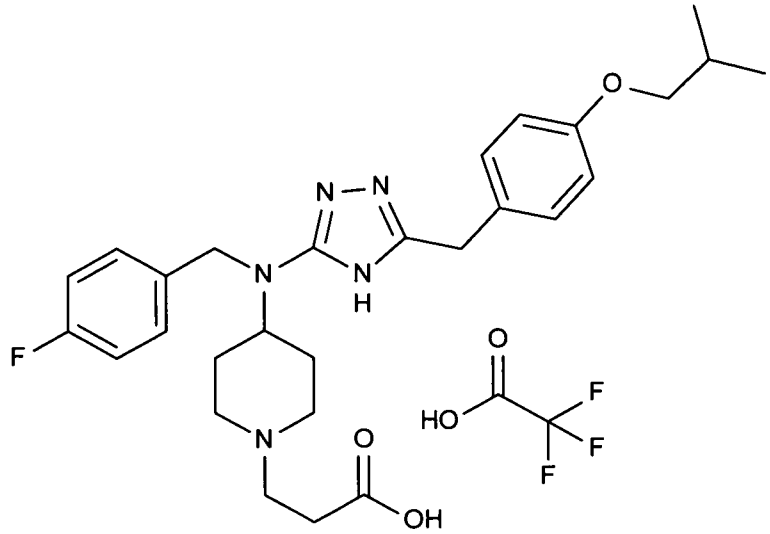
ml) in one portion. The reaction mixture was stirred for 40 minutes, then diluted with dichloromethane (20 ml) and washed with sodium hydrogen carbonate (20 ml, saturated aqueous). The water phase was extracted with dichloromethane (20 ml) and the combined organic phases were washed with brine (2x20 ml), dried over sodium sulfate, filtered, and concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 9-17 % methanol in dichloromethane to afford the desired intermediate (321 mg, 55 %).

[00324] methyl 3-(4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidin-1-yl)propanoate



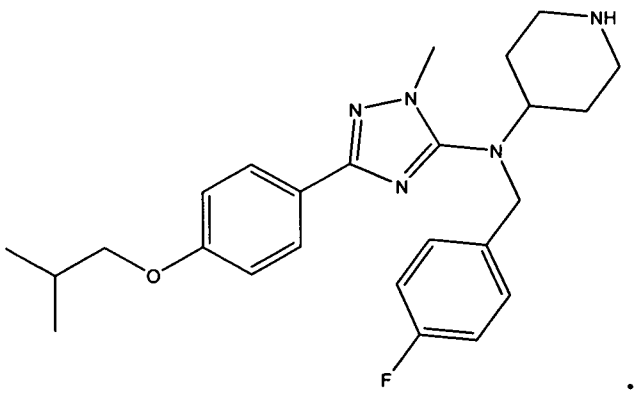
[00325] To a stirred solution of N-[(4-fluorophenyl)methyl]-N-(5-{[4-(2-methylpropoxy)-phenyl]methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine (26 mg, 0.0593 mmol) in acetonitrile (3 ml) at room temperature was added silicon dioxide (40 mg), and methyl acrylate (27 µl, 0.297 mmol). The mixture was heated to reflux, stirred for 4 hours, then additional methyl acrylate (30 µl, 0.33 mmol) was added and the mixture was stirred at room temperature for 36 hours. Additional methyl acrylate (30 µl, 0.33 mmol) was added, the mixture heated to reflux for 3 hours, filtered and concentrated. The residue was dissolved in acetonitrile (3 ml) and silicon dioxide (40 mg) and methyl acrylate (30 µl, 0.33 mmol) were added. The mixture was heated to reflux for 1 hour, then additional methyl acrylate (30 µl, 0.33 mmol) was added and the reaction was stirred overnight. The mixture was concentrated and purified by column chromatography using silicon dioxide gel, eluting with 5-29 % methanol in dichloromethane to afford the desired intermediate (9 mg, 34 %).

[00326] 3-(4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidin-1-yl)propanoic acid; trifluoroacetic acid

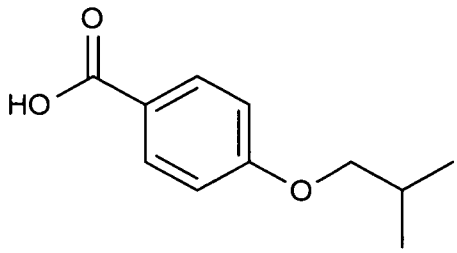


[00327] To a stirred solution of methyl 3-(4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidin-1-yl)propanoate (9 mg, 0.017 mmol) in tetrahydrofuran (2 ml) at room temperature was added a solution of lithium hydroxide (20 µl, 10 % aqueous). The mixture was stirred overnight and concentrated. The crude material was purified by HPLC, eluting with 35-70 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (2.5 mg, 23 %). ^{1}H NMR (400 MHz, Acetonitrile-*d3*) δ 7.93 (s, 1H), 7.32 – 7.24 (m, 2H), 7.19 (d, 2H), 7.05 (t, 2H), 6.86 (d, 2H), 4.57 (s, 2H), 4.23 – 4.07 (m, 2H), 3.94 (s, 2H), 3.73 (d, 2H), 3.56 – 3.46 (m, 2H), 3.30 – 3.23 (m, 2H), 3.06 – 2.94 (m, 2H), 2.81 – 2.73 (m, 2H), 2.33 – 2.14 (m, 2H), 2.08 – 1.99 (m, 2H), 0.99 (d, 6H); LC-MS: 510.4 $[M+H]^+$.

[00328] Example 9: N-[(4-fluorophenyl)methyl]-N-{1-methyl-3-[4-(2-methylpropoxy)-phenyl]-1H-1,2,4-triazol-5-yl}piperidin-4-amine; trifluoroacetic acid (9)

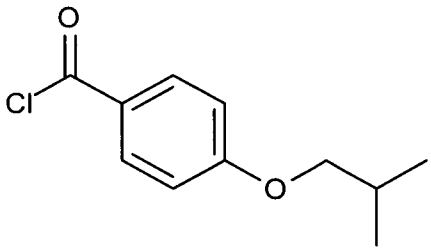


[00329] 4-(2-methylpropoxy)benzoic acid



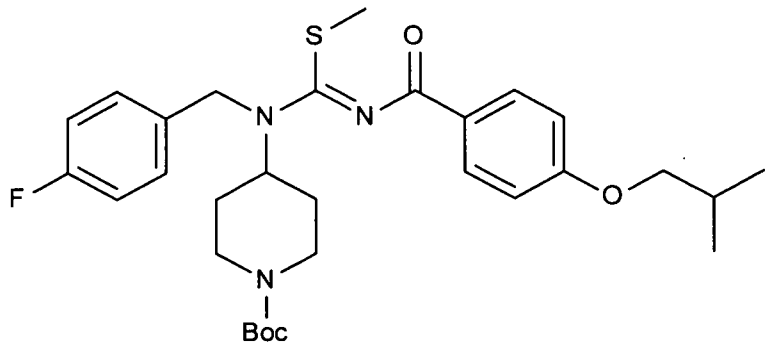
[00330] To a stirred solution of methyl 4-(2-methylpropoxy)-benzoate (3.35 g, 16.1 mmol) in methanol (80 ml) at room temperature was added a solution of sodium hydroxide (12.9 ml, 5 M aqueous) dropwise over 10 minutes. The mixture was stirred overnight, then additional sodium hydroxide solution (4.8 ml, 5M aqueous) was added and the mixture was heated to 37 °C. After 3 hours, hydrochloric acid (15 ml, 5 M aqueous) was added until the mixture reached pH 7. The mixture was concentrated, then diluted with water (40 ml). Hydrochloric acid (5 M aqueous) was added until the mixture reached pH 3 and the water phase was extracted with diethyl ether (4 x 50 ml). The combined organic phases were washed with water (70 ml), dried over magnesium sulfate, filtered, and concentrated to yield the desired intermediate (3.1 g) that was used without further purification.

[00331] 4-(2-methylpropoxy)benzoyl chloride



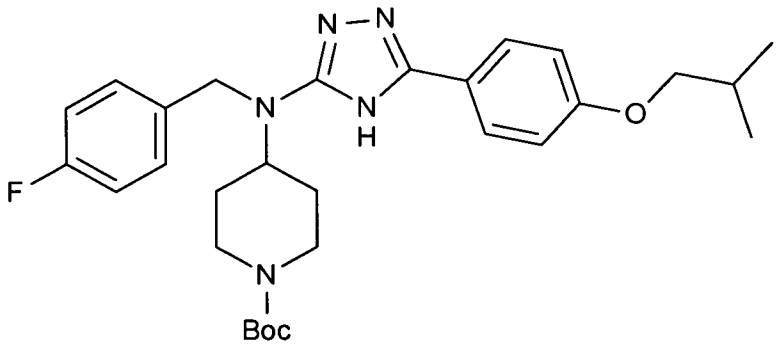
[00332] To a stirred suspension of 4-(2-methylpropoxy)benzoic acid (1.617 g, 8.292 mmol) in dichloromethane (6 ml) at room temperature was added thionyl chloride (6.02 ml, 82.92 mmol) dropwise. The mixture was stirred overnight, then concentrated to yield the desired intermediate (1.750 g) that was used without further purification.

[00333] tert-butyl 4-{[(4-fluorophenyl)methyl][(1Z)-{[(Z)-4-(2-methylpropoxy)benzoyl]-imino}(methylsulfanyl)methyl]amino}piperidine-1-carboxylate



[00334] To a stirred solution of 4-(2-methylpropoxy)benzoyl chloride (1.75 g, 8.25 mmol) in tetrahydrofuran (27 ml) at room temperature was added a solution of potassium thiocyanate (0.96 g, 9.90 mmol) in acetone (27 ml) dropwise, followed by tert-butyl 4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (prepared in analogy to intermediate 20) (2.54 g, 8.25 mmol). The mixture was heated to reflux for 2 hours, then potassium carbonate (1.37 g, 9.90 mmol) was added in portions followed by methyl iodide (1.23 ml, 19.8 mmol) dropwise over 10 minutes. The mixture was stirred overnight. Ethyl acetate (20 ml) was added, the solids were filtered off and washed with ethyl acetate (2 x 200 ml). The combined organic phases were concentrated to give the desired intermediate (4.46 g).

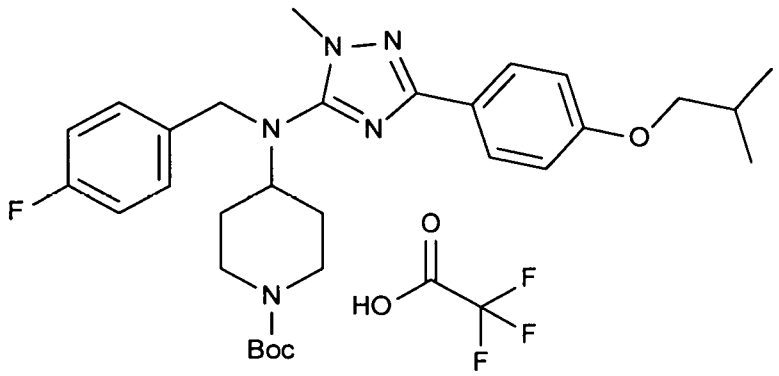
[00335] tert-butyl 4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidine-1-carboxylate



[00336] To a stirred solution of tert-butyl 4-{[(4-fluorophenyl)methyl][(1Z)-{[(Z)-4-(2-methylpropoxy)benzoyl]imino}(methylsulfanyl)methyl]amino}piperidine-1-carboxylate (4.45 g, 7.98 mmol) in dioxane (180 ml) at room temperature was added a hydrazine hydrate (388 µl, 7.98 mmol) dropwise over 5 minutes. The mixture was heated to reflux, stirred for 80 minutes, then additional hydrazine hydrate (388 µl, 7.98 mmol) was added. The mixture was stirred for 20 minutes, then additional hydrazine hydrate (388 µl, 7.98 mmol) was added. The mixture was stirred for 5 hours, then cooled to room temperature and stirred overnight.

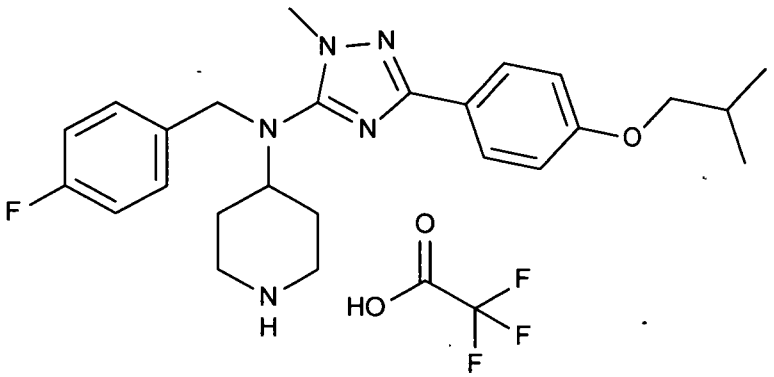
The mixture was concentrated and the crude material was purified by column chromatography using silicon dioxide gel, eluting with 1-2 % methanol in dichloromethane to afford the desired intermediate (1.64 g, 39 %).

[00337] tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-3-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-5-yl})amino}piperidine-1-carboxylate; trifluoroacetic acid



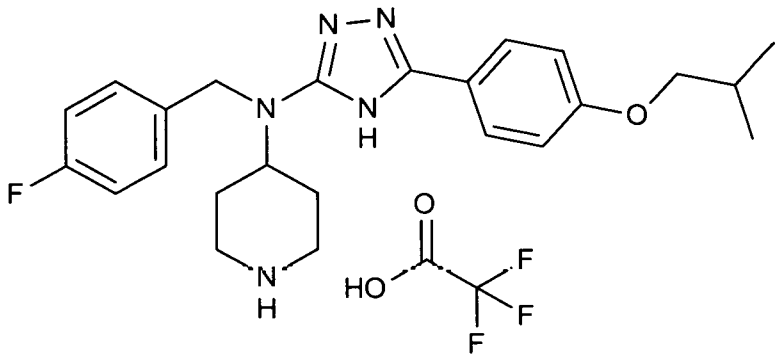
[00338] To a stirred solution of tert-butyl 4-{[(4-fluorophenyl)methyl]({5-[4-(2-methyl-propoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidine-1-carboxylate (235 mg, 0.450 mmol) in dimethylformamide (3.5 ml) at room temperature was added potassium tert-butoxide (60.6 mg, 0.540 mmol) in one portion. After 15 minutes methyl iodide (39 µl, 0.63 mmol) was added and the reaction mixture was stirred for 80 minutes. Brine (20 ml) was added and the reaction mixture extracted with ethyl acetate (3 x 20 ml). The combined organic phases were washed with water (30 ml) and concentrated. The crude material was purified by HPLC, eluting with 65-95 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the intermediate (55 mg, 19 %).

[00339] N-[(4-fluorophenyl)methyl]-N-{1-methyl-3-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-5-yl}piperidin-4-amine; trifluoroacetic acid



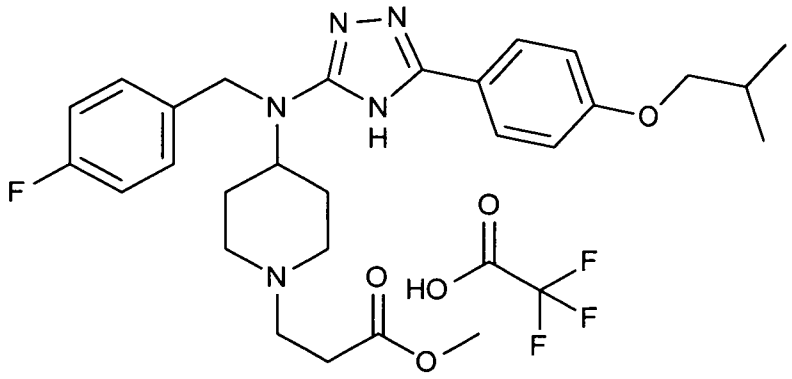
[00340] To a stirred solution of tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-3-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-5-yl})amino}piperidine-1-carboxylate; trifluoroacetic acid (57 mg, 0.106 mmol) in dichloromethane (3 ml) at room temperature was added trifluoroacetic acid (1 ml) in one portion. The reaction mixture was stirred for 1 hour, then concentrated and purified by HPLC, eluting with 35-80 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (38 mg, 78 %). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.87 (d, 2H), 7.30 (dd, 2H), 7.09 – 6.93 (m, 4H), 4.33 (s, 2H), 3.79 (d, 2H), 3.53 – 3.43 (m, 3H), 3.32 (s, 3H), 3.07 (t, 2H), 2.26 (d, 2H), 2.08 (dq, 1H), 2.01 – 1.84 (m, 2H), 1.06 (d, 6H); LC-MS: 438.4 $[M+H]^+$.

[00341] Example 10: N-[(4-fluorophenyl)methyl]-N-{5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl}piperidin-4-amine; trifluoroacetic acid (10)



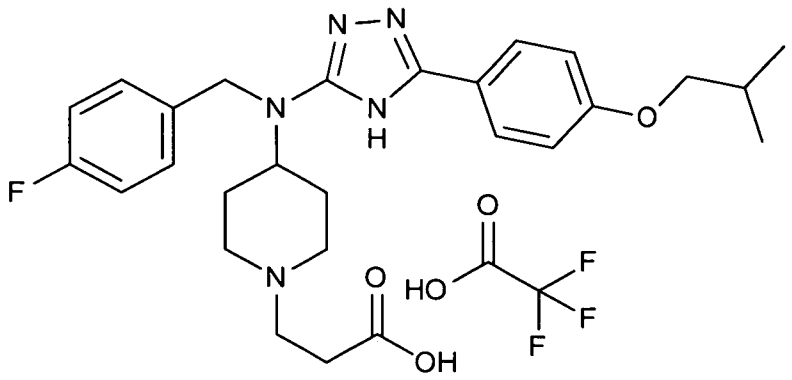
[00342] To a stirred solution of tert-butyl 4-{[(4-fluorophenyl)methyl]({5-[4-(2-methyl-propoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidine-1-carboxylate (1.38 g, 2.63 mmol) in dichloromethane (24 ml) at room temperature was added trifluoroacetic acid (8 ml) in one portion. The reaction mixture was stirred for 105 minutes, then concentrated to give crude material (2.34 g). A portion of the crude material (105 mg) was purified by HPLC, eluting with 40-95 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (38 mg, 60 %). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, 2H), 7.41 – 7.31 (m, 2H), 7.13 – 6.97 (m, 4H), 4.68 (s, 2H), 4.26 (dt, 1H), 3.81 (d, 2H), 3.47 (d, 2H), 3.09 (t, 2H), 2.21 – 1.98 (m, 5H), 1.05 (d, 6H); LC-MS: 424.3 $[M+H]^+$.

[00343] Example 11: methyl 3-(4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)-phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidin-1-yl)propanoate; trifluoroacetic acid (11)



[00344] To a stirred solution of N-[(4-fluorophenyl)methyl]-N-{5-[4-(2-methylpropoxy)-phenyl]-4H-1,2,4-triazol-3-yl}piperidin-4-amine (86 mg, 0.204 mmol) in acetonitrile (5 ml) at room temperature was added silicon dioxide (100 mg), and methyl acrylate (37 µl, 0.408 mmol). The mixture was heated to reflux, stirred overnight, filtered, and concentrated. The crude material was purified by HPLC, eluting with 35-75 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (78 mg, 61 %) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, 2H), 7.23 – 7.13 (m, 2H), 6.99 – 6.87 (m, 4H), 4.59 (s, 2H), 4.57 – 4.45 (m, 1H), 3.77 – 3.67 (m, 5H), 3.51 (d, 2H), 3.27 (t, 2H), 2.99 (t, 2H), 2.82 (t, 2H), 2.36 (q, 2H), 2.08 (m, 1H), 1.89 (d, 2H), 1.03 (d, 6H); LC-MS: 510.4 $[M+H]^+$.

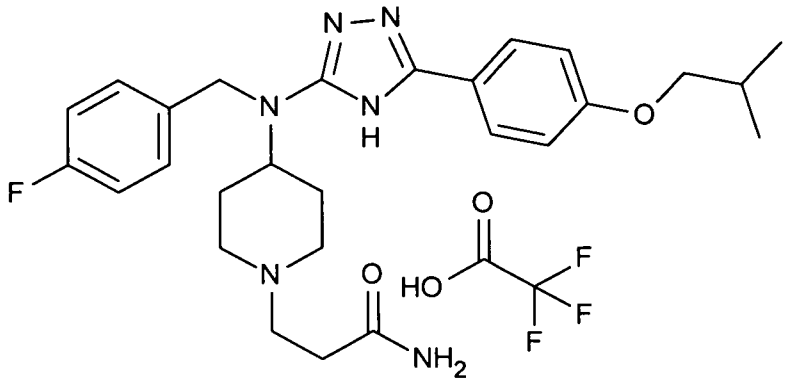
[00345] Example 12: 3-(4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidin-1-yl)propanoic acid; trifluoroacetic acid (12)



[00346] To a stirred solution of methyl 3-(4-{[(4-fluorophenyl)methyl]({5-[4-(2-methyl-propoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidin-1-yl)propanoate; trifluoroacetic acid (68 mg, 0.109 mmol) in tetrahydrofuran (2.5 ml) at room temperature was added a solution of lithium hydroxide (200 µl, 7.8 % aqueous). The mixture was stirred for 3 days, then diluted with methanol (15 ml), acidified with acetic acid to pH 7, and concentrated. The crude material was purified by HPLC, eluting with 35-90 % acetonitrile in water (containing

0.1 % trifluoroacetic acid) to afford the title compound (15 mg, 23 %). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (d, 2H), 7.40 – 7.29 (m, 2H), 7.10 – 6.95 (m, 4H), 4.65 (s, 2H), 4.22 (s, 1H), 3.79 (d, 2H), 3.62 (d, 2H), 3.40 (s, 2H), 3.21 – 3.04 (m, 2H), 2.82 (t, 2H), 2.21 (s, 2H), 2.07 (dt, 3H), 1.03 (d, 6H); LC-MS: 496.3 $[M+H]^+$.

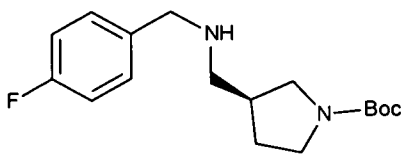
[00347] Example 13: 3-(4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidin-1-yl)propanamide; trifluoroacetic acid (13)



[00348] To a stirred solution of N-[(4-fluorophenyl)methyl]-N-{5-[4-(2-methylpropoxy)-phenyl]-4H-1,2,4-triazol-3-yl}piperidin-4-amine (86 mg, 0.204 mmol) in acetonitrile (5 ml) at room temperature was added silicon dioxide (100 mg), and acrylamide (29 mg, 0.408 mmol). The mixture was heated to reflux, stirred overnight, filtered, and concentrated. The crude material was purified by HPLC, eluting with 35-75 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (11.2 mg, 9 %) ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.85 (d, 2H), 7.44 – 7.34 (m, 2H), 7.13 – 6.99 (m, 4H), 4.68 (s, 2H), 4.32 – 4.18 (m, 1H), 3.82 (d, 2H), 3.67 (d, 2H), 3.40 (t, 2H), 3.12 (t, 2H), 2.74 (t, 2H), 2.22 (d, 2H), 2.09 (p, 3H), 1.06 (d, 6H); LC-MS: 495.4 $[M+H]^+$.

[00349] Example 14: N-[(4-fluorophenyl)methyl]-N-{[(3R)-1-methylpyrrolidin-3-yl]methyl}-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (14)

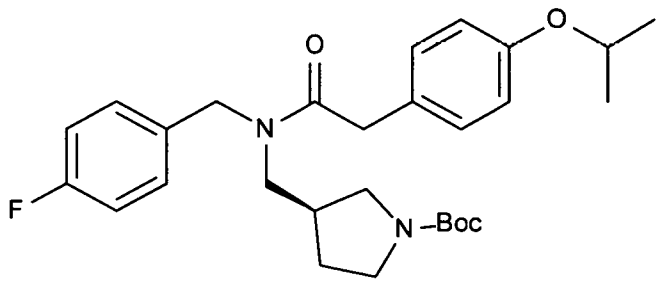
[00350] tert-butyl (3S)-3-({[(4-fluorophenyl)methyl]amino}methyl)pyrrolidine-1-carboxylate



[00351] 4-fluorobenzaldehyde (268 µl, 2.5 mmol) was added to a solution of tert-butyl (3S)-3-(aminomethyl)pyrrolidine-1-carboxylate (501 mg, 2.5 mmol) in ethanol (5 ml). After

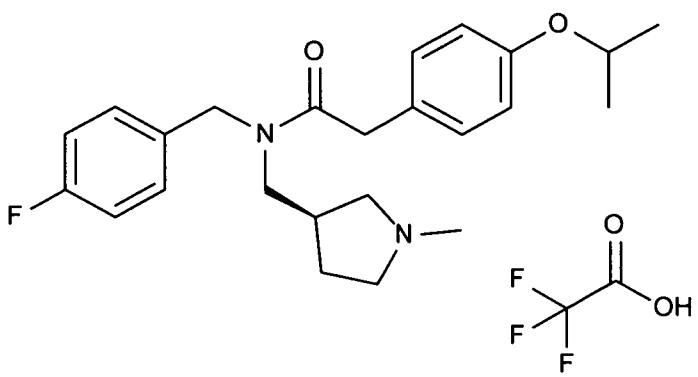
1 hour of stirring at ambient temperature sodium triacetoxyborohydride (795 mg, 3.75 mmol) was added. After additionally 18 hours of stirring the mixture was concentrated. Sodium hydroxide (1 M, 10 ml) was added and the resulting mixture was extracted with dichloromethane (2 x 10 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by column chromatography using silica gel, eluting with 5-10% methanol in dichloromethane to afford the title compound (619 mg, 80%).

[00352] tert-butyl (3S)-3-({N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}methyl)pyrrolidine-1-carboxylate



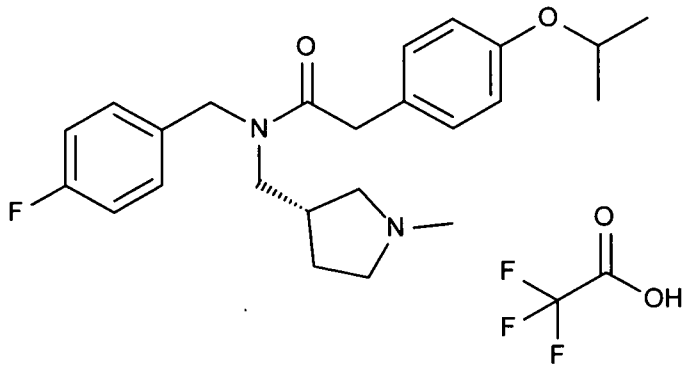
[00353] 2-[4-(propan-2-yloxy)phenyl]acetyl chloride (51.7 mg, 243 μmol) in dichloromethane (500 μl) was added to a solution of tert-butyl (3S)-3-({[(4-fluorophenyl)methyl]amino}methyl)pyrrolidine-1-carboxylate (50 mg, 162 μmol) and diisopropylethylamine (45.8 μl, 324 μmol) in dichloromethane (500 μl). After 1 hour of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with 25-50% ethyl acetate in petroleum ether to afford the title compound (77.2 mg, 98%).

[00354] N-[(4-fluorophenyl)methyl]-N-{[(3R)-1-methylpyrrolidin-3-yl]methyl}-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (14)



[00355] tert-butyl (3S)-3-({N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}methyl)pyrrolidine-1-carboxylate (77.2 mg, 159 μmol) was dissolved in dichloromethane (1.5 ml) and trifluoroacetic acid (500 μl) was added. After 15 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofuran (1 ml). Formaldehyde (37% aqueous, 17.8 μl, 239 μmol) and sodium triacetoxyborohydride (67.5 mg, 318 μmol) were added. After 15 minutes of stirring at ambient temperature more formaldehyde (37% aqueous, 17.8 μl, 239 μmol) was added. After additionally 3 hours more sodium triacetoxyborohydride (67.5 mg, 318 μmol) was added. The resulting mixture was stirred for 30 minutes before it was cooled to -20 °C and stored overnight. The mixture was heated to ambient temperature, diluted with sodium hydroxide (1 M, 5 ml) and extracted with dichloromethane (2 x 5 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 30-55% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (62 mg, 76%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.87 (bs, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.2 Hz, 4H), 6.84 (d, J = 8.5 Hz, 2H), 4.68 – 4.41 (m, 3H), 3.87 – 3.68 (m, 3H), 3.65 (s, 2H), 3.14 (dd, J = 13.8, 5.0 Hz, 1H), 2.95 – 2.69 (m, 6H), 2.26 – 2.05 (m, 1H), 1.88 – 1.69 (m, 1H), 1.33 (d, J = 6.1 Hz, 6H); LC-MS: 399.2 $[M+H]^+$.

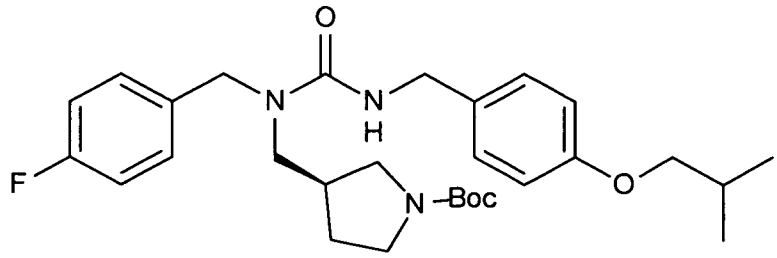
[00356] Example 15: N-[(4-fluorophenyl)methyl]-N-{[(3S)-1-methylpyrrolidin-3-yl]methyl}-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (15)



[00357] The compound was prepared in analogy with example 14 using tert-butyl (3R)-3-(aminomethyl)pyrrolidine-1-carboxylate. Yield: 55.4 mg, 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.83 (bs, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.0 Hz, 4H), 6.83 (d, J = 8.5 Hz, 2H), 4.68 – 4.39 (m, 3H), 3.83 – 3.68 (m, 3H), 3.65 (s, 2H), 3.14 (dd, J = 13.8, 5.1 Hz, 1H), 2.95 – 2.64 (m, 6H), 2.26 – 2.06 (m, 1H), 1.87 – 1.67 (m, 1H), 1.32 (d, J = 6.1 Hz, 6H); LC-MS: 399.2 $[M+H]^+$.

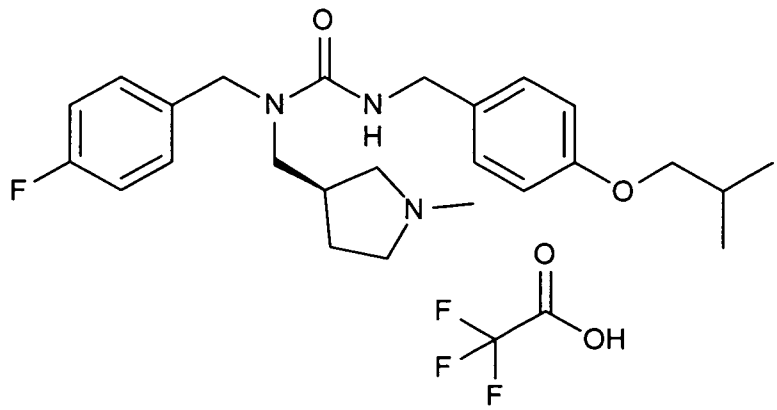
[00358] Example 16: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}-3-{[(3R)-1-methylpyrrolidin-3-yl]methyl}urea (16)

[00359] tert-butyl (3S)-3-({[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}methyl)pyrrolidine-1-carboxylate



[00360] 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (49.9 mg, 243 μmol) in dichloromethane (1 ml) was added to tert-butyl (3S)-3-({[(4-fluorophenyl)methyl]amino}-methyl)pyrrolidine-1-carboxylate (50 mg, 162 μmol (prepare in analogy with the intermediate in example 14). After 1 hour of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with 25-50% ethyl acetate in petroleum ether to afford the title compound (79.5 mg, 96%).

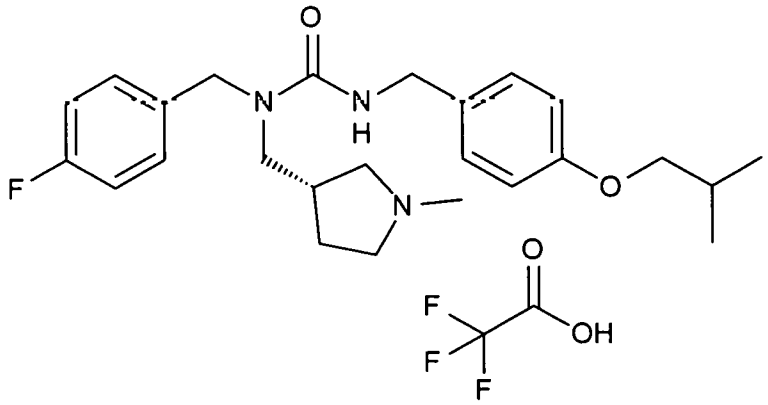
[00361] 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(3R)-1-methylpyrrolidin-3-yl]methyl}urea ; trifluoroacetic acid (16);



[00362] tert-Butyl (3S)-3-({[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}methyl)pyrrolidine-1-carboxylate (79.5 mg, 155 μmol) was dissolved in dichloromethane (1.5 ml) and trifluoroacetic acid (500 μl) was added. After 15 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofurane (1 ml). Formaldehyde (37% aqueous, 17.3 μl, 232 μmol) and sodium triacetoxyborohydride (65.6 mg, 310 μmol) were added. After 30 minutes of stirring at

ambient temperature more formaldehyde (37% aqueous, 17.3 µl, 232 µmol) was added. After additionally 1 hour more sodium triacetoxyborohydride (65.6 mg, 310 µmol) was added. The resulting mixture was stirred for 30 minutes before it was cooled to -20 °C and stored overnight. The mixture was heated to ambient temperature, diluted with sodium hydroxide (1 M, 5 ml) and extracted with dichloromethane (2 x 5 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 30-55% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (47.3 mg, 56%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.89 (d, 2H), 7.25 – 6.95 (m, 6H), 6.80 (dd, J = 8.5, 5.7 Hz, 2H), 4.64 – 4.24 (m, 4H), 3.89 – 3.73 (m, 2H), 3.69 (d, J = 6.6 Hz, 2H), 3.58 – 3.41 (m, 1H), 3.24 (dt, J = 15.1, 5.4 Hz, 1H), 3.00 – 2.62 (m, 6H), 2.34 – 1.97 (m, 2H), 1.92 – 1.71 (m, 1H), 1.01 (dd, J = 6.7, 1.7 Hz, 6H); LC-MS: 428.3 $[M+H]^+$.

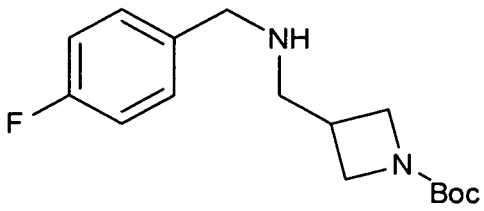
[00363] Example 17: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(3S)-1-methylpyrrolidin-3-yl]methyl}urea; trifluoroacetic acid (17)



[00364] The compound was prepared in analogy with example 16 using tert-butyl (3R)-3-({[(4-fluorophenyl)methyl]amino}methyl)pyrrolidine-1-carboxylate. Yield: 51.8 mg, 59%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.77 (d, 1H), 7.24 – 6.93 (m, 6H), 6.80 (dd, J = 8.5, 5.5 Hz, 2H), 4.61 – 4.26 (m, 4H), 3.90 – 3.73 (m, 2H), 3.69 (d, J = 6.6 Hz, 2H), 3.58 – 3.43 (m, 1H), 3.30 – 3.17 (m, 1H), 3.01 – 2.63 (m, 6H), 2.31 – 1.98 (m, 2H), 1.91 – 1.73 (m, 1H), 1.01 (dd, J = 6.7, 1.6 Hz, 6H); LC-MS: 428.3 $[M+H]^+$.

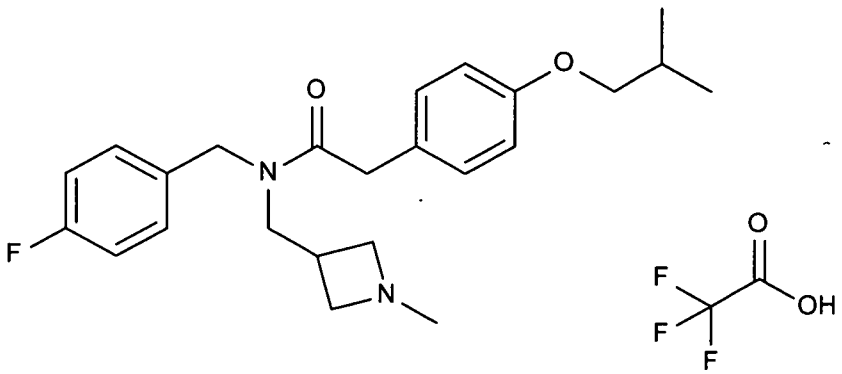
[00365] Example 18: N-[(4-fluorophenyl)methyl]-N-[(1-methylazetidin-3-yl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (18)

[00366] tert-butyl 3-({[(4-fluorophenyl)methyl]amino}methyl)azetidine-1-carboxylate

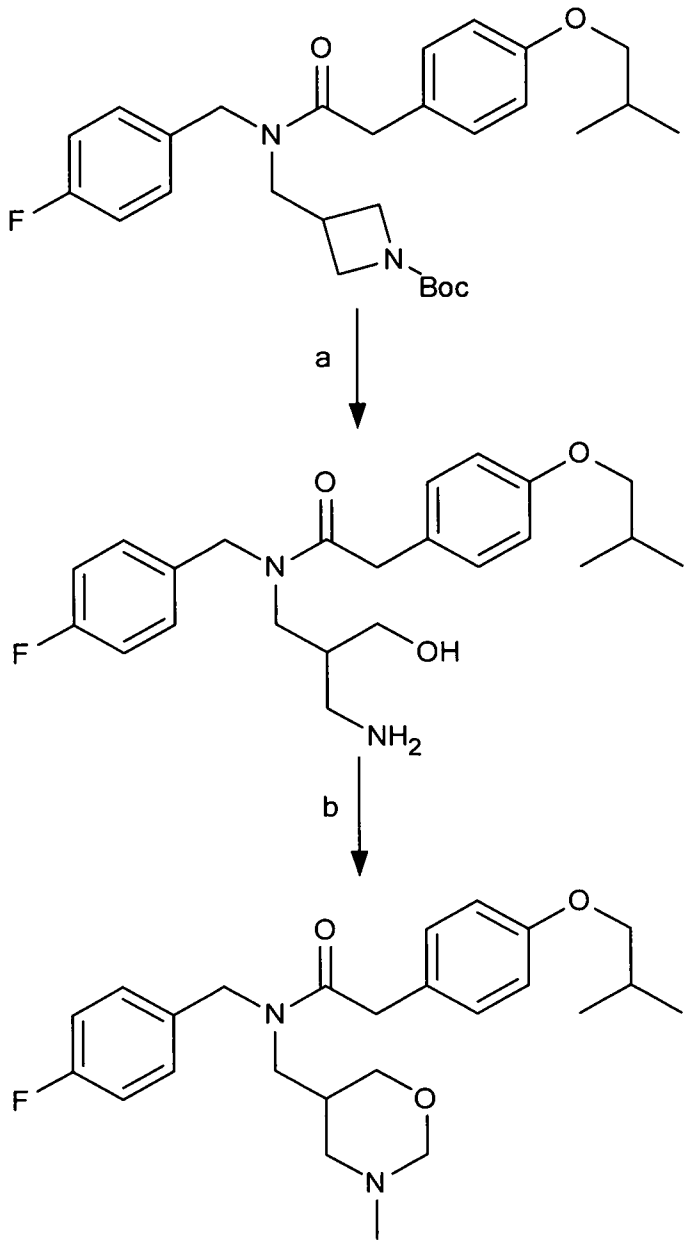


[00367] To a mixture of 4-fluorobenzaldehyde (268 µl, 2.5 mmol) and tert-butyl 3-(amino-methyl)azetidine-1-carboxylate (465.7 mg, 2.5 mmol) in dichloromethane (25 ml) sodium triacetoxyborohydride (795 mg, 3.75 mmol) was added at ambient temperature. After stirring for 24 hours the mixture was treated with sodium hydroxide (1M, 10 ml), separated and extracted with dichloromethane (2 x 10 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by column chromatography using silica gel, eluting with 2-5% methanol in dichloromethane to afford the title compound in 61% yield (471 mg).

[00368] N-[(4-fluorophenyl)methyl]-N-[(1-methylazetidin-3-yl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (18);



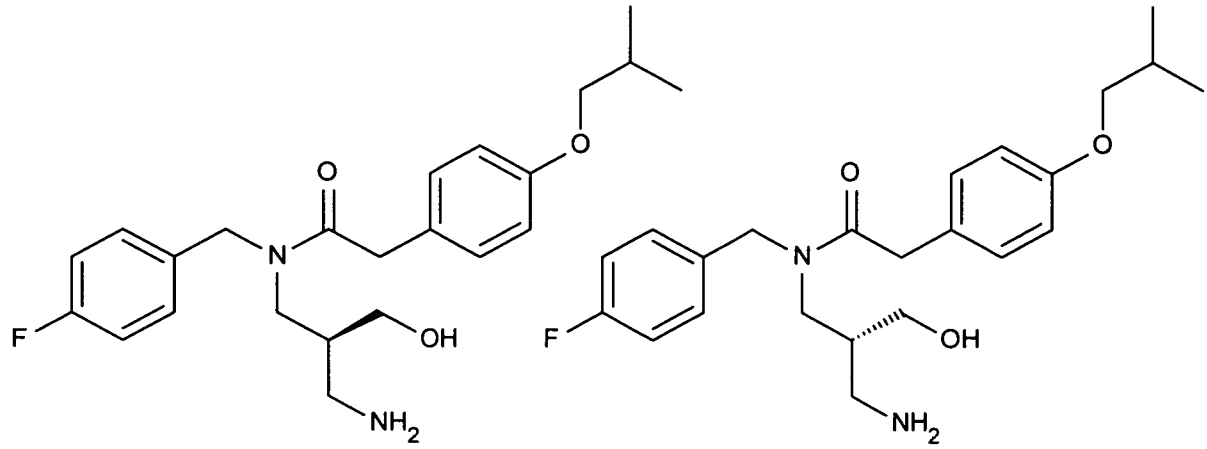
[00369] The compound was prepared in analogy with example 14, starting from 2-[4-(propan-2-yloxy)phenyl]acetyl chloride and tert-butyl 3-({[(4-fluorophenyl)methyl]-amino}methyl)azetidine-1-carboxylate to eventually give the title compound in 47% yield (12.6 mg): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 – 6.96 (m, 6H), 6.90 – 6.81 (m, 2H), 4.64 – 4.27 (m, 3H), 4.21 – 3.36 (m, 9H), 3.36 – 3.05 (m, 1H), 2.78 (s, 3H), 2.17 – 1.94 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 399.52 $[M+H]^+$.



[00370] Scheme 6. Reagents: a) trifluoroacetic acid; b) formaldehyde, sodium triacetoxyborohydride.

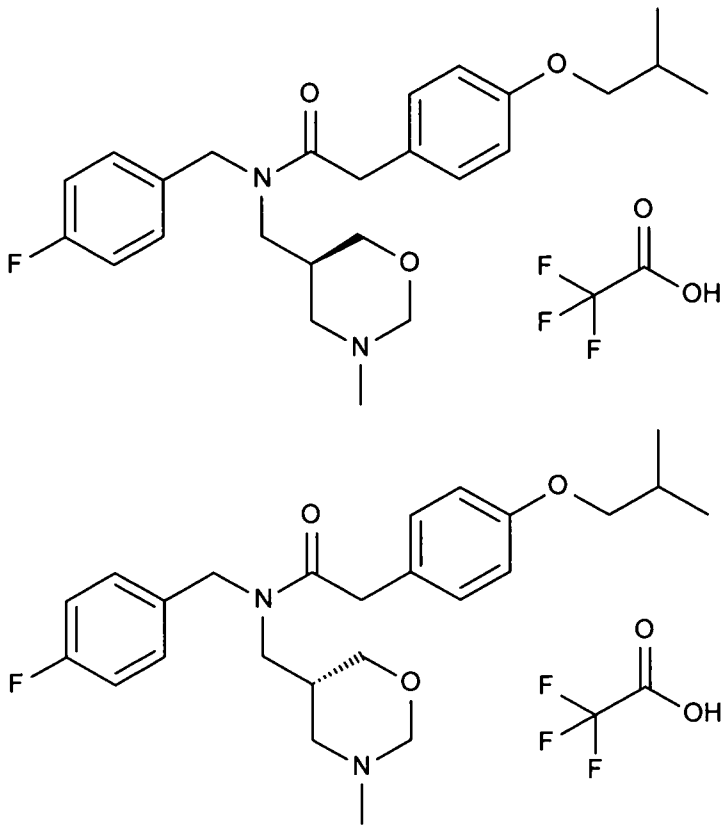
[00371] Example 19 (scheme 6): N-[(4-fluorophenyl)methyl]-N-{[(5R)-3-methyl-1,3-oxazinan-5-yl]methyl}-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (19a); and N-[(4-fluorophenyl)methyl]-N-{[(5S)-3-methyl-1,3-oxazinan-5-yl]methyl}-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (19b)

[00372] N-[(2R)-2-(aminomethyl)-3-hydroxypropyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide and N-[(2S)-2-(aminomethyl)-3-hydroxypropyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide



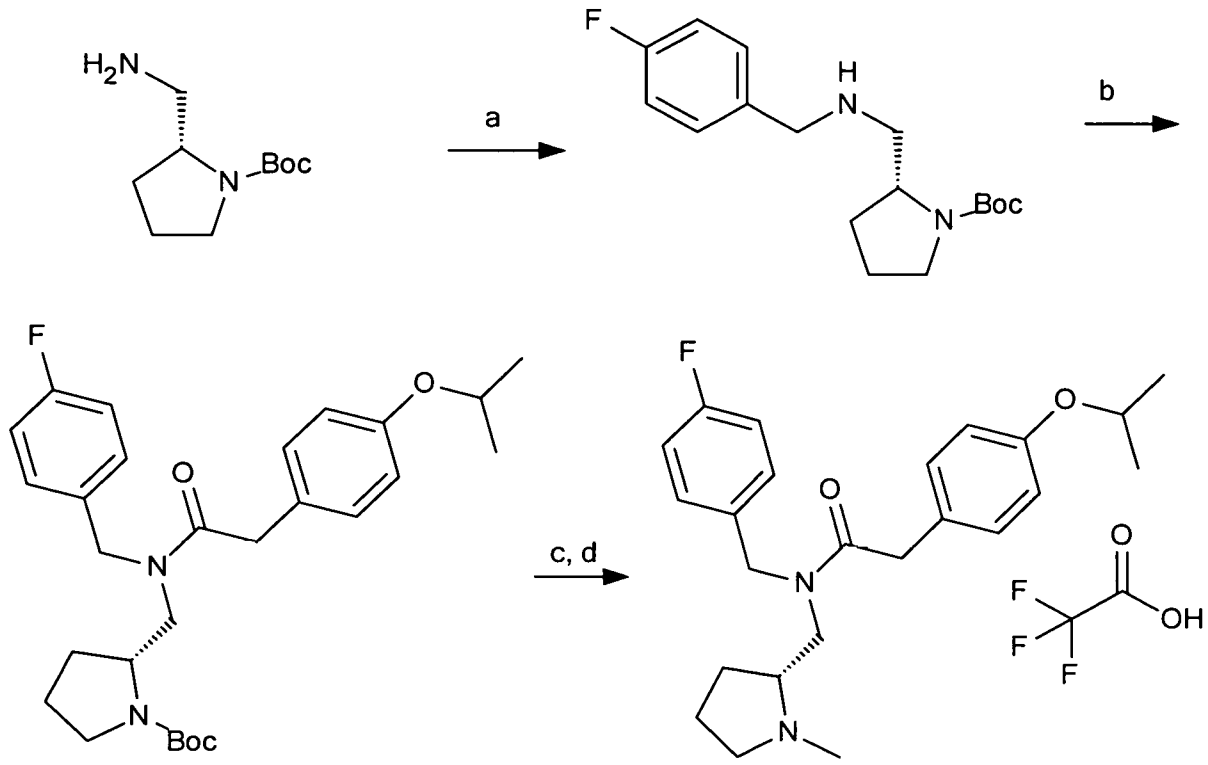
[00373] tert-butyl 3-({N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-acetamido}methyl)azetidine-1-carboxylate (20 mg, 41.3 μmol) was dissolved in dichloro-methane (1 ml), trifluoroacetic acid (50 μl) and water (50 μl) was added. After stirring for 24 hours at ambient temperature the mixture diluted with sodium hydroxide (aq. sat. 1 ml) and extracted with dichloromethane (2 x 3 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds (7 mg, 43%) as a 1:1 mixture of enantiomers.

[00374] N-[(4-fluorophenyl)methyl]-N-{[(5R)-3-methyl-1,3-oxazinan-5-yl]methyl}-2-[4-(2-methylpropoxy)phenyl]acetamide (19a); trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-{[(5S)-3-methyl-1,3-oxazinan-5-yl]methyl}-2-[4-(2-methylpropoxy)phenyl]acetamide (19b); trifluoroacetic acid



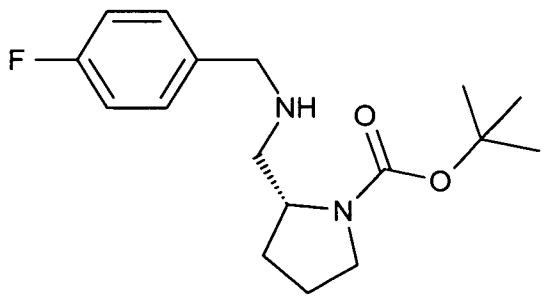
[00375] N-[2-(aminomethyl)-3-hydroxypropyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenacetamide (7mg, 17 μmol) was dissolved in tetrahydrofuran (1 ml). Formaldehyde (37% aqueous, 1.78 μl, 23.9 μmol) and sodium triacetoxyborohydride (6.75 mg, 31.8 μmol) were added. After 15 minutes of stirring at ambient temperature more formaldehyde (37% aqueous, 1.78 μl, 23.9 μmol) was added. After 2 hours more sodium triacetoxyborohydride (6.75 mg, 31.8 μmol) was added. The resulting mixture was stirred for 30 minutes before it was diluted with sodium hydrogen carbonate (aq. sat. 2 ml) and extracted with dichloromethane (2 x 5 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds (6.5 mg, 70%) as a 1:1 mixture of enantiomers: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.22 (m, 2H), 7.19 – 7.08 (m, 2H), 7.08 – 6.98 (m, 2H), 6.90 – 6.79 (m, 2H), 4.22 – 4.08 (m, 1H), 4.08 – 3.91 (m, 2H), 3.88 – 3.64 (m, 4H), 3.58 – 3.30 (m, 3H), 3.14 – 2.80 (m, 2H), 2.70 – 2.49 (m, 4H), 2.51 – 2.23 (m, 1H), 2.06 (hept, J = 6.0 Hz, 1H), 1.12 – 0.90 (m, 6H); LC-MS: 429.54 $[M+H]^+$.

[00376] Example 20: N-[(4-fluorophenyl)methyl]-N-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-2-[4-(propan-2-yloxy)phenyl]-acetamide; trifluoroacetic acid (20)



[00377] Scheme 7. Reagents: a) 4-fluorobenzaldehyde, sodium triacetoxyborohydride; b) 2-[4-(propan-2-yloxy)phenyl]acetyl chloride; diisopropylethylamine; c) trifluoroacetic acid; d) formaldehyde, sodium triacetoxyborohydride.

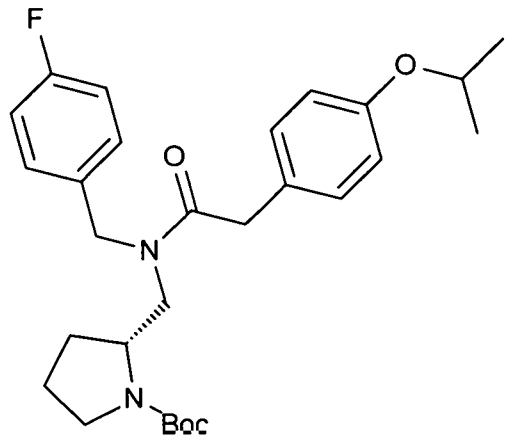
[00378] tert-butyl (2R)-2-({[(4-fluorophenyl)methyl]amino}methyl)pyrrolidine-1-carboxylate



[00379] To a solution of 4-fluorobenzaldehyde (248 mg, 2.00 mmol) in 3 ml dry tetrahydrofuran a solution of tert-butyl (2R)-2-(aminomethyl)pyrrolidine-1-carboxylate (421 mg, 2.10 mmol) in 3 ml dry tetrahydrofuran was added. After 20 minutes stirring, sodium triacetoxyborohydride (721 mg, 3.40 mmol) was added in one portion and stirring was continued for 3 hours. Diethyl ether (50 ml) was added to the reaction and the reaction was

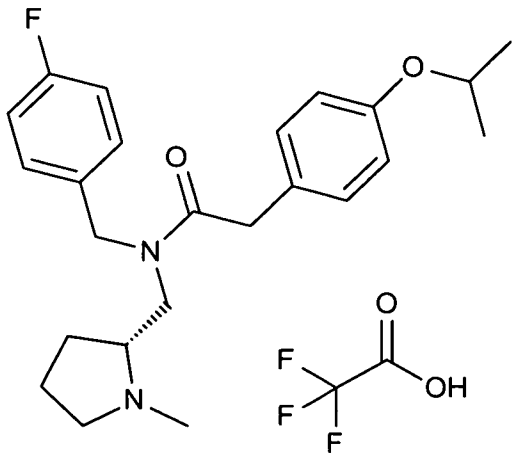
basified with sodium hydroxide (1 M, 1 ml) to pH 10. The water phase was extracted once with diethyl ether (150 ml), combined organic phase was washed once with brine (50 ml), dried over sodium sulfate, concentrated and the product was purified by column chromatography using silica gel, eluting with ethyl acetate:methanol 100:2 to give tert-butyl (2R)-2-({[(4-fluoro-phenyl)methyl]amino}methyl)pyrrolidine-1-carboxylate (360 mg, 58.4%) as light yellow oil.

[00380] tert-butyl (2R)-2-({N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-methyl)pyrrolidine-1-carboxylate



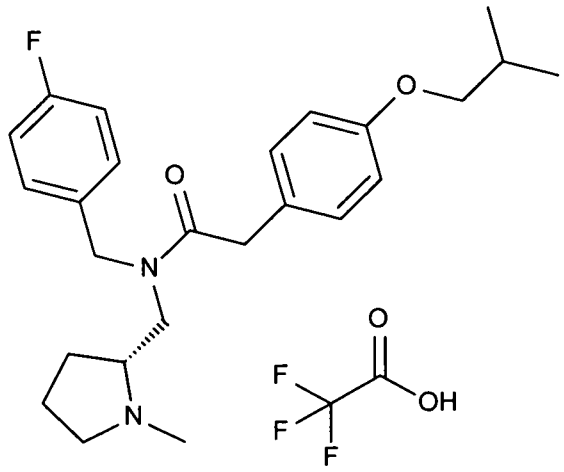
[00381] To a solution of tert-butyl (2R)-2-({[(4-fluoro-phenyl)methyl]amino}methyl)-pyrrolidine-1-carboxylate (99 mg, 0.321 mmol) in dry dichloromethane (1.0 ml) 2-[4-(propan-2-yloxy)phenyl]acetyl chloride (81.9 mg, 0.385 mmol) in dry dichloromethane (1 ml) was added followed by diisopropylethylamine (125 mg, 0.963 mmol) in dry dichloromethane (0.4 ml). The reaction was stirred for 20 hours before it was concentrated and purified by column chromatography using silica gel, eluting with petroleum ether:ethyl acetate 3:2 to give tert-butyl (2R)-2-({N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-methyl)pyrrolidine-1-carboxylate (136 mg, 87.4%) as a light yellow oil.

[00382] N-[(4-fluorophenyl)methyl]-N-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-2-[4-(propan-2-yloxy)phenyl]-acetamide; trifluoroacetic acid (20)



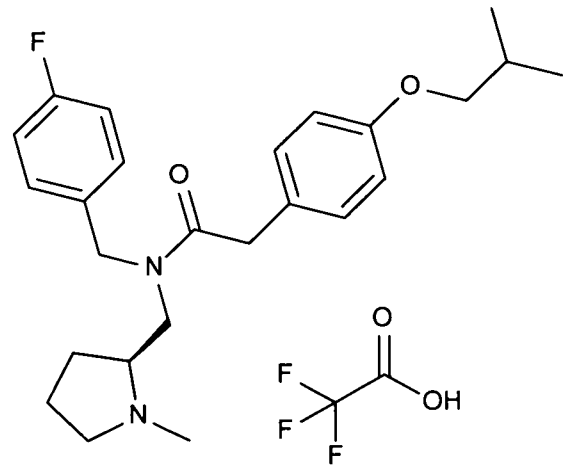
[00383] To a solution get tert-butyl (2R)-2-({N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-methyl)pyrrolidine-1-carboxylate (136 mg, 0.281 mmol) in dry dichloromethane (4.5 ml) trifluoroacetic acid (1.5 ml) was added dropwise. After 20 minutes stirring the reaction mixture was analyzed by LCMS to check deprotection is completed. The reaction solution was concentrated, dried and redissolved in tetrahydrofuran (3 ml). To that solution formaldehyde (30% solution in water, 77.2 µL, 0.842 mmol) was added. After 10 minutes of stirring sodium triacetoxyborohydride (119 mg, 0.561 mmol) was added. After 20 hours of stirring the reaction was quenched by sodium hydrogen carbonate (0.1 ml, aqueous, saturated), concentrated and diluted with dichloromethane (15 ml) and sodium hydrogen carbonate (10 ml, aqueous, saturated). Phases were separated and the water phase was extracted with dichloromethane (2 x 15 ml). Combined organic phase was washed with 20% brine (25 ml), dried over sodium sulfate and concentrated to give 121 mg crude product. The crude material was purified by HPLC, eluting with 30-55% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (88 mg, 78.7%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.13 (d, J = 8.4 Hz, 2H), 7.08 – 6.98 (m, 4H), 6.85 (d, J = 8.4 Hz, 2H), 4.72 (s, 2H), 4.57 – 4.50 (m, 1H), 3.90 – 3.80 (m, 1H), 3.78 – 3.68 (m, 4H), 3.68 – 3.60 (m, 1H), 2.91 – 2.83 (m, 1H), 2.76 (s, 3H), 2.16 – 2.08 (m, 2H), 2.07 – 1.97 (m, 1H), 1.87 – 1.77 (m, 1H), 1.33 (d, J = 6.0 Hz, 6H); LC-MS: 399.2 $[M+H]^+$.

[00384] Example 21: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-acetamide; trifluoroacetic acid (21)



[00385] The compound was prepared in analogy with example 20 (using 2-[4-(2-methylpropoxy)phenyl]acetyl chloride instead of 2-[4-(propan-2-yloxy)phenyl]acetyl chloride). Yield (46.0 mg, 54.2%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 - 7.12 (m, 2H), 7.11 - 7.00 (m, 4H), 6.88 – 6.83 (m, 2H), 4.71 (s, 2H), 3.89 – 3.80 (m, 1H), 3.79 – 3.68 (m, 6H), 3.68 – 3.60 (m, 1H), 2.90 – 2.80 (m, 1H), 2.76 (s, 3H), 2.17 – 1.96 (m, 4H), 1.88 – 1.78 (m, 1H), 1.06 – 1.00 (d, J = 6.7 Hz, 6H); LC-MS: 413.3 $[M+H]^+$.

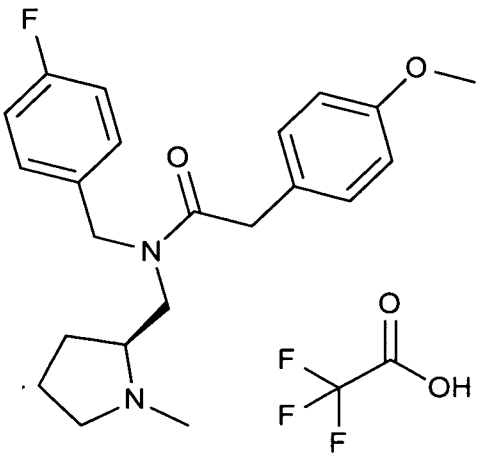
[00386] Example 22: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-{[(2S)-1-methylpyrrolidin-2-yl]methyl}acetamide; trifluoroacetic acid (22)



[00387] The compound was prepared in analogy with example 20 using sodium cyanoborohydride (3 equivalents) instead of sodium triacetoxyborohydride under the methylation step, and tert-butyl (2S)-2-(aminomethyl)pyrrolidine-1-carboxylate instead of tert-butyl (2R)-2-(aminomethyl)pyrrolidine-1-carboxylate. Yield 60.0 mg, 43.5%.^{1}H NMR (400 MHz, Chloroform-d) δ 7.12 (d, J = 8.6 Hz, 2H), 7.10 – 7.02 (m, 4H), 6.85 (d, J = 8.6

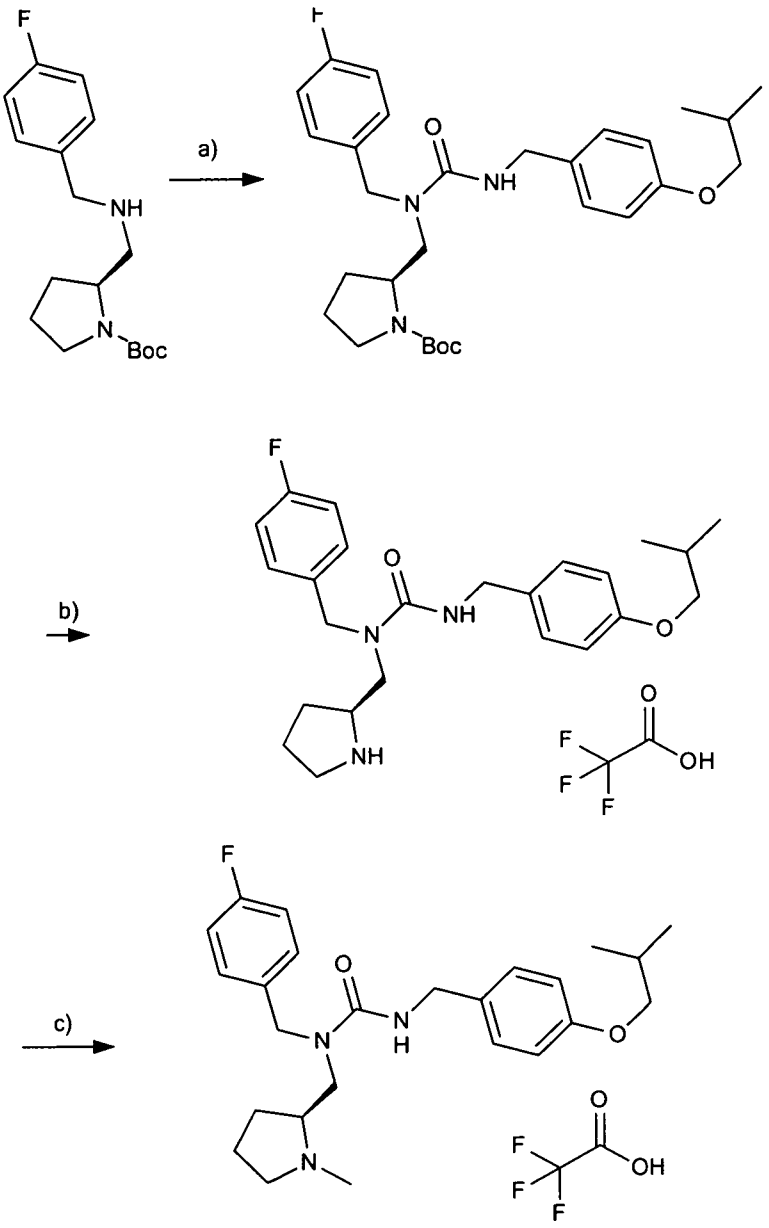
Hz, 2H), 4.70 (s, 2H), 3.89 - 3.82 (m, 1H), 3.79 – 3.60 (m, 7H), 2.91-2.82 (m, 1H), 2.76 (s, 3H), 2.18 – 1.94 (m, 4H), 1.87 – 1.75 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 413.3 $[M+H]^+$.

[00388] Example 23: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-{[(2S)-1-methylpyrrolidin-2-yl]methyl}acetamide; trifluoroacetic acid (23)



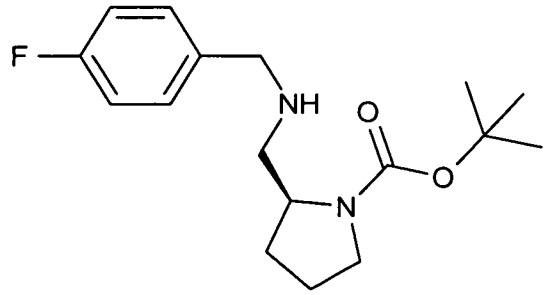
[00389] The compound was prepared in analogy with example 20 using sodium cyanoborohydride (3 equivalents) instead of sodium triacetoxyborohydride under the methylation step tert-butyl (2S)-2-(aminomethyl)pyrrolidine-1-carboxylate instead of tert-butyl (2S)-2-(aminomethyl)pyrrolidine-1-carboxylate, and 2-(4-methoxyphenyl)acetyl chloride instead of 2-[4-(propan-2-yloxy)phenyl]acetyl chloride. Yield 3.2 mg, 6.8%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 - 7.10 (m, 4H), 7.05 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.78 (q, J= 16.6 Hz, 2H), 3.90 - 3.82 (m, 1H), 3.80 (s, 3H), 3.76 - 3.65 (m, 5H), 2.88 - 2.79 (m, 1H), 2.73 (s, 3H), 2.21 – 2.09 (m, 2H), 2.05-1.93 (m, 1H), 1.89 - 1.79 (m, 1H); LC-MS: 371.1 [M+H].

[00390] Example 24: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}-3-{[(2S)-pyrrolidin-2-yl]methyl}urea; trifluoroacetic acid (24a) and 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2S)-1-methylpyrrolidin-2-yl]methyl}urea; trifluoroacetic acid (24b)



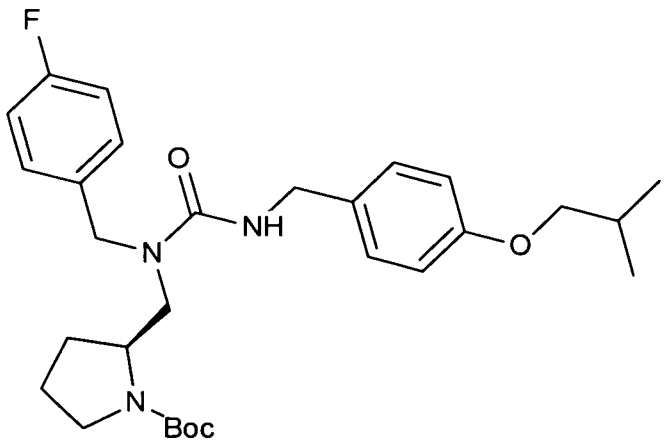
[00391] Scheme 8. Reagents: a) 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene; b) trifluoroacetic acid; c) formaldehyde, sodium cyanoborohydride.

[00392] Tert-butyl (2S)-2-({[(4-fluorophenyl)methyl]amino}methyl)pyrrolidine-1-carboxylate



[00393] To a solution of 4-fluorobenzaldehyde (248 mg, 2.00 mmol) in 3 ml dry tetrahydrofuran a solution of tert-butyl (2S)-2-(aminomethyl)pyrrolidine-1-carboxylate (421 mg, 2.10 mmol) in 3 ml dry tetrahydrofuran was added. After 20 minutes stirring sodium triacetoxyborohydride (721 mg, 3.40 mmol) was added in one portion and stirring was continued for 3 hours. Diethyl ether (50 ml) was added to the reaction and the reaction was basified with sodium hydroxide (1 M, 1 ml) to pH 10. The water phase was extracted once with diethyl ether (150 ml), combined organic phase was washed once with brine (50 ml), dried over sodium sulfate and concentrated. The product was purified by column chromatography using silica gel, eluting with ethyl acetate:methanol 100:2 to give tert-butyl (2S)-2-({[(4-fluoro-phenyl)methyl]amino}methyl)pyrrolidine-1-carboxylate (360 mg, 58.4%) as light yellow oil.

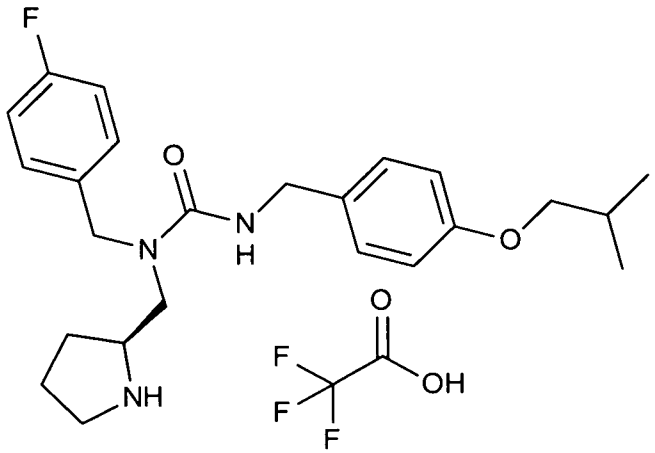
[00394] Tert-butyl (2S)-2-({[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)amino}methyl)pyrrolidine-1-carboxylate



[00395] To a solution of tert-butyl (2S)-2-({[(4-fluoro-phenyl)methyl]amino}methyl)-pyrrolidine-1-carboxylate (90 mg, 0.292 mmol) in dry dichloromethane (1.5 ml) 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (71.9 mg, 0.350 mmol) in dry dichloromethane (1 ml) was added. The reaction was stirred for 20 hours before it was

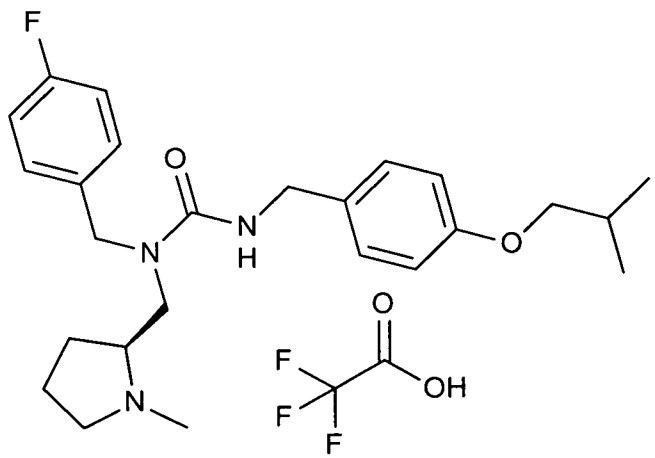
concentrated and purified by column chromatography using silica, eluting with petroleum ether:ethyl acetate 1:1 to give tert-butyl (2S)-2-({[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)amino} methyl)pyrrolidine-1-carboxylate (132 mg, 88%) as a colourless oil.

[00396] 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2S)-pyrrolidin-2-yl]methyl}urea; trifluoroacetic acid (24a)



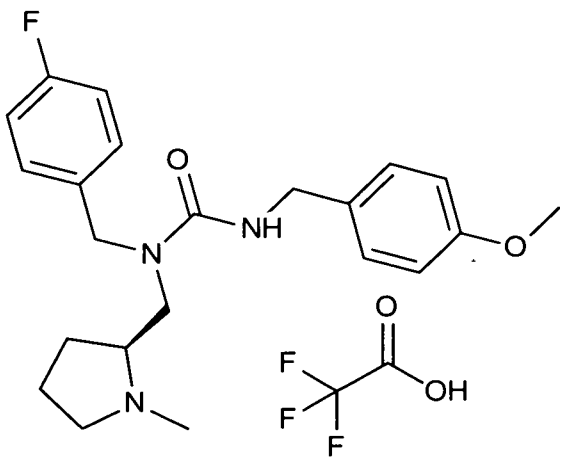
[00397] To a solution of tert-butyl (2S)-2-({[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)amino}methyl)pyrrolidine-1-carboxylate (132 mg, 0.257 mmol) in dry dichloromethane (3.6 ml) trifluoroacetic acid (1.2 ml) was added dropwise. After 20 minutes stirring the reaction mixture was concentrated to give 3-[(4-fluorophenyl)-methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2S)-pyrrolidin-2-yl]methyl}urea; trifluoroacetic acid with quantitative yield.

[00398] 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2S)-1-methyl-pyrrolidin-2-yl]methyl}urea; trifluoroacetic acid (24b)



[00399] 3-[(4-Fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2S)-pyrrolidin-2-yl]methyl}urea; trifluoroacetic acid (35.2 mg, 0.085 mmol) was dissolved in tetrahydrofuran (5 ml). To that solution formaldehyde (30% solution in water, 12.8 µL, 0.170 mmol) was added, after 10 minutes followed by sodium cyanoborohydride (16.0 mg, 0.255 mmol). During the next several hours folmaldehyde/sodium cyanoborohydride addition was repeated twice more in order to complete methylation (LCMS control). After 20 hours of stirring the reaction was quenched by sodium hydrogen carbonate (0.1 ml, aqueous, saturated), concentrated and diluted with dichloromethane (30 ml) and sodium hydrogen carbonate (12 ml, aqueous, saturated). Phases were separated and the water phase was extracted once with dichloromethane (8 ml). Combined organic phase was washed with water (15 ml), dried over sodium sulfate and concentrated. The crude material was purified by HPLC, eluting with 25-75% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (22.5 mg, 61.9 %): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.15 (dd, J = 8.5, 5.3 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.02 (t, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.31 (bs, 1H, NH), 4.65 (d, J = 17.0 Hz, 1H), 4.49 (d, J = 17.0 Hz, 1H), 4.30 (s, 2H), 3.93 - 3.82 (m, 2H), 3.78 – 3.63 (m, 4H), 2.95 - 2.88 (m, 1H), 2.85 (s, 3H), 2.28-2.19 (m, 1H), 2.20– 2.12 (m, 1H), 2.10-2.00 (m, 2H), 1.98 – 1.83 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 428.3 $[M+H]^+$.

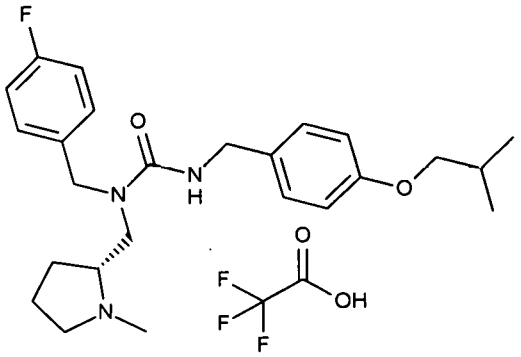
[00400] Example 25: 3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-{[(2S)-1-methylpyrrolidin-2-yl]methyl}-urea; trifluoroacetic acid (25)



[00401] The compound was prepared in analogy with example 24 using 1-(isocyanato-methyl)-4-methoxybenzene instead of 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene . Yield 20.6 mg (27.5%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 – 7.11 (m, 2H), 7.11-7.06 (m, 2H), 7.01 (t, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.60 (bs, 1H, NH), 4.54 (q , J =

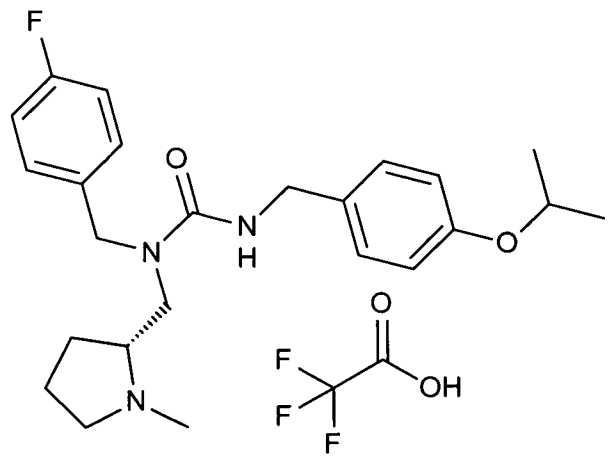
17.0 Hz, 2H), 4.29 (s, 2H), 3.88 – 3.77 (m, 5H), 3.74 – 3.61 (m, 2H), 2.98 – 2.90 (m, 1H), 2.87 (s, 3H), 2.27 – 2.19 (m, 1H), 2.13 – 2.02 (m, 2H), 1.92 – 1.84 (m, 1H); LC-MS: 386.1 $[M+H]^+$.

[00402] Example 26: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}-3-{[(2R)-1-methylpyrrolidin-2-yl]methyl}urea; trifluoroacetic acid (26)



[00403] The compound was prepared in analogy with example 24 using sodium triacetoxyborohydride, and tert-butyl (2R)-2-(aminomethyl)pyrrolidine-1-carboxylate instead of tert-butyl (2S)-2-(aminomethyl)pyrrolidine-1-carboxylate. Yield 20.6 mg, 27.5%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 – 7.12 (m, 2H), 7.11 – 7.06 (m, 2H), 7.05 – 7.00 (m, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.04 (bs, 1H, NH), 4.64 – 4.46 (m, 2H), 4.29 (s, 2H), 3.90 – 3.80 (m, 2H), 3.78 – 3.72 (m, 1H), 3.72 – 3.58 (m, 3H), 2.98 – 2.92 (m, 1H), 2.89 (s, 3H), 2.30 – 2.20 (m, 1H), 2.19 – 2.00 (m, 3H), 1.90 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 428.3 $[M+H]^+$.

[00404] Example 27: 3-[(4-fluorophenyl)methyl]-3-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-1-{[4-(propan-2-yloxy)phenyl]-methyl}urea; trifluoroacetic acid (27)

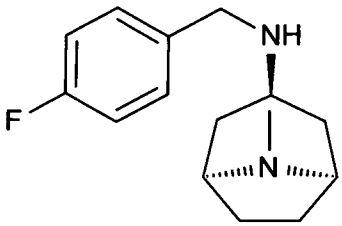


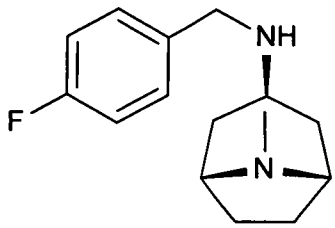
[00405] The compound was prepared in analogy with example 24 using sodium triacetoxyborohydride, and 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene instead of 1-

(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield 20.0 mg, 18.4%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 – 7.12 (m, 2H), 7.08 – 6.99 (m, 4H), 6.79 (d, J = 8.3 Hz, 2H), 4.90 (bs, 1H, NH), 4.61 – 4.48 (m, 3H), 4.29 (s, 2H), 3.88 – 3.78 (m, 2H), 3.73 – 3.64 (m, 2H), 2.97 – 3.90 (m, 1H), 2.88 (s, 3H), 2.28 - 2.19 (m, 1H), 2.18 – 2.00 (m, 2H), 1.95 – 1.85 (m, 1H), 1.39 – 1.22 (d, J = 6.5 Hz, 6H); LC-MS: 414.4 $[M+H]^+$.

[00406] Example 28: N-[(4-fluorophenyl)methyl]-N-[(1R,3r,5S)-8-methyl-8-azabicyclo-[3.2.1]octan-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (28)

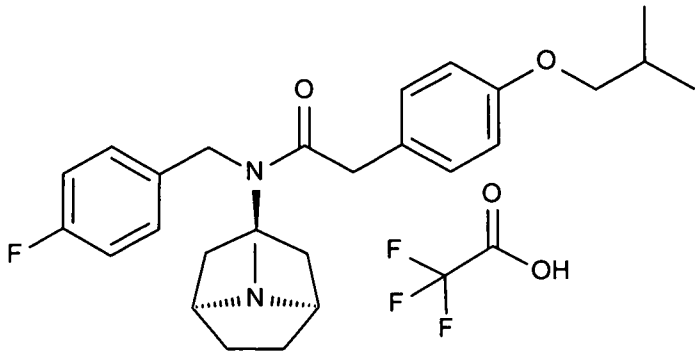
[00407] (1R,3r,5S)-N-[(4-fluorophenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-amine and (1R,3s,5S)-N-[(4-fluorophenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-amine





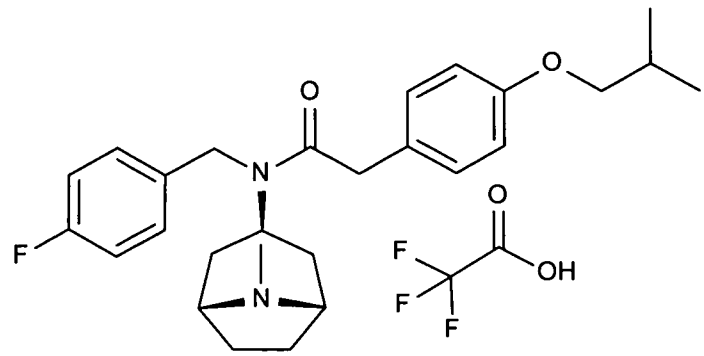
[00408] Sodium cyanoborohydride (628 mg, 10 mmol) was added to 4-fluorobenzylamine (571 µl, 5 mmol), 8-methyl-8-azabicyclo[3.2.1]octan-3-one (696 mg, 5 mmol) and acetic acid (750 µl) in methanol (10 ml). After 3 hours of stirring at ambient temperature the mixture was concentrated. Sodium hydroxide (1M, 10 ml) was added and the resulting mixture was extracted with dichloromethane (3 x 10 ml). The organic phase was dried using a phase separator and concentrated. Oxalic acid (446 mg, 4.95 mmol) was added and the resulting salt was recrystallized from methanol. The formed crystals were suspended in sodium hydroxide (1M, 30 ml) and extracted with dichloromethane (2 x 30 ml). The organic phase was dried using a phase separator and concentrated. The material was purified by column chromatography using silica gel, eluting with 5-10% methanol in dichloromethane (containing 1% triethylamine) to afford (1R,3r,5S)-N-[(4-fluorophenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (291 mg, 24%, faster eluting material) and (1R,3s,5S)-N-[(4-fluorophenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (93 mg, 8%, slower eluting material).

[00409] N-[(4-fluorophenyl)methyl]-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (28)



[00410] 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (27.4 mg, 121 μmol) in dichloromethane (1 ml) was added to (1R,3r,5S)-N-[(4-fluorophenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (25 mg, 101 μmol) and triethylamine (28.1 μl, 201 μmol). After 1 hour of stirring at ambient temperature water (1 ml) was added. The organic phase was separated. The aqueous phase was extracted with dichloromethane (1 ml). The combined organic phase was dried using a phase separator 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 (13 mg, 23%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.80 (s, 1H), 7.19 – 7.08 (m, 2H), 7.08 – 6.93 (m, 4H), 6.92 – 6.83 (m, 2H), 4.41 (s, 2H), 3.75 – 3.58 (m, 7H), 2.62 (s, 3H), 2.50 – 2.17 (m, 8H), 2.09 (dp, J = 13.4, 6.6 Hz, 1H), 1.03 (d, J = 6.7 Hz, 6H); LC-MS: 439.3 $[M+H]^+$.

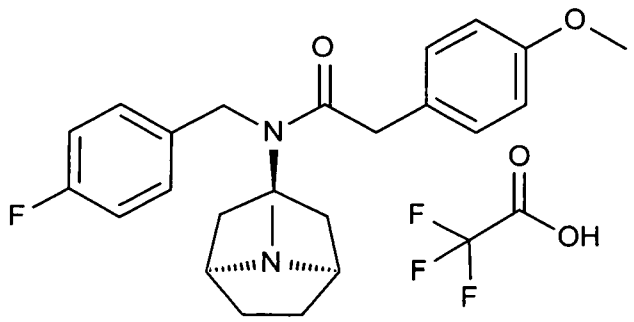
[00411] Example 29: N-[(4-fluorophenyl)methyl]-N-[(1R,3s,5S)-8-methyl-8-azabicyclo-[3.2.1]octan-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (29)



[00412] The compound was prepared in analogy with example 28 using (1R,3s,5S)-N-[(4-fluorophenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-amine and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 64.2 mg, 64%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.34 (bs, 1H), 7.15 (dd, J = 8.6, 5.3 Hz, 2H), 7.09 – 6.99 (m, 4H), 6.83 (d, J

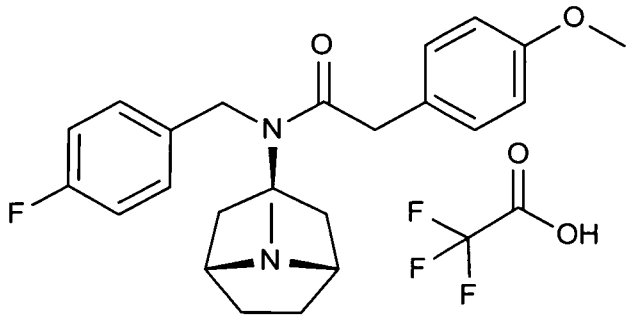
= 8.6 Hz, 2H), 5.23 (tt, J = 11.7, 5.8 Hz, 1H), 4.58 (s, 2H), 3.80 – 3.65 (m, 4H), 3.55 (s, 2H), 2.75 – 2.64 (m, 3H), 2.33 – 2.11 (m, 6H), 2.07 (dq, J = 13.3, 6.7 Hz, 1H), 1.78 – 1.64 (m, 2H), 1.03 (dd, J = 6.6, 3.8 Hz, 6H); LC-MS: 439.3 $[M+H]^+$.

[00413] Example 30: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]acetamide; trifluoroacetic acid (30)



[00414] The compound was prepared in analogy with example 28 using (1R,3r,5S)-N-[(4-fluorophenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-amine and 2-(4-methoxyphenyl)-acetyl chloride. Yield: 23.9 mg, 25%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.93 (bs, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 6.9 Hz, 4H), 6.89 (d, J = 8.6 Hz, 2H), 4.42 (s, 2H), 3.81 (s, 3H), 3.76 (s, 2H), 3.71 (s, 2H), 3.61 (p, J = 9.7 Hz, 1H), 2.62 (d, J = 4.4 Hz, 3H), 2.48 – 2.17 (m, 8H); LC-MS: 397.3 $[M+H]^+$.

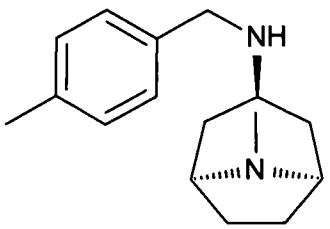
[00415] Example 31: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]acetamide; trifluoroacetic acid (31)

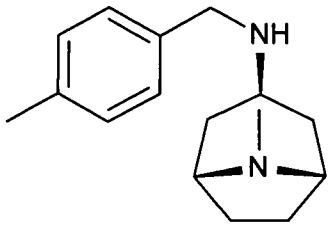


[00416] The compound was prepared in analogy with example 28 using (1R,3s,5S)-N-[(4-fluorophenyl)methyl]-8-methyl-8-azabicyclo[3.2.1]octan-3-amine and 2-(4-methoxyphenyl)-acetyl chloride. Yield: 21.3 mg, 23%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.70 (s, 1H), 7.20 – 7.11 (m, 2H), 7.10 – 7.00 (m, 4H), 6.88 – 6.79 (m, 2H), 5.23 (tt, J = 11.7, 5.6 Hz, 1H), 4.59 (s, 2H), 3.80 (s, 3H), 3.78 – 3.72 (m, 2H), 3.55 (s, 2H), 2.69 (d, J = 4.7 Hz, 3H), 2.42 – 2.06 (m, 6H), 1.76 – 1.62 (m, 2H); LC-MS: 397.3 $[M+H]^+$.

[00417] Example 32: 2-(4-methoxyphenyl)-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide; trifluoroacetic acid (32)

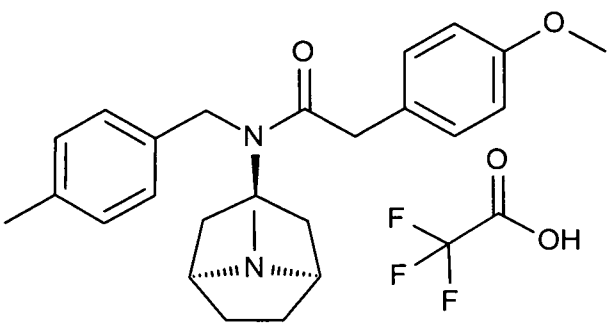
[00418] (1R,3r,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine and (1R,3s,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine





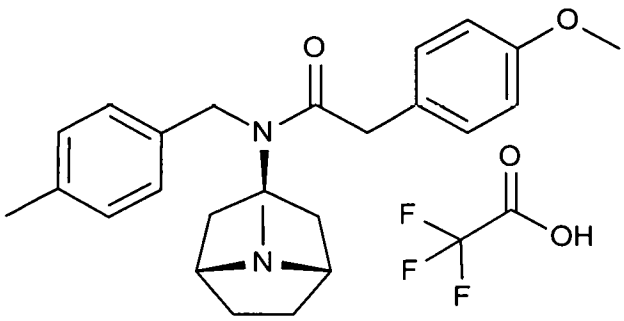
[00419] 4-Methylbenzylamine (1.26 ml, 10 mmol) was added to 8-methyl-8-azabicyclo-[3.2.1]octan-3-one (1.39 g, 10 mmol) in toluene (50 ml). The mixture was heated to reflux with azeotropic removal of water. After 3.5 hours the mixture was cooled to ambient temperature and concentrated. The crude material was dissolved in methanol (50 ml) and sodium borohydride (567 mg, 15 mmol) was added. After stirring at ambient for 15 hours the mixture was concentrated. Sodium hydroxide (1M, 50 ml) was added and the resulting mixture was extracted with dichloromethane (3 x 50 ml). The organic phase was dried using a phase separator and concentrated. The material was purified by column chromatography using silica gel, eluting with 5% diethylamine in ethyl acetate to afford (1R,3r,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine (1.02 g, 18%, faster eluting material) and (1R,3s,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine (340 mg, 10%, slower eluting material).

[00420] 2-(4-methoxyphenyl)-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide; trifluoroacetic acid (32)



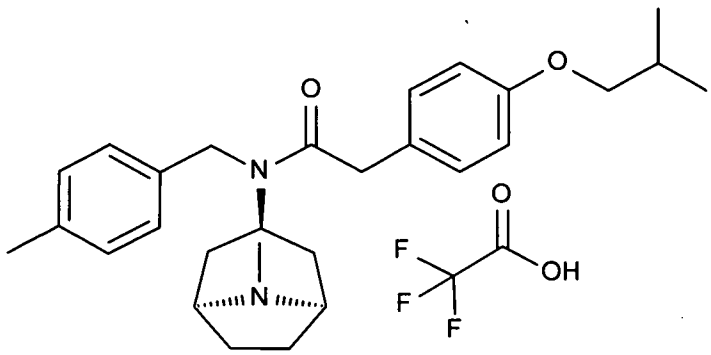
[00421] The compound was prepared in analogy with example 28 using (1R,3r,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine and 2-(4-methoxyphenyl)acetyl chloride. Yield: 40.0 mg, 38%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.11 (bs, 1H), 7.19 – 7.06 (m, 4H), 7.00 – 6.93 (m, 2H), 6.91 – 6.84 (m, 2H), 4.39 (s, 2H), 3.80 (s, 3H), 3.76 – 3.58 (m, 5H), 2.59 (s, 3H), 2.50 – 2.38 (m, 2H), 2.39 – 2.29 (m, 5H), 2.30 – 2.14 (m, 4H); LC-MS: 393.2 $[M+H]^+$.

[00422] Example 33: 2-(4-methoxyphenyl)-N-[(1R,3s,5S)-8-methyl-8-azabicyclo-[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide; trifluoroacetic acid (33)



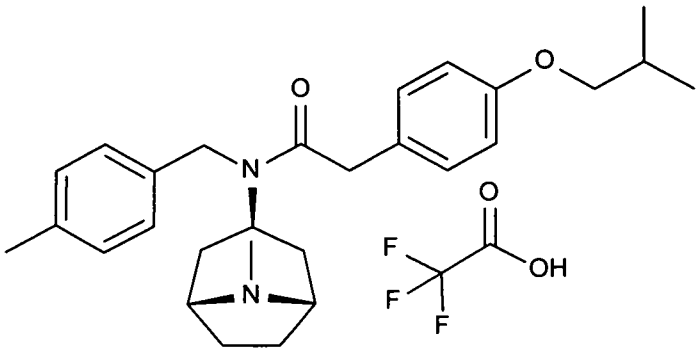
[00423] The compound was prepared in analogy with example 28 using (1R,3s,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine and 2-(4-methoxyphenyl)acetyl chloride. Yield: 44.7 mg, 44%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.38 (bs, 1H), 7.16 (d, J = 7.9 Hz, 2H), 7.11 – 7.02 (m, 4H), 6.84 (d, J = 8.7 Hz, 2H), 5.21 (tt, J = 11.9, 5.8 Hz, 1H), 4.56 (s, 2H), 3.87 – 3.68 (m, 6H), 3.56 (s, 2H), 2.68 (d, J = 3.8 Hz, 3H), 2.34 (s, 3H), 2.32 – 2.07 (m, 6H), 1.71 (dd, J = 14.6, 3.0 Hz, 2H); LC-MS: 393.1 $[M+H]^+$.

[00424] Example 34: N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (34)



[00425] The compound was prepared in analogy with example 28 using (1R,3r,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 48.0 mg, 42%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.51 (s, 1H), 7.12 (dd, J = 8.0, 4.5 Hz, 4H), 6.95 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.39 (s, 2H), 3.73 (s, 2H), 3.71 (d, J = 6.6 Hz, 2H), 3.69 – 3.56 (m, 3H), 2.60 (d, J = 3.9 Hz, 3H), 2.48 – 2.16 (m, 11H), 2.07 (dq, J = 13.3, 6.6 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 435.4 $[M+H]^+$.

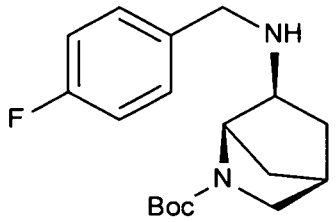
[00426] Example 35: N-[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (35)

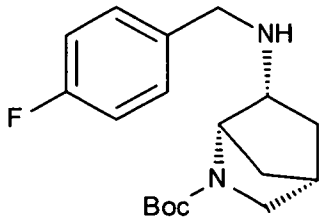


[00427] The compound was prepared in analogy with example 28 using (1R,3s,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 69.0 mg, 63%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.11 (s, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.09 – 7.00 (m, 4H), 6.83 (d, J = 8.6 Hz, 2H), 5.22 (tt, J = 12.0, 5.8 Hz, 1H), 4.55 (s, 2H), 3.77 (s, 2H), 3.70 (d, J = 6.6 Hz, 2H), 3.57 (s, 2H), 2.69 (d, J = 4.8 Hz, 3H), 2.34 (s, 3H), 2.34 – 1.96 (m, 7H), 1.79 – 1.64 (m, 2H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 435.3 $[M+H]^+$.

[00428] Example 36: 1-[(4-fluorophenyl)methyl]-1-[(1R,4S,6S)-2-methyl-2-azabicyclo-[2.2.1]heptan-6-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (36a) and 1-[(4-fluorophenyl)methyl]-1-[(1S,4R,6R)-2-methyl-2-azabicycl-o[2.2.1]heptan-6-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (36b)

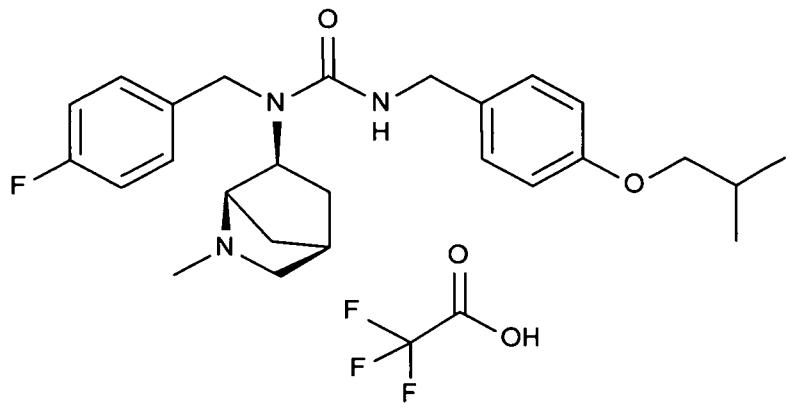
[00429] tert-butyl (1R,4R,6S)-6-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]-heptane-2-carboxylate and tert-butyl (1S,4S,6R)-6-{[(4-fluorophenyl)methyl]amino}-2-aza-bicyclo[2.2.1]heptane-2-carboxylate

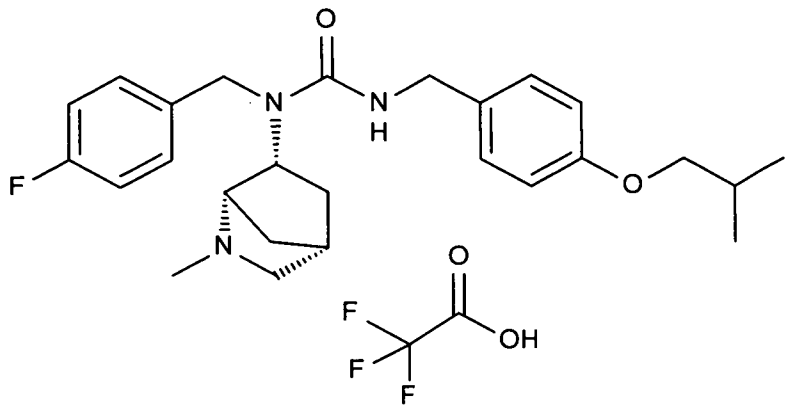




[00430] Sodium triacetoxyborohydride (201 mg, 947 μmol) was added to 4-fluorobenzylamine (64.9 μl, 568 μmol) and tert-butyl 6-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (100 mg, 473 μmol) in ethanol (2 ml). After 2 hours of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with ethyl acetate to afford the title compounds (154.6 mg, quantitative) as a 1:1 mixture of enantiomers.

[00431] 1-[(4-fluorophenyl)methyl]-1-[(1R,4S,6S)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (36a) and 1-[(4-fluorophenyl)methyl]-1-[(1S,4R,6R)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (36b)

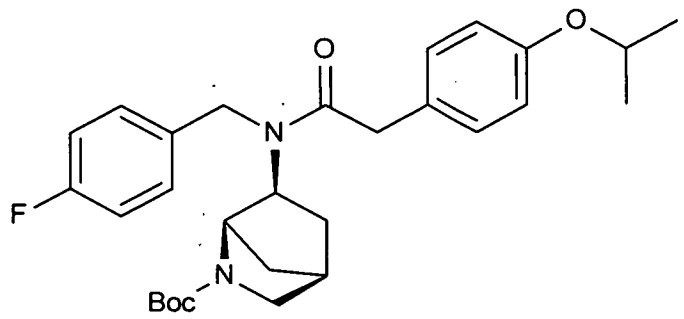


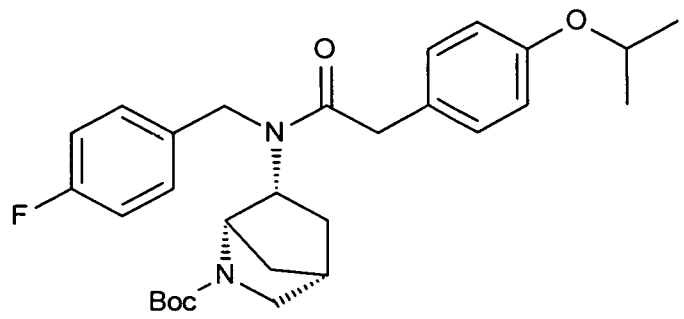


[00432] The compounds were prepared by adding tert-butyl (1R,4R,6S)-6-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]heptane-2-carboxylate and tert-butyl (1S,4S,6R)-6-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]heptane-2-carboxylate (1:1) to 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (1.5 equivalents) in 1 ml dichloromethane. After 1 hour of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with 25-50% ethyl acetate in petroleum ether to afford the title compounds. Yield: 8.6 mg, 22%. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.25 (dd, J = 8.6, 5.3 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.10 (t, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.55 (dd, J = 17.4, 3.5 Hz, 2H), 4.35 (d, J = 14.9 Hz, 1H), 4.29 (d, J = 14.9 Hz, 1H), 3.81 (s, 1H), 3.77 – 3.63 (m, 4H), 2.94 (dt, J = 10.5, 2.8 Hz, 1H), 2.85 (s, 3H), 2.69 (s, 1H), 2.12 – 1.91 (m, 3H), 1.84 – 1.72 (m, 2H), 1.03 (d, J = 6.7 Hz, 6H); LC-MS: 440.3 $[M+H]^+$.

[00433] Example 37: N-[(4-fluorophenyl)methyl]-N-[(1R,4S,6S)-2-methyl-2-azabicyclo-[2.2.1]heptan-6-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (37a) and N-[(4-fluorophenyl)methyl]-N-[(1S,4R,6R)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (37b)

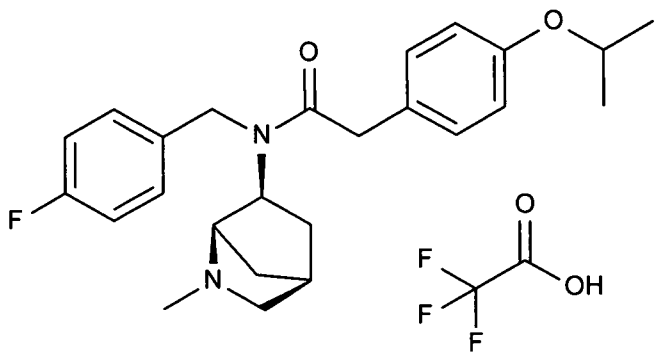
[00434] tert-butyl (1R,4R,6S)-6-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)-phenyl]acetamido}-2-azabicyclo[2.2.1]heptane-2-carboxylate; tert-butyl (1S,4S,6R)-6-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-2-azabicyclo[2.2.1]-heptane-2-carboxylate

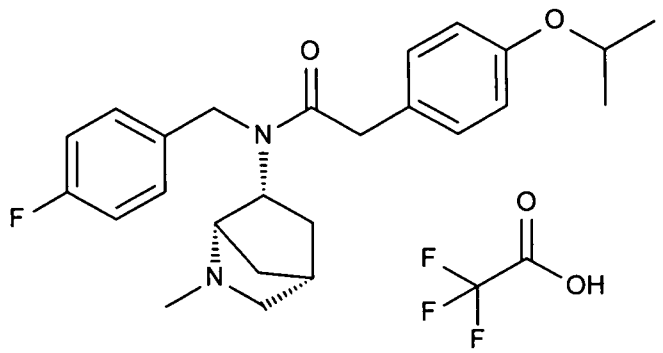




[00435] 2-[4-(propan-2-yloxy)phenyl]acetyl chloride (29.9 mg, 140 μmol) was added to a solution of tert-butyl (1R,4R,6S)-6-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]-heptane-2-carboxylate and tert-butyl (1S,4S,6R)-6-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]heptane-2-carboxylate (1:1, 30 mg, 93.6 μmol) and triethylamine (26.1 μl, 187 μmol) in dichloromethane (1 ml). After 1 hour of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with 25-50% ethyl acetate in petroleum ether to afford the title compound (34 mg, 73%).

[00436] N-[(4-fluorophenyl)methyl]-N-[(1R,4S,6S)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (37a) and N-[(4-fluorophenyl)methyl]-N-[(1S,4R,6R)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (37b)



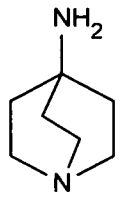


[00437] Tert-butyl (1R,4R,6S)-6-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-2-azabicyclo[2.2.1]heptane-2-carboxylate; tert-butyl (1S,4S,6R)-6-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-2-azabicyclo[2.2.1]heptane-2-carboxylate (1:1, 34.0 mg, 68.5 μmol) was dissolved in dichloromethane (1.5 ml) and trifluoroacetic acid (500 μl) was added. After 20 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofurane (1 ml). Formaldehyde (37% aqueous, 10.2 μl, 137 μmol) and sodium triacetoxyborohydride (29.0 mg, 137 μmol) were added. After 2.5 hours of stirring at ambient temperature more formaldehyde (37% aqueous, 5.1 μl, 68.5 μmol) and sodium triacetoxyborohydride (14.5 mg, 68.5 μmol) were added. The resulting mixture was stirred for 1 hour before it was concentrated. The crude material was diluted with sodium hydroxide (1M, 1 ml) and extracted with dichloromethane (2 x 1 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 25-55% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (25.0 mg, 70%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.37 (bs, 1H), 7.08 (d, J = 8.6 Hz, 2H), 7.05 – 6.92 (m, 4H), 6.79 (d, J = 8.6 Hz, 2H), 4.89 (d, J = 18.0 Hz, 1H), 4.69 (d, J = 18.1 Hz, 1H), 4.60 (s, 1H), 4.48 (hept, J = 6.0 Hz, 1H), 4.16 – 3.98 (m, 2H), 3.83 (d, J = 15.9 Hz, 1H), 3.66 (d, J = 15.9 Hz, 1H), 2.87 (s, 3H), 2.76 (d, J = 11.1 Hz, 1H), 2.69 (s, 1H),

1.94 (d, J = 12.0 Hz, 1H), 1.88 – 1.73 (m, 3H), 1.31 (d, J = 6.0 Hz, 6H); LC-MS: 411.2 $[M+H]^+$.

[00438] Example 38: 3-{1-azabicyclo[2.2.2]octan-4-yl}-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea hydrochloride (38)

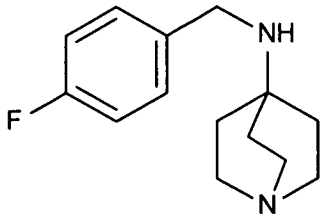
[00439] 4-aminoquinuclidine dihydrochloride



x 2HCl

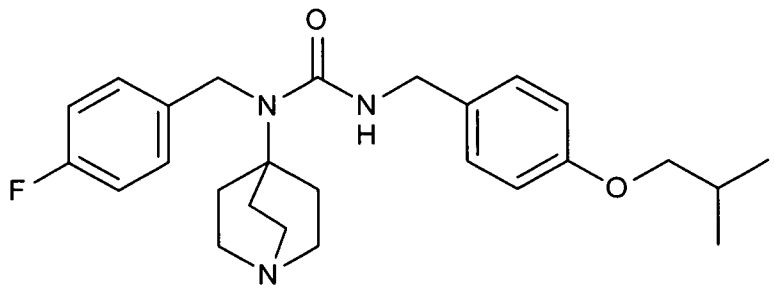
[00440] Ethyl quinuclidine-4-carboxylate (900 mg, 4.91 mmol) was hydrolyzed in a mixture of ethanol (2 mL) and sodium hydroxide (aq) (2M, 7.5 mL) at 50 °C. The reaction was followed by TLC (methanol/diethylamine 20/1). After 3 hours the mixture was neutralized with HCl (2 M) to pH=5 and evaporated. The residue was extracted with methanol which however also extracted NaCl. The extract was evaporated and the solid was extracted with ethanol which was not very effective in extracting the desired zwitterionic amino acid. All extracts and solids were combined and HCl (2 M) was added to pH< 1 and the mixture was evaporated until it was completely dry. The solid residue was suspended in dichloromethane (10 mL) and oxalyl chloride (25 mmol, 2.3 mL) was added followed by two drops of N,N-dimethylformamide. The mixture was refluxed for 6 hours and then evaporated to dryness. To the residue was added N,N-dimethylformamide (10 mL) and sodium azide (10.4 mmol, 680 mg) and the mixture was stirred at 50 °C for 20 h, then partitioned between saturated sodium carbonate and toluene. A three phase liquid system was formed. The toluene phase (on top) was collected, dried, and heated at reflux for 1 hours (visible gas formation occurred before reaching the reflux temperature), then cooled and extracted three times with HCl (5M, 3 x 20 mL). The aqueous phases were combined and heated at reflux for 1 h, then evaporated to almost dryness and triturated with abs. ethanol. The precipitate was collected and gave the desired 4-aminoquinuclidine as the dihydrochloride (173 mg, 0.87 mmol, 18% yield). ^{1}H NMR (400 MHz, deuterium oxide) δ 3.68 – 3.52 (m, 4H), 2.37 – 2.23 (m, 4H).

[00441] N-[(4-fluorophenyl)methyl]-1-azabicyclo[2.2.2]octan-4-amine



[00442] 4-aminoquinuclidine dihydrochloride (73 mg, 0.366 mmol) was stirred in abs. ethanol (2 mL) and sodium hydroxide (5M, 0.7 mmol, 0.14 mL) was added (pH 11). Sodium triacetoxyborohydride (1.464 mmol, 320 mg) was added followed by 4-fluorobenzaldehyde (0.403 mmol, 44 uL) dissolved in ethanol (0.5 mL) dropwise during 20 minutes (pH was 5). The reaction was followed by TLC (methanol/diethylamine 10/1) and samples were taken out and partitioned between dichoromethane and aqueous sodium hydroxide (1 M). TLC was run on both the aqueous phase and the organic phase. The 4-aminoquinuclidine is in the aqueous phase and the bensylated product is mainly in the organic phase. After adding extra sodium triacetoxyborohydride (250 mg), acetic acid (84 uL), and 4-fluorobenzaldehyde (12 uL), and stirring for 20 hours the reaction was judged to be complete. The mixture was partitioned between aqueous sodium hydroxide (1 M) and dichloromethane, pH was checked (>12) and the aqueous phase was extracted with dichloromethane (4 x 10 mL). The combined organic extracts were dried and evaporated to give 79 mg of the desired product as an oil that was contaminated with 4-fluorobenzaldehyde. LCMS confirmed the formation of product (235 $[M+H]^+$).

[00443] 3-{1-azabicyclo[2.2.2]octan-4-yl}-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea hydrochloride (38)



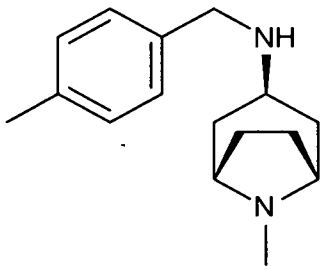
HCl

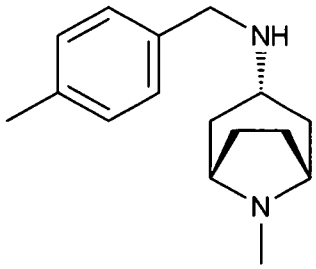
[00444] N-[(4-fluorophenyl)methyl]-1-azabicyclo[2.2.2]octan-4-amine (79 mg, 0.337 mmol) was dissolved in dichloromethane (1 mL) and 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (0.67 mmol, 144 mg) dissolved in dichloromethane (1 mL) was

added and the mixture was stirred at room temperature. TLC (methanol/diethylamine; 10/1) showed complete reaction after 10 minutes and water followed by aqueous sodium hydroxide (1 M) was added to pH>12. The mixture was extracted with dichloromethane (2 x 5 mL), the combined organic extract was dried and the solvents were removed. Chromatography (silicon dioxide, methanol/diethylamine; 1/0-20/1) gave fractions 7-11 and fractions 12-13. Fraction 7-11 had correct mass (LC-MS) and was subjected to another chromatography (silicon dioxide, column length 25 mm, eluted with methanol) and gave fractions 10-17 of the title compound (26 mg as the free base, 16% yield). ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.29 – 7.16 (m, 2H), 7.12 – 6.95 (m, 4H), 6.78 (d, J = 8.6 Hz, 2H), 4.54 (s, 2H), 4.18 (s, 2H), 3.68 (d, J = 6.5 Hz, 2H), 2.99 – 2.82 (m, 6H), 2.18 – 1.90 (m, 7H), 1.01 (d, J = 6.7 Hz, 6H). This material (26 mg) was dissolved in methanol and a solution of hydrochloric acid in methanol (2M, 0.24 mmol, 120 uL) was added and the solvent was evaporated to give the title compound as a white solid HCl-salt (31 mg). LC-MS: 440 $[M+H]^+$.

[00445] Example 39: 2-(4-methoxyphenyl)-N-[(1R,3S,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide; oxalic acid (39a) and 2-(4-methoxyphenyl)-N-[(1R,3R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide; oxalic acid (39b)

[00446] (1R,3s,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine and (1R,3r,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine

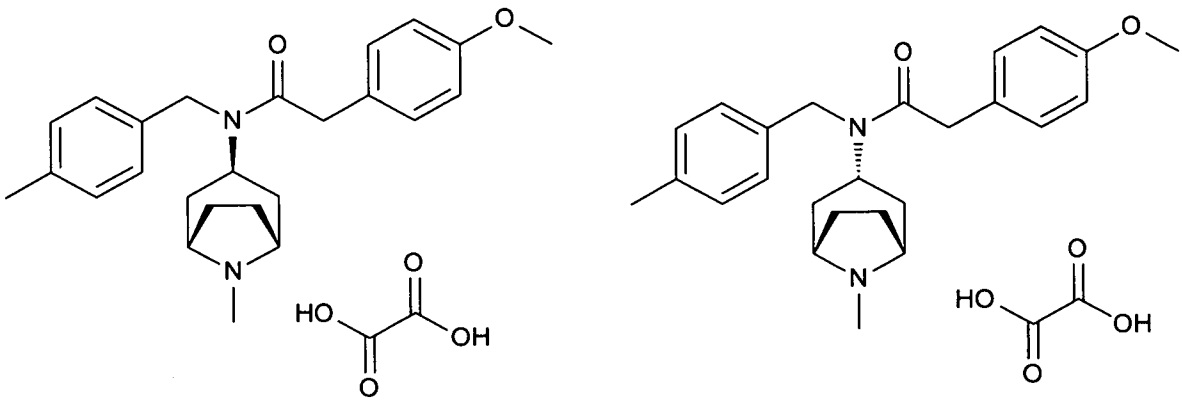




[00447] (4-methylphenyl)methanamine (606 mg, 5 mmol) in ethanol (10ml) was added to a solution of (1R,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-one (696 mg, 5 mmol) in ethanol (10ml). Acetic acid (858 µl, 10 mmol) was added. After 30 min of stirring at ambient temperature sodium cyanoborohydride (628 mg, 10 mmol) was added. After additionally 18 hours of stirring the mixture diluted with dichloromethane (20 ml) and water (20 ml). The pH was adjusted to pH 10 using sodium hydroxide (2M). The phases were separated and the water phase was extracted with dichloromethane (2 x 20 ml). The combined organic phases

were dried over magnesium sulfate and concentrated to afford the title compounds (1.07 g, 88%).

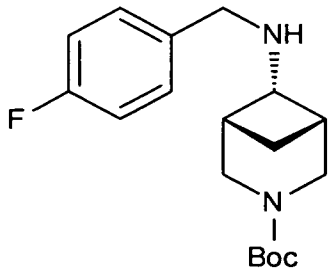
[00448] 2-(4-methoxyphenyl)-N-[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide; oxalic acid (39a) and 2-(4-methoxyphenyl)-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide; oxalic acid (39b)

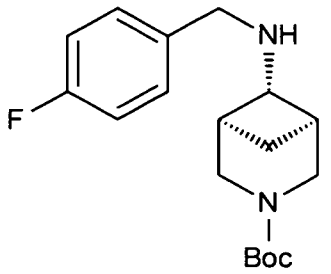


[00449] 2-(4-methoxyphenyl)acetyl chloride (203 mg, 1.1 mmol) in dichloromethane (5 ml) was added to a solution of (1R,3s,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine and (1R,3r,5S)-8-methyl-N-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-amine (244 mg, 1 mmol) in dichloromethane (5 ml). After 2 hours of stirring at ambient temperature the mixture was filtered over an ion exchange column (SCX) and purified by column chromatography using silica gel, eluting with 5% methanol in dichloromethane. The material was dissolved in dichloromethane (1 ml), oxalic acid (61.6 mg, 0.68 μmol) was added followed by pentane (1 ml). The resulting salt was filtered off to afford the title compounds (300 mg, 62%) as a 1:1 mixture of diastereomers: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (s, 4H), 7.10 – 7.01 (m, 2H), 6.89 – 6.75 (m, 2H), 4.71 (s, 1H), 4.43 (s, 1H), 3.80 – 3.74 (m, 3H), 3.72 – 3.40 (m, 5H), 2.71 – 2.45 (m, 6H), 2.31 (s, 3H), 2.25 – 2.00 (m, 5H), 1.84 – 1.26 (m, 2H); LC-MS: 393.2 $[M+H]^+$.

[00450] Example 40: N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,6r)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide; trifluoroacetic acid (40a) and N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,6s)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide; trifluoroacetic acid (40b)

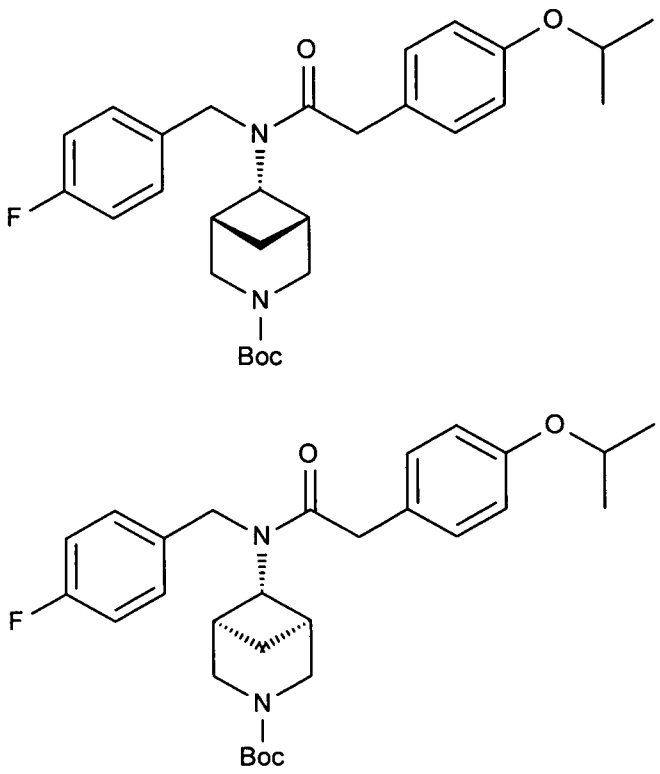
[00451] tert-butyl (1R,5S,6r)-6-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate and tert-butyl (1R,5S,6s)-6-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate





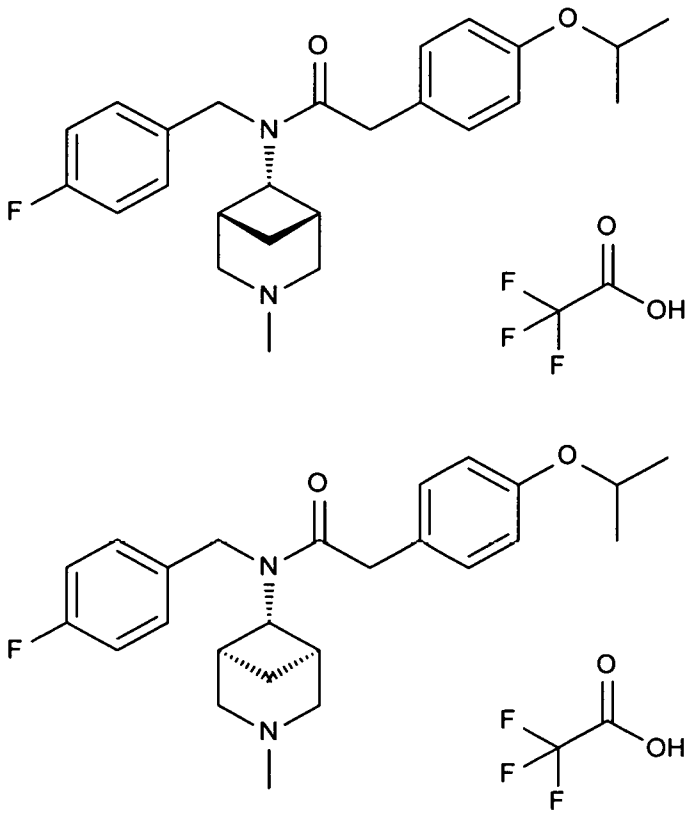
[00452] To a mixture of 4-fluorobenzylamine (64.9 µl, 568 µmol) and tert-butyl 6-oxo-3-azabicyclo[3.1.1]heptane-3-carboxylate (113 mg, 539 µmol) in dichloromethane (5 ml) sodium triacetoxyborohydride (201 mg, 947 µmol) was added. After stirring for 2 hours at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with dichloromethane:methanol (97:3) to afford the title compounds (172 mg, quantitative) as a 1:1 mixture of isomers.

[00453] Tert-butyl (1R,5S,6r)-6-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-3-azabicyclo[3.1.1]heptane-3-carboxylate and tert-butyl (1R,5S,6s)-6-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-3-azabicyclo[3.1.1]heptane-3-carboxylate



[00454] To a solution of tert-butyl (1R,5S,6r)-6-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate and tert-butyl (1R,5S,6s)-6-{[(4-fluorophenyl)-methyl]amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate (172mg, 538 μmol) and diisopropylethylamine (92 μl, 648 μmol) in dichloromethane (2 ml) a solution of 2-[4-(propan-2-yloxy)phenyl]acetyl chloride (117.7 mg, 550 μmol) in dichloromethane (500 μl) was added dropwise. After stirring for 1 hour at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with 10-30% ethyl acetate in petroleum ether to afford the title compounds (250.8 mg, 94 %) as a 1:1 mixture of diastereomers.

[00455] N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,6r)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide; trifluoroacetic acid (40a) and N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,6s)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide; trifluoroacetic acid (40b)

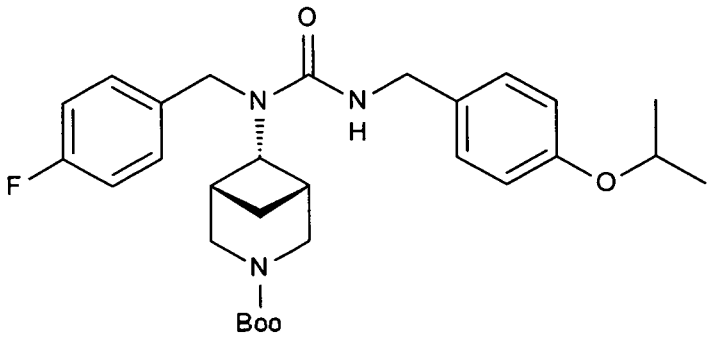


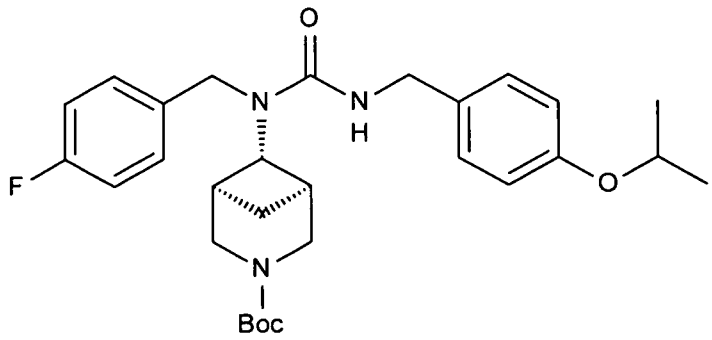
[00456] Tert-butyl (1R,5S,6r)-6-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-3-azabicyclo [3.1.1]heptane-3-carboxylate and tert-butyl (1R,5S,6s)-6-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}-3-azabicyclo[3.1.1]heptane-3-carboxylate (25.0 mg, 50.57 μmol) was dissolved in dichloromethane (10 ml) and trifluoroacetic acid (1 ml) was added. After stirring for 3 hours at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofurane (1 ml). Formaldehyde (37% aqueous, 7.12 μl, 96.0 μmol) and sodium triacetoxyborohydride (13.5 mg, 63.6 μmol) were added. After 15 minutes of stirring at ambient temperature more formaldehyde (37% aqueous, 1.78 μl, 23.9 μmol) was added. After 2 hours more sodium triacetoxyborohydride (6.75 mg, 31.8 μmol) was added. The resulting mixture was stirred for 30 minutes before it was diluted with sodium hydrogen carbonate (aq. sat. 5 ml) and extracted with dichloromethane (2 x 15 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds (20.06 mg, 76%) as a 1:1 mixture of diastereomers: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 (d, J = 8.5 Hz, 1H), 7.16 – 6.96 (m, 5H), 6.92 – 6.79 (m, 2H), 4.73 (s, 1H), 4.60 – 4.41 (m, 2H), 4.11 (d, J = 10.8 Hz, 1H), 3.88 – 3.62 (m, 4H), 3.58 (t, J = 5.5 Hz, 1H), 3.17 – 3.00

(m, 1H), 2.88 – 2.78 (m, 2H), 2.71 (dd, J = 12.1, 6.9 Hz, 1H), 2.58 (s, 1H), 2.31 (d, J = 3.0 Hz, 2H), 2.17 – 2.00 (m, 1H), 1.34 – 1.29 (m, 6H); LC-MS: 411.53 $[M+H]^+$.

[00457] Example 41: 3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}-3-[(1R,5S,6r)-3-methyl-3-azabicyclo [3.1.1]heptan-6-yl]urea; trifluoroacetic acid (41a) and 3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}-3-[(1R,5S,6s)-3-methyl-3-azabicyclo [3.1.1]heptan-6-yl]urea; trifluoroacetic acid (41b)

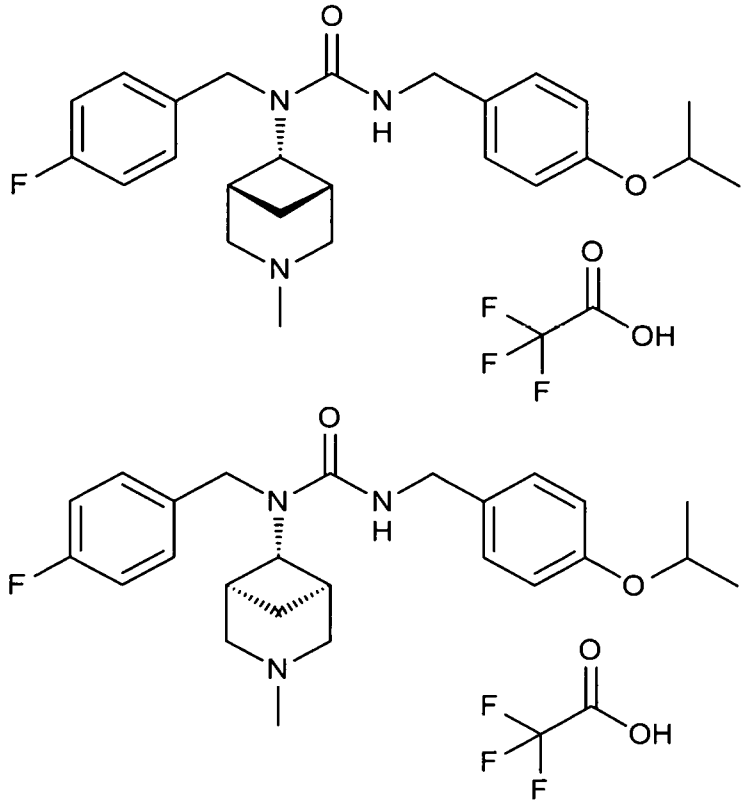
[00458] Tert-butyl (1R,5S,6r)-6-{[(4-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]-methyl}carbamoyl)amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate and tert-butyl (1R,5S,6s)-6-{[(4-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl}carbamoyl)-amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate





[00459] A solution of 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene (50 mg, 261 μmol) and tert-butyl (1R,5S,6r)-6-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate and tert-butyl (1R,5S,6s)-6-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate (50 mg, 156 μmol) in dichloromethane (2 ml) was stirred for 1 hour at ambient temperature and concentrated. The crude material was purified by column chromatography using silica gel, eluting with 15-40% ethyl acetate in petroleum ether to afford the title compounds (73.4 mg, 92%) as a 1:1 mixture of diastereomers.

[00460] 3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}-3-[(1R,5S,6r)-3-methyl-3-azabicyclo [3.1.1]heptan-6-yl]urea; trifluoroacetic acid (41a) and 3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}-3-[(1R,5S,6s)-3-methyl-3-azabicyclo [3.1.1]heptan-6-yl]urea; trifluoroacetic acid (41b)

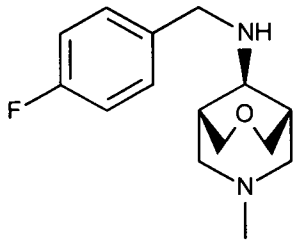


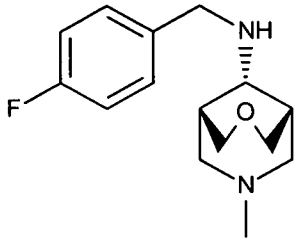
[00461] Tert-butyl (1R,5S,6r)-6-{[(4-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]-methyl}carbamoyl)amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate and tert-butyl (1R,5S,6s)-6-{[(4-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl}carbamoyl)-amino}-3-azabicyclo[3.1.1]heptane-3-carboxylate (73.4 mg, 142 μmol) was dissolved in dichloromethane (10 ml) and trifluoroacetic acid (1 ml) was added. After stirring for 3 hours at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofurane (1 ml). Formaldehyde (37% aqueous, 7.12 μl, 96.0 μmol) and sodium triacetoxyborohydride (13.5 mg, 63.6 μmol) were added. After 15 minutes of stirring at ambient temperature more formaldehyde (37% aqueous, 1.78 μl, 23.9 μmol) was added. After 2 hours more sodium triacetoxyborohydride (6.75 mg, 31.8 μmol) was added. The resulting mixture was stirred for 30 minutes before it was diluted with sodium hydrogen carbonate (aq. sat. 5 ml) and extracted with dichloromethane (2 x 15 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (60.7

mg, 64%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 6.90 (m, 6H), 6.85 – 6.76 (m, 2H), 4.92 – 4.68 (m, 1H), 4.62 – 4.25 (m, 5H), 4.25 – 3.84 (m, 2H), 3.81 – 3.51 (m, 1H), 3.39 – 3.00 (m, 4H), 3.00 – 2.58 (m, 5H), 2.45 – 1.80 (m, 1H), 1.37 – 1.20 (m, 6H); LC-MS: 426.54 $[M+H]^+$.

[00462] Example 42: N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,9s)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]acetamide; trifluoroacetic acid (42)

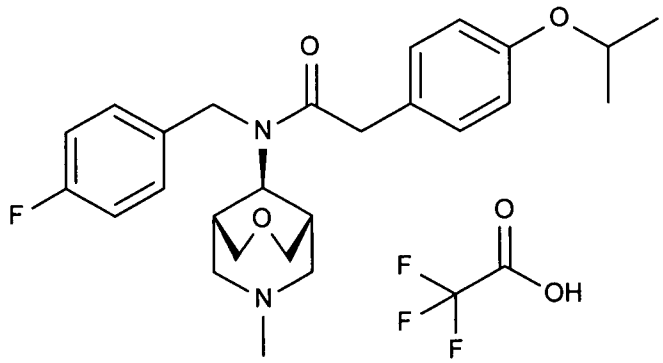
[00463] 7-methyl-(1R,5S,9r)-9-{[(4-fluorophenyl)methyl]amino}-3-oxa-7-azabicyclo-[3.3.1]nonane and 7-methyl-(1R,5S,9s)-9-{[(4-fluorophenyl)methyl]amino}-3-oxa-7-azabicyclo[3.3.1]nonane





[00464] The compounds were prepared in analogy with example 40 using tert-butyl 9-oxo-3-oxa-7-azabicyclo[3.3.1]nonane-7-carboxylate as an undefined mixture of diastereomers.

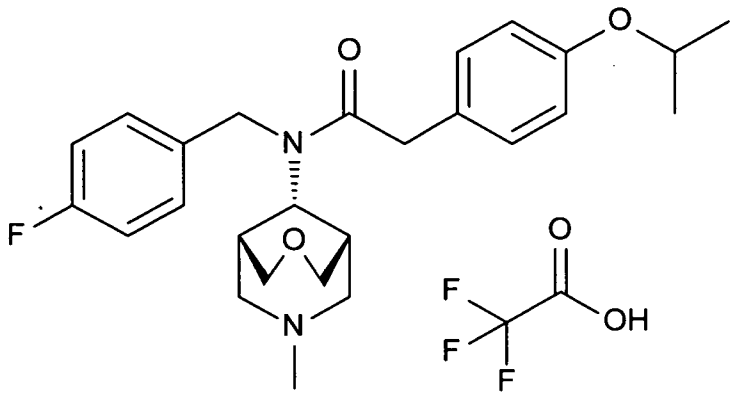
[00465] N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,9s)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]acetamide; trifluoroacetic acid (42)



[00466] The compound was prepared in analogy with example 40 using (1R,5S,9r)-N-[(4-fluorophenyl)methyl]-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-amine and (1R,5S,9s)-N-[(4-fluorophenyl)methyl]-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-amine (undefined mixture) and 2-[4-(propan-2-yloxy)phenyl]acetyl chloride. Yield: 16.8 mg, 47%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 6.96 (m, 6H), 6.83 (d, J = 8.6 Hz, 2H), 4.77 (s, 2H), 4.52

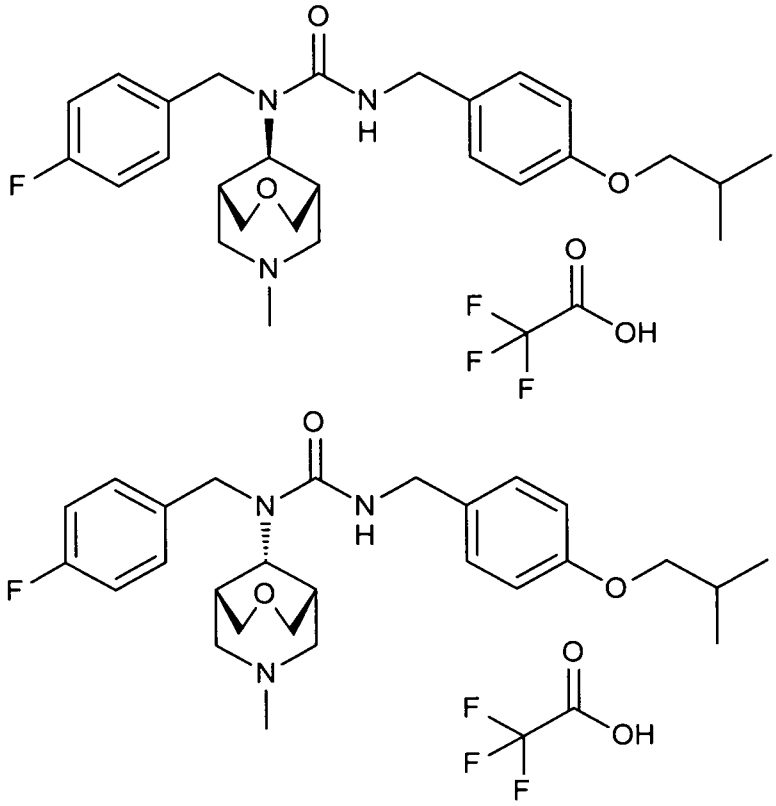
(p, J = 6.1 Hz, 1H), 4.24 – 4.07 (m, 5H), 3.80 (d, J = 12.3 Hz, 2H), 3.69 (s, 2H), 3.09 (d, J = 12.2 Hz, 2H), 2.89 (s, 3H), 2.45 (s, 2H), 1.33 (d, J = 6.1 Hz, 6H); LC-MS: 441.56 $[M+H]^+$.

[00467] Example 43: N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,9r)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]acetamide; trifluoroacetic acid (43)



[00468] The compound was prepared in analogy with example 42 using 7-methyl-(1R,5S,9r)-9-{[(4-fluorophenyl)methyl]amino}-3-oxa-7-azabicyclo[3.3.1]nonane and 7-methyl-(1R,5S,9s)-9-{[(4-fluorophenyl)methyl]amino}-3-oxa-7-azabicyclo[3.3.1]nonane (undefined mixture) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 19.7 mg, 52%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.01 (m, 6H), 6.86 (d, J = 8.5 Hz, 2H), 4.62 (s, 2H), 4.52 (p, J = 6.1 Hz, 1H), 4.21 (d, J = 11.8 Hz, 2H), 3.95 – 3.79 (m, 3H), 3.73 (s, 2H), 3.65 (d, J = 11.8 Hz, 2H), 2.95 (d, J = 12.6 Hz, 2H), 2.69 – 2.56 (m, 5H), 1.33 (d, J = 6.0 Hz, 6H); LC-MS: 441.56 $[M+H]^+$.

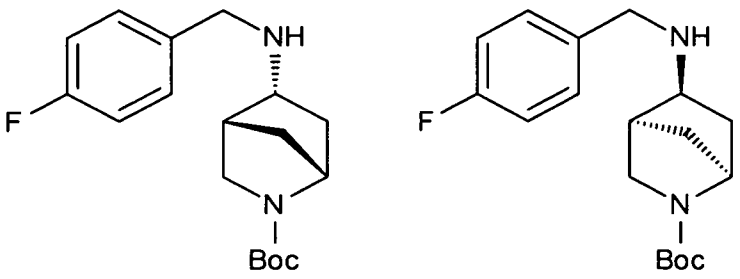
[00469] Example 44: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}-3-[(1R,5S,9r)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]urea; trifluoroacetic acid (44a) and 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9s)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]urea; trifluoroacetic acid (44b)



[00470] The compound was prepared as a 1:1 mixture of diastereomers in analogy with example 41 using 7-methyl-(1R,5S,9r)-9-{[(4-fluorophenyl)methyl]amino}-3-oxa-7-azabicyclo[3.3.1]nonane and 7-methyl-(1R,5S,9s)-9-{[(4-fluorophenyl)methyl]amino}-3-oxa-7-azabicyclo[3.3.1]nonane (undefined mixture) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 22.3 mg, 61%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 – 6.91 (m, 6H), 6.77 (d, *J* = 8.6 Hz, 2H), 4.48 (s, 1H), 4.42 (s, 1H), 4.28 (t, *J* = 4.4 Hz, 2H), 4.10 (d, *J* = 11.5 Hz, 1H), 4.00 – 3.81 (m, 3H), 3.71 – 3.54 (m, 5H), 3.25 (d, *J* = 12.4 Hz, 1H), 3.07 (d, *J* = 12.6 Hz, 1H), 2.78 (s, 2H), 2.75 (s, 1H), 2.54 (s, 1H), 2.45 (s, 1H), 2.05 (heptd, *J* = 6.8, 2.4 Hz, 1H), 1.00 (dd, *J* = 6.7, 1.6 Hz, 6H); LC-MS: 470.60 $[M+H]^+$.

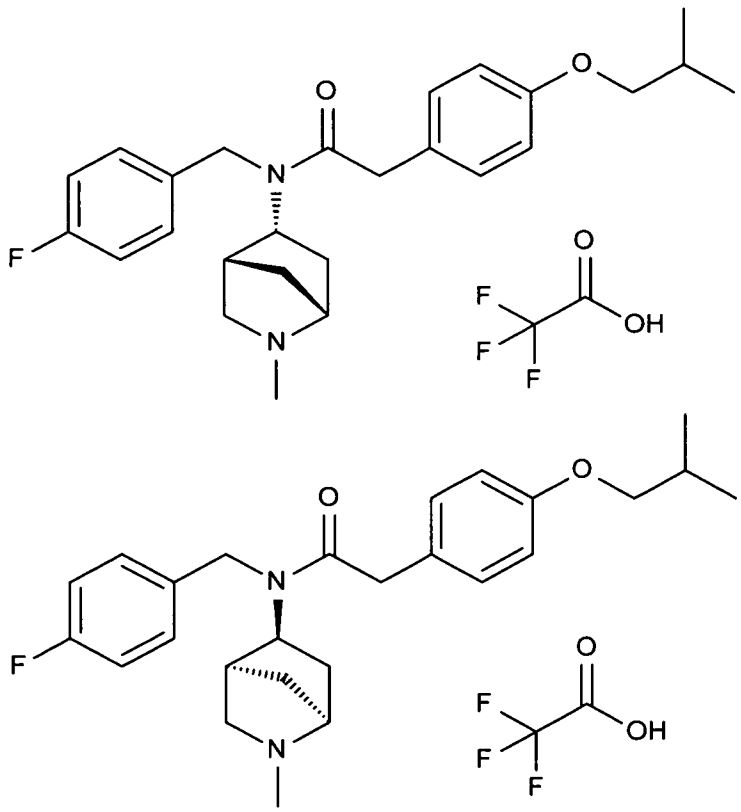
[00471] Example 45: N-[(4-fluorophenyl)methyl]-N-[(1R,4R,5R)-2-methyl-2-azabicyclo-[2.2.1]heptan-5-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (45a) and N-[(4-fluorophenyl)methyl]-N-[(1S,4S,5S)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (45b)

[00472] Tert-butyl (1R,4R,5R)-5-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]-heptane-2-carboxylate and tert-butyl (1S,4S,5S)-5-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]heptane-2-carboxylate



[00473] The compounds were prepared in analogy with example 40 using tert-butyl 5-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate as a 1:1 mixture of enantiomers.

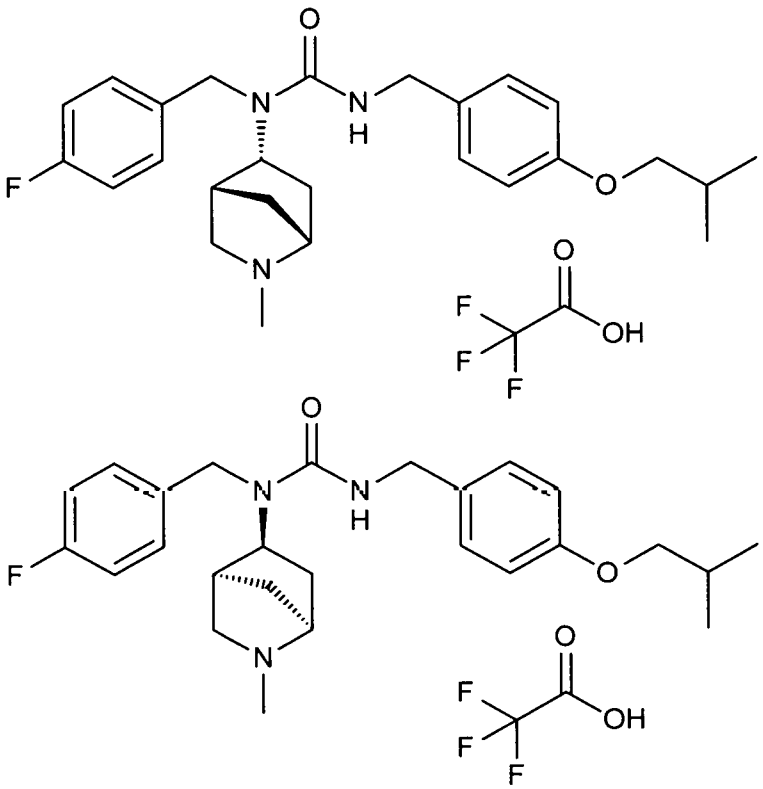
[00474] N-[(4-fluorophenyl)methyl]-N-[(1R,4R,5R)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (45a) and N-[(4-fluorophenyl)methyl]-N-[(1S,4S,5S)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (45b)



[00475] The compounds were prepared in analogy with example 40 using tert-butyl (1R,4R,5R)-5-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]heptane-2-carboxylate and tert-butyl (1S,4S,5S)-5-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]heptane-2-carboxylate (1:1) and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride as a 1:1 mixture of enantiomers. Yield: 21.2 mg, 70%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.07 – 6.97 (m,

6H), 6.81 (d, J = 8.3 Hz, 2H), 4.95 – 4.72 (m, 2H), 4.57 – 4.46 (m, 1H), 3.78 – 3.57 (m, 6H), 3.32 (s, 1H), 2.80 (d, J = 4.4 Hz, 3H), 2.64 (d, J = 12.1 Hz, 1H), 2.14 – 1.89 (m, 3H), 1.88 – 1.70 (m, 2H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 425.56 $[M+H]^+$.

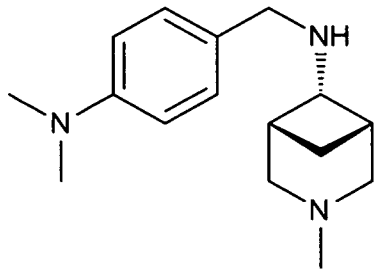
Example 46: 3-[(4-fluorophenyl)methyl]-3-[(1R,4R,5R)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (46a) and 3-[(4-fluorophenyl)methyl]-3-[(1S,4S,5S)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-1-{[4-(2-methylpropoxy)phenyl] methyl}urea; trifluoroacetic acid (46b)



[00476] The compound was prepared in analogy with example 41 using tert-butyl (1R,4R,5R)-5-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]heptane-2-carboxylate and tert-butyl (1S,4S,5S)-5-{[(4-fluorophenyl)methyl]amino}-2-azabicyclo[2.2.1]heptane-2-carboxylate and 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene as a 1:1 mixture of enantiomers. Yield: 28.6 mg, 59%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 – 6.93 (m, 6H), 6.80 (d, J = 8.3 Hz, 2H), 4.91 (s, 1H), 4.83 – 4.69 (m, 1H), 4.57 – 4.44 (m, 2H), 4.28 (qd, J = 14.3, 4.7 Hz, 2H), 3.98 (dd, J = 11.7, 5.7 Hz, 1H), 3.72 (d, J = 15.9 Hz, 3H), 3.40 – 3.07 (m, 3H), 2.93 – 2.78 (m, 4H), 2.68 (d, J = 11.9 Hz, 1H), 2.20 – 1.80 (m, 2H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 440.57 $[M+H]^+$.

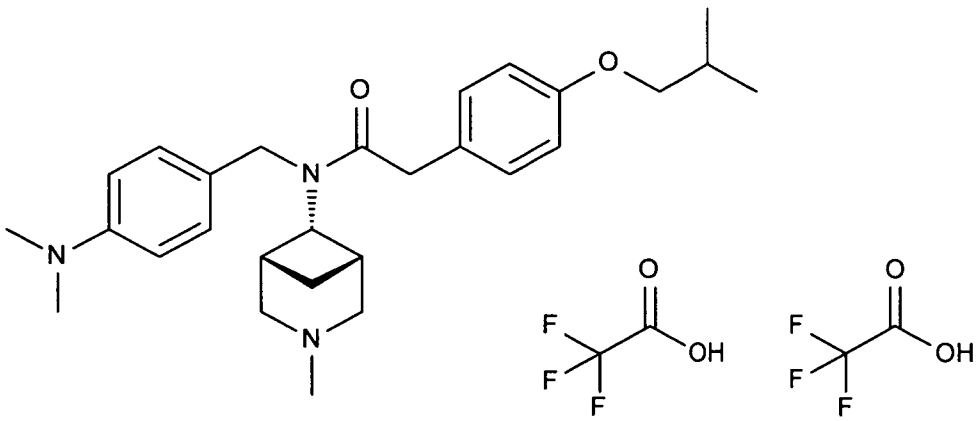
[00477] Example 47: N-{[4-(dimethylamino)phenyl]methyl}-2-[4-(2-methylpropoxy)phenyl]-N-[(1R,5S,6r)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide; bis(trifluoroacetic acid) (47)

[00478] (1R,5S,6r)-N-{[4-(dimethylamino)phenyl]methyl}-3-methyl-3-azabicyclo[3.1.1]heptan-6-amine



[00479] The compound was prepared in analogy with example 40 using 3-methyl-3-azabicyclo[3.1.1]heptan-6-one and 4-(aminomethyl)-N,N-dimethylaniline.

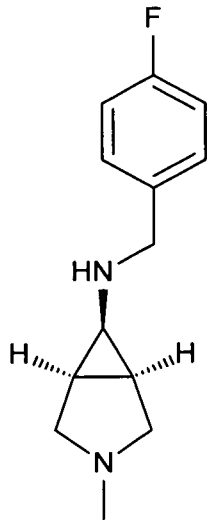
[00480] N-{[4-(dimethylamino)phenyl]methyl}-2-[4-(2-methylpropoxy)phenyl]-N-[(1R,5S,6r)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide; bis(trifluoroacetic acid) (47)



[00481] The compound was prepared in analogy with example 28 using (1R,5S,6r)-N-{[4-(dimethylamino)phenyl]methyl}-3-methyl-3-azabicyclo[3.1.1]heptan-6-amine and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 8.9 mg, 32%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.01 (m, 6H), 6.90 (d, J = 8.4 Hz, 1H), 6.87 – 6.75 (m, 1H), 5.06 (s, 4H), 4.79 – 4.60 (m, 1H), 4.55 – 4.43 (m, 1H), 4.35 – 4.06 (m, 1H), 3.89 – 3.63 (m, 5H), 3.63 – 3.38 (m, 1H), 3.19 – 3.03 (m, 3H), 2.97 – 2.79 (m, 3H), 2.79 – 2.67 (m, 1H), 2.59 (s, 1H), 2.38 – 2.17 (m, 2H), 2.15 – 1.96 (m, 2H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 450.64 $[M+H]^+$.

[00482] Example 48: 3-[(4-fluorophenyl)methyl]-3-[(1R,5S,6s)-3-methyl-3-azabicyclo-[3.1.0]hexan-6-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (48)

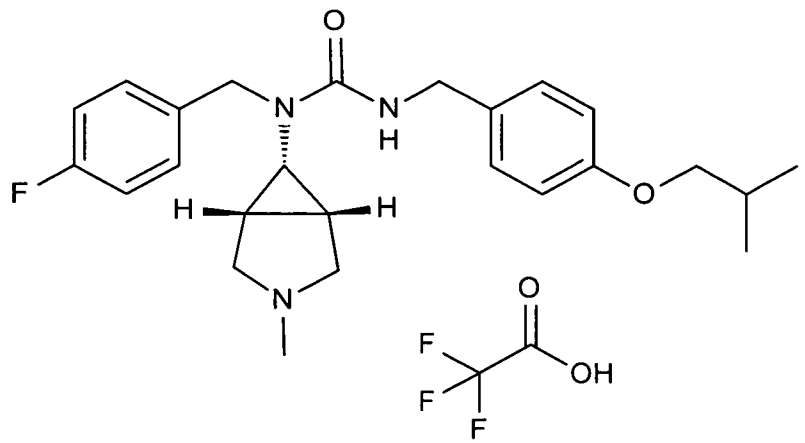
[00483] (1R,5S,6s)-N-[(4-fluorophenyl)methyl]-3-methyl-3-azabicyclo[3.1.0]hexan-6-amine



[00484] *N*-Methyl-4-piperidone (9.88 g) in toluene (200 ml) was reacted with diallylamine (42.3 ml) in the presence of titanium tetrachloride (4.5 ml) at 20 °C for 20 hours. The mixture was filtered and the filtrate was distilled (0.2 mbar, 90 °C) to give the enamine (oil, 12.6 g) which was chlorinated at - 50 °C with *N*-chlorosuccinimide (8.48 g) in dichloromethane (220 ml) for 2 hours. Evaporation and extraction of the residue with hexane (2 x 75 ml) gave an extract that upon evaporation gave the chloroenamine as an oil (12.23 g). The chloroenamine (12.23 g) was stirred for 48 hours at room temperature in a solution prepared from sodium (3.73 g) and methanol (300 ml). The mixture was evaporated and stirred in hexane/toluene (10/1, 150 ml), then filtered and the filtrate was concentrated and distilled (0.2 mbar, 90 °C) to give the hemiaminal ether as an oil (9.13 g). 4.0 g of this oil in tetrahydrofuran (40 ml) was added slowly into a suspension of lithium aluminum hydride (36.4 mmol, 1.38 g) in tetrahydrofuran (30 ml). The mixture was heated at 55 °C for 5 hours, then stirred at room temperature for 17 hours. The reaction was quenched by cooling and cautious addition of ethyl acetate (7.13 ml) followed by water (1.38 ml), sodium hydroxide (15% aqueous, 1.38 ml), and finally water (4.14 ml). The suspension was stirred for 30 min, then filtered and the filtrate was evaporated. The residue was distilled (0.2 mbar 62-67 °C) to give the corresponding diallylamine (3.07 g). The diallylamine (2.42 g) was dissolved in dichloromethane (16 ml) and added slowly to a mixture of 1,3-dimethylbarbituric acid (6.36 g) and tetrakis(triphenylphosphine)palladium(0) (292 mg). After 5 hours stirring at 40 °C the mixture was evaporated and diethyl ether and potassium carbonate (6.0 g) were added. The mixture was

stirred 1 hour, a small sample was taken out and diluted with water and showed pH> 10. The mixture was filtered and the solids were washed with diethyl ether. The solids were then dissolved in water and aqueous sodium hydroxide (1M) was added to give a solution at pH 13. The aqueous phase was extracted 3 times with diethyl ether, the organic phases were combined and extracted with hydrochloric acid (2M aqueous). The acidic aqueous phase was washed three times with ethyl acetate. To the acidic (pH< 1) aqueous phase was added solid potassium carbonate and solid sodium hydroxide to give pH >12 and the solution was extracted with diethyl ether three times. The combined organic phases were evaporated to give an oil (142 mg). The oil was dissolved in pyridine (3 ml), cooled to 0 °C and 4-fluorobenzoyl chloride (2.0 eq. 2.53 mmol, 305 µl) was added slowly. The mixture was evaporated and dissolved in a solution of sodium methoxide in methanol (1M, 3 ml), then concentrated and partitioned between dichloromethane and water. The organic phase was evaporated and the residue was purified by column chromatography using silica gel, eluting with 25% methanol in ethyl acetate to give fractions the benzamide (23 mg). The benzamide (23 mg) was treated with lithium aluminum hydride (15 mg) in tetrahydrofuran (1.0 ml) overnight, then quenched with excess sodium sulfate decahydrate, filtered and evaporated to give the title compound as an oil (20 mg). LCMS (M+H=221.1) and ^{1}H NMR corroborated the structure in about 50% purity.

[00485] 3-[(4-fluorophenyl)methyl]-3-[(1R,5S,6s)-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (48)

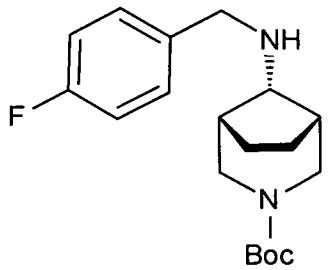


[00486] (1R,5S,6s)-N-[(4-fluorophenyl)methyl]-3-methyl-3-azabicyclo[3.1.0]hexan-6-amine (50 % purity, 20 mg, approximately 0.024 mmol) was dissolved in dichloromethane (1.0 ml) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (40 µl, approximately 0.19 mmol) was added. The solution was stirred for 30 min, then partitioned between dichloro-

methane and aqueous sodium hydroxide (0.5M). The organic phase was separated, dried with sodium sulfate and evaporated. The crude product was purified on a short silicon dioxide column using methanol as eluent to give 17 mg of a crystalline solid. The solid was purified by HPLC, eluting with 40-80% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (8 mg). The material was partitioned between dichloromethane and sodium hydroxide (0.5M aqueous), the organic phase was dried and evaporated to give the title compound as the free base (6 mg), ^{1}H NMR (400 MHz, $CDCl_3$) δ, 7.29 (m, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.99 (t, J = 8.6 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 4.50 (bs, 2H), 4.40 (d, J = 4.7 Hz, 2H), 3.71 (d, J = 6.5 Hz, 2H), 2.85 (bs, 2H), 2.75 (bs, 2H), 2.46 (bs, 1H), 2.27 (bs, 3H), 2.07 (non, J = 6.5 Hz, 1H), 1.75 (bs, 2H), 1.03 (d, J = 6.5 Hz, 6H). The material was dissolved in dichloromethane and trifluoroacetic acid (2 µl) was added. The solvents were evaporated to give 6.8 mg of the title compound LCMS: $[M+H=426.2]^+$.

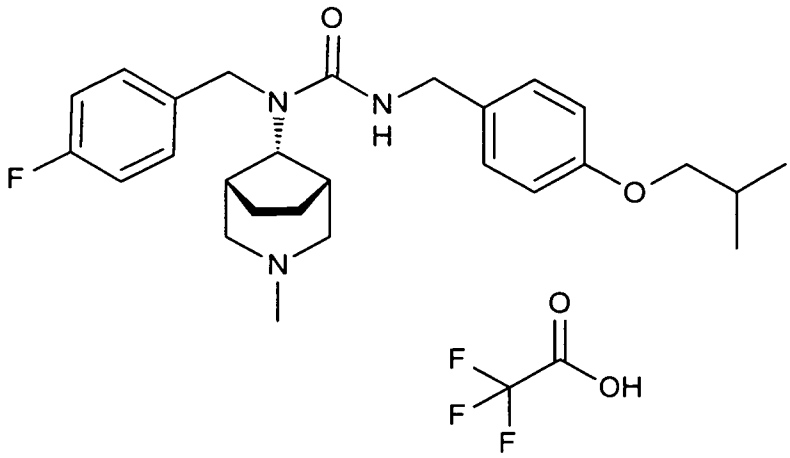
[00487] Example 49: 1-[(4-fluorophenyl)methyl]-1-[(1R,5S,8r)-3-methyl-3-azabicyclo[3.2.1]octan-8-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (49)

[00488] Tert-butyl (1R,5S,8r)-8-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.2.1]octane-3-carboxylate



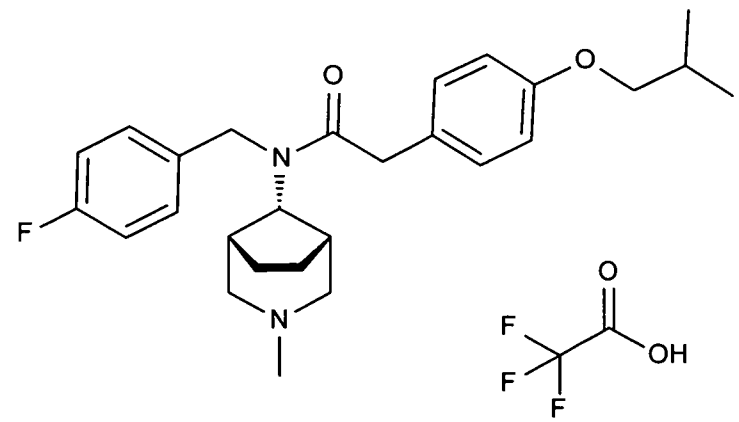
[00489] The compound was prepared in analogy with example 40 using tert-butyl 8-oxo-3-azabicyclo[3.2.1]octane-3-carboxylate.

[00490] 1-[(4-fluorophenyl)methyl]-1-[(1R,5S,8r)-3-methyl-3-azabicyclo[3.2.1]octan-8-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (49)



[00491] The compound was prepared in analogy with example 36 using tert-butyl (1R,5S,8r)-8-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.2.1]octane-3-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 12 mg, 20%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.14 (bs, 1H), 7.18 – 7.01 (m, 6H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.05-5.00 (m, 1H), 4.43 (s, 2H), 4.33 (d, *J* = 5.1 Hz, 2H), 3.70 (d, *J* = 6.5 Hz, 2H), 3.48 –3.34 (m, 3H), 3.00 – 2.87 (m, 4H), 2.70 (s, 3H), 2.15 – 2.01 (m, 2H), 1.93 – 1.79 (m, 2H), 1.03 (d, *J* = 6.7 Hz, 6H); LC-MS: 454.4 $[M+H]^+$.

[00492] Example 50: N-[(4-fluorophenyl)methyl]-N-[(1R,5S,8r)-3-methyl-3-azabicyclo[3.2.1]octan-8-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (50)

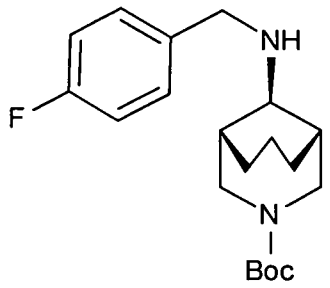


[00493] The compound was prepared in analogy with example 37 using tert-butyl (1R,5S,8r)-8-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.2.1]octane-3-carboxylate and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 17 mg, 20%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.76 (bs, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.16 – 7.06 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 2H), 3.70 (d, *J* = 6.5 Hz, 2H), 3.38 (d, *J* = 11.9 Hz, 2H), 3.28 – 3.21 (m,

1H), 2.98 (s, 2H), 2.78 (br. s, 1H), 2.69 – 2.59 (m, 2H), 2.51 (s, 3H), 2.15 – 1.93 (m, 3H), 1.83 – 1.69 (m, 2H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 439.4 $[M+H]^+$.

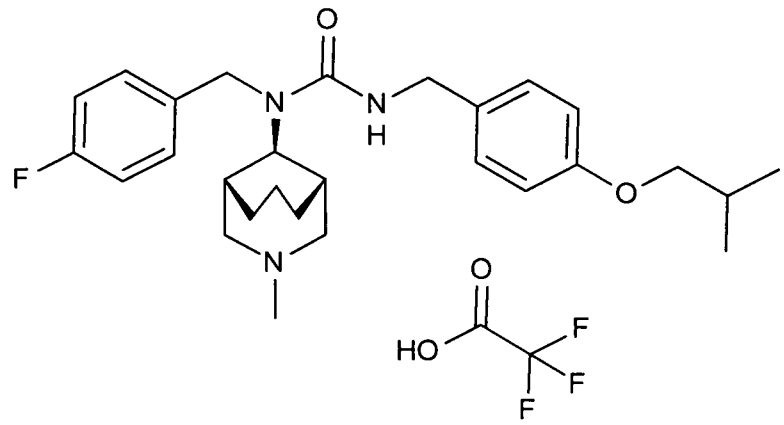
[00494] Example 51: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9s)-3-methyl-3-azabicyclo[3.3.1]nonan-9-yl]urea; trifluoroacetic acid (51)

[00495] Tert-butyl (1R,5S,9s)-9-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.3.1]-nonane-3-carboxylate



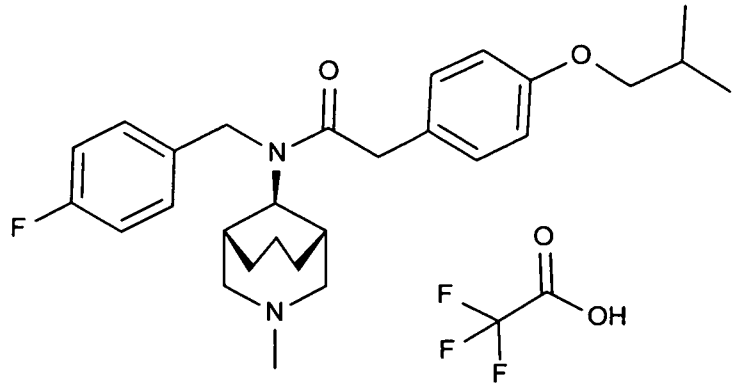
[00496] The compound was prepared in analogy with example 37 using tert-butyl 9-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate.

[00497] 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9s)-3-methyl-3-azabicyclo[3.3.1]nonan-9-yl]urea; trifluoroacetic acid (51)



The compound was prepared in analogy with example 36 using tert-butyl (1R,5S,9s)-9-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.3.1]nonane-3-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 116 mg, 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.78 (bs, 1H), 7.18 – 7.10 (m, 2H), 7.08 – 6.97 (m, 4H), 6.79 (d, J = 8.6 Hz, 2H), 4.91 (t, J = 5.3 Hz, 1H), 4.52 (s, 2H), 4.28 (d, J = 5.3 Hz, 2H), 4.06 (s, 1H), 3.90 (d, J = 12.6 Hz, 2H), 3.69 (d, J = 6.5 Hz, 2H), 3.05 (d, J = 12.1 Hz, 2H), 2.80 (s, 3H), 2.55 (s, 2H), 2.20 – 2.00 (m, 2H), 1.96 – 1.76(m, 4H), 1.70 – 1.56 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 468.3 $[M+H]^+$.

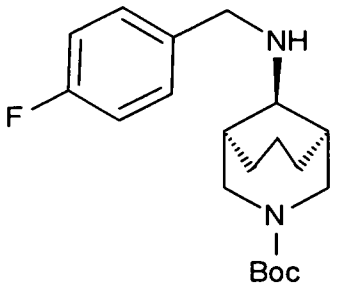
[00498] Example 52: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(1R,5S,9s)-3-methyl-3-azabicyclo[3.3.1]nonan-9-yl]acetamide; trifluoroacetic acid (52)



[00499] The compound was prepared in analogy with example 37 using tert-butyl (1R,5S,9s)-9-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.3.1]nonane-3-carboxylate and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 91 mg, 49%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.48 (bs, 1H), 7.12 – 7.00 (m, 6H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.75 (s, 2H), 4.31 (s, 1H), 3.87 (d, *J* = 12.4 Hz, 2H), 3.70 (d, *J* = 6.5 Hz, 2H), 3.64 (s, 2H), 3.06 (d, *J* = 11.7 Hz, 2H), 2.80 (s, 3H), 2.47 (s, 2H), 2.15 – 1.93 (m, 2H), 1.89 – 1.73 (m, 4H), 1.69 – 1.55 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 6H); LC-MS: 453.3 $[M+H]^+$.

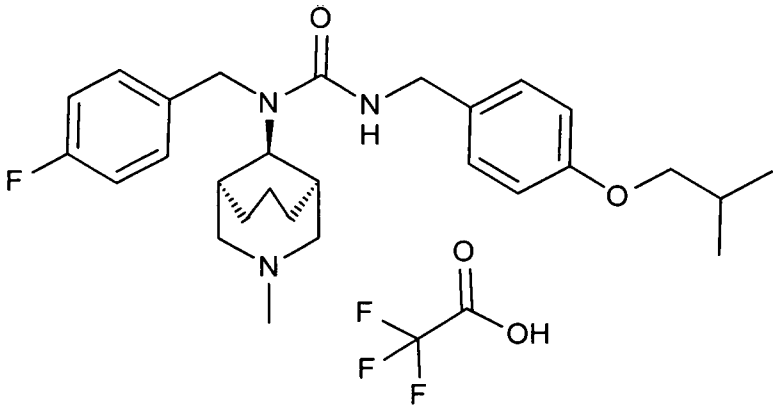
[00500] Example 53: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9r)-3-methyl-3-azabicyclo[3.3.1]nonan-9-yl]urea; trifluoroacetic acid (53)

[00501] Tert-butyl (1R,5S,9r)-9-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.3.1]nonane-3-carboxylate



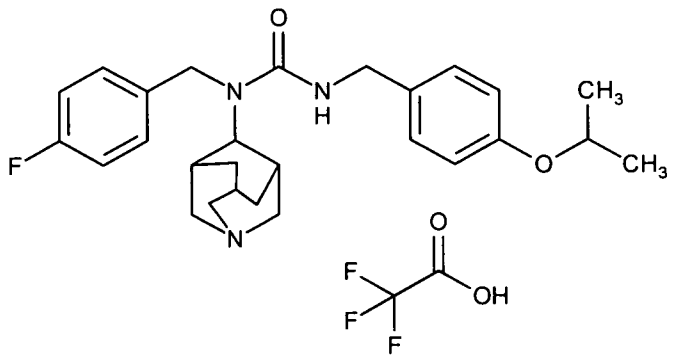
[00502] The compound was prepared in analogy with example 40 using tert-butyl 9-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate.

[00503] 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9r)-3-methyl-3-azabicyclo[3.3.1]nonan-9-yl]urea; trifluoroacetic acid (53)



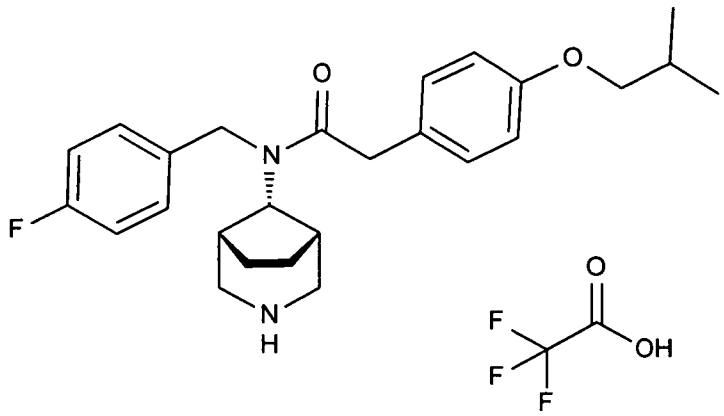
[00504] The compound was prepared in analogy with example 38 using tert-butyl (1R,5S,9r)-9-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.3.1]nonane-3-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 10 mg, 15%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.54 (bs, 1H), 7.22 – 6.89 (m, 6H), 6.85 – 6.76 (m, 2H), 4.88 – 4.79 (m, 1H), 4.54 – 4.35 (m, 2H), 4.29 (d, *J* = 5.0 Hz, 2H), 3.93 – 3.77 (m, 1H), 3.69 (d, *J* = 6.4 Hz, 2H), 3.66 – 3.55 (m, 2H), 3.37 – 2.77 (m, 3H), 2.72 – 2.49 (m, 4H), 2.16 – 1.95 (m, 3H), 1.91 – 1.41 (m, 4H), 1.02 (d, *J* = 6.6 Hz, 6H); LC-MS: 468.3 $[M+H]^+$.

[00505] Example 54: 3-{1-azatricyclo[3.3.1.1^{3,7}]decan-4-yl}-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (54)



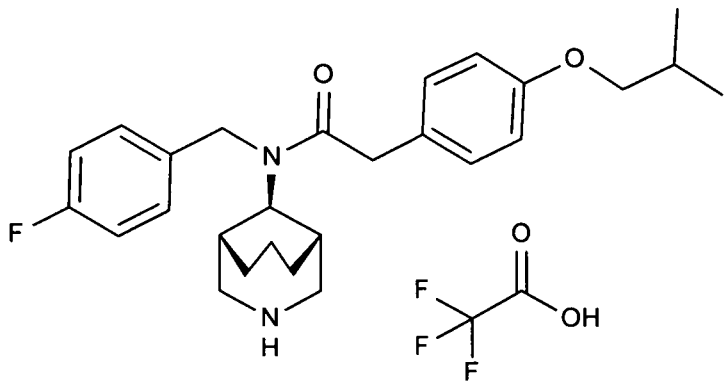
[00506] The title compounds were prepared in analogy with example 38, using N-[(4-fluorophenyl)methyl]-1-azatricyclo[3.3.1.1^{3,7}]decan-4-amine (made in analogy with intermediate 9) and 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene. Isolated as an undefined mixture of stereoisomers. Yield: 68 %: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 6.95 (m, 6H), 6.77 (dd, 2H), 5.24 – 4.79 (m, 1H), 4.49 (dd, 3H), 4.35 – 4.17 (m, 3H), 3.73 (d, 1H), 3.53 (s, 2H), 3.44 (d, 2H), 3.28 (d, 1H), 2.66 (d, 2H), 2.21 – 1.98 (m, 4H), 1.85 (d, 1H), 1.32 (d, 6H); LC-MS: 452.6 $[M+H]^+$.

[00507] Example 55: N-[(1R,5S,8r)-3-azabicyclo[3.2.1]octan-8-yl]-N-[(4-fluorophenyl)-methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (55)



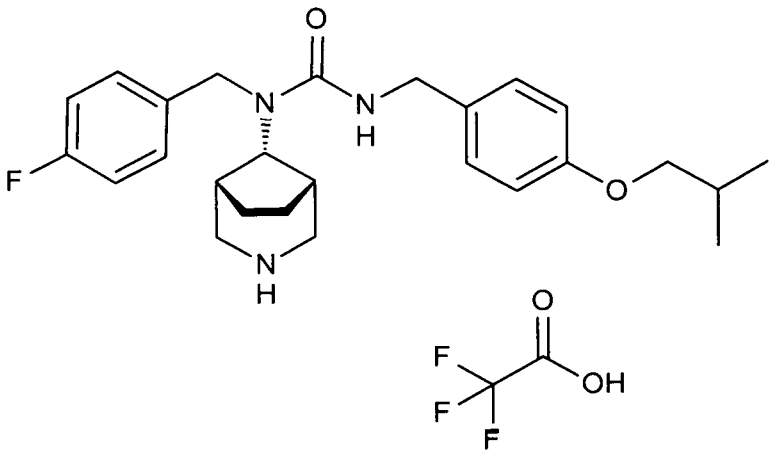
[00508] To a stirred solution of tert-butyl (1R,5S,8r)-8-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.2.1]octane-3-carboxylate (1 equivalent) and diisopropylethylamine (2 equivalents) in dichloromethane was slowly added 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (1.1 equivalents) as a solution in dichloromethane. After stirring at room temperature for 2 hours, the mixture was washed with water and extracted with dichloromethane. The organic phase was dried and concentrated. The residue was re-dissolved in dichloromethane and treated with trifluoroacetic acid at room temperature. After 3 hours, the mixture was concentrated. The crude was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Yield: 146 mg, 91%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.39 (bs, 1H), 8.88 (bs, 1H), 7.16 – 7.01 (m, 6H), 6.90 – 6.81 (m, 2H), 4.69 (s, 2H), 3.79 (s, 2H), 3.69 (d, 2H), 3.50 – 3.34 (m, 2H), 3.29 – 3.17 (m, 2H), 3.06 – 2.93 (m, 4H), 2.13 – 2.00 (m, 1H), 1.97- 1.78 (m, 3H), 1.01 (d, 6H); LC-MS: 425.3 $[M+H]^+$.

[00509] Example 56: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(1R,5S,9s)-3-azabicyclo[3.3.1]nonan-9-yl]acetamide; trifluoroacetic acid (56)



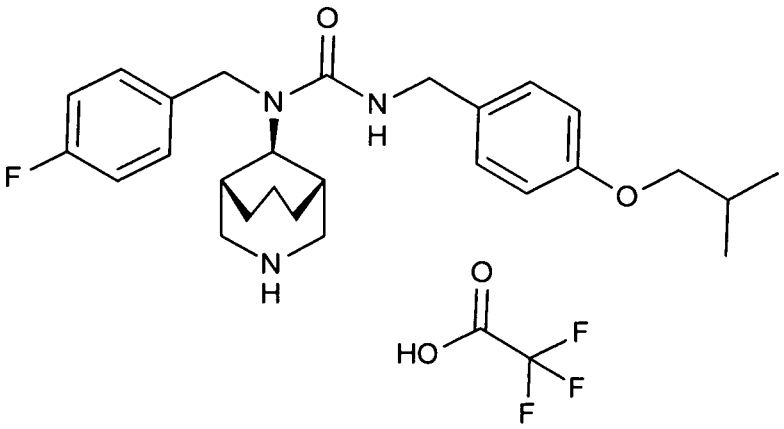
[00510] The compound was prepared in analogy with example 55 using tert-butyl (1R,5S,9s)-9-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.3.1]nonane-3-carboxylate and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 227.0 mg, 99%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.50 (bs, 1H), 7.60 (bs, 1H), 7.14 – 6.97 (m, 6H), 6.88 – 6.77 (m, 2H), 4.75 (s, 2H), 4.36 (s, 1H), 3.70 (d, 2H), 3.65 (s, 2H), 3.41 (bs, 4H), 2.44 (bs, 2H), 2.08 (m, 1H), 1.93 – 1.66 (m, 6H), 1.03 (d, 6H). LC-MS: 439.4 $[M+H]^+$.

[00511] Example 57: 3-[(1R,5S,8R)-3-azabicyclo[3.2.1]octan-8-yl]-3-[(4-fluorophenyl)-methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (57)



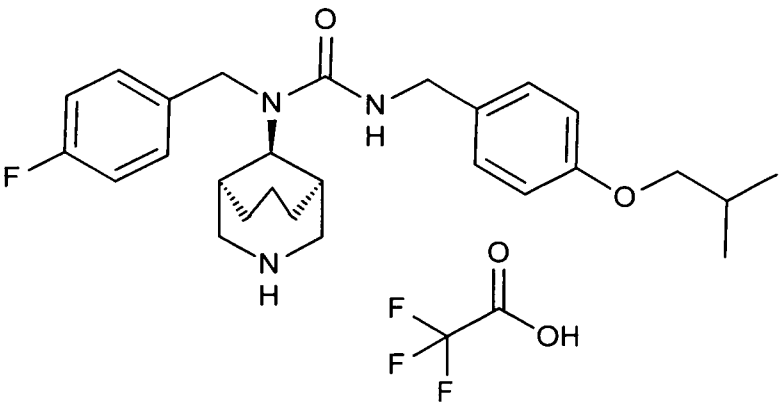
[00512] 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (1.2 equivalents) in dichloromethane was added dropwise to tert-butyl (1R,5S,8r)-8-{[(4-fluorophenyl)methyl]-amino}-3-azabicyclo[3.2.1]octane-3-carboxylate (1 equivalent) in dichloromethane at room temperature. The mixture was stirred for 2.5 hours, then additional isocyanate (0.6 equivalents) was added in one potion. The mixture was stirred for 1.5 hours, then concentrated and re-dissolved in dichloromethane. Trifluoroacetic acid was added. After 1 hour, the mixture was concentrated and the crude was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Yield: 88 mg, 80%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.28 (bs, 1H), 8.74 (bs, 1H), 7.18 – 6.96 (m, 6H), 6.85 – 6.76 (m, 2H), 5.33 (bs, 1H), 4.43 (s, 2H), 4.31 (s, 2H), 3.70 (d, 2H), 3.43 – 3.29 (m, 3H), 3.09 – 2.81 (m, 7H), 2.15 – 2.00 (m, 1H), 1.92 (s, 1H), 1.02 (d, 6H); LC-MS: 440.3 $[M+H]^+$.

[00513] Example 58: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}-3-[(1R,5S,9s)-3-azabicyclo[3.3.1]nonan-9-yl]urea; trifluoroacetic acid (58)



[00514] The compound was prepared in analogy with example 57 using tert-butyl (1R,5S,9s)-9-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.3.1]nonane-3-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 180.0 mg, 99%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.83 (bs, 1H), 8.20 (bs, 1H), 7.19 – 7.11 (m, 2H), 7.08 – 6.98 (m, 4H), 6.82 – 6.75 (m, 2H), 4.91 – 4.82 (m, 1H), 4.52 (s, 2H), 4.31 – 4.23 (m, 2H), 4.08 (s, 1H), 3.69 (d, 2H), 3.41 (bs, 4H), 2.68 – 2.48 (m, 2H), 2.15 – 1.85 (m, 4H), 1.81 – 1.64 (m, 3H), 1.02 (d, 6H). LC-MS: 454.4 $[M+H]^+$.

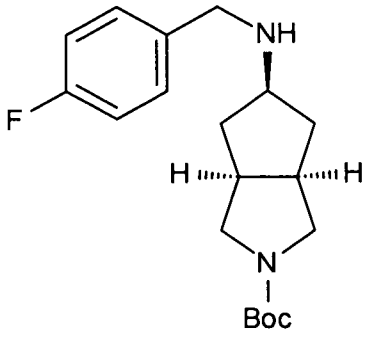
[00515] Example 59: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}-3-[(1R,5S,9r)-3-azabicyclo[3.3.1]nonan-9-yl]urea; trifluoroacetic acid (59)



[00516] The compound was prepared in analogy with example 57 using tert-butyl (1R,5S,9r)-9-{[(4-fluorophenyl)methyl]amino}-3-azabicyclo[3.3.1]nonane-3-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 50.0 mg, 49%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.56 (bs, 1H), 8.46 (bs, 1H), 7.18 – 7.09 (m, 2H), 7.07 – 6.96 (m, 4H), 6.81 – 6.74 (m, 2H), 5.52 – 5.42 (m, 1H), 4.45 (s, 2H), 4.30 – 4.22 (m, 2H), 3.75 – 3.64 (m, 3H), 3.55 – 3.42 (m, 2H), 3.16 – 3.05 (m, 2H), 2.54 (bs, 2H), 2.12 – 2.00 (m, 1H), 1.94 – 1.60 (m, 6H), 1.02 (d, 6H). LC-MS: 454.4 $[M+H]^+$.

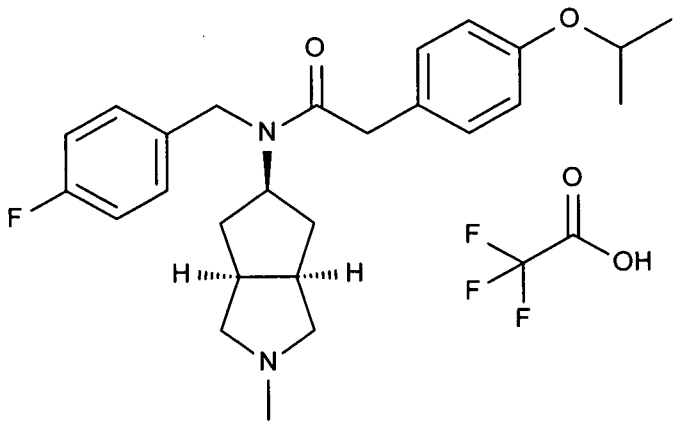
[00517] Example 60: N-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (60)

[00518] Tert-butyl (3aR,5s,6aS)-5-{[(4-fluorophenyl)methyl]amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate



[00519] To a mixture of 4-fluorobenzylamine (64.9 µl, 568 µmol) tert-butyl 5-oxo-octahydrocyclopenta[c]pyrrole-2-carboxylate (121.4 mg, 539 µmol) in dichloromethane (5 ml) sodium triacetoxyborohydride (201 mg, 947 µmol) was added. After stirring for 2 hours at ambient temperature, the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with dichloromethane:methanol (97:3) to afford the title compounds.

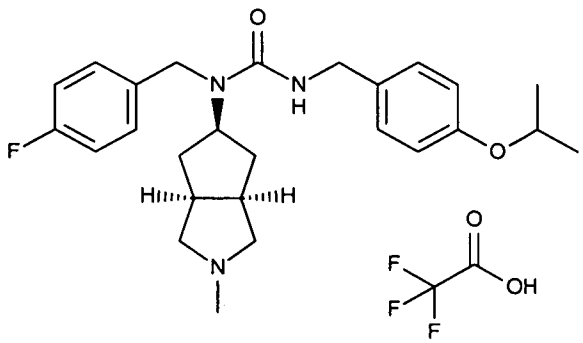
[00520] N-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid



[00521] To a solution of tert-butyl (3aR,5s,6aS)-5-{[(4-fluorophenyl)methyl]amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate (25.5 mg, 764 µmol) and diisopropylethylamine (11.9 mg, 917 µmol) in dichloromethane (2.5 ml) a solution of 2-[4-(propan-2-yloxy)phenyl]acetyl chloride (16.6 mg, 781 µmol) in 2.5 ml dichloromethane was

added dropwise. After stirring for 1h at ambient temperature, the mixture was concentrated. The crude material was purified by column chromathography using silica gel, eluting with 10-30 % ethyl acetate in petroleum ether to afford the intermediate amide. The intermediate was dissolved in dry dichloromethane (4.5 ml) and trifluoroacetic acid (1.5 ml) was added dropwise. After 60 minutes stirring the reaction mixture was concentrated, dried and dissolved in tetrahydrofuran (3 ml). To that solution formaldehyde (37% solution in water, 20.4 µL, 274 µmol) was added. After 15 minutes stirring sodium triacetoxyborohydride (58.1 mg, 274 µmol). After 20 h stirring the reaction was concentrated and diluted with dichloromethane (15 ml) and sodium hydrogen carbonate (15 ml, aqueous, saturated). Phases were separated and the water phase was extracted with dichloromethane (2 x 15 ml). The combined organic phase was washed with 20% brine (25 ml), dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC , eluting with 30-70% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound Yield: 32.1 mg, 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 6.92 (m, 6H), 6.89 – 6.72 (m, 2H), 5.02 – 4.84 (m, 1H), 4.63 – 4.38 (m, 3H), 3.67 – 3.43 (m, 5H), 2.94 – 2.67 (m, 7H), 2.04 (dt, *J* = 13.1, 6.6 Hz, 1H), 1.74 – 1.44 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 6H); LC-MS: 425.56 $[M+H]^+$.

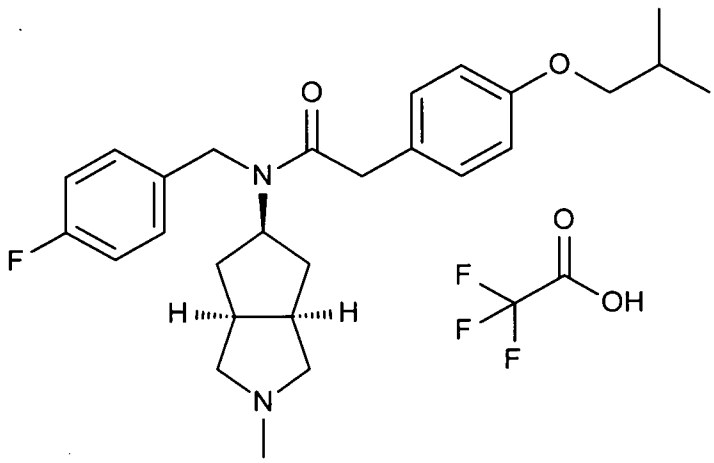
[00522] Example 61: 3-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (61)



[00523] A solution of tert-butyl (3aR,5s,6aS)-5-{[(4-fluorophenyl)methyl]amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate (77.4 mg , 231 µmol) and 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene (75.1 mg, 393 µmol)in dichloromethane (2.5 ml) was stirred for 1h at ambient temperature and thereafter concentrated. The crude material was purified by column chromatography using silica gel, eluting with 15-40% ethyl acetate in petroleum ether to afford the intermediate urea. The intermediate was dissolved in dry dichloromethane (4.5 ml) and trifluoroacetic acid (1.5 ml) was added dropwise. After 60

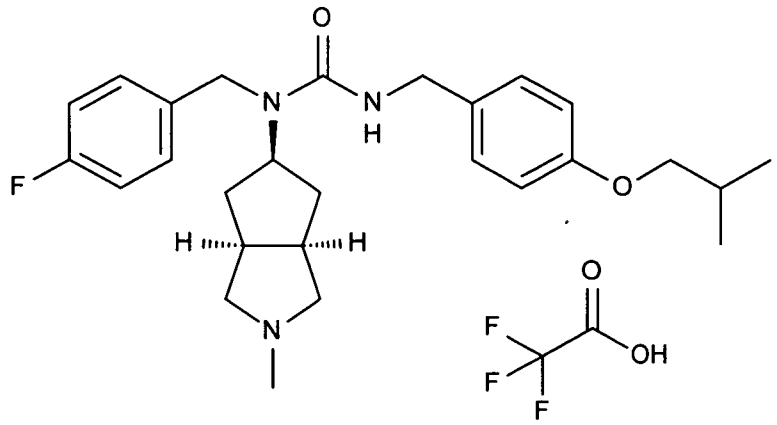
minutes stirring the reaction mixture was concentrated, dried and dissolved in tetrahydrofuran (3 ml). To that solution formaldehyde (37% solution in water, 25.5 µL, 342 µmol) was added. After 15 minutes stirring sodium triacetoxyborohydride (72.6 mg, 342 µmol). After 20 h stirring the reaction was concentrated and diluted with dichloromethane (15 ml) and sodium hydrogen carbonate (15 ml, aqueous, saturated). Phases were separated and the water phase was extracted with dichloromethane (2 x 15 ml). The combined organic phase was washed with 20% brine (25 ml), dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC , eluting with 30-70% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound. Yield: 11.4 mg, 89%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 – 7.09 (m, 2H), 7.06 – 6.93 (m, 4H), 6.83 – 6.68 (m, 2H), 4.85 (d, *J* = 6.1 Hz, 1H), 4.63 – 4.39 (m, 4H), 4.39 – 4.17 (m, 2H), 3.61 (dd, *J* = 11.1, 3.4 Hz, 2H), 3.01 – 2.73 (m, 7H), 2.11 (d, *J* = 7.3 Hz, 2H), 1.71 – 1.51 (m, 2H), 1.32 (d, *J* = 6.0 Hz, 6H); LC-MS: 440.57 $[M+H]^+$.

[00524] Example 62: N-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (62)



[00525] The compound was prepared in analogy with example 60 using tert-butyl (3aR,5s,6aS)-5-{[(4-fluorophenyl)methyl]amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 25.1 mg, 59%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.10 (m, 3H), 7.10 – 6.93 (m, 4H), 6.87 – 6.76 (m, 2H), 4.94 (d, *J* = 6.1 Hz, 1H), 4.58 (s, 2H), 4.10 – 3.75 (m, 1H), 3.69 (d, *J* = 6.5 Hz, 2H), 3.66 – 3.54 (m, 2H), 3.50 (s, 1H), 2.92 – 2.67 (m, 6H), 2.17 – 1.90 (m, 3H), 1.78 – 1.41 (m, 2H), 1.01 (d, *J* = 6.7 Hz, 6H); LC-MS: 439.58 $[M+H]^+$.

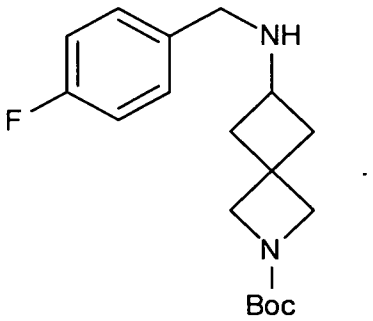
[00526] Example 63: 3-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (63)



[00527] The compound was prepared in analogy with example 61 using tert-butyl (3aR,5s,6aS)-5-{[(4-fluorophenyl)methyl]amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 14.8 mg, 73%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 (dd, *J* = 8.5, 5.3 Hz, 2H), 7.03 – 6.92 (m, 4H), 6.76 (d, *J* = 8.6 Hz, 2H), 5.18 (s, 1H), 5.08 (s, 1H), 4.91 – 4.77 (m, 1H), 4.55 (s, 1H), 4.44 (s, 2H), 4.25 (d, *J* = 3.1 Hz, 2H), 3.71 – 3.57 (m, 4H), 2.88 (dd, *J* = 21.1, 4.9 Hz, 7H), 2.09 (ddd, *J* = 20.0, 13.3, 6.8 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 6H); LC-MS: 454.60 $[M+H]^+$.

[00528] Example 64: N-[(4-fluorophenyl)methyl]-N-{2-methyl-2-azaspiro[3.3]heptan-6-yl}-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (64)

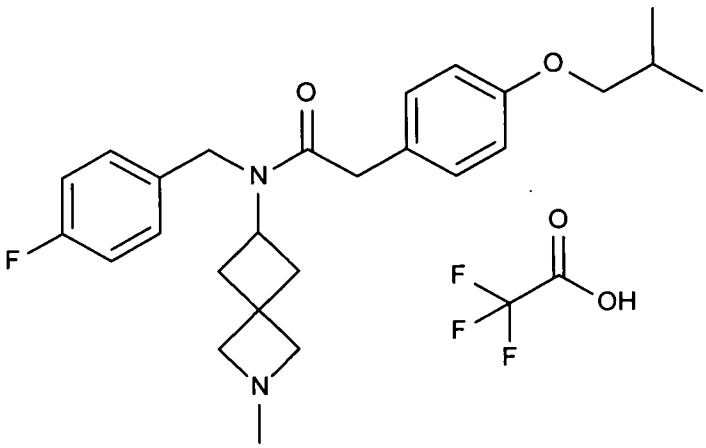
[00529] Tert-butyl 6-{[(4-fluorophenyl)methyl]amino}-2-azaspiro[3.3]heptane-2-carboxylate



[00530] To a mixture of 4-fluorobenzaldehyde (268 µl, 2.5 mmol) and tert-butyl 6-amino-2-azaspiro[3.3]heptane-2-carboxylate (530.7 mg, 2.5 mmol) in dichloromethane (25 ml) sodium triacetoxyborohydride (795 mg, 3.75 mmol) was added at ambient temperature. After stirring for 24 hours the mixture was treated with sodium hydroxide (1M, 10 ml), separated

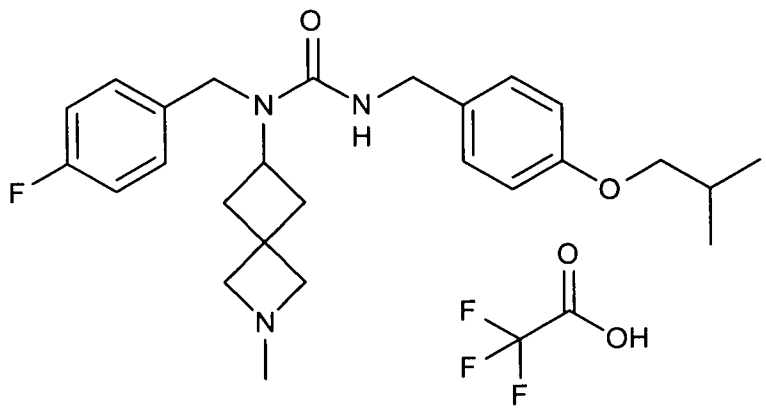
and extracted with dichloromethane (2 x 10 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by column chromatography using silica gel, eluting with 2-5% methanol in dichloromethane to afford the title compound (736.9 mg, 92%).

[00531] N-[(4-fluorophenyl)methyl]-N-{2-methyl-2-azaspiro[3.3]heptan-6-yl}-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid



[00532] The compound was prepared in analogy with example 60 using tert-butyl 6-{[(4-fluorophenyl)methyl]amino}-2-azaspiro[3.3]heptane-2-carboxylate and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield 24.6 mg, 67%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 6.91 (m, 6H), 6.91 – 6.75 (m, 2H), 4.46 (s, 4H), 4.37 – 4.12 (m, 1H), 3.79 – 3.47 (m, 6H), 2.79 (d, *J* = 3.9 Hz, 3H), 2.53 (dd, *J* = 24.0, 9.3 Hz, 3H), 2.07 (hept, *J* = 6.5 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 6H); LC-MS: 425.56 $[M+H]^+$.

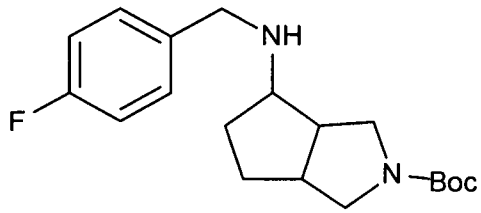
[00533] Example 65: 3-[(4-fluorophenyl)methyl]-3-{2-methyl-2-azaspiro[3.3]heptan-6-yl}-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (65)



[00534] The compound was prepared in analogy with example 61 using tert-butyl 6-{[(4-fluorophenyl)methyl]amino}-2-azaspiro[3.3]heptane-2-carboxylate and 1-(isocyanato-methyl)-4-(2-methylpropoxy)benzene. Yield: 20.4 mg (73%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 6.95 (m, 6H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.64 – 4.18 (m, 8H), 3.75 – 3.54 (m, 4H), 2.77 (s, 3H), 2.71 – 2.60 (m, 1H), 2.55 – 2.44 (m, 1H), 2.38 (d, *J* = 11.2 Hz, 2H), 2.13 – 1.95 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 6H); LC-MS: 440.57 $[M+H]^+$.

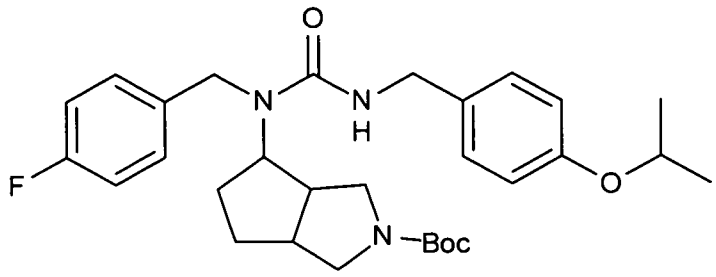
[00535] Example 66: 3-[(4-fluorophenyl)methyl]-3-{2-methyl-octahydrocyclo-penta[c]pyrrol-4-yl}-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (66)

[00536] Tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate



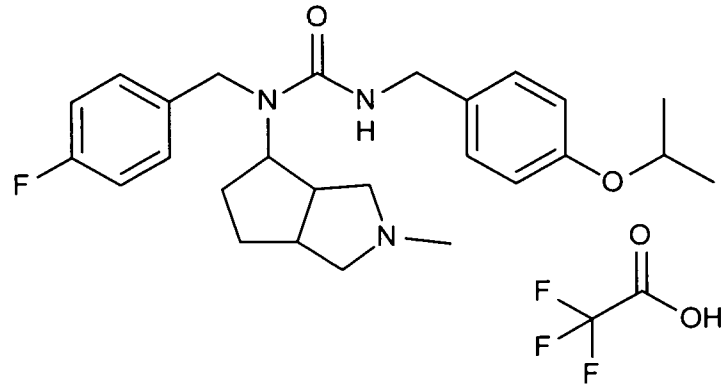
To a solution of tert-butyl 4-oxo-octahydrocyclopenta[c]pyrrole-2-carboxylate (450 mg, 2.00 mmol) in ethanol (5 ml) a solution of 4-fluorobenzylamine (263 mg, 2.10 mmol) in ethanol (4 ml) was added in one portion. After 20 minutes stirring sodium triacetoxyborohydride (717 mg, 3.40 mmol) was added in one portion and stirring was continued for 20 hours. The reaction was quenched with sodium hydroxide (1M, 1.1 ml) and concentrated. The residue was diluted with 20% brine (30 ml), basified with sodium hydroxide (1 M) to pH 10 and extracted with dichloromethane (4 x 40 ml). Combined organic phase was washed once with 20% brine (100 ml), dried over sodium sulfate and concentrated. The product was purified by column chromatography using silica gel, eluting with ethyl acetate:methanol 10:1 to afford the title compound (367 mg, 55.1%) as light yellow oil.

[00537] Tert-butyl 4-{[(4-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl}-carbamoyl)-amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate



[00538] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate (105 mg, 0.315 mmol) in dry dichloromethane (2.0 ml) 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene (72.2 mg, 0.378 mmol) in dichloromethane (1.5 ml) was added. Stirring was continued for 20 hours before the reaction was concentrated. The crude product was purified by column chromatography using silica gel, eluting with petroleum ether:ethyl acetate 3:2 to afford the title compound (124 mg, 74.9%) as light yellow oil.

[00539] 3-[(4-fluorophenyl)methyl]-3-{2-methyl-octahydrocyclopenta[c]pyrrol-4-yl}-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid

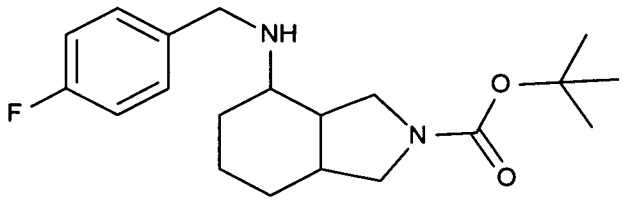


[00540] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl]({[4-(propan-2-yloxy)phenyl]methyl}carbamoyl)-amino}-octahydrocyclopenta[c]pyrrole-2-carboxylate (120 mg, 0.229 mmol) in dry dichloromethane (4.5 ml) trifluoroacetic acid (1.5 ml) was added dropwise. After 20 minutes stirring the reaction mixture was concentrated, dried and dissolved in tetrahydrofuran (3 ml). To that solution formaldehyde (30% solution in water, 104.7 µL, 1.142 mmol) was added. After 15 minutes stirring sodium triacetoxyborohydride (96.7 mg, 0.458 mmol). After 20 h stirring the reaction was quenched by sodium hydrogen carbonate (0.1 ml, aqueous, saturated), concentrated and diluted with dichloromethane (15 ml) and sodium hydrogen carbonate (15 ml, aqueous, saturated). Phases were separated and the water phase was extracted with dichloromethane (2 x 15 ml). The combined organic

phase was washed with 20% brine (25 ml), dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC , eluting with 35-75% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (44.0 mg, 45.0%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 – 7.04 (m, 4H), 7.05 – 6.96 (m, 2H), 6.84 – 6.75 (m, 2H), 4.82 (bs, 1H, NH), 4.72 – 4.65 (d, *J* = 16.2 Hz, 1H), 4.58 – 4.48 (m, 1H), 4.46 – 4.36 (d, *J* = 16.2 Hz, 1H), 4.35 – 4.20 (m, 2H), 3.90 – 3.80 (m, 1H), 3.73 – 3.59 (m, 1H), 3.57 – 3.47 (d, *J* = 11.5 Hz, 1H), 3.17 – 2.93 (m, 4H), 2.80 (s, 3H), 2.50 – 2.40 (m, 1H), 2.05 – 1.89 (m, 1H), 1.75 – 1.56 (m, 2H), 1.32 (d, *J* = 5.9 Hz, 6H); LC-MS: 440.3 $[M+H]^+$.

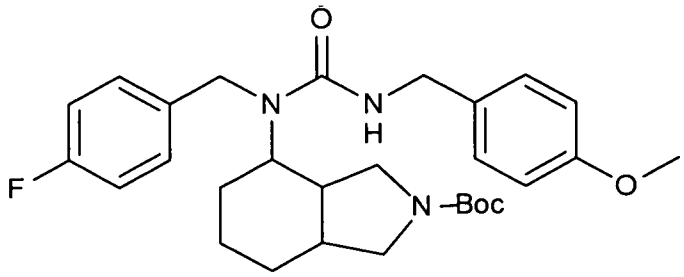
[00541] Example 67: 3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-(2-methyl-octahydro-1H-isoindol-4-yl)urea; trifluoroacetic acid (67)

[00542] Tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-octahydro-1H-isoindole-2-carboxylate



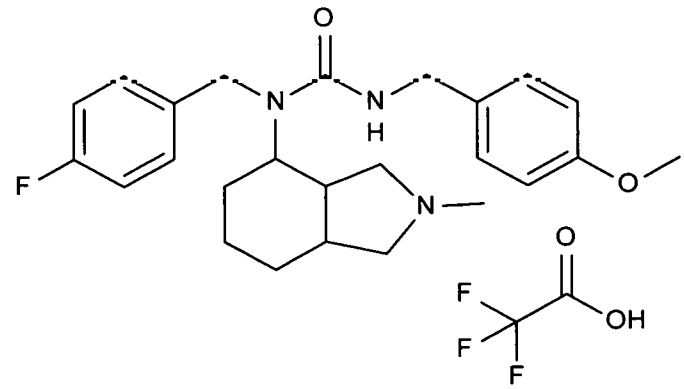
[00543] To a solution of tert-butyl 4-oxo-octahydro-1H-isoindole-2-carboxylate (480 mg, 2.01 mmol) in dry tetrahydrofuran (3 ml) a solution of 4-fluorobenzylamine (264 mg, 2.11 mmol) in dry tetrahydrofuran (3 ml) was added. After 20 min stirring sodium triacetoxyborohydride (850 mg, 4.01 mmol) was added in one portion and stirring was continued for 20 hours. Diethyl ether (100 ml) was added to the reaction and the reaction was basified with sodium hydroxide (1M, 1 ml) to pH 10. The phases were separated and the water phase was extracted once more with 150 ml diethyl ether. The combined organic phase was washed once with brine (50 ml), dried over sodium sulfate, concentrated and the product was purified by column chromatography using silica gel, eluting with ethylacetate:methanol (20:1) to afford the title compound (430 mg, 61.5%).

[00544] Tert-butyl 4-{[(4-fluorophenyl)methyl]({[(4-methoxyphenyl)methyl]-carbamoyl})amino}-octahydro-1H-isoindole-2-carboxylate



[00545] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-octahydro-1H-isoindole-2-carboxylate (94 mg, 0.270 mmol) in dry dichloromethane (1.5 ml) 1-(isocyanato-methyl)-4-methoxybenzene (52.8 mg, 0.324 mmol) in dry dichloromethane (0.5 ml) was added. The reaction was stirred for 20 hours before it was concentrated and purified by column chromatography using silica gel, eluting with petroleum ether:ethyl acetate 3:2 to petroleum ether:ethyl acetate 1:1 to afford the title compound (115 mg, 83.3%).

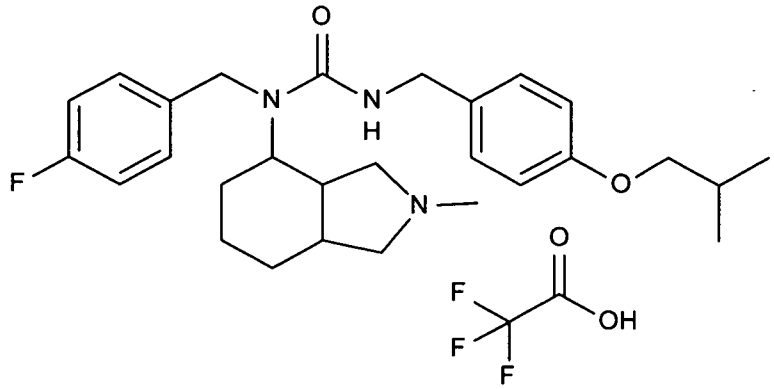
[00546] 3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-(2-methyl-octahydro-1H-isoindol-4-yl)urea; trifluoroacetic acid



[00547] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl]({[(4-methoxyphenyl)-methyl]carbamoyl})amino}-octahydro-1H-isoindole-2-carboxylate (115 mg, 0.225 mmol) in dry dichloromethane (4.5 ml) trifluoroacetic acid (1.5 ml) was added dropwise. After 20 minutes the mixture was concentrated and redissolved in tetrahydrofuran (3 ml). To that solution formaldehyde (30% solution in water, 61.9 µL, 0.674 mmol) was added. After 15 minutes stirring sodium triacetoxyborohydride (98.2 mg, 0.450 mmol) was added. After 20 h stirring the reaction was quenched by sodium hydrogen carbonate (aqueous, saturated, 0.1 ml), concentrated and diluted with dichloromethane (15 ml) and sodium hydrogen carbonate (aqueous, saturated, 15 ml). Phases were separated and the water phase was extracted with dichloromethane (2 x 15 ml). The combined organic phase was washed with brine (20%, 25 ml), dried over sodium sulfate and concentrated to get crude product. The residue was

purified by HPLC, eluting with 22-52% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (74.0 mg, 61.0 %) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 – 7.10 (m, 2H), 7.07 – 6.92 (m, 4H), 6.83 – 6.76 (m, 2H), 4.78 – 4.62 (m, 1H), 4.57 (bs, 1H, NH), 4.38 – 4.28 (m, 2H), 4.25 – 4.12 (m, 3H), 3.78 (s, 3H), 3.76 – 3.66 (m, 1H), 3.63 (dd, J = 11.2, 5.2 Hz, 1H), 3.28 – 3.18 (m, 1H), 2.94 – 2.84 (m, 3H), 2.85 – 2.77 (m, 1H), 2.60 – 2.47 (m, 1H), 2.43 – 2.23 (m, 1H), 1.93 – 1.80 (m, 1H), 1.68 – 1.59 (m, 2H), 1.43 – 1.22 (m, 2H). LC-MS: 426.2 $[M+H]^+$.

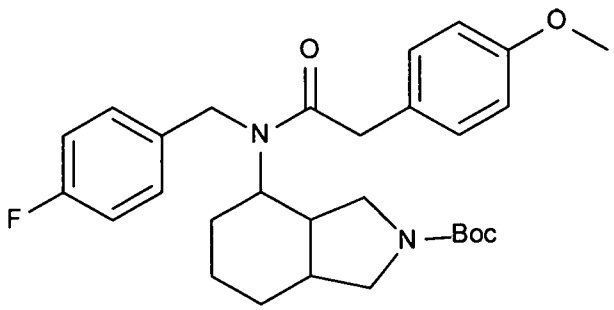
[00548] Example 68: 3-[(4-fluorophenyl)methyl]-3-(2-methyl-octahydro-1H-isoindol-4-yl)-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (68)



[00549] The compound was prepared in analogy with example 67 using tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-octahydro-1H-isoindole-2-carboxylate and 1-(isocyanato-methyl)-4-(2-methylpropoxy)benzene. Yield: 26.0 mg, 28.2 %, white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.21 – 7.09 (m, 2H), 7.06 – 6.92 (m, 4H), 6.81 – 6.73 (m, 2H), 4.79 – 4.69 (m, 1H), 4.35 - 4.29 (m, 2H), 4.22 – 4.12 (m, 3H), 3.79 – 3.71 (m, 1H), 3.71 – 3.63 (m, 2H), 3.63 (dd, J = 11.3, 5.4 Hz, 1H), 3.30 – 3.20 (m, 1H), 2.95 – 2.83 (m, 3H), 2.83 – 2.75 (m, 1H), 2.56 – 2.43 (m, 1H), 2.45 – 2.35 (m, 1H), 2.15 - 2.03 (m, 1H), 1.94 – 1.83 (m, 1H), 1.70 – 1.60 (m, 2H), 1.44 – 1.30 (m, 2H), 1.03 (d, J = 6.7 Hz, 6H). LC-MS: 468.4 $[M+H]^+$.

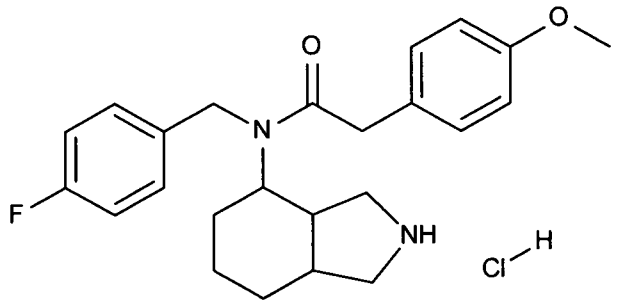
[00550] Example 69a: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-(octahydro-1H-isoindol-4-yl)acetamide; hydrochloride (69a)

[00551] Tert-butyl 4-{N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)acetamido}-octahydro-1H-isoindole-2-carboxylate



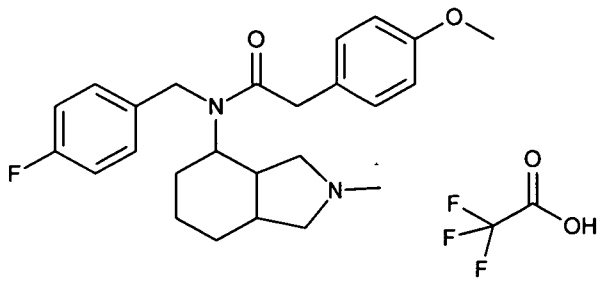
[00552] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-octahydro-1H-isoindole-2-carboxylate (109 mg, 0.313 mmol) in dry dichloromethane (1.0 ml) 2-(4-methoxyphenyl)acetyl chloride (69.3 mg, 0.375 mmol) in dry dichloromethane (1 ml) was added under nitrogen flow followed by diisopropylethylamine (122 mg, 0.938 mmol) in dry dichloromethane (0.4 ml). The reaction was stirred for 20 hours before it was concentrated and purified by column chromatography using silica gel, eluting with petroleum ether:ethyl acetate 1:1 to afford the title compound (106 mg, 68.2 %) as a light yellow oil.

[00553] N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-(octahydro-1H-isoindol-4-yl)acetamide; hydrochloride



[00554] Tert-butyl 4-{N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)acetamido}-octahydro-1H-isoindole-2-carboxylate (106.0 mg, 0.213 mmol) was dissolved in hydrogen chloride in dry ether (2M, 3 ml) and left at stirring for 18 hours. The white suspension was filtered slowly. The white solid was washed with ether (2 x 2.5 ml) and dried to afford the title compound (82 mg, 88.7 %) as white solid. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.32 – 7.21 (m, 2H), 7.21 – 6.97 (m, 4H), 6.97 – 6.88 (m, 2H), 4.70 – 4.46 (m, 2H), 4.38 – 4.28 (m, 1H), 3.78 (s, 3H), 3.64 – 3.56 (m, 2H), 3.53 – 3.39 (m, 1H), 3.23 (dd, J = 11.7, 6.0 Hz, 1H), 3.09 – 2.99 (m, 2H), 2.81 – 2.71 (m, 1H), 2.44 – 2.34 (m, 1H), 2.07 – 1.94 (m, 1H), 1.86 – 1.76 (m, 1H), 1.65 – 1.50 (m, 2H), 1.36 (q, J =13.5 Hz, 1H), 1.25 – 1.10 (m, 1H). LC-MS: 397.3 $[M+H]^+$.

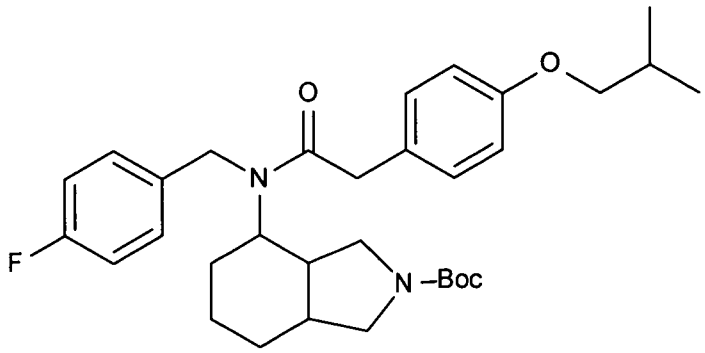
[00555] Example 69b: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-(2-methyl-octahydro-1H-isoindol-4-yl)acetamide; trifluoroacetic acid (69b)



[00556] Formaldehyde (42.2 μL, 30% aqueous, 0.460 mmol) was added to a solution of N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-(octahydro-1H-isoindol-4-yl)acetamide hydrochloride (67.0 mg, 0.153 mmol) in tetrahydrofuran (4.0 ml). After 15 min stirring sodium triacetoxyborohydride (64.9 mg, 0.306 mmol) was added in one portion and stirring was continued. After 2 h stirring the reaction was quenched by sodium hydrogen carbonate (aqueous, saturated, 0.1 ml), concentrated and diluted with dichloromethane (15 ml) and sodium hydrogen carbonate (aqueous, saturated, 15 ml). Phases were separated and the water phase was extracted more with dichloromethane (2 x 15 ml). The combined organic phase was washed with brine (20%, 20 ml), dried over sodium sulfate and concentrated. The residue was purified by HPLC, eluting with 23-60% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (55.0 mg, 87.5%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.18 – 7.06 (m, 6H), 6.92 – 6.82 (m, 2H), 4.78 – 4.72 (m, 1H), 4.60 – 4.50 (m, 1H), 4.45 – 4.30 (m, 1H), 4.07 – 4.97 (m, 1H), 3.75 (s, 3H), 3.70 – 3.60 (m, 2H), 3.55 – 3.37 (m, 2H), 2.90 – 2.77 (m, 4H), 2.55 – 2.40 (m, 3H), 1.85 – 1.75 (m, 1H), 1.68 – 1.50 (m, 2H), 1.38 – 1.27 (m, 1H), 1.25 – 1.15 (m, 1H). LC-MS: 3.97 min – 411.2 $[M+H]^+$.

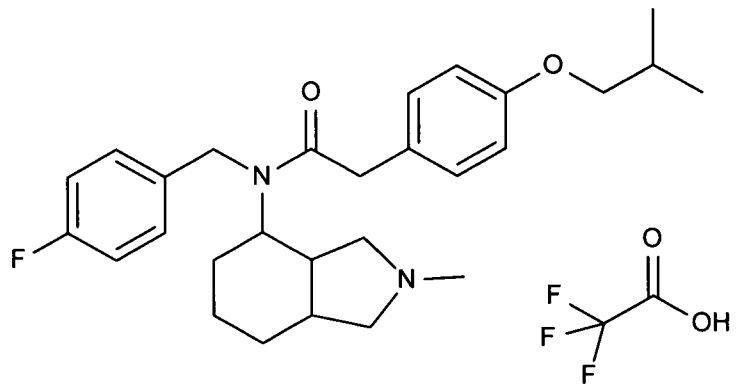
[00557] Example 70: N-[(4-fluorophenyl)methyl]-N-(2-methyl-octahydro-1H-isoindol-4-yl)-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (70)

[00558] Tert-butyl 4-{N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-acetamido}-octahydro-1H-isoindole-2-carboxylate



[00559] To a solution of tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-octahydro-1H-isoindole-2-carboxylate (101 mg, 0.290 mmol) in dry dichloromethane (1.0 ml) 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (78.9 mg, 0.348 mmol) in dichloromethane (1 ml) was added, followed by diisopropylethylamine (113.0 mg, 0.870 mmol) in dichloromethane (0.4 ml). Stirring was continued for 20 hours before the reaction was concentrated. The residue was purified by column chromatography using silica gel, eluting with petroleum ether:ethyl acetate 3:2 to afford the title compound (123.0 mg, 78.8 %) as off-white foam.

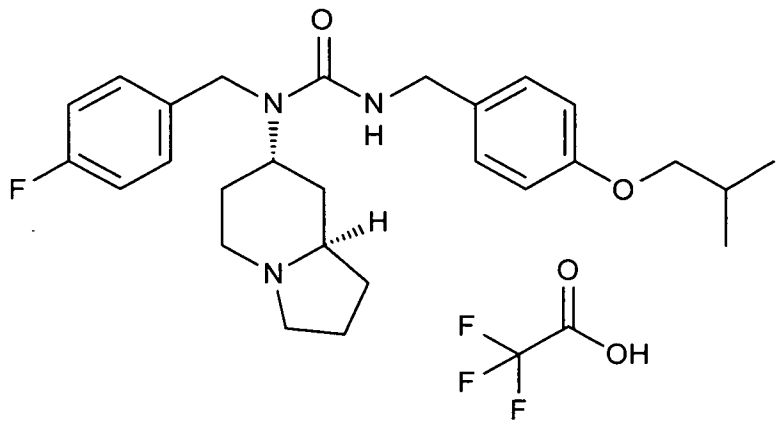
[00560] N-[(4-fluorophenyl)methyl]-N-(2-methyl-octahydro-1H-isoindol-4-yl)-2-[4-(2-methyl-propoxy)phenyl]acetamide; trifluoroacetic acid



[00561] To a solution of tert-butyl 4-{N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamido}-octahydro-1H-isoindole-2-carboxylate (123.0 mg, 0.228 mmol) in dry dichloromethane (4.5 ml) trifluoroacetic acid (1.5 ml) was added dropwise. After 20 min stirring the reaction mixture concentrated and redissolved in tetrahydrofuran (3 ml). To that solution formaldehyde (30% aqueous, 62.8.0 µL, 0.685 mmol) was added. After 15 min stirring sodium triacetoxyborohydride (96.8 mg, 0.457 mmol) was added. After 2 hours of stirring the reaction was quenched by sodium hydrogen carbonate (aqueous, saturated, 0.1 ml), concentrated and diluted with dichloromethane (15 ml) and sodium

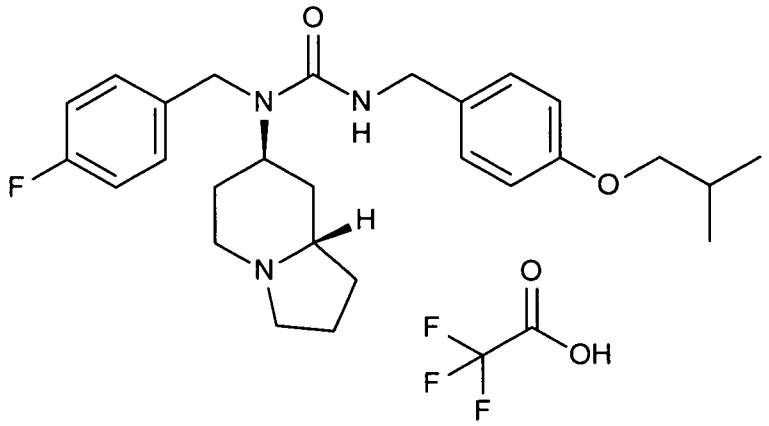
hydrogen carbonate (aqueous, saturated, 15 ml). Phases were separated and the water phase was extracted with dichloromethane (2 x 15 ml). The combined organic phase was washed with brine (20%, 25 ml), dried over sodium sulfate and concentrated to get crude product. The residue was purified by HPLC, eluting with 25-60% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (80.5 mg, 77.9 %) as a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.20 – 7.02 (m, 6H), 6.88 – 6.78 (m, 2H), 4.80 - 4.70 (m, 1H), 4.56 – 4.48 (m, 1H), 4.35 (dd, J =39.8, 17.6 Hz, 1H), 4.10 - 3.95 (m, 1H), 3.76 - 3.67 (m, 2H), 3.64 – 3.58 (m, 2H), 3.55 – 3.45 (m, 1H), 3.42 – 3.32 (m, 1H), 3.25 - 3.15 (m, 1H), 2.91 – 2.75 (m, 4H), 2.57 - 2.45 (m, 2H), 2.14 – 2.00 (m, 1H), 1.85 – 1.75 (m, 1H), 1.78 – 1.50 (m, 2H), 1.35 – 1.25 (m, 1H), 1.23 – 1.13 (m, 1H), 1.03 (d, J = 6.7 Hz, 6H). LC-MS: 453.4 $[M+H]^+$.

[00562] Example 71: 3-[(7S,8aR)-octahydroindolizin-7-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (71)



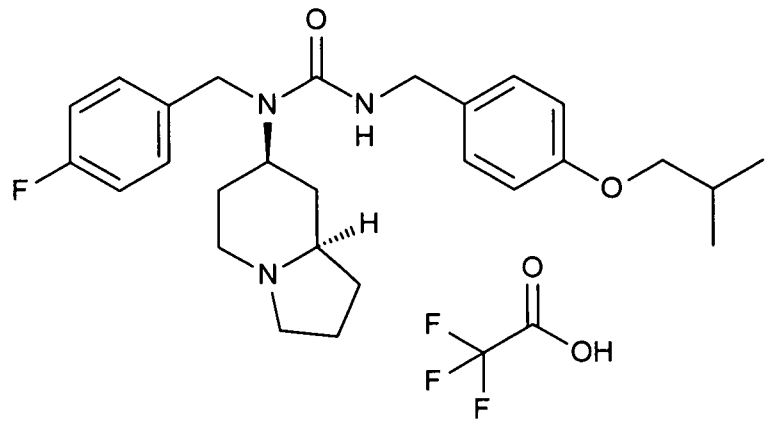
[00563] 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (27.3 mg, 133 µmol) was added to (7S,8aR)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine (30.0 mg, 121 µmol) in dichloromethane (1 ml). After 1.5 hours of stirring at ambient temperature the mixture was concentrated. The crude material was purified by HPLC, eluting with 50-85% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (50 mg, 73%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.17 (bs, 1H), 7.21 – 7.11 (m, 2H), 7.07 – 6.92 (m, 4H), 6.78 (d, J = 8.5 Hz, 2H), 4.91 (t, J = 12.6 Hz, 1H), 4.64 (s, 1H), 4.35 (s, 2H), 4.26 (s, 2H), 3.96 (s, 1H), 3.68 (d, J = 6.6 Hz, 2H), 3.60 – 3.48 (m, 1H), 3.43 (d, J = 11.1 Hz, 1H), 3.17 – 3.05 (m, 1H), 3.05 – 2.88 (m, 1H), 2.34 – 2.02 (m, 7H), 1.98 (d, J = 14.7 Hz, 1H), 1.86 (d, J = 13.3 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 454.3 $[M+H]^+$.

[00564] Example 72: 3-[(7R,8aS)-octahydroindolizin-7-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (72)



[00565] The compound was prepared in analogy with example 71 using (7R,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 69%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.31 (bs, 1H), 7.22 – 7.11 (m, 2H), 7.08 – 6.93 (m, 4H), 6.78 (d, J = 8.5 Hz, 2H), 4.91 (t, J = 12.7 Hz, 1H), 4.63 (s, 1H), 4.35 (s, 2H), 4.26 (s, 2H), 3.96 (s, 1H), 3.68 (d, J = 6.5 Hz, 2H), 3.61 – 3.47 (m, 1H), 3.43 (d, J = 10.4 Hz, 1H), 3.18 – 3.04 (m, 1H), 3.04 – 2.89 (m, 1H), 2.36 – 2.02 (m, 7H), 1.98 (d, J = 13.3 Hz, 1H), 1.86 (d, J = 13.9 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 454.3 $[M+H]^+$.

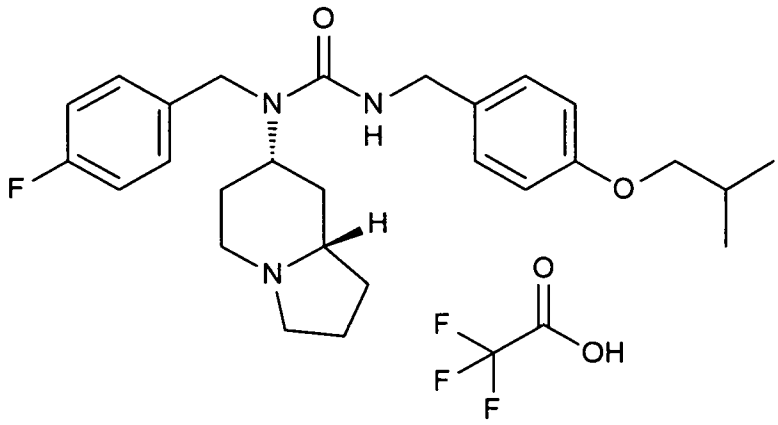
[00566] Example 73: 3-[(7R,8aR)-octahydroindolizin-7-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (73)



[00567] The compound was prepared in analogy with example 71 using (7R,8aR)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 80%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.08 (bs, 1H), 7.18 (dd, J = 8.3, 5.2 Hz, 2H), 7.07 – 6.93 (m, 4H), 6.79 (d, J = 8.5 Hz, 2H), 4.85 (t, J = 11.7 Hz, 1H), 4.65 (s, 1H), 4.41 (s, 2H), 4.27 (d, J = 4.1 Hz, 2H), 3.80 – 3.70 (m, 2H), 3.69 (d, J =

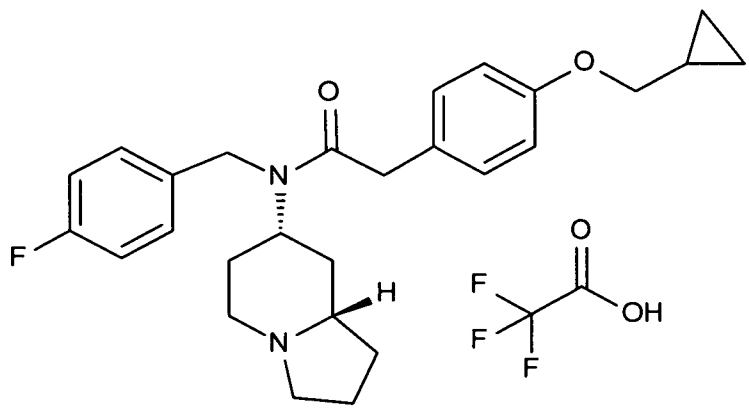
6.5 Hz, 2H), 3.03 – 2.89 (m, 1H), 2.72 (d, J = 10.3 Hz, 1H), 2.31 – 1.85 (m, 9H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 454.3 $[M+H]^+$.

[00568] Example 74: 3-[(7S,8aS)-octahydroindolizin-7-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (74)



[00569] The compound was prepared in analogy with example 71 using (7S,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 14%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.13 (m, 2H), 7.01 (m, 4H), 6.79 (m, 2H), 4.85 (m, 1H), 4.64 (m, 1H), 4.41 (s, 2H), 4.27 (d, 2H), 3.73 (m, 2H), 3.69 (d, 2H), 2.96 (m, 1H), 2.71 (m, 1H), 2.30 – 1.85 (m, 9H), 1.02 (d, 6H); LC-MS: 454.3 $[M+H]^+$.

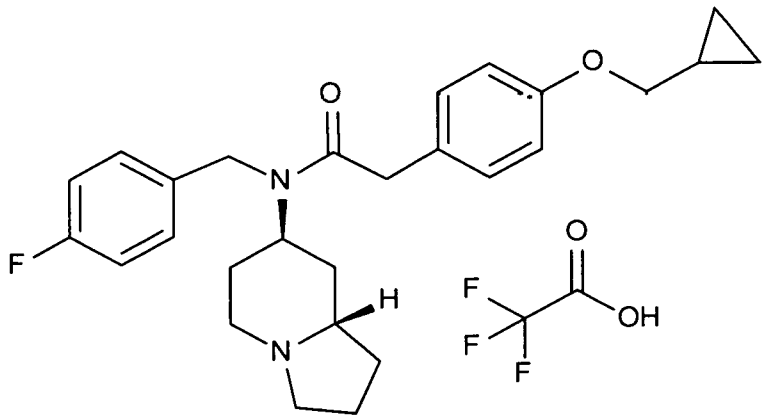
[00570] Example 75: N-[(7S,8aS)-octahydroindolizin-7-yl]-2-[4-(cyclopropylmethoxy)-phenyl]-N-[(4-fluoro-phenyl)methyl]acetamide; trifluoroacetic acid (75)



[00571] 2-[4-(Cyclopropylmethoxy)phenyl]acetic acid (10,5 mg, 51,1 µmol) was added to 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (21.4 mg, 56,2 µmol) and diisopropylethylamine (19.8 mg, 153 µmol)

in dry dimethylformamide (0.5 ml). The mixture was stirred for 30 minutes before (7S,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine (12.7 mg, 51.1 μmol) in dry dimethylformamide (0.4 ml) was added. After 18 hours, the mixture was diluted with brine (5 ml) and extracted with diethyl ether (5 x 5 ml). The combined organic phase was washed with brine (3 x 5 ml), dried over sodium sulfate, filtered and concentrated. The crude material was purified by HPLC, eluting with 30-80% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (11.0 mg, 49%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 (dd, J = 8.4, 5.3 Hz, 2H), 7.06 (t, J = 8.2 Hz, 4H), 6.84 (d, J = 8.6 Hz, 2H), 4.95 (m, 1H), 4.56 (s, 2H), 3.78 (d, J = 6.9 Hz, 2H), 3.77 – 3.66 (m, 2H), 3.59 (s, 2H), 2.95 – 2.87 (m, 1H), 2.75 – 2.60 (m, 2H), 2.26 – 1.85 (m, 7H), 1.78 (d, J = 12.9 Hz, 1H), 1.30 – 1.22 (m, 1H), 0.69 – 0.62 (q, J = 4.7 Hz, 2H), 0.35 (q, J = 4.7 Hz, 2H); LC-MS: 437.3 $[M+H]^+$.

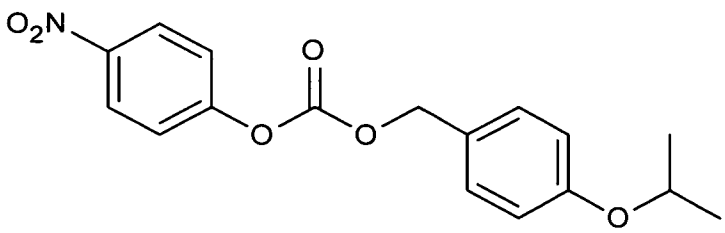
[00572] Example 76: N-[(7R,8aS)-octahydroindolizin-7-yl]-2-[4-(cyclopropylmethoxy)-phenyl]-N-[(4-fluorophe-nyl)methyl]acetamide; trifluoroacetic acid (76)



[00573] The compound was prepared in analogy with example 75 using (7R,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine and 2-[4-(cyclopropylmethoxy)phenyl]acetic acid. Yield: 16%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 (d, J = 8.5 Hz, 2H), 7.10 – 7.02 (m, 4H), 6.84 (d, J = 8.6 Hz, 2H), 4.99 (t, J = 14.4 Hz, 1H), 4.52 (s, 2H), 3.96 – 3.88 (m, 1H), 3.78 (d, J = 6.9 Hz, 2H), 3.59 (s, 2H), 3.50 (m, 1H), 3.43 – 3.35 (m, 1H), 3.13 – 3.03 (m, 1H), 2.90 (d, J = 14.9 Hz, 1H), 2.26 – 2.20 (m, 1H), 2.16 (m, 4H), 2.05 (d, J = 13.3 Hz, 1H), 1.86 (d, J = 20.3 Hz, 1H), 1.72 (d, J = 20.7 Hz, 1H), 1.27 (t, J = 7.9 Hz, 1H), 0.65 (q, J = 4.7 Hz, 2H), 0.38 – 0.32 (m, 2H); LC-MS: 437.3 $[M+H]^+$.

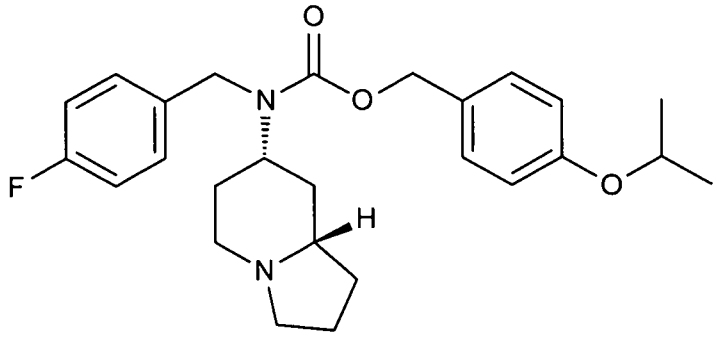
[00574] Example 77: [4-(propan-2-yloxy)phenyl]methyl N-[(7S,8aS)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]carbamate (77)

[00575] 4-nitrophenyl [4-(propan-2-yloxy)phenyl]methylcarbonate



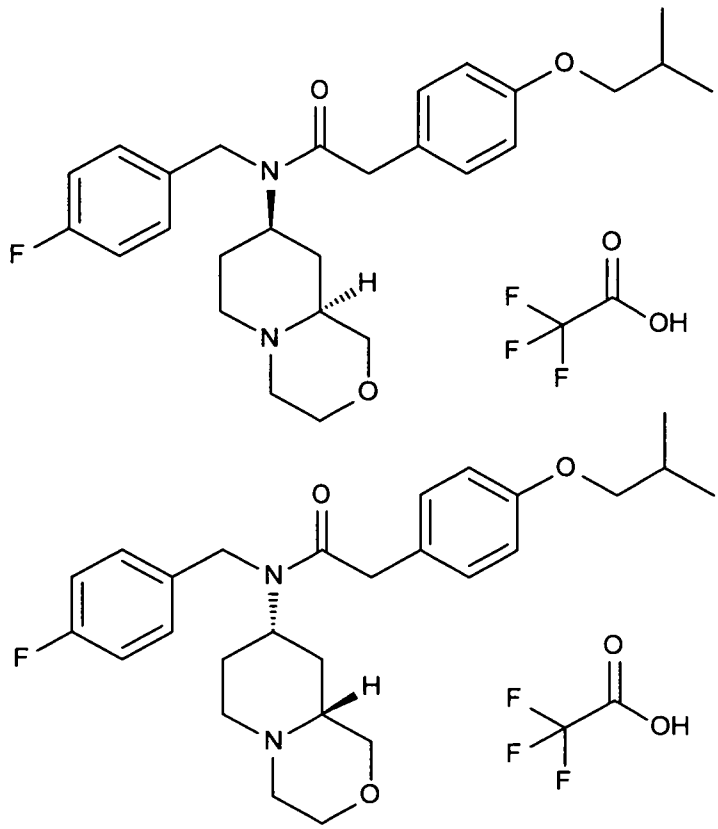
[00576] Ethyl 4-hydroxybenzoic acid (5.0 g, 30 mmol), potassium carbonate (12.5 g, 90 mmol), and 2-iodopropane (7.45 ml, 75 mmol) were stirred in dimethylformamide (20 mL) at 65 °C for 31 h. More 2-iodopropane (3 ml) was added and stirring at 65 °C was continued for another 21 h. The mixture was partitioned between water and diethyl ether. The organic phase was washed two times with water and one time with brine. The organic phase was dried and evaporated to give ethyl 4-isopropoxybenzoic acid (6.13 g). This material (5.63 g, 27 mmol) was dissolved in tetrahydrofuran (15 ml) and added slowly to a mixture of lithium aluminum hydride (1.54 g, 40.5 mmol) in tetrahydrofuran (50 ml). After 20 hours, the reaction was quenched with ethyl acetate (7 ml, 70 mmol). Silicon dioxide (15.4 g) was added and the mixture was stirred for 30 min. The resulting suspension was filtered and the filtrate was evaporated and give a residue that was partitioned between diethyl ether and sodium hydroxide (aqueous, 1M). The organic phase was separated, dried and evaporated to give 4-isopropoxybenzyl alcohol (3.46 g). The alcohol (6 mmol, 1.0 g) was dissolved in dichloromethane (10 mL) and p-nitrophenyl chloroformate (1.25 g, 6 mmol) was added. Pyridine (510 µl, 6 mmol) dissolved in dichloromethane (5 ml) was added dropwise. After 1 hour, the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 20% ethyl acetate in petroleum ether to afford the desired carbonate (1.56 g).

[00577] [4-(propan-2-yloxy)phenyl]methyl N-[(7S,8aS)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]carbamate (19)



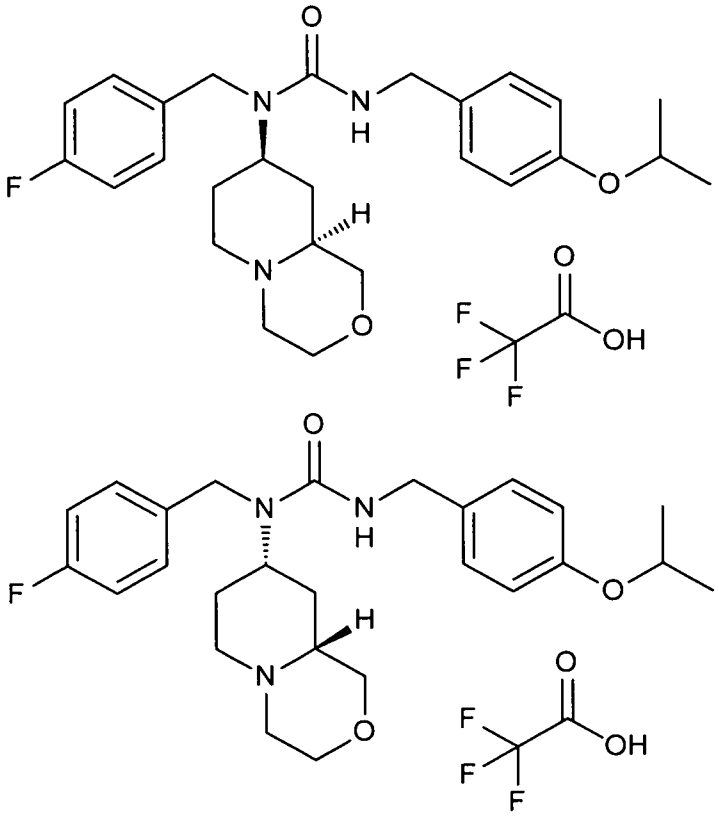
[00578] 4-Nitrophenyl [4-(propan-2-yloxy)phenyl]methylcarbonate (60 mg, 0.18 mmol) was added to (7S,8aS)-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine (30 mg, 0.12 mmol) in pyridine (1.0 ml). The mixture was stirred at 55 °C for 20 h and then cooled to ambient temperature and concentrated. The crude was partitioned between diethyl ether and sodium hydroxide (aqueous, 1M). The organic phase was evaporated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 0-10% methanol in ethyl acetate. Fractions containing product were pooled, concentrated and further purified by column chromatography using silicon dioxide gel, eluting with 25% methanol in ethyl acetate to afford the title compound (10 mg); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.42 – 7.01 (m, 4H), 7.00-6.67 (m, 4H), 5.21-4.95 (m, 2H), 4.63 – 3.84 (m, 4H), 3.06 (d, 1H), 3.00 (t, 1H), 2.17 – 1.97 (m, 2H), 1.97 – 1.21 (m, 9H), 1.33 (d, 6H); LC-MS: 441.4 $[M+H]^+$.

[00579] Example 78: N-[(8R,9aS)-octahydropyrido[2,1-c]morpholin-8-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (78a) and N-[(8S,9aR)-octahydropyrido[2,1-c]morpholin-8-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (78b)



[00580] To a solution of (8R,9aS)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine and (8S,9aR)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine (1:1, 20 mg, 75 μmol) and diisopropylethylamine (22 μl, 150 μmol) in dichloromethane (2 ml), a solution of 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (17.4 mg, 80 μmol) in dichloromethane (500 μl) was added dropwise. After stirring for 1 hour at ambient temperature the mixture was concentrated. The crude material was purified by preparative HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds in 68% yield (23.4 mg). Isolated as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 6.99 (m, 6H), 6.84 (d, J = 7.7 Hz, 2H), 4.50 (s, 2H), 4.17 – 2.86 (m, 15H), 2.42 – 1.81 (m, 2H), 1.75 – 1.62 (m, 2H), 1.03 (d, J = 6.7 Hz, 6H); LC-MS: 455.5 $[M+H]^+$.

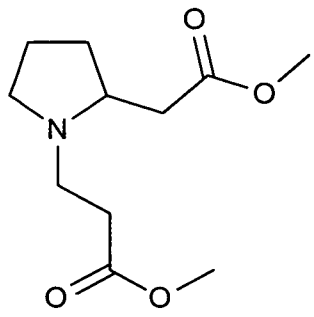
[00581] Example 79: 3-[(8R,9aS)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (79a) and 3-[(8S,9aR)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (79b)



[00582] The compounds were prepared in analogy with example 71 using (8R,9aS)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine and (8S,9aR)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine (1:1) and 1-(isocyanato-methyl)-4-(propan-2-yloxy)benzene. Isolated as a racemic mixture. Yield: 27.3 mg, 73%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.11 (m, 2H), 7.08 – 6.91 (m, 4H), 6.78 (d, J = 7.7 Hz, 2H), 4.78 (s, 1H), 4.64 (s, 1H), 4.50 (p, J = 5.9 Hz, 1H), 4.33 (s, 2H), 4.26 (s, 2H), 4.12 (t, J = 12.3 Hz, 1H), 3.95 – 3.79 (m, 4H), 3.70 (s, 1H), 3.58 (s, 1H), 3.34 (d, J = 11.0 Hz, 1H), 3.04 (d, J = 13.4 Hz, 1H), 2.59 – 2.12 (m, 2H), 2.07 – 1.87 (m, 1H), 1.73 (d, J = 14.3 Hz, 1H), 1.32 (d, J = 6.0 Hz, 6H); LC-MS: 456.6 $[M+H]^+$.

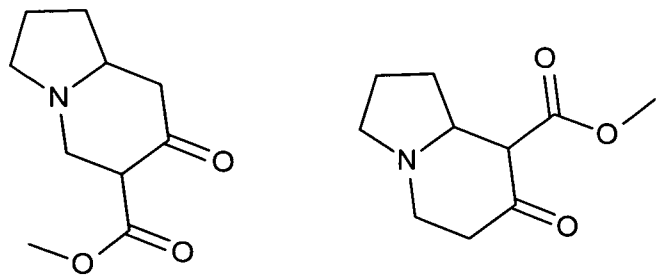
[00583] Example 80: 1-[(6S,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluoro-phenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (80a) and 1-[(6R,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (80b); 1-[(7R,8R,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}urea; trifluoroacetic acid (80c) and 1-[(7S,8S,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (80d)

[00584] Methyl 3-[2-(2-methoxy-2-oxoethyl)pyrrolidin-1-yl]propanoate



[00585] A solution of tert-butyl 2-(2-methoxy-2-oxoethyl)pyrrolidine-1-carboxylate (2.4 g, 9.82 mmol) in dichloromethane (4 ml) was cooled to 0 °C. Trifluoroacetic acid (2.2 ml, 30 mmol) was added. The cooling bath was removed and the reaction was stirred at room temperature for 2 hours. The mixture was concentrated and re-dissolved in ethanol (16 ml). Methyl acrylate (2.65 ml, 29.5 mmol) and triethylamine (8.2 ml, 59 mmol) were added. The reaction was stirred at room temperature under nitrogen for 90 hours. The mixture was concentrated. The crude was dissolved in diethyl ether and sodium hydrogen carbonate (aqueous, saturated). After shaking the ether phase was collected. The water phase was extracted once more with ether. The combined organic phases were dried over magnesium sulfate, filtered and the solvent was evaporated to give crude methyl 3-[2-(2-methoxy-2-oxoethyl)pyrrolidin-1-yl]propanoate, which was used without further purification.

[00586] Methyl 7-oxo-octahydroindolizine-6-carboxylate and methyl 7-oxo-octahydroindolizine-8-carboxylate

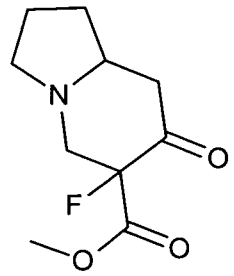


[00587] Lithium bis(trimethylsilyl)amide (13.7 ml, 1.0 M in tetrahydrofuran, 13.7 mmol) was added dropwise to a stirred solution of methyl 3-[2-(2-methoxy-2-oxoethyl)pyrrolidin-1-yl]propanoate (2.1 g, 9.2 mmol) in anhydrous tetrahydrofuran (15 ml) at -78 °C under a nitrogen atmosphere. The reaction was stirred at -78 °C for 2 hours. A solution of hydrochloric acid (12 M in water, 1.2 ml) was added and the solution was warmed to room temperature. The solvent was evaporated. The crude material was purified by column

chromatography using silicon dioxide gel, eluting with methanol in ethyl acetate with 0.5 % triethyl amine added.

[00588] Two fractions were collected, one more lipophilic, fraction 1, 928 mg, and one more polar, fraction 2, 525 mg. According to NMR, fraction 1 was enriched on methyl 7-oxo-octahydroindolizine-6-carboxylate and fraction 2 was a mixture of methyl 7-oxo-octahydroindolizine-6-carboxylate and methyl 7-oxo-octahydroindolizine-8-carboxylate.

[00589] Methyl 6-fluoro-7-oxo-octahydroindolizine-6-carboxylate

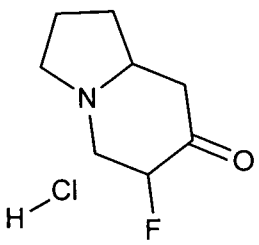


[00590] Fraction 1 (500 mg, 2.54 mmol) from the synthesis of methyl 7-oxo-octahydroindolizine-6-carboxylate was dissolved in anhydrous tetrahydrofuran (14.5 ml). Sodium hydride (57-63%, oil dispersion, 101 mg, 2.5 mmol) was added portionwise. The mixture was stirred at room temperature for 30 minutes before it was cooled to 0 °C in an ice bath. Grinded Selectfluor (898 mg, 2.54 mmol) was added portionwise. After 1 hour, the mixture was filtered and the solid was washed with ethyl acetate. The solvent was evaporated.

[00591] The crude material was purified by column chromatography using silicon dioxide gel, eluting with a gradient of ethyl acetate in petroleum ether.

[00592] Three spots on TLC giving the right mass on LCMS were isolated. In eluting order they were fraction 1, 118 mg, fraction 2, 49 mg and fraction 3, 71 mg.

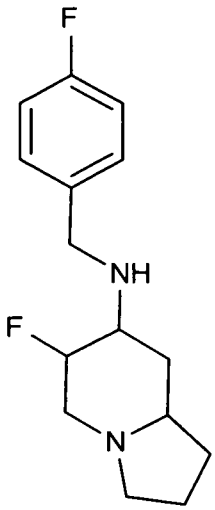
[00593] 6-Fluoro-octahydroindolizin-7-one hydrochloride



[00594] Fraction 1 (118 mg, 0.55 mmol) from the synthesis of methyl 6-fluoro-7-oxo-octahydroindolizine-6-carboxylate was mixed with hydrochloric acid (6 M, aqueous, 2 ml).

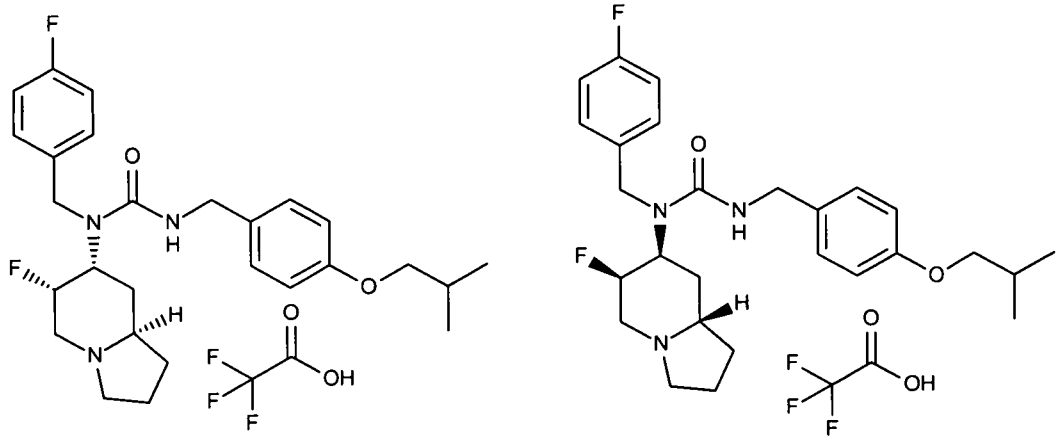
The reaction was refluxed for 20 hours, then cooled to room temperature and concentrated. The residue was used without any further purification.

[00595] 6-Fluoro-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine

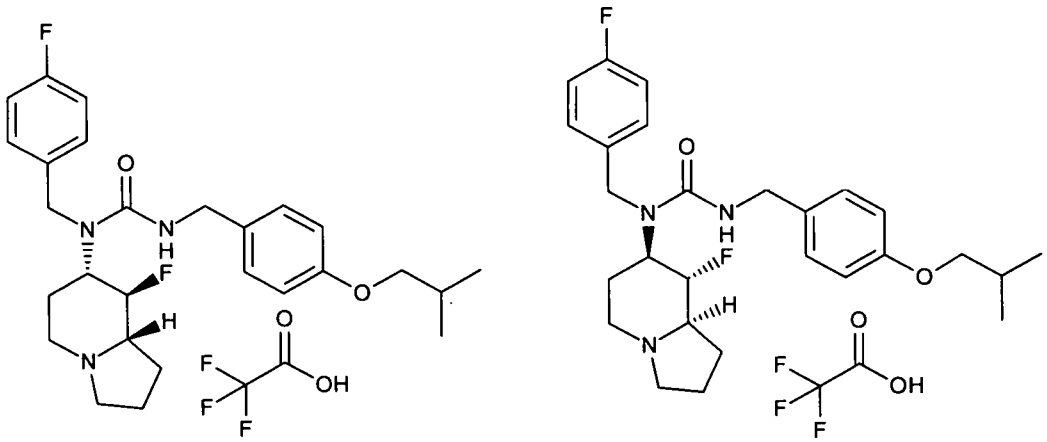


[00596] The crude 6-fluoro-octahydroindolizin-7-one hydrochloride (106 mg, 0.55 mmol) was dissolved in ethanol (2 ml). (4-fluorophenyl)-methanamine (76 mg, 0.61 mmol) was added and the mixture was stirred for 30 minutes. Sodium triacetoxyborohydride (174 mg, 0.83 mmol) was added portion wise and the resulting mixture was stirred for 2.5 hours. The solvent was evaporated. The residue was dissolved in dichloromethane and sodium hydroxide (1M, aqueous). After shaking, the organic phase was collected. The aqueous phase was extracted twice with dichloromethane. The combined 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 methanol in ethyl acetate (containing 0.5 % triethyl amine). Two spots on TLC giving the correct mass on LCMS were isolated. In eluting order fraction 1, 60 mg, and fraction 2, 62 mg.

(F) 1-[(6S,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 1-[(6R,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}urea; trifluoroacetic acid



[00597] and (G) 1-[(7R,8R,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)-methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (22c) and 1-[(7S,8S,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (22d)

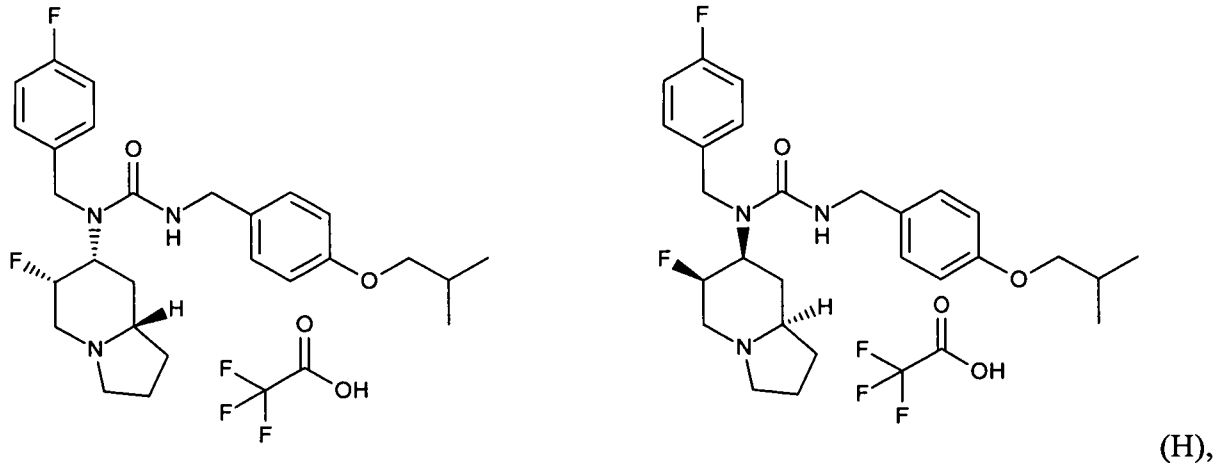


[00598] Fraction 1 (60 mg, 0.22 mmol) from the synthesis of 6-fluoro-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine was dissolved in dichloromethane (0.9 ml). 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (50.8 mg, 0.24 mmol) dissolved in dichloromethane (0.5 ml) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated. The crude material was purified by HPLC, eluting with 25-40% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford (F) 1-[(6S,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea; trifluoroacetic acid and 1-[(6R,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (13 mg, 10%, isomeric purity 99%) in a first fraction, as a racemic mixture: 1H NMR (500 MHz, Chloroform-d) δ 7.15 (dd, 2H), 7.03 (t, 2H), 6.96 (d, 2H), 6.82 – 6.76 (m, 2H), 5.12 – 4.88 (m, 2H), 4.71 (s, 1H), 4.63 – 4.43 (m, 2H), 4.31 – 4.21 (m, 2H), 4.17 (s, 1H), 3.75

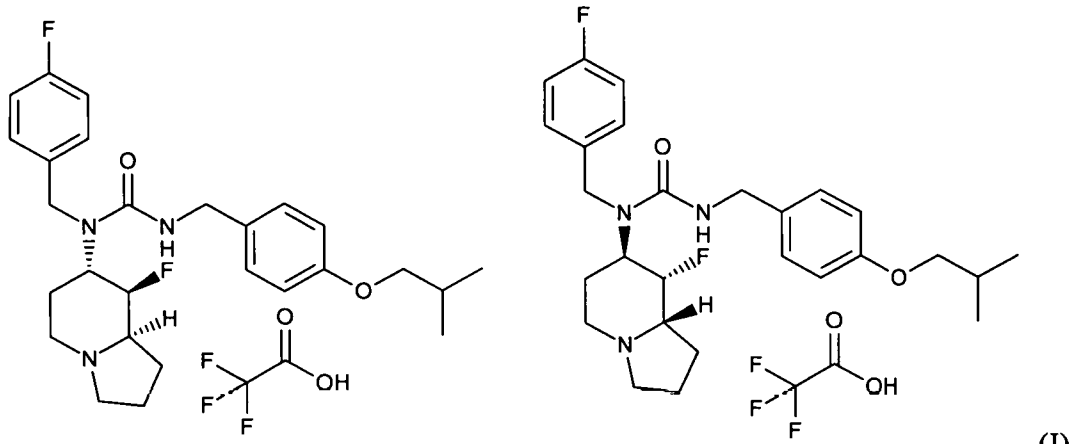
(t, 1H), 3.68 (d, 2H), 3.65 (m, 1H), 3.16 (d, 1H), 3.05 (dd, 1H), 2.73 (td, 1H), 2.21 (s, 4H), 2.07 (dh, 1H), 1.83 (d, 1H), 1.02 (d, 6H); ^{19}F NMR (aliphatic fluorides) (470 MHz, Chloroform-*d*) δ -204.70 – -205.11 (m); LC-MS: 472.2 $[M+H]^+$.

[00599] In a second fraction (G) 1-[(7R,8R,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 1-[(7S,8S,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (4 mg, 6%, isomeric purity 69%) were isolated as a racemic mixture: ^{19}F NMR (aliphatic fluorides) (470 MHz, Chloroform-*d*) δ -186.43 (d, J = 53.2 Hz); LC-MS: 472.2 $[M+H]^+$.

[00600] Example 81: 1-[(6R,7S,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (21) and 1-[(6S,7R,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (81b); 1-[(7R,8R,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea; trifluoroacetic acid (81c) and 1-[(7S,8S,8aR)-8-fluoro-octahydro-indolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (81d)



(H),



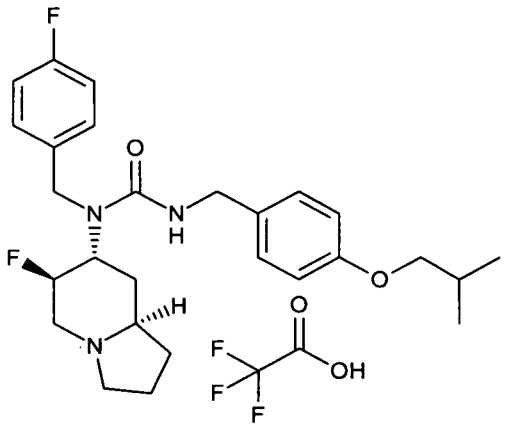
and (I)

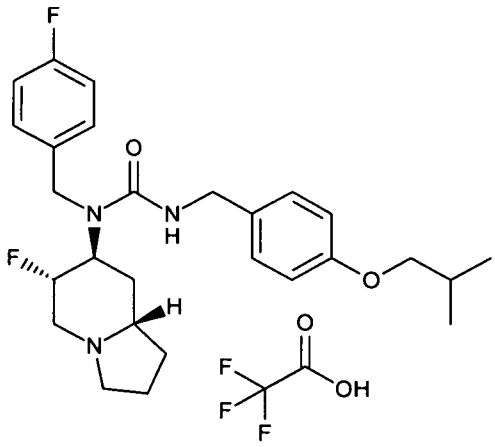
[00601] The compounds were prepared in analogy with example 80, from isolated fraction 2 in the synthesis of 6-fluoro-N-[(4-fluorophenyl)methyl]-octahydroindolizin-7-amine (60 mg, 0.226 mmol) dissolved in dichloromethane (0.9 ml) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (50.8 mg, 0.24 mmol) dissolved in dichloromethane (0.50 ml).The crude material was purified by HPLC, eluting with 30-50% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford (H) 1-[(6R,7S,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 1-[(6S,7R,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (13 mg, 13%, isomeric purity 89%), as a racemic mixture in a first eluting fraction: ^{19}F NMR (aliphatic fluorides) (470 MHz, Chloroform-*d*) δ -197.13 (q, *J* = 37.7 Hz), -199.68 (q, *J* = 36.0 Hz); LC-MS: 472.2 $[M+H]^+$

[00602] In a second eluting fraction, (I) 1-[(7R,8R,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 1-[(7S,8S,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (7 mg, 5%, isomeric purity 49%)

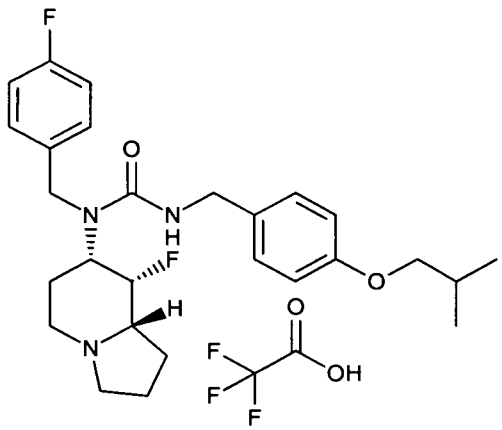
were isolated as a racemic mixture: ^{19}F NMR (aliphatic fluorides) (470 MHz, Chloroform-*d*) δ -191.07 (d, J = 54.2 Hz); LC-MS: 472.2 $[M+H]^+$

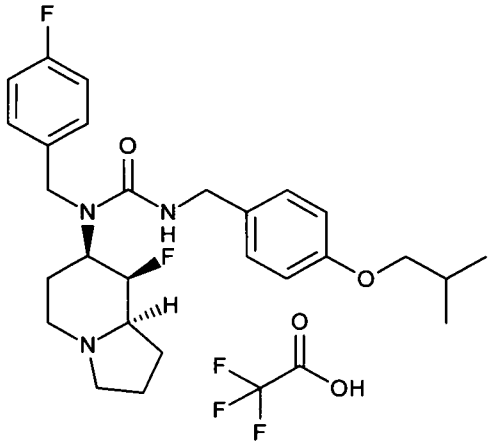
[00603] Example 82: 1-[(6R,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (82a) and 1-[(6S,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2 methylpropoxy)phenyl]methyl} urea; trifluoroacetic acid (82b); 1-[(6R,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea; trifluoroacetic acid (82c) and 1-[(6S,7S,8aS)-6-fluoro-octahydro-indolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2 methylpropoxy)phenyl]methyl} urea; trifluoroacetic acid (82d)





(B), and





(C).

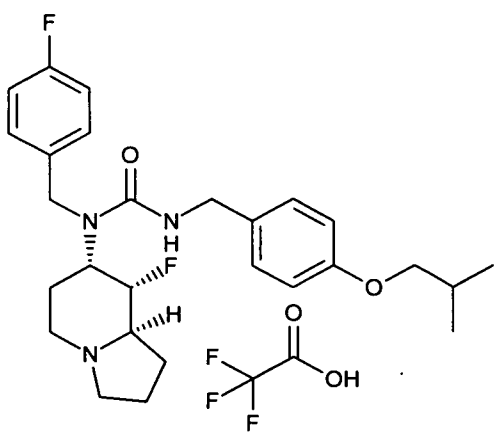
[00604] The compounds were prepared in analogy with example 80, starting from the isolated fraction 2 and 3 (120 mg, 0.56 mmol,) in the synthesis of methyl 6-fluoro-7-oxo-octahydroindolizine-6-carboxylate. The combined fractions were heated with aqueous hydrochloric acid (6M, aqueous, 2 ml) for 20 hours. After cooling and evaporation of the solvent the crude residue was treated with (4-fluorophenyl) methanamine (76 mg, 0.61 mmol) followed by sodium triacetoxyborhydride (174 mg, 0.83 mmol) in ethanol (2 ml). After work-

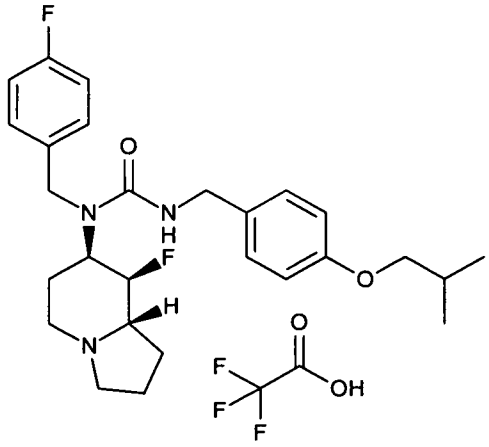
up the crude material was purified by column chromatography using silicon dioxide gel, eluting with a gradient of methanol in ethyl acetate (containing 0.5 % triethyl amine).

[00605] Two spots on TLC were isolated. In eluting order fraction 1, 47 mg, and fraction 2, 17 mg. Fraction 1 (40 mg, 0.150 mmol) was treated with 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (33.8 mg, 0.165 mmol) in dichloromethane (0.6 ml). The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford (B) 1-[(6R,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 1-[(6S,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2 methylpropoxy)phenyl]methyl} urea; trifluoroacetic acid (3 mg, 3%, isomeric purity 20%), as a racemic mixture: ^{19}F NMR (aliphatic fluorides) (470 MHz, Chloroform-*d*) δ -183.73(bd); LC-MS: 472.2 $[M+H]^+$

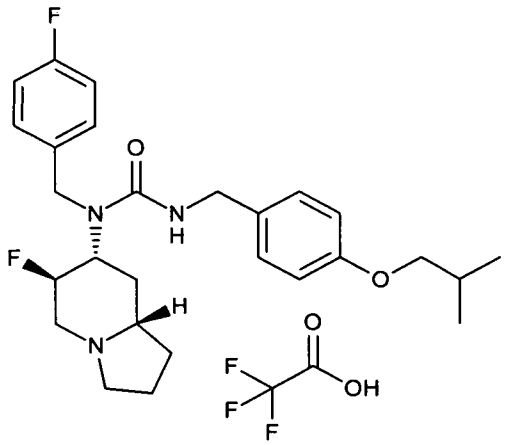
[00606] Fraction 2 (10 mg, 0.38 mmol) was treated with 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (8.5 mg, 0.41 mmol) in dichloromethane (0.15 ml). The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford (C) 1-[(6R,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 1-[(6S,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2 methylpropoxy)phenyl]methyl} urea; trifluoroacetic acid (5 mg, 23 %, isomeric purity 16%), as a racemic mixture: ^{19}F NMR (aliphatic fluorides) (470 MHz, Chloroform-*d*) δ -213.14 – -213.66 (m); LC-MS: 472.2 $[M+H]^+$

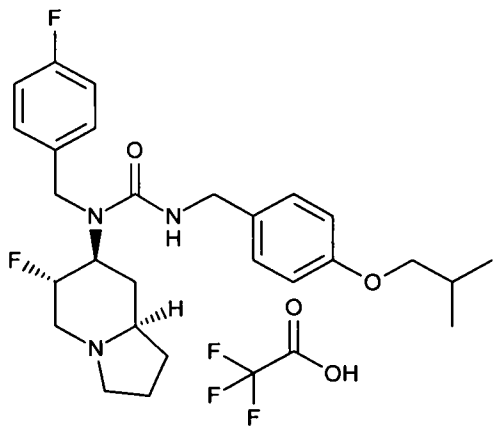
[00607] Example 83: 1-[(7R,8S,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluoro-phenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (83a) and 1-[(7S,8R,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (83b); 1-[(6R,7R,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}urea; trifluoroacetic acid (83c) and 1-[(6S,7S,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (83d)





(D), and





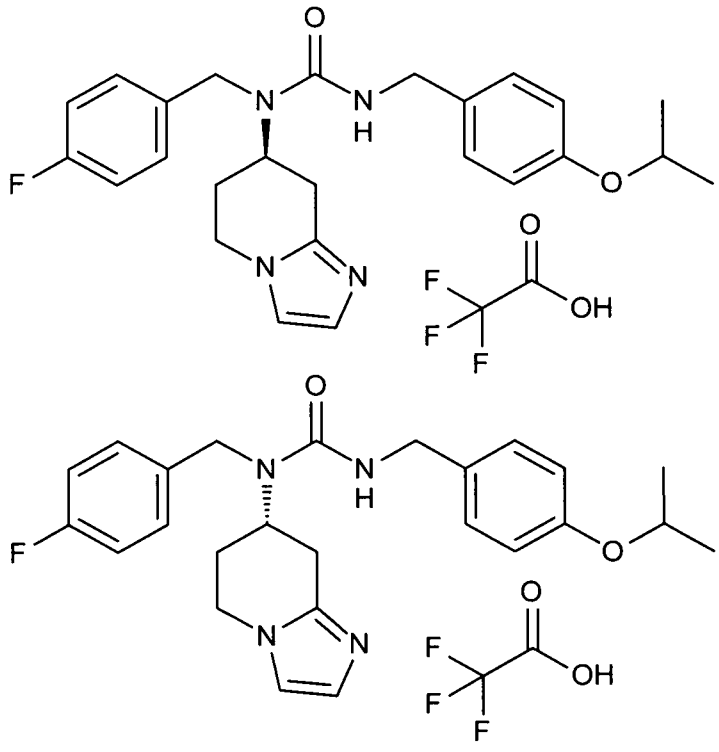
(E).

[00608] The compounds were prepared in analogy with example 80, starting from the isolated fraction 2 (325 mg, 1.65 mmol) in the synthesis of methyl 7-oxo-octahydro-indolizine-8-carboxylate and its regioisomer. The mixture dissolved in anhydrous tetrahydrofuran (9.5 ml) was treated with sodium hydride (57-63%, oil dispersion, 66 mg, 1.65 mmol), cooled to 0 °C and treated with Selectfluor (584 mg, 1.65 mmol). The crude material was purified by column chromatography using silicon dioxide gel, eluting with a gradient of ethyl acetate in petroleum ether. Three spots on TLC giving the right mass on LC-MS were isolated. In eluting order they were fraction 1, 24 mg, fraction 2, 38 mg and fraction 3, 75 mg. Fraction 3 (75 mg, 0.35 mmol) was heated with aqueous hydrochloric acid (6M, aqueous, 2 ml) for 20 hours. After cooling and evaporation of the solvent the crude residue was treated with (4-fluorophenyl) methanamine (48 mg, 0.39 mmol) followed by sodium triacetoxyborohydride (111 mg, 0.53 mmol) in ethanol (1 ml). After work-up the crude material was purified by column chromatography using silicon dioxide gel, eluting with a gradient of methanol in ethyl acetate (containing 0.5 % triethyl amine), to give one fraction 44 mg, 0.16 mmol. The isolated product was treated with 1-(isocyanatomethyl)-4-(2-

methylpropoxy)benzene (36 mg, 0.176 mmol) in dichloromethane (1 ml). The crude material was purified by HPLC, eluting with 30-60% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford (D) 1-[(7R,8S,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 1-[(7S,8R,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (8 mg, 8%, isomeric purity 62%) in a first fraction, as a racemic mixture: ^{19}F NMR (aliphatic fluorides) (470 MHz, Chloroform-*d*) -192.55 (ddd, J = 48.9, 34.0, 16.2 Hz); LC-MS: 472.2 $[M+H]^+$.

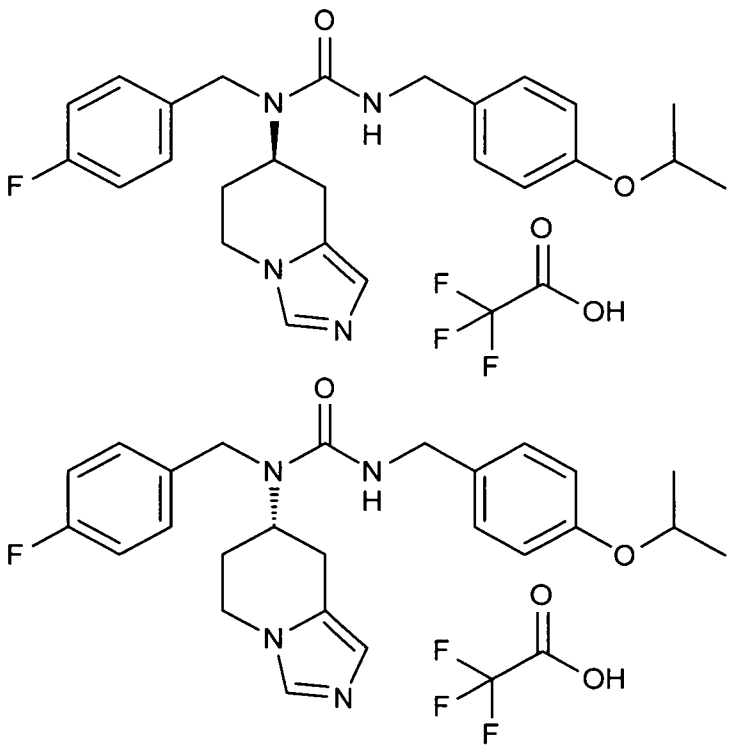
[00609] In a second fraction (E) 1-[(6R,7R,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 1-[(6S,7S,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (3 mg, 3%, isomeric purity 34%) were isolated as a racemic mixture: ^{19}F NMR (aliphatic fluorides) (470 MHz, Chloroform-*d*) δ -183.61 (bd); LC-MS: 472.2 $[M+H]^+$.

[00610] Example 84: 3-[(4-fluorophenyl)methyl]-3-[(7R)-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (84a) and 3-[(4-fluorophenyl)methyl]-3-[(7S)-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (84b)



[00611] (7R)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-amine; (7S)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-amine (1:1) (1 equivalent) in dichloromethane was added to 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene (2 equivalents) in dichloromethane. The solution was stirred for 1 hour and then partitioned between dichloromethane and sodium hydroxide (aqueous, 0.5 M). The organic phase was separated, dried (sodium sulfate), filtered and evaporated. The crude product was purified by column chromatography using silicon dioxide gel, and isolated as a racemic mixture. Yield: 52 %: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (s, 4H), 7.10 (d, 3H), 7.04 (s, 1H), 6.85 (s, 2H), 5.16 (s, 1H), 4.83 (s, 1H), 4.60 – 4.20 (m, 7H), 3.57 (dd, 1H), 3.27 (dd1H), 2.48 – 2.19 (m, 2H), 1.38 (d, 6H); LC-MS: 437.5 $[M+H]^+$.

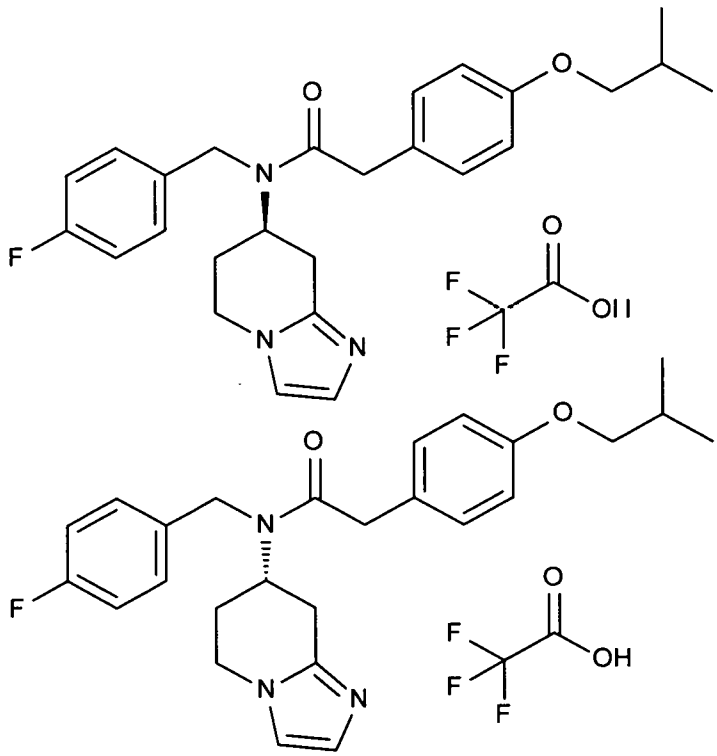
[00612] Example 85: 3-[(4-fluorophenyl)methyl]-3-[(7R)-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (85a) and 3-[(4-fluorophenyl)methyl]-3-[(7S)-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (85b)



[00613] (7R)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-amine; (7S)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-amine (1:1) (1 equivalent) in dichloromethane was added to 1-(isocyanatomethyl)-4-(propan-2-yloxy)-benzene (2 equivalents) in dichloromethane. The solution was stirred for 1 hour and then partitioned between dichloromethane and sodium hydroxide (aqueous, 0.5 M). The organic

phase was separated, dried (sodium sulfate), filtered and evaporated. The crude product was purified by column chromatography using silicon dioxide gel, and isolated as a racemic mixture. Yield: 66 %:^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 (s, 1H), 7.25 – 7.17 (m, 2H), 7.05 (dt 5H), 6.79 (d, 2H), 4.86 – 4.65 (m, 2H), 4.50 (dt, 2H), 4.40 (s, 2H), 4.30 (s, 2H), 4.21 (td, 1H), 3.19 (dd, 1H), 3.01 – 2.80 (m, 1H), 2.36 – 2.15 (m, 2H), 1.32 (d, 6H); LC-MS: 437.5 $[M+H]^+$.

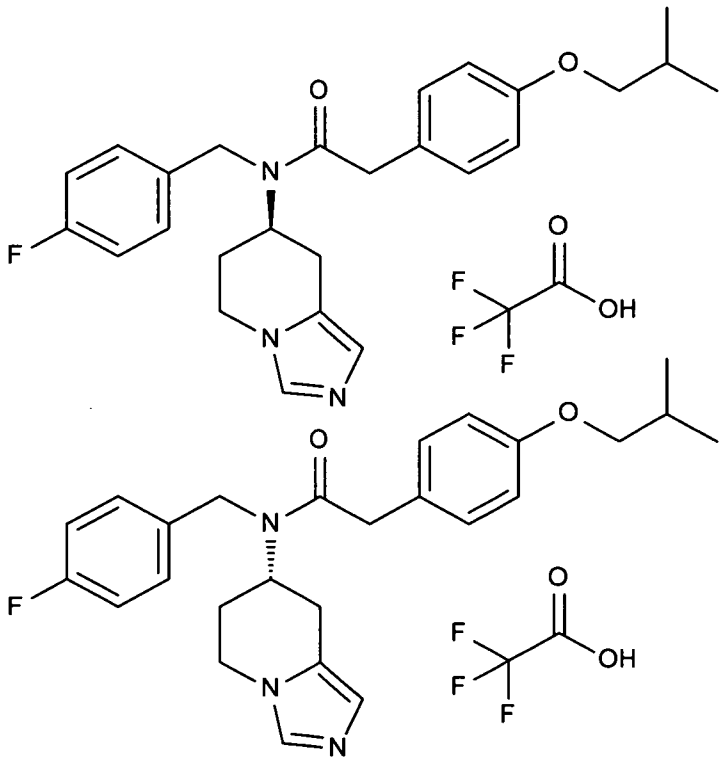
[00614] Example 86: N-[(4-fluorophenyl)methyl]-N-[(7R)-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (86a) and N-[(4-fluorophenyl)methyl]-N-[(7S)-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (86b)



[00615] (7R)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-amine; (7S)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-amine (1:1) (1 equivalent) was dissolved in dichloromethane. Pyridine (3 equivalents) was added followed by 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (1.2 equivalents) dissolved in dichloromethane. The mixture was stirred for 20 hours and then partitioned between dichloromethane and sodium hydroxide (aqueous, 0.5 M). The organic phase was dried and evaporated. The residue was purified by column chromatography using silicon dioxide gel, and isolated as a racemic mixture. Yield: 56 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 –

7.04 (m, 7H), 6.97 (s, 1H), 6.90 (d, 2H), 4.57 (s, 2H), 4.39 (s, 1H), 4.18 (d, 1H), 4.04 (d, 1H), 3.81 – 3.62 (m, 4H), 3.48 (d, 2H), 2.54 (d, 1H), 2.10 (tt, 2H), 1.06 (d, 6H); LC-MS: 436.5 $[M+H]^+$.

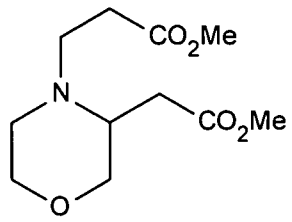
[00616] Example 87: N-[(4-fluorophenyl)methyl]-N-[(7R)-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (87a) and N-[(4-fluorophenyl)methyl]-N-[(7S)-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (87b)



[00617] The title compounds were prepared in analogy with example 86, using (7R)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-amine; (7S)-N-[(4-fluorophenyl)methyl]-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-amine (1:1) and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Isolated as a racemic mixture. Yield: 47 %: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 7.27 (s, 1H), 7.16 – 7.07 (m, 6H), 6.87 (d, 2H), 4.48 (m, 3H), 4.08 (t, 1H), 3.92 – 3.62 (m, 4H), 3.14 – 2.93 (m, 2H), 2.76 – 2.29 (m, 1H), 2.18 – 1.93 (m, 3H), 1.03 (d, 6H); LC-MS: 436.5 $[M+H]^+$.

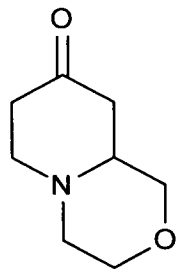
[00618] Example 88: 3-[(8S,9aR)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (88a) and 3-[(8R,9aS)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (88b)

[00619] Methyl 3-[3-(2-methoxy-2-oxoethyl)morpholin-4-yl]propanoate



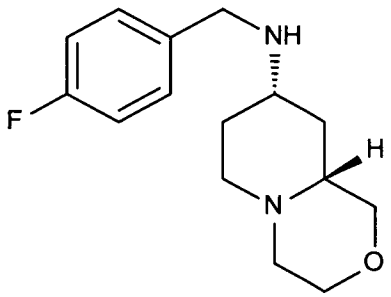
[00620] A mixture of methyl 2-(morpholin-3-yl)acetate hydrochloride (2 g, 10.2 mmol), methyl prop-2-enoate (1.389 ml, 15.31 mmol) and triethylamine (2.85 ml, 20.4 mmol) in methanol (50 ml) was stirred for 24 hours at ambient temperature. Solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (10 ml), washed with brine, dried and concentrated to yield the diester (1.72 g, 68.6 %), which was used directly in the next step without further purification.

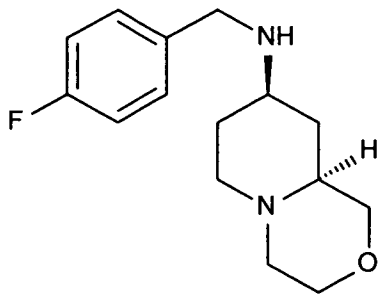
[00621] Octahydropyrido[2,1-c]morpholin-8-one



[00622] A solution of methyl 3-[3-(2-methoxy-2-oxoethyl)morpholin-4-yl]propanoate (1.72 g, 6.93 mmol) in tetrahydrofuran (30 mL) was cooled to -78 °C and treated with lithium bis(trimethylsilyl)amide in tetrahydrofuran (1M, 13.9 mL, 13.9 mmol). After stirring for 4 hours the mixture was allowed to warm to ambient temperature, quenched with sodium bicarbonate (aqueous, saturated, 5 ml), extracted with ethyl acetate (3 x 20 ml), washed with brine, dried and concentrated. Hydrochloric acid (concentrated, 15 ml) was added and the mixture was heated to 50 °C. After 12 hours, the mixture was allowed to cool to ambient temperature, treated with sodium hydroxide (5M, aqueous, 50 ml) and extracted with ethyl acetate (3 x 15 ml). The organic phase was dried and concentrated to yield the desired ketone (750 mg, 70 %).

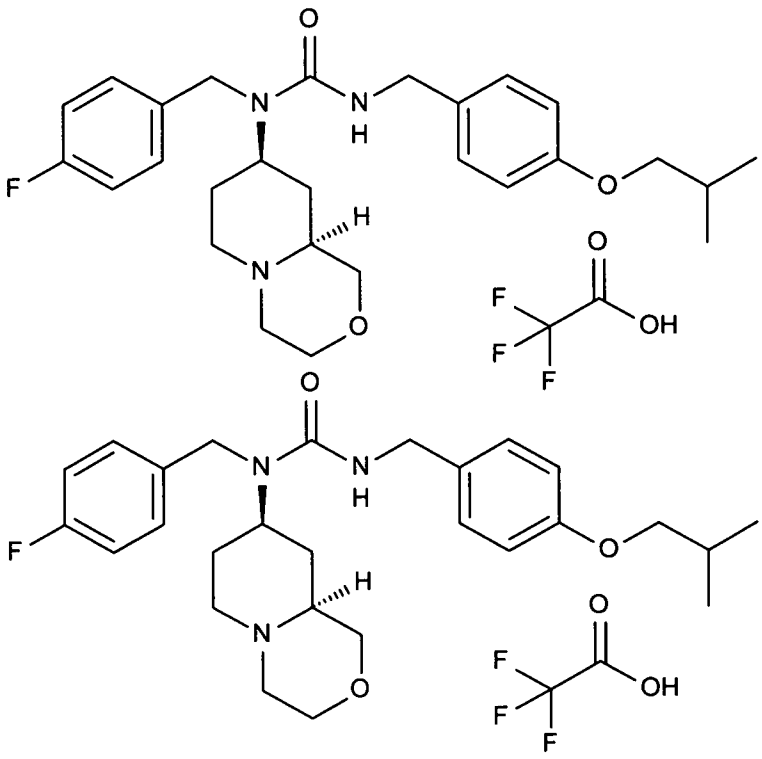
[00623] (8R,9aS)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine and (8S,9aR)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine





[00624] To 4-fluorobenzylamine (1 equivalent) and octahydropyrido[2,1-c]morpholin-8-one (1 equivalent) in ethanol at room temperature was added sodium triacetoxyborohydride (2 equivalents) in portions. The mixture was stirred for 4 hours, then sodium hydroxide (aqueous, 5 M) was added. The resulting mixture was stirred for 1 hour and then partitioned between diethyl ether and water. The organic phase was collected, the aqueous phase was extracted once again with diethyl ether. The combined organic phases were dried and evaporated to give the desired intermediate as an oil.

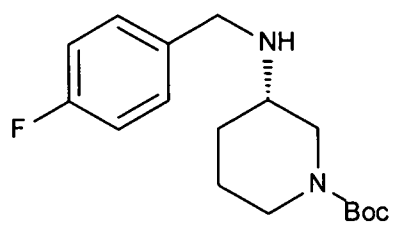
[00625] 3-[(8S,9aR)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 3-[(8R,9aS)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid.



[00626] (8R,9aS)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine and (8S,9aR)-N-[(4-fluorophenyl)methyl]-octahydropyrido[2,1-c]morpholin-8-amine (1:1) (1 equivalent) in dichloromethane was added to 1-(isocyanatomethyl)-4-(2-methylpropoxy)-benzene (2 equivalents) in dichloromethane. The solution was stirred for 1 hour and then partitioned between dichloromethane and sodium hydroxide (aqueous, 0.5 M). The organic phase was separated, dried (sodium sulfate), filtered and evaporated. The crude product was purified by column chromatography using silicon dioxide gel, and isolated as a racemic mixture. Yield: 74 %: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 7.12 (m, 2H), 7.01 (dd, 4H), 6.79 (d, 2H), 4.85 – 4.53 (m, 2H), 4.30 (m, 4H), 4.10 (d, 1H), 3.99 – 3.51 (m, 9H), 3.43 – 2.90 (m, 2H), 2.24 (d, 2H), 2.07 (dt, 1H), 1.02 (d, 7H); LC-MS: 470.6 $[M+H]^+$.

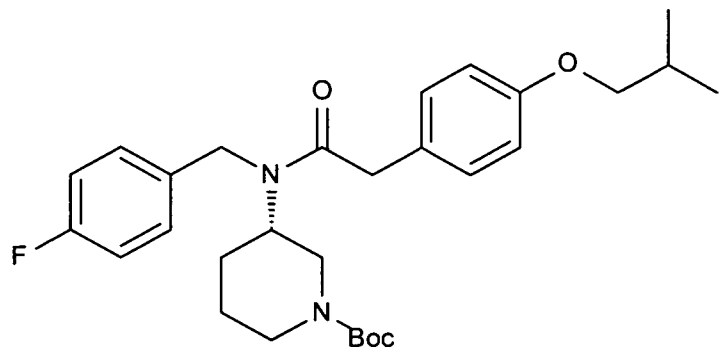
[00627] Example 89: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide hydrochloride (89)

[00628] Tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate



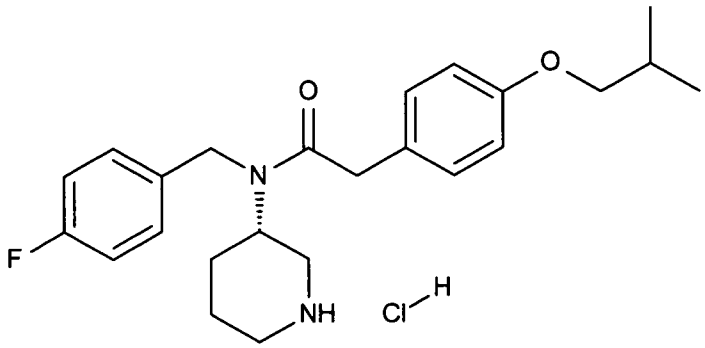
[00629] To a solution of 4-fluorobenzaldehyde (507 mg, 4.00 mmol) in tetrahydrofuran (6 ml) a solution of tert-butyl (3S)-3-aminopiperidine-1-carboxylate (834 mg,4.08 mmol) in tetrahydrofuran (6 ml) was added dropwise. After 20 minutes stirring sodium triacetoxy-borohydride (1440 mg, 6.80 mmol) was added in one portion and stirring was continued for 4 hours. The reaction suspension was quenched with sodium hydroxide (1M, 1 ml). The mixture was concentrated, the residue was diluted with 20% brine (25 ml), basified with sodium hydroxide (1 M) to pH 10 and extracted with dichloromethane (4 x 40 ml). Combined organic phase was washed once with 20% brine (50 ml), dried over sodium sulfate and concentrated. The product was purified by column chromatography using silica gel, eluting with ethyl acetate:methanol 1:0.1 to give tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1020 mg, 82.7%) as light yellow oil, easily crystallized to white crystals.

[00630] Tert-butyl (3S)-3-{N-[(4-fluorophenyl)methyl]-2-[4-(2-ethylpropoxy)phenyl]acet-amido}-piperidine-1-carboxylate



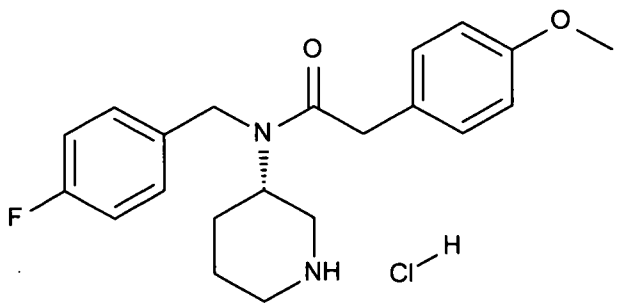
[00631] To a solution of tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (171 mg, 0.554 mmol) in dry dichloromethane (2.5 ml) 2-[4-(2-methylpropoxy)-phenyl]acetyl chloride (138 mg, 0.610 mmol) in dichloromethane (2 ml) was added, followed by diisopropylethylamine (216 mg) in dichloromethane (0.8 ml). Stirring was continued for 20 hours before the reaction was concentrated and the crude product was purified by column chromatography using silica gel, eluting with petroleum ether:ethyl acetate 1:1 to give tert-butyl (3S)-3-{N-[(4-fluorophenyl)methyl]-2-[4-(2-ethylpropoxy)phenyl]acetamido}-piperidine-1-carboxylate (149 mg, 53.9%) as colourless oil.

[00632] N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide hydrochloride



[00633] Tert-butyl (3S)-3-{N-[(4-fluorophenyl)methyl]-2-[4-(2-ethylpropoxy)phenyl]acetamido}-piperidine-1-carboxylate (148 mg, 0.297 mmol) was dissolved in hydrochloric acid (2 M) solution in dry diethyl ether (3 ml) and left at stirring for 18 hours. The white suspension was filtered and the solid was washed with diethyl ether (3 x 2 ml) and dried to give N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide hydrochloride (110 mg, 85.2%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.15 (m, 2H), 7.12 – 7.00 (m, 4H), 6.96 – 6.80 (m, 2H), 4.70 - 4.50 (m, 3H), 4.42 – 4.25 (m, 1H), 3.78 -3.62 (m, 3H), 3.57 – 3.47 (m, 2H), 3.21 (d, *J* = 10.9 Hz, 1H), 3.06 (d, *J* = 11.4 Hz, 1H), 2.73 – 3.63 (m, 1H), 2.08 – 1.99 (m, 1H), 1.90 – 1.70 (m, 4H), 1.01 (t, *J* = 6.7 Hz, 6H); LC-MS: 399.2 $[M+H]^+$.

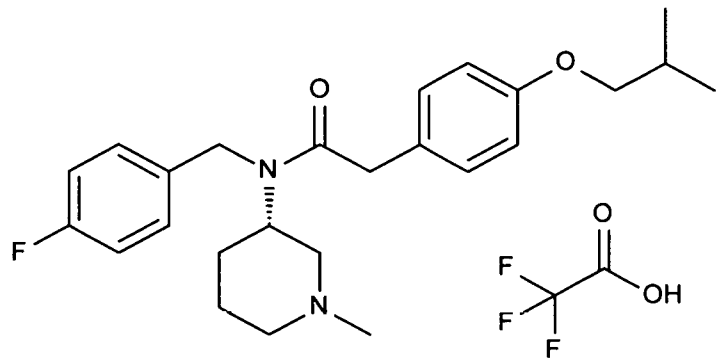
[00634] Example 90: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]acetamide hydrochloride (90)



The compound was prepared in analogy with example 89 using tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 2-(4-methoxyphenyl)acetyl chloride. Yield: 125.0 mg, 98.1%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.18 (m, 2H), 7.14 – 7.02 (m, 4H), 6.99 – 6.89 (m, 2H), 4.55 – 4.50 (m, 2H), 4.50 – 4.40 (m, 1H), 4.35 – 4.25 (m, 1H), 3.78 (s, 3H), 3.74 – 3.55 (m, 1H), 3.52 – 3.42 (m, 1H), 3.42 – 3.30 (m, 1H), 3.30 – 3.18

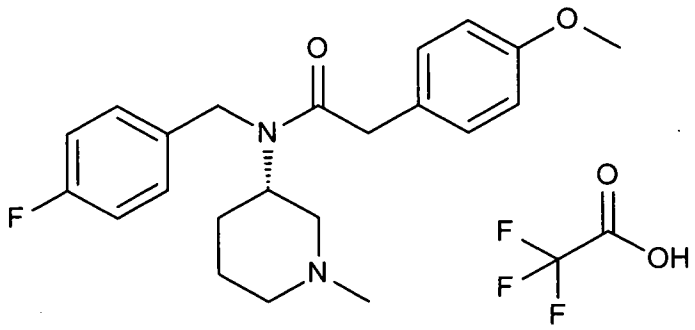
(m, 1H), 3.15 – 3.05 (m, 1H), 2.84 - 2.70 (m, 1H), 1.98 – 1.85 (m, 1H), 1.85 – 1.74 (m, 3H); LC-MS: 357.2 $[M+H]^+$.

[00635] Example 91: N-[(4-fluorophenyl)methyl]-N-[(3S)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)-phenyl]acetamide; trifluoroacetic acid (91)



[00636] Water solution of formaldehyde (82.7 μL, 30%, 0.901 mmol) was added to a solution of N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide hydrochloride (98.0 mg, 0.225 mmol) in tetrahydrofuran (2.5 ml). After 15 minutes stirring sodium triacetoxyborohydride (95.5 mg, 0.451 mmol) was added in one portion and stirring was continued. After 18 hours of stirring the reaction was quenched by sodium hydrogen carbonate (0.1 ml, aqueous, saturated), concentrated and diluted with dichloromethane (15 ml) and sodium hydrogen carbonate (15 ml, aqueous, saturated). Phases were separated and the water phase was extracted more with dichloromethane (2 x 15 ml). Combined organic phase was washed with 20% brine (20 ml), dried over sodium sulfate and concentrated. The crude material was purified by HPLC, eluting with 30-55% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (56.0 mg, 47.2%) as white solid: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.13 (t, J = 8.7 Hz, 4H), 7.03 (t, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.61 (d, J = 16.1 Hz, 1H), 4.39 (d, J = 16.1 Hz, 1H), 3.80 - 3.75 (m, 1H), 3.74 – 3.67 (m, 4H), 3.55 - 3.35 (m, 3H), 2.73 (s, 3H), 2.65 - 2.49 (m, 2H), 2.13 - 2.06 (m, 1H), 1.92 - 1.75 (m, 2H), 1.53 (d, J = 13.2 Hz, 1H), 1.06 – 1.00 (m, 6H); LC-MS: 413.3 $[M+H]^+$.

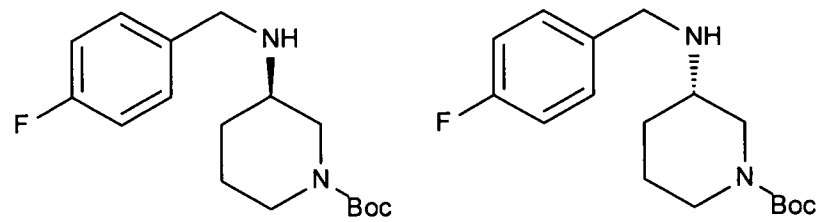
[00637] Example 92: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]acetamide; trifluoroacetic acid (92)



[00638] The compound was prepared in analogy with example 91 using N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]acetamide hydrochloride. Yield: 57.0 mg, 39.2%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.12 (d, J = 7.4 Hz, 4H), 7.08 – 6.93 (m, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.60 (d, J = 16.0 Hz, 1H), 4.35 (d, J = 16.1 Hz, 1H), 3.79 (s, 3H), 3.73 - 3.63 (m, 3H), 3.59 - 3.50 (m, 1H), 3.50 - 3.38 (m, 2H), 2.72 (s, 3H), 2.62 - 3.52 (m, 1H), 2.53 - 2.44 (m, 1H), 1.87 - 1.75 (m, 2H), 1.58 - 1.50 (m, 1H); LC-MS: 371.3 $[M+H]^+$.

[00639] Example 93: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide hydrochloride (93a) and N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide hydrochloride (93b)

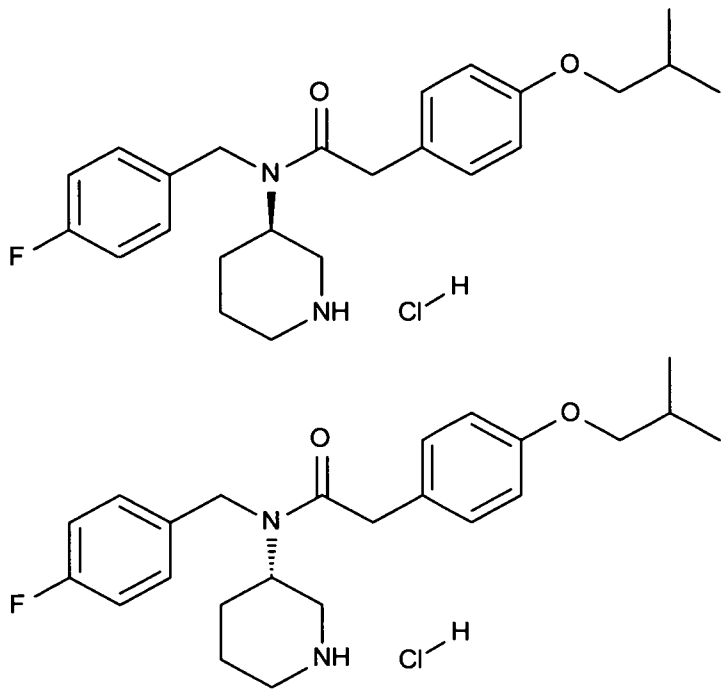
[00640] Tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate



[00641] To a solution of tert-butyl 3-aminopiperidine-1-carboxylate (461 mg, 2.20 mmol) in dichloroethane (5 ml) a solution of 4-fluorobenzylamine (357 mg, 2.31 mmol) in dichloroethane (4 ml) was added in one portion. After 20 minutes stirring sodium triacetoxyborohydride (817 mg, 3.74 mmol) was added in one portion and stirring was continued for 20 hours. The reaction was quenched with sodium hydroxide (1M, 1.1 ml), diluted with 20% brine (30 ml), basified with sodium hydroxide (1 M) to pH 10 and extracted with dichloromethane (4 x 40 ml). Combined organic phase was washed once with 20% brine (100 ml), dried over sodium sulfate and concentrated. The product was purified by column chromatography using silica gel, eluting with ethyl acetate:methanol 10:1 to give tert-butyl 3-

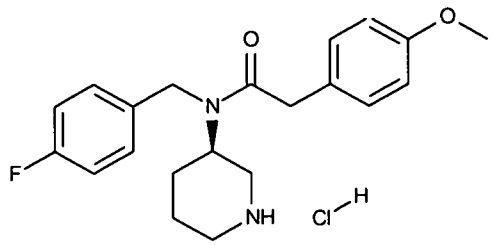
{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (611 mg, 90.1%) as light yellow oil as a 1:1 mixture of enantiomers.

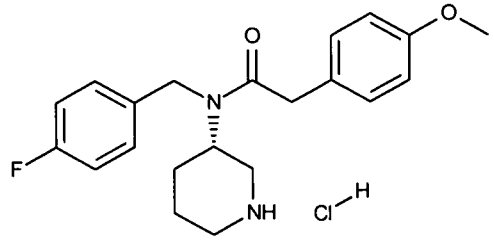
[00642] N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide hydrochloride and N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide hydrochloride



[00643] The compounds were prepared in analogy with example 89 using tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride as a 1:1 mixture of enantiomers. Yield: 77.0 mg, 82.0%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.33 - 7.21 (m, 2H), 7.18 – 7.00 (m, 4H), 6.95 – 6.83 (m, 2H), 4.69 – 4.51 (m, 2H), 4.42 – 4.25 (m, 1H), 3.76 – 3.62 (m, 4H), 3.29 – 3.09 (m, 3H), 2.84 (t, J = 13.1 Hz, 1H), 2.08 – 2.00 (m, 1H), 2.00 – 1.91 (m, 2H), 1.91 – 1.77 (m, 1H), 1.71 (d, J = 10.7 Hz, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 399.2 $[M+H]^+$.

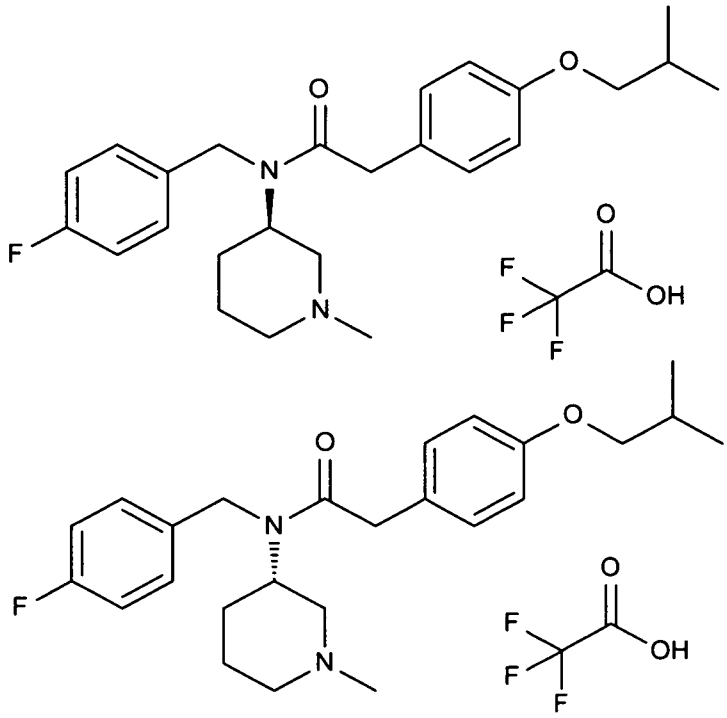
[00644] Example 94: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]acetamide hydrochloride (94a) and N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]acetamide hydrochloride (94b)





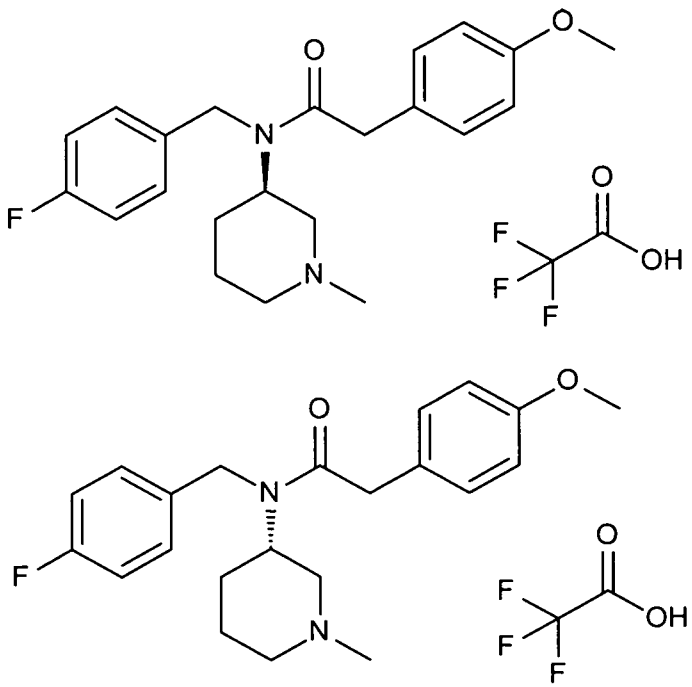
[00645] The compound was prepared in analogy with example 89 using tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 2-(4-methoxyphenyl)acetyl chloride as a 1:1 mixture of enantiomers. Yield: 72.0 mg, 96.2%. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.30 – 7.19 (m, 2H), 7.18 – 7.04 (m, 4H), 6.91 – 6.82 (m, 2H), 4.63 (s, 2H), 4.33 – 4.27 (m, 1H), 3.78 (s, 3H), 3.68 (s, 2H), 3.29 – 3.09 (m, 3H), 2.84 (t, J = 12.8 Hz, 1H), 2.04 – 1.90 (m, 2H), 1.82 – 1.66 (m, 2H); LC-MS: 357.2 $[M+H]^+$.

[00646] Example 95: N-[(4-fluorophenyl)methyl]-N-[(3R)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (95a) and N-[(4-fluorophenyl)-methyl]-N-[(3S)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (95b)



[00647] The compound was prepared in analogy with example 91 using N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide hydrochloride and N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide hydrochloride (1:1). Yield 23.0 mg, 50.0%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.15 - 7.08 (m, 4H), 7.06 - 7.00 (m, 2H), 6.90 - 6.85 (m, 2H), 4.61 (d, J = 16.1 Hz, 1H), 4.35 (d, J = 16.1 Hz, 1H), 3.78 (t, J = 10.7 Hz, 1H), 3.76 - 3.69 (m, 4H), 3.54 - 3.35 (m, 3H), 2.74 (s, 3H), 2.67 – 2.48 (m, 2H), 2.15 - 2.05 (m, 1H), 1.90 - 1.77 (m, 2H), 1.58 - 1.51 (m, 1H), 1.08 – 0.99 (m, 6H); LC-MS: 413.3 $[M+H]^+$.

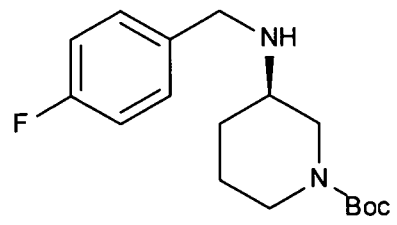
[00648] Example 96: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]acetamide; trifluoroacetic acid (96a) and N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]acetamide; trifluoroacetic acid (96b)



[00649] The compound was prepared in analogy with example 91 using N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]acetamide hydrochloride and N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]acetamide hydrochloride (1:1). Yield: 47.0 mg, 80.4%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.16 – 7.09 (m, 4H), 7.04 (t, J = 8.5 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.62 (d, J= 16.0 Hz, 1H), 4.37 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H), 3.75 – 3.68 (m, 3H), 3.55 - 3.40 (m, 3H), 2.76 (s, 3H), 2.62 (t, J = 10.8 Hz, 1H), 2.50 (qd, J = 12.6, 4.8 Hz, 1H), 1.90 - 1.75 (m, 2H), 1.57 (d, J = 12.4 Hz, 1H); LC-MS: 371.3 $[M+H]^+$.

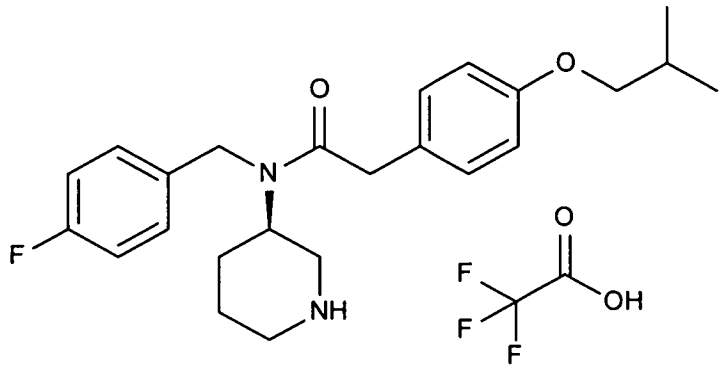
[00650] Example 97: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide; trifluoroacetic acid (97)

[00651] Tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate



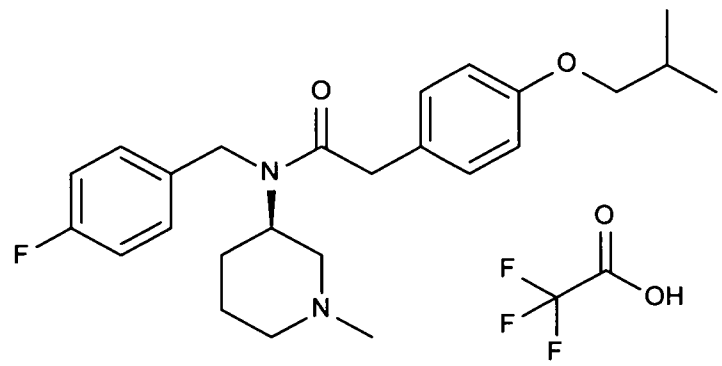
[00652] The compound was prepared in analogy with example 89 using tert-butyl (3R)-3-aminopiperidine-1-carboxylate.

[00653] N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide; trifluoroacetic acid



[00654] The compound was prepared in analogy with example 89 using tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 2-[4-(2-methylpropoxy)-phenyl]acetyl chloride. Additional purification by preparative HPLC, eluting with 30-79% acetonitrile in water (containing 0.1% trifluoroacetic acid) yielded the title trifluoroacetic acid salt (59 mg) as fine white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.34 – 7.17 (m, 4H), 7.15 – 7.02 (m, 2H), 6.94 - 6.82 (m, 2H), 4.62 (s, 1H), 4.51 - 4.27 (m, 2H), 3.79 – 3.65 (m, 3H), 3.52 (d, J = 7.7 Hz, 2H), 3.21 - 3.02 (m, 2H), 3.00 - 2.90 (m, 1H), 2.77 - 2.64 (m, 1H), 2.03 - 1.97 (m, 1H), 1.84 - 1.71 (m, 2H), 1.71 - 1.57 (m, 2H), 1.02 – 0.93 (m, 6H); LC-MS: 399.2 $[M+H]^+$.

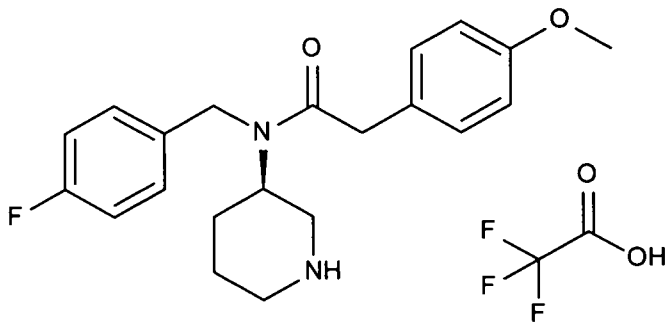
[00655] Example 98: N-[(4-fluorophenyl)methyl]-N-[(3R)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)phenyl]-acetamide; trifluoroacetic acid (98)



[00656] The compound was prepared in analogy with example 91 using N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide; trifluoroacetic acid. Yield: 51.0 mg, 34.4%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.16 – 7.09 (m, 4H), 7.03 (t, J = 8.5 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.62 (d, J= 16.0 Hz, 1H), 4.36 (d,

J= 16.0 Hz, 1H), 3.82 - 3.75 (m, 1H), 3.74 - 3.68 (m, 4H), 3.52 - 3.40 (m, 2H), 3.40 - 3.34 (m, 1H), 2.75 (s, 3H), 2.66 - 3.56 (m, 1H), 2.55 - 2.46 (m, 1H), 2.13 - 2.03 (m, 1H), 1.87 - 1.77 (m, 2H), 1.58 - 1.50 (m, 1H), 1.03 (d, J = 6.7 Hz, 6H); LC-MS: 413.3 $[M+H]^+$.

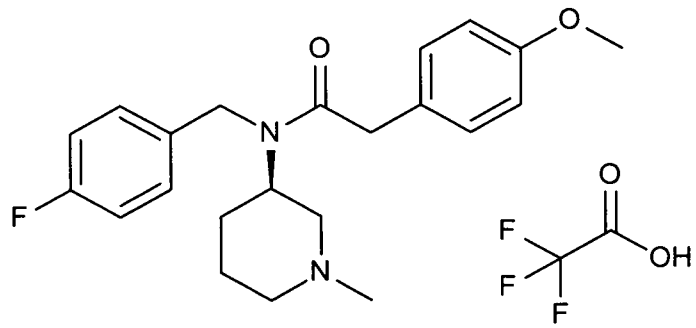
[00657] Example 99: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]acetamide; trifluoroacetic acid (99)



[00658] The compound was prepared in analogy with example 89 using tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 2-(4-methoxyphenyl)acetyl chloride.

[00659] Additional purification by preparative HPLC, eluting with 30-79% acetonitrile in water (containing 0.1% trifluoroacetic acid) yielded the title trifluoroacetic acid salt (42 mg) as fine white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.34 – 7.17 (m, 4H), 7.14 – 7.00 (m, 2H), 6.97 – 6.82 (m, 2H), 4.62 (s, 1H), 4.54 – 4.42 (m, 2H), 3.76 – 3.68 (m, 4H), 3.57 – 3.50 (m, 2H), 3.20 – 3.02 (m, 2H), 3.01 – 2.89 (m, 1H), 2.77 - 2.64 (m, 1H), 1.85 – 1.67 (m, 2H), 1.66 - 11 .53 (m, 2H); LC-MS: 357.2 $[M+H]^+$.

[00660] Example 100: N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]acetamide; trifluoroacetic acid (100)

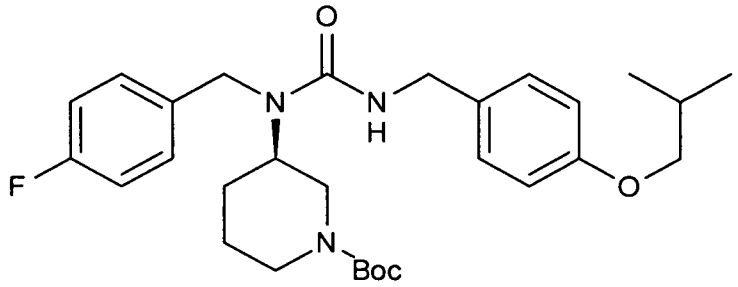


[00661] The compound was prepared in analogy with example 91 using N-[(4-fluoro-phenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]acetamide; trifluoroacetic acid. Yield: 52.0 mg, 40.5%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.16 – 7.10 (m, 4H), 7.04 (t, J

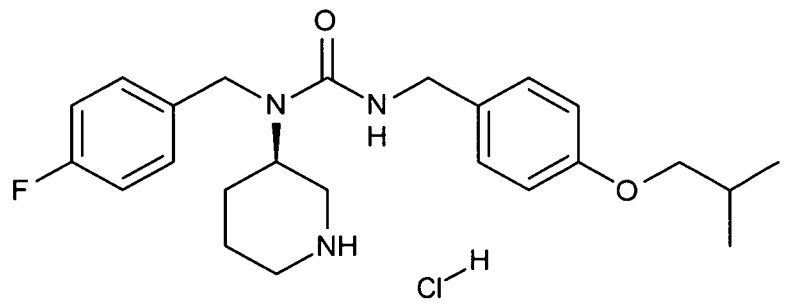
= 8.4 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 4.62 (d, J = 16.2 Hz, 1H), 4.36 (d, J = 16.2 Hz, 1H), 3.79 (s, 3H), 3.78 - 3.72 (m, 1H), 3.71 (s, 2H), 3.55 - 3.43 (m, 2H), 3.41 - 3.34 (m, 1H), 2.75 (s, 3H), 2.65 - 2.55 (m, 1H), 2.54 - 2.46 (m, 1H), 1.88 – 1.74 (m, 2H), 1.55 (d, J = 12.7 Hz, 1H); LC-MS: 371.3 $[M+H]^+$.

[00662] Example 101: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}-3-[(3R)-piperidin-3-yl]urea hydrochloride (101)

[00663] Tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}piperidine-1-carboxylate



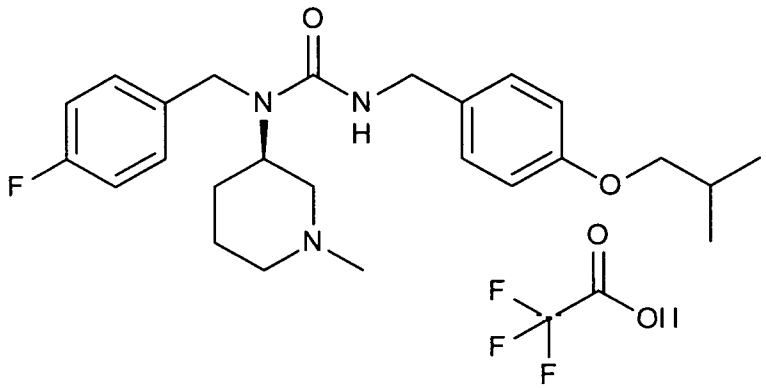
[00664] To a solution of tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (148 mg, 0.478 mmol) in dry dichloromethane (2.5 ml) 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (118 mg, 0.574 mmol) in dichloromethane (2 ml) was added. Stirring was continued for 20 hours before the reaction was concentrated and the crude product was purified by column chromatography using silica gel, eluting with petroleum ether:ethyl acetate 1:1 to give tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]({[4-(2-methyl-propoxy)phenyl]-methyl}carbamoyl)amino}piperidine-1-carboxylate (240 mg, 97.7%) as light yellow oil.



[00665] Tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}piperidine-1-carboxylate (240 mg, 0.470 mmol) was dissolved in hydrochloric acid solution in dry diethyl ether (2M, 2.5 ml) and reaction was left at stirring overnight. The reaction mixture was cooled by ice bath. The solution was decanted from a

sticky light yellow mass. The residue was washed with diethyl ether (2 x 3 ml) and dried to produce a foam of 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(3R)-piperidin-3-yl]urea; hydrochloride (210 mg, 98%): ^{1}H NMR (400 MHz, DMSO-d6) δ 7.28 – 7.21 (m, 2H), 7.14 (t, J = 8.8 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.82 (d, J =8.0 Hz, 2H), 4.47 (s, 2H), 4.41 – 4.31 (m, 1H), 4.17 (d, J = 5.1 Hz, 2H), 3.70 (d, J = 6.4 Hz, 2H), 3.13 (d, J = 11.7 Hz, 1H), 2.99 (d, J = 10.6 Hz, 1H), 2.89 (q, J = 11.2 Hz, 1H), 2.72 – 2.61 (m, 1H), 1.98 (dq, J = 13.0, 6.5 Hz, 1H), 1.83 –1.74 (m, 1H), 1.74 – 1.60 (m, 3H), 0.96 (d, J = 6.6 Hz, 6H); LC-MS: 414.4 $[M+H]^+$.

[00666] Example 102: 3-[(4-fluorophenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)-phenyl]methyl}urea; trifluoroacetic acid (102)

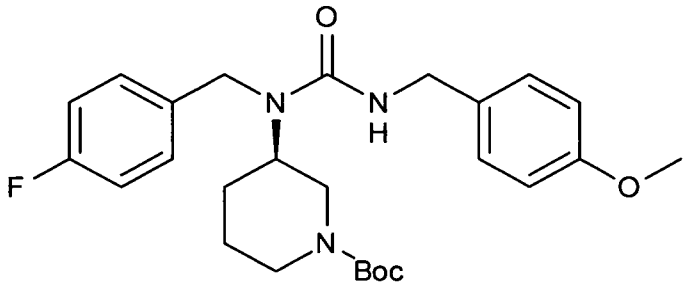


[00667] Water solution of formaldehyde (200.0 μL, 30%, 2.18 mmol) was added to a solution of 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(3R)-piperidin-3-yl]urea; hydrochloride (196.0 mg, 0.436 mmol) in tetrahydrofuran (4.0 ml). After 15 minutes stirring sodium triacetoxyborohydride (190.0 mg, 0.871 mmol) was added in one portion and stirring was continued. After 18 hours of stirring the reaction was quenched by sodium hydrogen carbonate (0.1 ml, aqueous, saturated) and concentrated. The crude was diluted with dichloromethane (15 ml) and sodium hydrogen carbonate (15 ml, aqueous, saturated). Phases were separated and the water phase was extracted more with dichloromethane (2 x 15 ml). Combined organic phase was washed with 20% brine (25 ml), dried over sodium sulfate and concentrated. Crude product was purified by preparative HPLC, eluting with 40-70% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (140.0 mg, 57.6%) as a white solid: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.23 – 7.13 (m, 4H), 7.01 (t, J = 8.5 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 5.60 (bs, 1H, NH), 4.56 – 4.37 (m, 2H), 4.37 – 4.27 (m, 2H), 3.98 (t, J = 11.2 Hz, 1H), 3.70 (d, J = 6.5 Hz, 2H), 3.58 – 3.50 (d, J= 11.0 Hz, 1H), 3.41 (d, J= 11.6 Hz, 1H), 3.16 – 3.03 (m, 1H),

2.74 (s, 3H), 2.63 - 2.53 (m, 1H), 2.15 – 2.00 (m, 2H), 1.98 – 1.83 (s, 3H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 428.3 $[M+H]^+$.

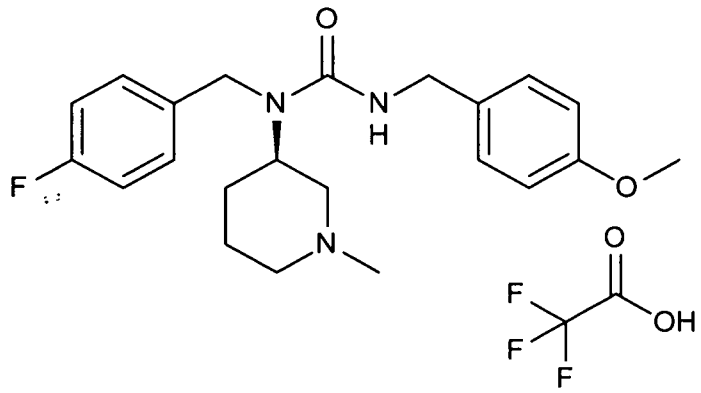
[00668] Example 103: 3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]urea; trifluoroacetic acid (103)

[00669] Tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]({[(4-methoxyphenyl)methyl]-carbamoyl})-amino}piperidine-1-carboxylate



[00670] To a solution of tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (107 mg, 0.347 mmol) in dry dichloromethane (2.0 ml) 1-(isocyanatomethyl)-4-methoxybenzene (67.9 mg, 0.414 mmol) in dichloromethane (1.5 ml) was added. Stirring was continued for 20 hours before the reaction was concentrated and the crude product was purified by column chromatography using silica gel, eluting with petroleum ether:ethyl acetate 1:1 to give tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]({[4-methoxyphenyl]-methyl}-carbamoyl)amino}piperidine-1-carboxylate (185 mg, 96.1%) as light yellow oil.

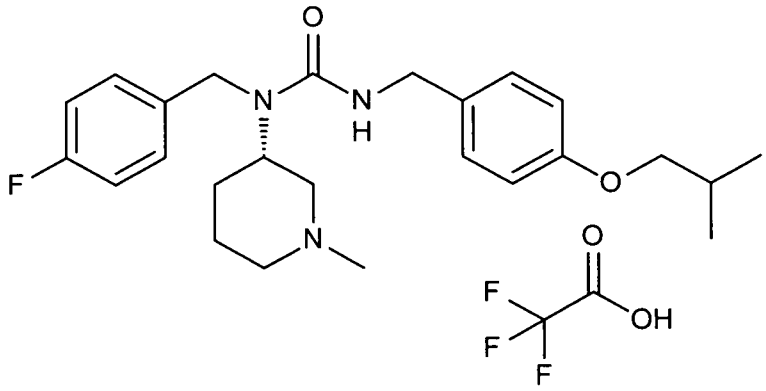
[00671] 3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]urea; trifluoroacetic acid



[00672] To a solution of tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]({[4-methoxyphenyl]-methyl}carbamoyl)amino}piperidine-1-carboxyláte (185 mg, 0.333 mmol) in dry dichloromethane (3.0 ml) trifluoroacetic acid (1.0 ml) was added dropwise. After 20 minutes

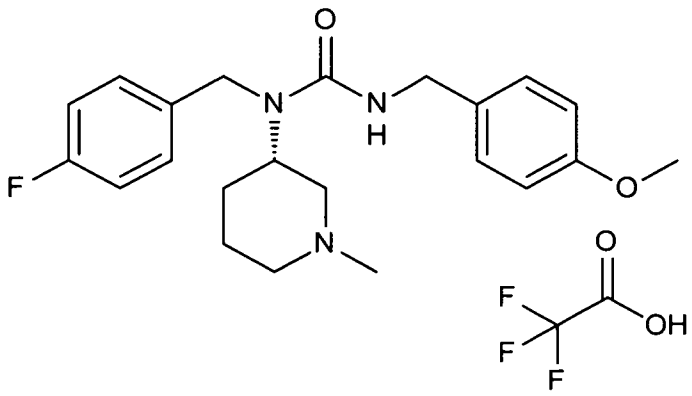
stirring the reaction mixture was analyzed by LCMS to check deprotection completed. The reaction solution was concentrated, dried and dissolved in tetrahydrofuran (3 ml). To that solution formaldehyde (30% solution in water, 153.0 µL, 1.670 mmol) was added. After 15 minutes stirring sodium triacetoxyborohydride (146 mg, 0.667 mmol). After 20 hours of stirring the reaction was quenched by 0.1 ml saturated sodium hydrogen carbonate solution, concentrated and diluted with dichloromethane (15 ml) and saturated sodium hydrogen carbonate solution (15 ml). Phases were separated and the water phase was extracted with dichloromethane (2 x 15 ml). Combined organic phase was washed with 20% brine (25 ml), dried over sodium sulfate and concentrated to give crude product. The crude product was purified by preparative HPLC, eluting with 30-60% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (105.0 mg, 60.8%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.23 - 7.13 (m, 4H), 7.08 – 6.98 (m, 2H), 6.82 (d, J = 8.0 Hz, 2H), 5.72 (bs, 1H, NH), 4.56 - 4.38 (m, 2H), 4.37 - 4.25 (m, 2H), 4.00 - 3.92 (m, 1H), 3.80 (s, 3H), 3.56 (d, J = 10.5 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.11 (m, 1H), 2.75 (s, 3H), 2.63 - 2.53 (m, 1H), 2.14 - 2.02 (m, 1H), 1.99 - 1.87 (m, 3H); LC-MS: 386.3 $[M+H]^+$.

[00673] Example 104: 3-[(4-fluorophenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (104)



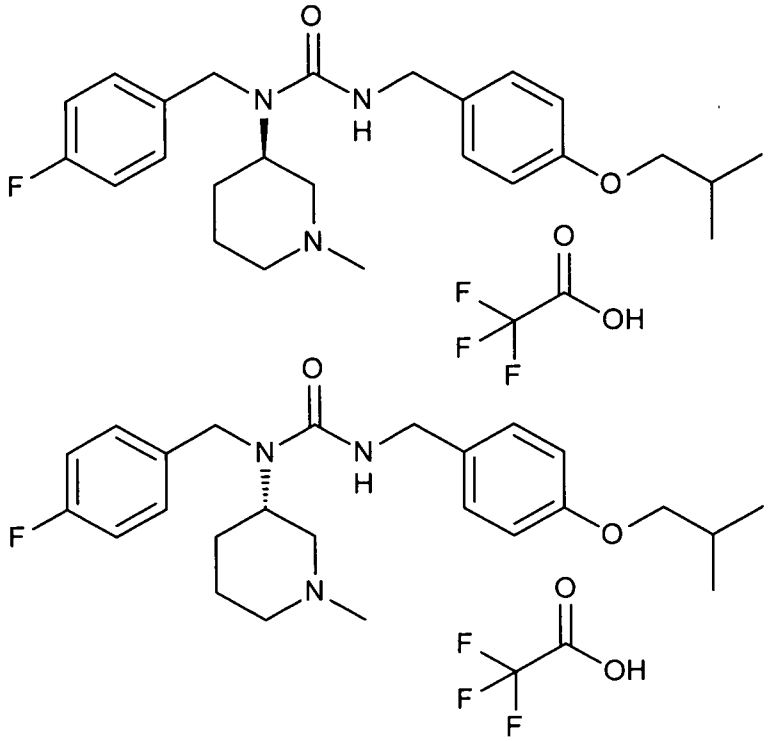
[00674] The compound was prepared in analogy with example 103 using tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 50.0 mg, 55.4%, sticky white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.21 – 7.14 (m, 4H), 7.04 – 6.97 (m, 2H), 6.85 – 6.81 (m, 2H), 5.87 (bs, 1H, NH), 4.56 – 4.36 (m, 2H), 4.30 (tt, J = 14.4, 7.2 Hz, 2H), 3.99 (t, J = 11.2 Hz, 1 H), 3.70 (d, J = 6.5 Hz, 2H), 3.52 (d, J = 10.2 Hz, 1H), 3.39 (d, J = 11.7 Hz, 1H), 3.06 – 2.93 (m, 1H), 2.72 (s, 3H), 2.59 - 2.50 (m, 1H), 2.12 - 1.98 (m, 2H), 1.98 – 1.85 (m, 3H), 1.06 – 0.98 (m, 6H); LC-MS: 428.3 $[M+H]^+$.

[00675] Example 105: 3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]urea; trifluoroacetic acid (105)



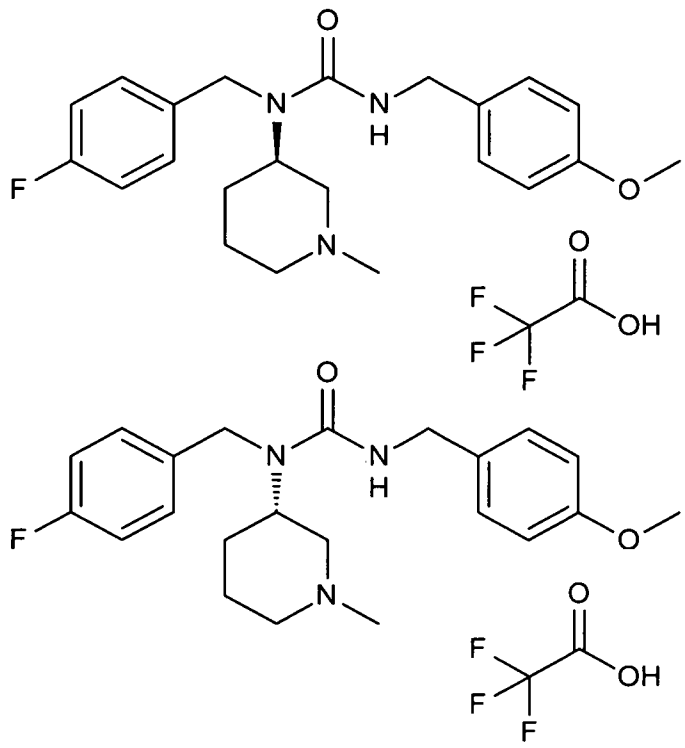
[00676] The compound was prepared in analogy with example 103 using tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 1-(isocyanatomethyl)-4-methoxybenzene. Yield: 40.0 mg, 43.6%, colourless solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.23 - 7.16 (m, 4H), 7.08 – 6.97 (m, 2H), 6.82 (d, J = 8.0 Hz, 2H), 5.80 (bs, 1H, NH), 4.54 - 4.37 (m, 2H), 4.37 – 4.24 (m, 2H), 3.97 (t, J = 11.5 Hz, 1H), 3.79 (s, 3H), 3.54 (d, J =10.4 Hz, 1H), 3.54 (d, J =10.4 Hz, 1H), 3.12 – 3.07 (m, 1H), 2.75 (s, 3H), 2.63 – 2.57 (m, 1H), 2.08 – 2.00 (m, 1H), 1.97 - 1.87 (m, 3H); LC-MS: 386.3 $[M+H]^+$.

[00677] Example 106: 3-[(4-fluorophenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (106a) and 3-[(4-fluorophenyl)-methyl]-3-[(3S)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (106b)



[00678] The compound was prepared in analogy with example 103 using tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and (3S)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene as a 1:1 mixture of enantiomers. Yield: 21.0 mg, 46.1%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.21 - 7.14 (m, 4H), 7.05 - 6.98 (m, 2H), 6.85 - 6.81 (m, 2H), 5.70 (bs, 1H, NH), 4.55 - 4.35 (m, 2H), 4.35 - 4.25 (m, 2H), 4.00 - 3.91 (m, 1H), 3.70 (d, J = 6.5 Hz, 2H), 3.53 (d, J = 10.4 Hz, 1H), 3.42 (d, J = 11.5 Hz, 1H), 3.21 - 3.11 (m, 1H), 2.76 (s, 3H), 2.64 - 2.55 (m, 1H), 2.16-2.02 (m, 2H), 1.99 - 1.87 (m, 3H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 428.3 $[M+H]^+$.

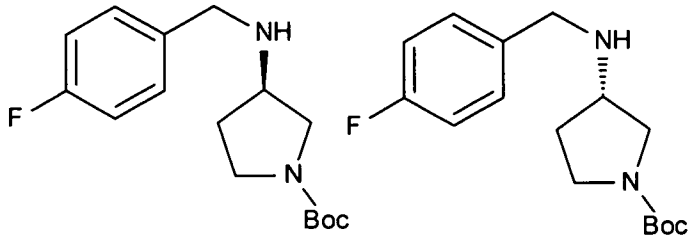
[00679] Example 107: 3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]urea; trifluoroacetic acid (107a) and 3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]urea; trifluoroacetic acid (107b)



[00680] The compounds were prepared in analogy with example 103 using tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and (3S)-3-{[(4-fluorophenyl)-methyl]amino}piperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-methoxybenzene as a 1:1 mixture of enantiomers. Yield: 23.0 mg, 52.1%, colourless solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 - 7.16 (m, 4H), 7.04 – 6.99 (m, 2H), 6.86 - 6.77 (m, 2H), 5.85 (bs, 1H, NH), 4.56 - 4.37 (m, 2H), 4.37 – 4.24 (m, 2H), 4.04 – 3.96 (m, 1H), 3.79 (s, 3H), 3.57 – 3.50 (m, 1H), 3.40 (d, J =11.6 Hz, 1H), 3.07 – 2.96 (m, 1H), 2.73 (s, 3H), 2.60 - 2.52 (m, 1H), 2.08 – 1.97 (m, 1H), 1.97 - 1.87 (m, 3H); LC-MS: 386.1 $[M+H]^+$.

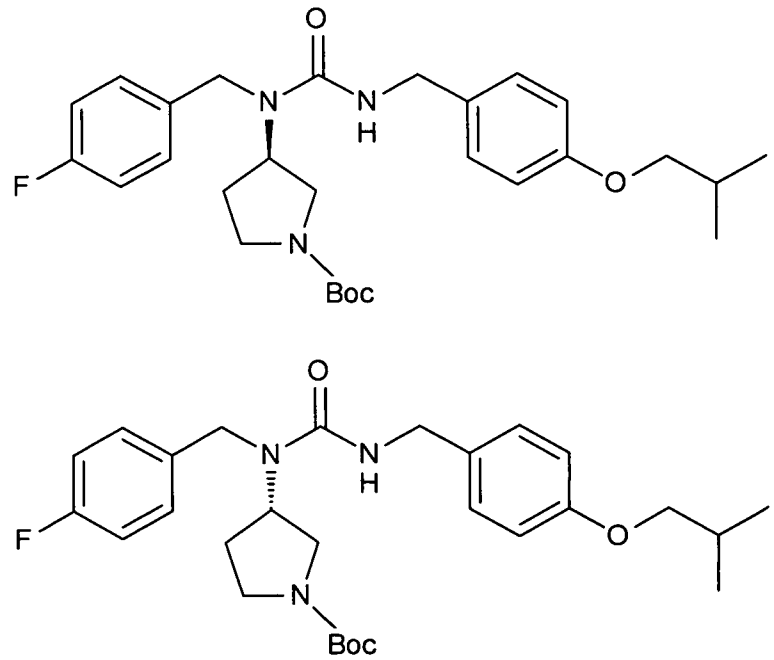
[00681] Example 108: 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}-1-[(3R)-pyrrolidin-3-yl]urea; trifluoroacetic acid (108a) and 1-[(4-fluorophenyl)-methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3S)-pyrrolidin-3-yl]urea; trifluoroacetic acid (108b)

[00682] Tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}pyrrolidine-1-carboxylate and tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}pyrrolidine-1-carboxylate



[00683] Sodium triacetoxyborohydride (1.14 g, 5.40 mmol) was added to 4-fluorobenzylamine (34 µl, 2.97 mmol) and tert-butyl 3-oxopyrrolidine-1-carboxylate (500 mg, 2.7 mmol) in ethanol (50 ml). After 4 hours of stirring at ambient temperature sodium hydroxide (1M , 75 ml) was added and the mixture was extracted with ethyl acetate (3 x 75 ml). The organic phase was dried using sodium sulfate, filtered and concentrated. The crude material was purified by column chromatography using silica gel, eluting with 0-10% methanol (containing 1% triethyl amine) in ethyl acetate to afford the title compounds as a 1:1 mixture of enantiomers (280 mg, 35%).

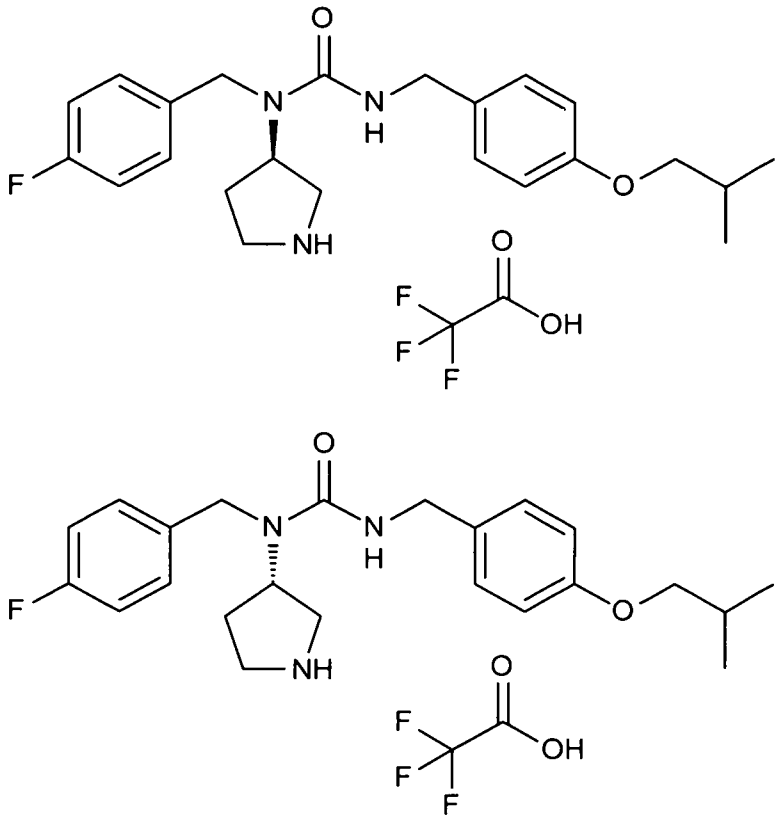
[00684] Tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}pyrrolidine-1-carboxylate and tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}pyrrolidine-1-carboxylate



[00685] 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (153 mg, 0.75 mmol) in dichloromethane (5 ml) was added to tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]amino}-

pyrrolidine-1-carboxylate and tert-butyl (3S)-3-{[(4-fluorophenyl)methyl]amino}pyrrolidine-1-carboxylate (200 mg, 0.68 mmol) in dichloromethane (15 ml). After 1 hour of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with 10% methanol in ethyl acetate to afford the title compounds as a 1:1 mixture of enantiomers (252 mg, 74%).

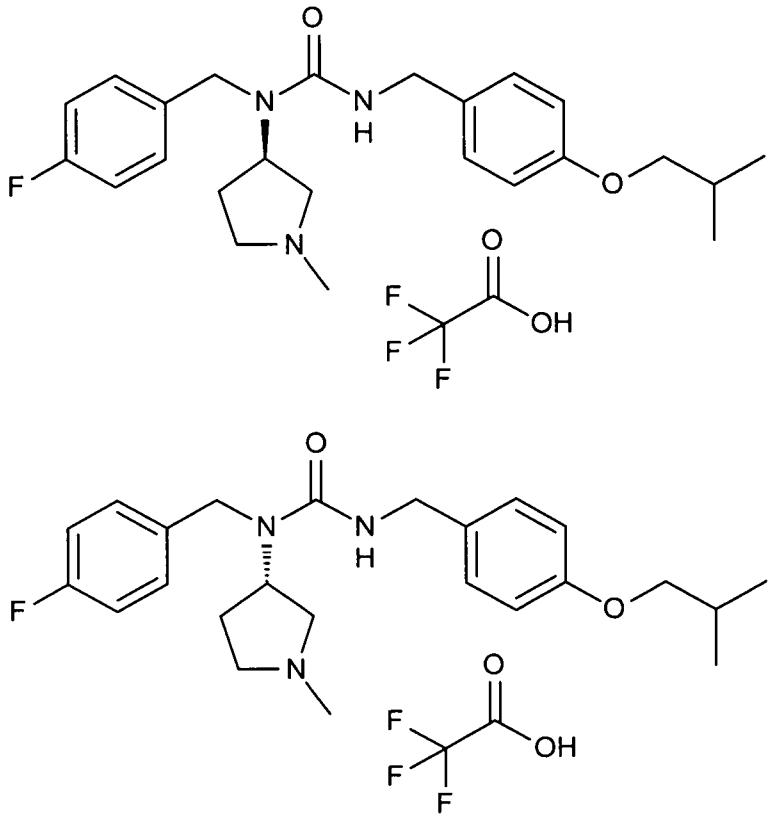
[00686] 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R)-pyrrolidin-3-yl]urea trifluoroacetic acid and 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3S)-pyrrolidin-3-yl]urea trifluoroacetic acid



[00687] Tert-butyl (3R)-3-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}pyrrolidine-1-carboxylate and tert-butyl (3S)-3-{[(4-fluoro-phenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}pyrrolidine-1-carboxylate (94.4 mg, 189 μmol) were dissolved in dichloromethane (4 ml) and trifluoroacetic acid (300 μl) was added. After 2 hours of stirring at ambient temperature the mixture was concentrated to afford the title compounds as a 1:1 mixture of enantiomers (95 mg, 98%): ^{1}H NMR (400 MHz, Chloroform-d) δ 10.37 (s, 1H), 8.77 (s, 1H), 7.15 – 7.06 (m, 2H), 7.06 – 6.94 (m, 4H), 6.78 (d, 2H), 4.78 (s, 1H), 4.49 – 4.39 (m, 1H), 4.36 (s, 2H), 4.21

(d, 2H), 3.67 (d, 2H), 3.55 (s, 1H), 3.45 (s, 1H), 3.35 (s, 1H), 3.15 (s, 2H), 2.32 – 2.21 (m, 1H), 2.20 – 2.11 (m, 1H), 2.05 (tt, 1H), 1.01 (d, 6H); LC-MS: 400.3 $[M+H]^+$.

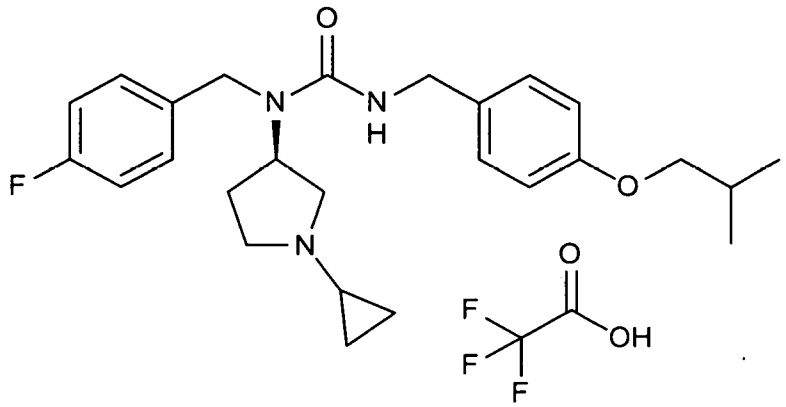
[00688] Example 109: 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}-1-[(3R)-1-methylpyrrolidin-3-yl]urea; trifluoroacetic acid (109a) and 1-[(4-fluoro-phenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3S)-1-methylpyrrolidin-3-yl]urea; trifluoroacetic acid (109b)

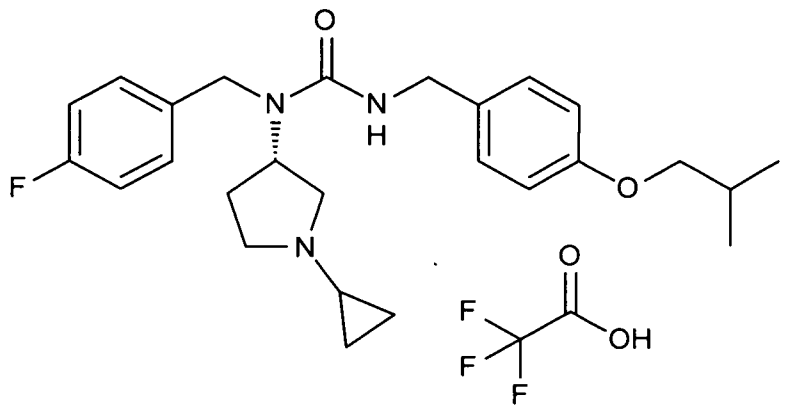


[00689] 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R)-pyrrolidin-3-yl]urea trifluoroacetic acid and 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methyl-propoxy)phenyl]methyl}-1-[(3S)-pyrrolidin-3-yl]urea trifluoroacetic acid (18.8 mg, 36.6 μmol) were dissolved in tetrahydrofuran (0.5 ml). Formaldehyde (37% aqueous, 4.13 μl, 54.9 μmol) and sodium cyanoborohydride (4.6 mg, 73.2 μmol) were added. After 30 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in methanol (1 ml). The mixture was heated to 65 °C and stirred for 1.5 hours before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds as a 1:1 mixture of enantiomers (8.6 mg, 45%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 – 7.10 (m, 2H), 7.09 – 6.97 (m, 4H), 6.82 (t, 2H), 5.92 (s, 2H), 5.19 – 4.68 (m, 1H),

4.51 (q1H), 4.40 (s, 1H), 4.26 (s, 2H), 3.91 – 3.76 (m, 1H), 3.70 (dd, 3H), 3.67 – 3.27 (m, 2H), 2.94 (s, 3H), 2.54 – 2.17 (m, 2H), 2.13 – 2.00 (m, 1H), 1.03 (d, 6H); LC-MS: 414.2 $[M+H]^+$.

[00690] Example 110: 1-[(3R)-1-cyclopropylpyrrolidin-3-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (110a) and 1-[(3S)-1-cyclopropylpyrrolidin-3-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea; trifluoroacetic acid (110b)



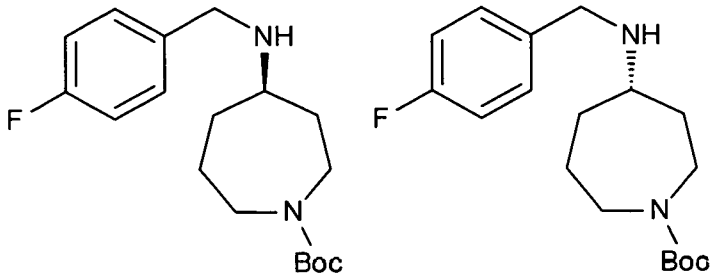


[00691] 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R)-pyrrolidin-3-yl]urea trifluoroacetic acid and 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methyl-propoxy)phenyl]methyl}-1-[(3S)-pyrrolidin-3-yl]urea trifluoroacetic acid (18.8 mg, 36.6 μmol) were dissolved in tetrahydrofuran (0.5 ml). (1-ethoxycyclopropoxy)trimethylsilane (9.6 mg, 54.9 μmol), acetic acid (2.3 μl, 40.3 μmol) and sodium cyanoborohydride (4.6 mg, 73.2 μmol) was added. After 30 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in methanol (1 ml). The mixture was heated to 65 °C and stirred for 1.5 hours before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds as a 1:1 mixture of enantiomers (6.9 mg,

34%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.20 – 7.11 (m, 2H), 7.09 – 6.98 (m, 4H), 6.82 (d, 2H), 4.75 (s, 1H), 4.58 – 4.38 (m, 2H), 4.31 – 4.22 (m, 2H), 3.91 – 3.78 (m, 1H), 3.70 (d, 4H), 3.66 – 3.53 (m, 1H), 3.23 (s, 1H), 2.72 (s, 1H), 2.64 – 2.39 (m, 1H), 2.30 – 2.15 (m, 1H), 2.08 (dp, 1H), 1.22 – 1.04 (m, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.87 (d, 1H); LC-MS: 440.2 $[M+H]^+$.

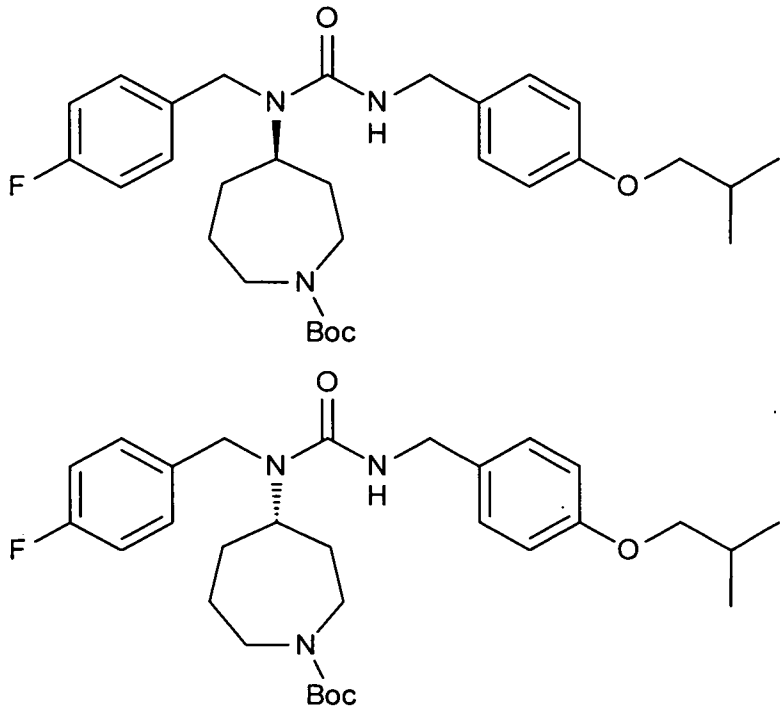
[00692] Example 111: 1-[(4R)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (111a) and 1-[(4S)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (111b)

[00693] Tert-butyl (4R)-4-{[(4-fluorophenyl)methyl]amino}azepane-1-carboxylate and tert-butyl (4S)-4-{[(4-fluorophenyl)methyl]amino}azepane-1-carboxylate



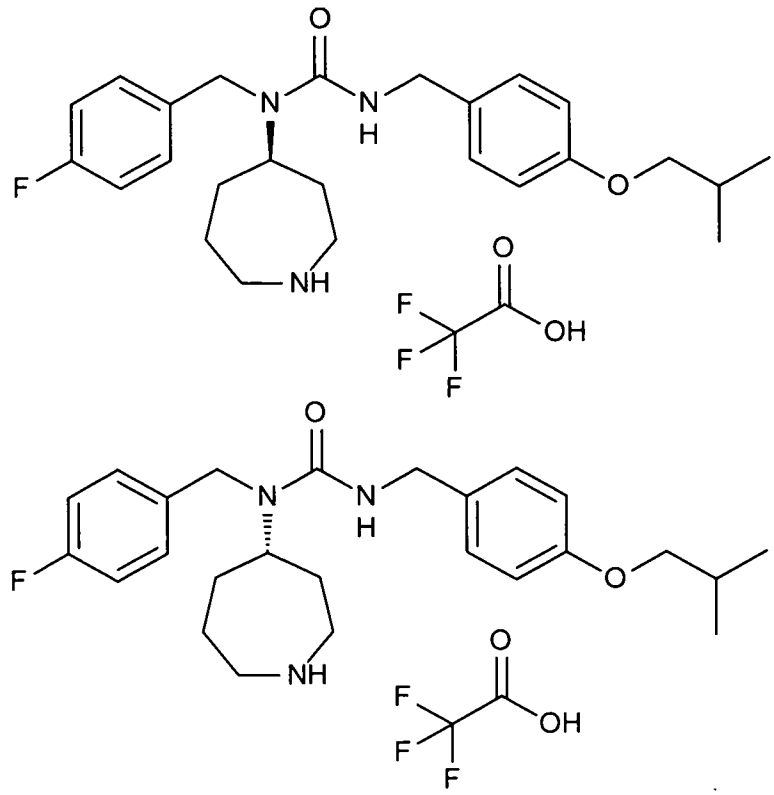
[00694] Sodium triacetoxyborohydride (994 mg, 4.69 mmol) was added to 4-fluorobenzylamine (30 µl, 2.58 mmol) and tert-butyl 4-oxoazepane-1-carboxylate (500 mg, 2.34 mmol) in ethanol (50 ml). After 4 hours of stirring at ambient temperature sodium hydroxide (1M, 75 ml) was added and the mixture was extracted with ethyl acetate (3 x 75 ml). The organic phase was dried using sodium sulfate, filtered and concentrated. The crude material was purified by column chromatography using silica gel, eluting with 0-10% methanol (containing 1% triethyl amine) in ethyl acetate to afford the title compounds as a 1:1 mixture of enantiomers (450 mg, 60%).

[00695] Tert-butyl (4R)-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}azepane-1-carboxylate and tert-butyl (4S)-4-{[(4-fluorophenyl)-methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}azepane-1-carboxylate



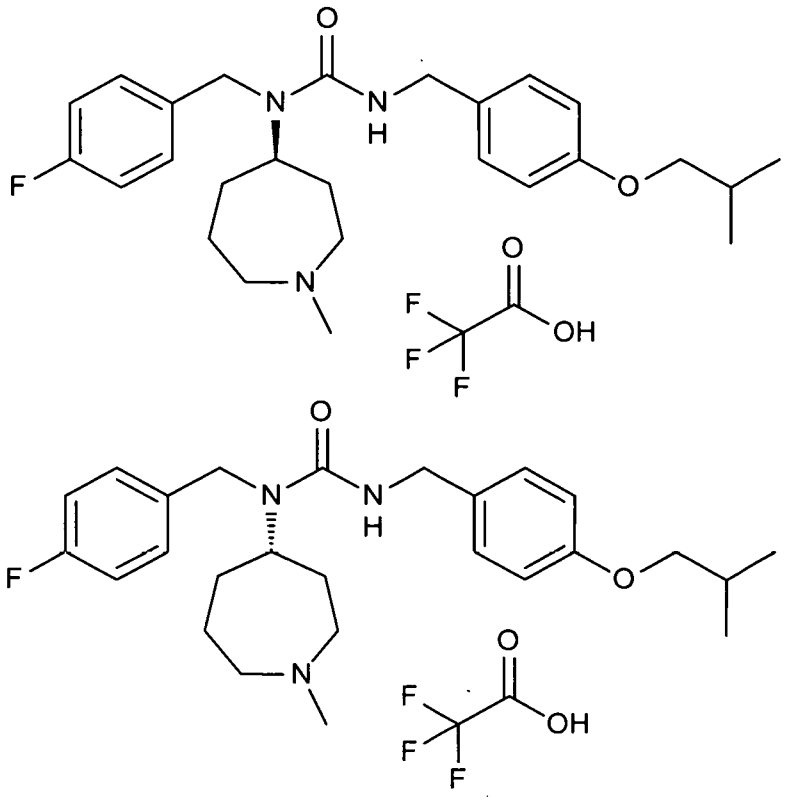
[00696] 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (140 mg, 682 μmol) in dichloromethane (5 ml) was added to tert-butyl (4R)-4-{[(4-fluorophenyl)methyl]amino}-azepane-1-carboxylate and tert-butyl (4S)-4-{[(4-fluorophenyl)methyl]amino}azepane-1-carboxylate (200 mg, 620 μmol) in dichloromethane (15 ml). After 1 hour of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silica gel, eluting with 10% methanol in ethyl acetate to the title compounds as a 1:1 mixture of enantiomers (318 mg, 97%).

[00697] 1-[(4R)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea trifluoroacetic acid and 1-[(4S)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea trifluoroacetic acid



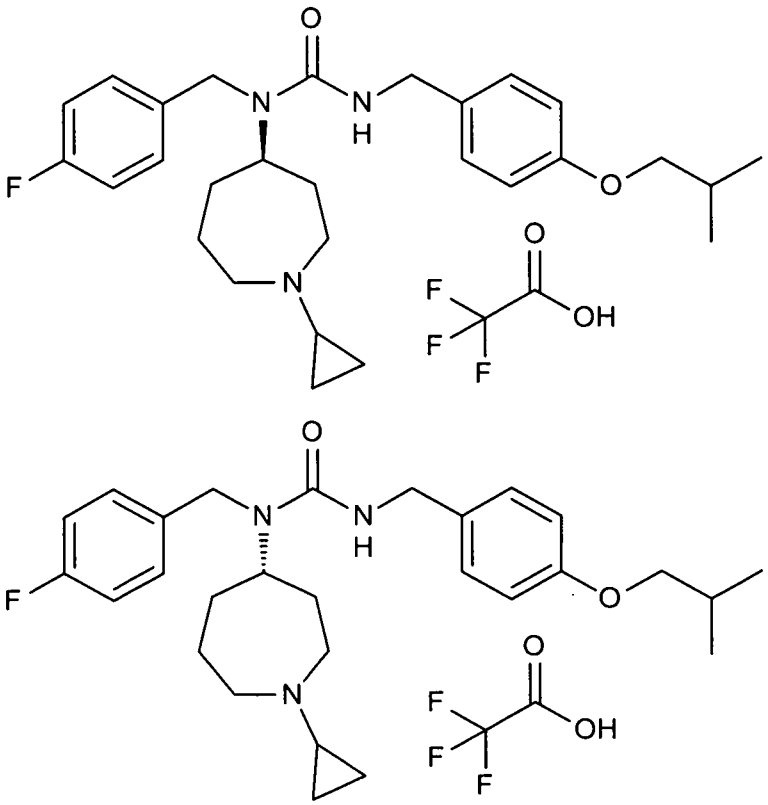
[00698] tert-butyl (4R)-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}azepane-1-carboxylate and tert-butyl (4S)-4-{[(4-fluorophenyl)-methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}azepane-1-carboxylate (249 mg, 472 μmol) were dissolved in dichloromethane (4 ml) and trifluoroacetic acid (600 μl) was added. After 3 hours of stirring at ambient temperature the mixture was concentrated to afford the title compounds as a 1:1 mixture of enantiomers (256 mg, 100%): ^{1}H NMR (400 MHz, Chloroform-d) δ 8.87 (s, 2H), 7.17 (dd, 2H), 7.03 (t, 2H), 6.96 (d, 2H), 6.79 (d, 2H), 4.50 – 4.32 (m, 3H), 4.24 (s, 2H), 3.82 (ddd, 2.5 Hz, 1H), 3.68 (d, 2H), 3.43 – 3.20 (m, 2H), 3.19 – 3.04 (m, 2H), 2.16 – 2.09 (m, 2H), 2.06 (dd, 6.7 Hz, 1H), 2.02 – 1.95 (m, 2H), 1.93 – 1.89 (m, 1H), 1.89 – 1.76 (m, 2H), 1.02 (d, 6H); LC-MS: 428.3 $[M+H]^+$.

[00699] Example 112: 1-[(4-fluorophenyl)methyl]-1-[(4R)-1-methylazepan-4-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (112a) and 1-[(4-fluorophenyl)-methyl]-1-[(4S)-1-methylazepan-4-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (112b)



[00700] 1-[(4R)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea trifluoroacetic acid and 1-[(4S)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea trifluoroacetic acid (40 mg, 73.9 μmol) were dissolved in tetrahydrofuran (0.5 ml). Formaldehyde (37% aqueous, 8.32 μl, 111 μmol) and sodium cyanoborohydride (9.3 mg, 148 μmol) were added. After 30 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in methanol (1 ml). The mixture was heated to 65 °C and stirred for 1.5 hours before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds as a 1:1 mixture of enantiomers (8.6 mg, 45%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.86 (s, 1H), 7.16 (dd, 2H), 7.01 (ddd, 4H), 6.79 (dd, 2H), 4.73 – 4.56 (m, 1H), 4.35 (d, 2H), 4.25 (d, 2H), 3.69 (dd, 2H), 3.73 – 3.55 (m, 2H), 3.51 – 3.38 (m, 1H), 3.11 – 2.92 (m, 1H), 2.84 (d, 3H), 2.52 – 2.16 (m, 2H), 2.14 – 1.94 (m, 4H), 1.94 – 1.76 (m, 2H), 1.01 (d, 6H).; LC-MS: 442.3 $[M+H]^+$.

[00701] Example 113: 1-[(4R)-1-cyclopropylazepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (113a) and 1-[(4S)-1-cyclopropylazepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea; trifluoroacetic acid (113b)

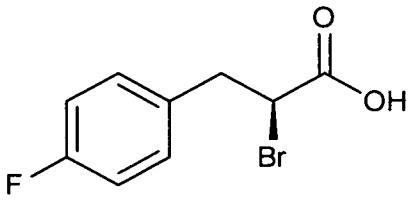


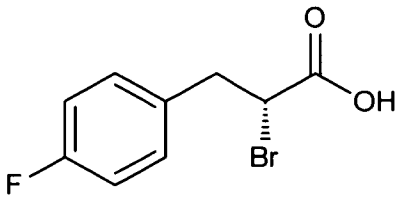
[00702] 1-[(4R)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea trifluoroacetic acid and 1-[(4S)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea trifluoroacetic acid (40 mg, 73.9 μmol) were dissolved in tetrahydrofuran (0.5 ml). (1-ethoxycyclopropoxy)trimethylsilane (19.3 mg, 111 μmol), acetic acid (2.3 μl, 40.3 μmol) and sodium cyanoborohydride (4.6 mg, 73.2 μmol) was added. After 30 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in methanol (1 ml). The mixture was heated to 65 °C and stirred for 1.5 hours before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds as a 1:1 mixture of enantiomers (12 mg, 28%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 (dt, 2H), 7.08 – 6.96 (m, 4H), 6.84 – 6.78 (m, 2H), 4.82 – 4.60 (m, 1H), 4.40 (s, 3H), 4.25 (dd, 2H), 3.70 (dd, 2H), 3.68 – 3.48 (m, 2H), 3.43 – 3.25 (m, 1H), 2.80 – 2.62 (m, 1H), 2.47 – 2.18 (m, 3H), 2.13 – 1.96 (m, 5H), 1.28 (d, 1H), 1.22 – 1.13 (m, 2H), 1.02 (d, 7H), 0.88 – 0.80 (m, 1H); LC-MS: 468.4 $[M+H]^+$.

[00703] Example 114: (2R)-3-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide; trifluoroacetic acid (114a) and (2S)-3-(4-

fluorophenyl)-2-(4-methylpiperazin-1-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-propanamide; trifluoroacetic acid (114b)

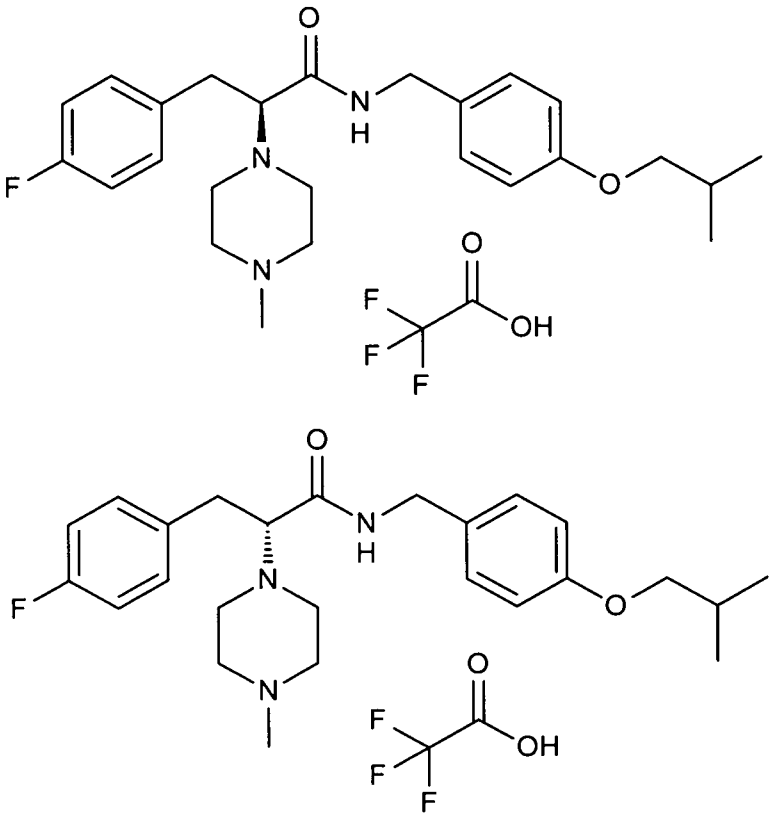
[00704] (2R)-2-bromo-3-(4-fluorophenyl)propanoic acid and (2S)-2-bromo-3-(4-fluorophenyl)propanoic acid





[00705] 2-amino-3-(4-fluorophenyl)propanoic acid (5.49 g, 30 mmol) was dissolved in hydrobromic acid (48%, 30 ml) and water (27 ml). The solution was cooled with ice/water. Then a solution of sodium nitirite (3.31 g, 48 mmol) in water (11 ml) was added dropwise. After completed addition the mixture was stirred at ambient temperature for 2.5 hours, concentrated to half volume and extracted with ether (3 x 200 ml). The organic phase is washed with brine, dried (sodium sulfate) and evaporated to give a yellow oil which solidified after half a day (7.00 g, 94 %).

[00706] (2R)-3-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)-N-{[4-(2-methylpropoxy)-phenyl]methyl}propanamide; trifluoroacetic acid and (2S)-3-(4-fluorophenyl)-2-(4-methyl-piperazin-1-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide; trifluoroacetic acid

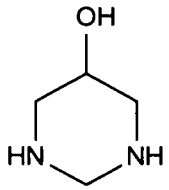


[00707] (2R)-2-bromo-3-(4-fluorophenyl)propanoic acid and (2S)-2-bromo-3-(4-fluorophenyl)propanoic acid (1:1, 1.98 g, 8.0 mmol), potassium carbonate (2.21 g, 16.0mmol) and 1-methylpiperazine (881 mg, 8.8 mmol) were mixed in tetrahydrofuran (dry, 60 ml) and stirred under nitrogen over night. The solvent was evaporated, sodium hydroxide solution (1M, 9ml) was added and the aqueous phase was extracted with diethyl ether (150ml). The aqueous phase was neutralized with hydrochloric acid and extracted with diethyl ether. The organic solvent was evaporated and the residue acidified with hydrochloric acid and freeze dried to give a crude hydrochloric salt of 3-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)propanoic (266 mg). The crude material was dissolved in N,N-dimethylformamide (4 ml) and diisopropylethylamine (342 mg, 2.6 mmol) and 1-[bis(dimet-hylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (335 mg, 880 μmol) were added. After 10 minutes [4-(2-methylpropoxy)phenyl]methanamine (157 mg, 880 μmol) was added. The reaction mixture was stirred over night. After addition of water (10 ml), the reaction mixture was extracted with diethyl ether. The organic phase is washed with brine, dried (sodium sulfate) and concentrated. The crude material was purified by HPLC to afford the title compound (5 mg, 0.1%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.14 (dd, *J* = 8.1, 5.5 Hz, 2H), 6.96 (t, *J* = 8.1 Hz, 4H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.22 (d, *J* =

16.0 Hz, 1H), 4.29 (dd, J = 14.4, 5.9 Hz, 1H), 4.20 (dd, J = 14.4, 5.2 Hz, 1H), 3.70 (d, J = 6.5 Hz, 2H), 3.60 – 2.24 (m, 13H), 2.08 (hept, J = 13.3, 6.7 Hz, 1H), 1.03 (d, J = 6.7 Hz, 6H). LC-MS: 428.3 $[M+H]^+$.

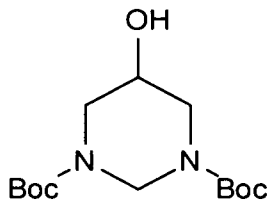
[00708] Example 115: 1-(1-acetyl-1,3-diazinan-5-yl)-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (115)

[00709] 1,3-diazinan-5-ol



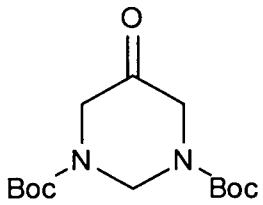
[00710] 1,3-diaminopropan-2-ol (3.0 g, 33.3 mmol) and paraformaldehyde (950 mg, 31.6 mmol) were dissolved in methanol (45 mL). The reaction was heated under reflux for 48 h. The solvent was evaporated and the residue was recrystallized from acetonitrile to give the intermediate (2.33g, 72 %).

[00711] 1,3-di-tert-butyl 5-hydroxy-1,3-diazinane-1,3-dicarboxylate



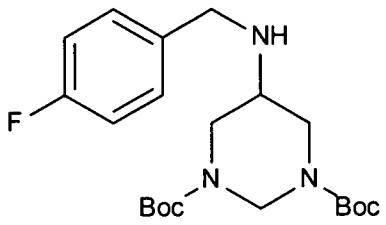
[00712] 1,3-diazinan-5-ol (2.33g, 22.8 mmol) and potassium carbonate (9.46 g, 68.4 mmol) were dissolved in water (90 mL) and cooled to 0 °C. A solution of di-tert-butyl dicarbonate (12.4 g, 57.0 mmol) in tetrahydrofuran (50 mL) was added dropwise with stirring. The cooling bath was removed and the reaction was stirred at room temperature overnight. Dichloromethane was added. After shaking the organic phase was collected. The water phase was extracted two more times using dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and evaporated. The crude was recrystallized from ethyl acetate and petroleum ether. The solids were collected. An extra crop was collected from the supernatant. The two isolated solids were pooled to give the desired intermediate (6.03 g, 87%).

[00713] 1,3-di-tert-butyl 5-oxo-1,3-diazinane-1,3-dicarboxylate



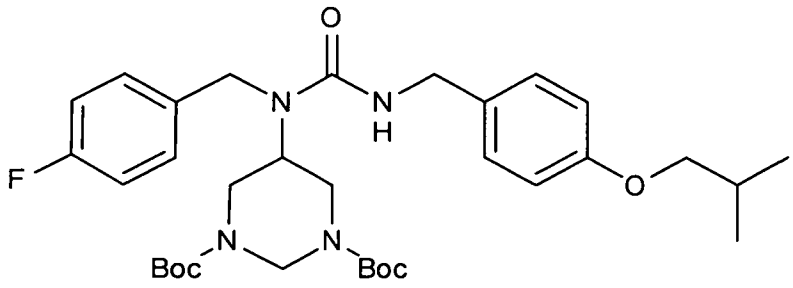
[00714] 1,3-di-tert-butyl 5-hydroxy-1,3-diazinane-1,3-dicarboxylate (2.0 g, 6.61 mmol) was dissolved in dichloromethane (66 mL). Dess-Martin periodinane (4.77 g, 11.2 mmol) was added portion wise. The mixture was stirred at room-temperature overnight. The reaction mixture was added to diethyl ether (216 mL). A precipitation was formed. A saturated solution of sodium bicarbonate in water (100 mL) was added followed by sodium thiosulfate (5.82 g, 33.1 mmol). After 15 minutes of stirring two clear phases had formed. The organic layer was separated and treated with sodium bicarbonate (5% in water), water and finally magnesium sulfate. The solid was filtered of and the solvent was evaporated to give the ketone (1.89 g, 95 %).

[00715] 1,3-di-tert-butyl 5-{[(4-fluorophenyl)methyl]amino}-1,3-diazinane-1,3-dicarboxylate



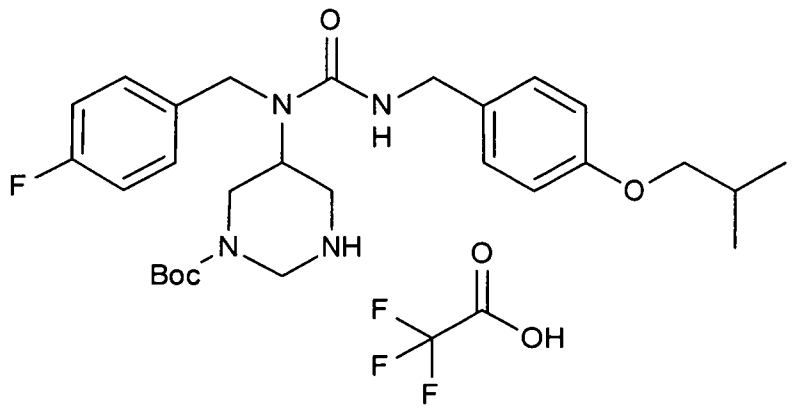
[00716] To 4-fluorobenzylamine (0.87g, 6.92 mmol) and 1,3-di-tert-butyl 5-oxo-1,3-diazinane-1,3-dicarboxylate (1.89g, 6.29 mmol) in ethanol at room temperature was added sodium triacetoxyborohydride (2 equivalents) in portions. The mixture was stirred for 4 hours, then sodium hydroxide (aqueous, 5 M) was added. The resulting mixture was stirred for 1 hour and then partitioned between diethyl ether and water. The organic phase was collected, the aqueous phase was extracted once again with diethyl ether. The combined organic phases were dried and evaporated to give the desired intermediate as an oil. Yield 1.17 g, 45%

[00717] 1,3-di-tert-butyl 5-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}-1,3-diazinane-1,3-dicarboxylate



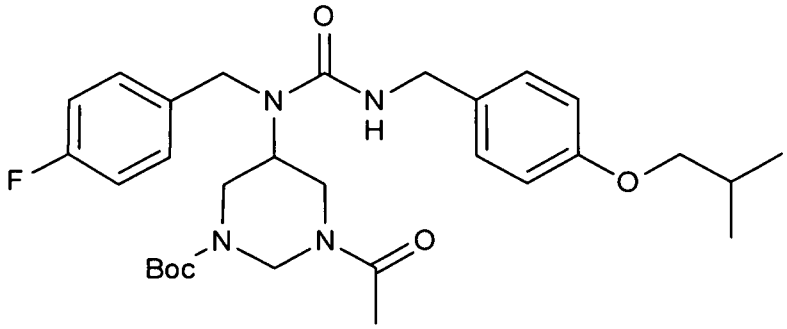
[00718] 1,3-di-tert-butyl 5-{[(4-fluorophenyl)methyl]amino}-1,3-diazinane-1,3-dicarboxylate (1.17 g, 2.86 mmol) was dissolved in dichloromethane (10 ml). 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (0.645 g, 3.14 mmol) dissolved in dichloromethane (6 ml) and was added. The mixture was stirred at ambient temperature overnight. The material was purified by column chromatography using silicon dioxide gel, eluting with ethyl acetate in petroleum ether to give the desired urea (0.59 g, 33 %)

[00719] tert-butyl 5-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)amino}-1,3-diazinane-1-carboxylate; trifluoroacetic acid



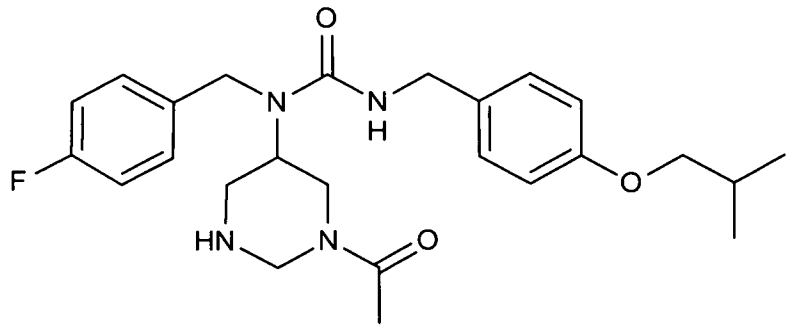
[00720] 1,3-di-tert-butyl 5-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}-1,3-diazinane-1,3-dicarboxylate (0.59 g, 0.96 mmol) was dissolved in dichloromethane (5.9 ml) and cooled to 0 °C. A solution of trifluoroacetic acid (10 % in dichloromethane, 7 ml) was added. After stirring at ambient temperature overnight the mixture was concentrated. The crude material was purified by HPLC, eluting with 35-65% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford monodeprotected product (154 mg, 25%).

[00721] tert-butyl 3-acetyl-5-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}-1,3-diazinane-1-carboxylate



[00722] tert-butyl 5-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)amino}-1,3-diazinane-1-carboxylate (77 mg, 0.122 mmol) was dissolved in tetrahydrofuran (0.8 ml). Pyridine (39 µl, 0.49 mmol) followed by acetic anhydride (23 µL, 0.245 mmol) were added. After stirring at ambient temperature overnight the mixture was concentrated to remove most of the solvent. Diethyl ether and ammonium chloride (aqueous, 1M) were added. The ether phase was separated, washed with ammonium chloride (2 x, aqueous, saturated), dried over sodium sulfate, filter and evaporated to give the desired compound.

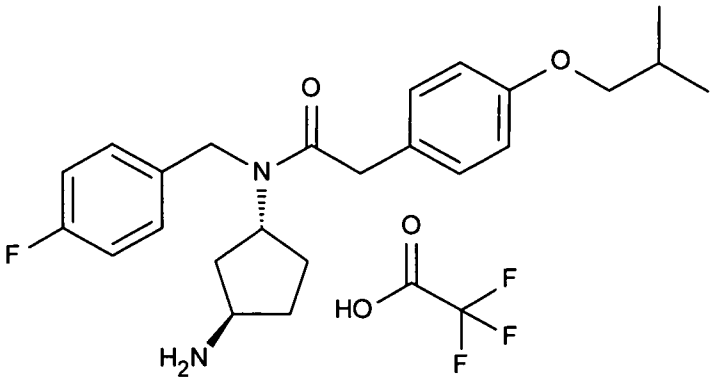
[00723] 1-(1-acetyl-1,3-diazinan-5-yl)-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea

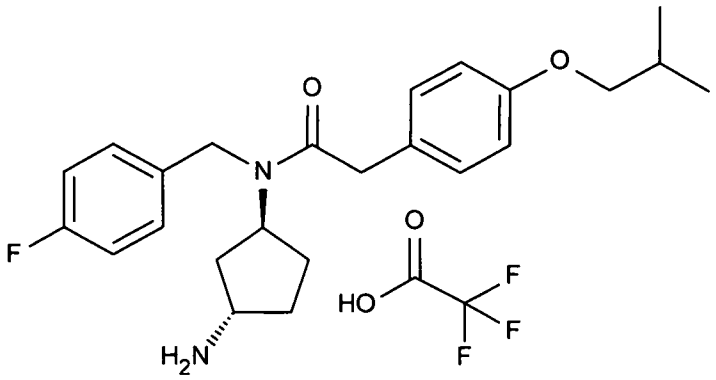


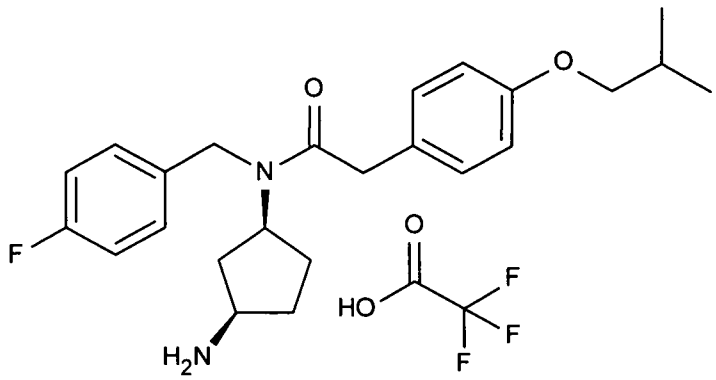
[00724] tert-butyl 3-acetyl-5-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}-1,3-diazinane-1-carboxylate (68 mg, 0.122 mmol) was dissolved in dichloromethane (0.76 ml) and cooled to 0 °C. A solution of trifluoroacetic acid (10 % in dichloromethane, 0.84 ml) was added. After stirring at ambient temperature overnight the mixture was concentrated. The product was purified by column chromatography using silicon dioxide gel, eluting with methanol in ethyl acetate (containing 0.5 % triethylamine) to afford the title compound (13 mg, 23 %). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 – 7.15 (m, 2H), 7.12 – 6.95 (m, 4H), 6.80 (d, 2H), 4.81 – 4.52 (m, 2H), 4.47 – 4.35 (m, 2H), 4.35 – 4.15 (m,

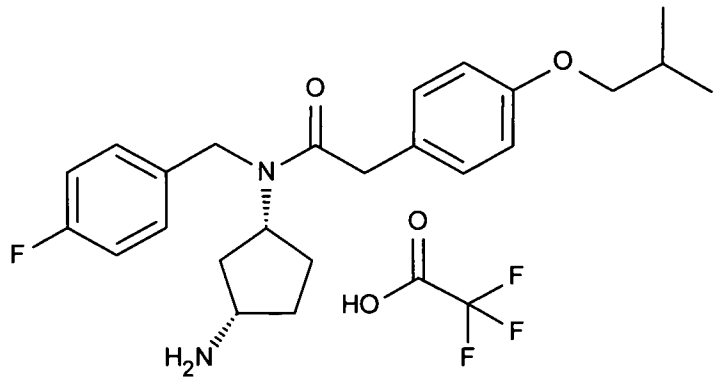
3H), 3.98 – 3.84 (m, 1H), 3.69 (d, 2H), 3.61 – 2.84 (m, 3H), 2.15 – 1.96 (m, 4H), 1.01 (d, 6H). LC-MS: 457.3 $[M+H]^+$.

[00725] Example 116: N-[(1R,3R)-3-aminocyclopentyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (116a) and N-[(1S,3S)-3-aminocyclopentyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (116b); N-[(1R,3S)-3-aminocyclopentyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (116c) and N-[(1S,3R)-3-aminocyclopentyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (116d)







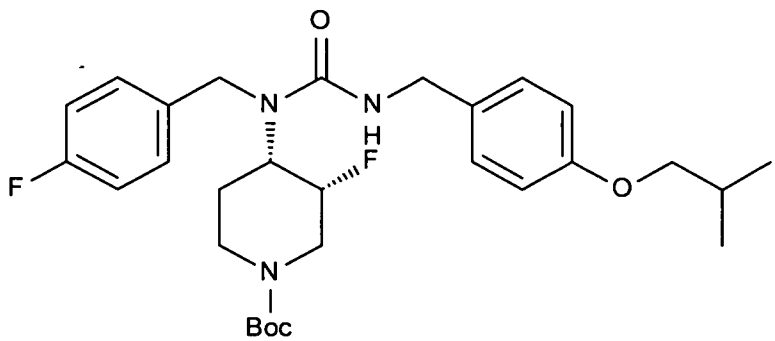


[00726] To a stirred solution of tert-butyl N-(3-{[(4-fluorophenyl)methyl]amino}-cyclopentyl)carbamate (1 equivalent) and diisopropylethylamine (2 equivalents) in dichloromethane was slowly added 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (1.1 equivalents) as a solution in dichloromethane. After stirring at room temperature for 2 hours,

the mixture was washed with water and extracted with dichloromethane. The organic phase was dried and concentrated. The residue was re-dissolved in dichloromethane and treated with trifluoroacetic acid at room temperature. After 3 hours, the mixture was concentrated. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford N-[(1R,3R)-3-aminocyclopentyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid and N-[(1S,3S)-3-aminocyclopentyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (58 %, racemic mixture, faster eluting product). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (s, 2H), 7.06 (m, 4H), 6.96 (m, 2H), 6.82 – 6.76 (m, 2H), 4.54 (m, 1H), 4.42 (d, 2H), 3.66 (d, 3H), 3.50 (s, 2H), 2.06 (s, 2H), 1.95 (s, 2H), 1.81 (s, 1H), 1.62 (d, 1H), 1.51 (s, 1H), 1.06 – 0.95 (m, 6H); LC-MS: 399.2 $[M+H]^+$ and N-[(1R,3S)-3-aminocyclopentyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid and N-[(1S,3R)-3-aminocyclopentyl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (32 %, racemic mixture, slower eluting product) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (s, 2H), 7.08 (m, 2H), 7.01 (m, 4H), 6.86 (m, 2H), 4.50 (s, 2H), 3.73 (m, 1H), 3.70 (s, 2H), 3.64 (s, 2H), 3.60 (m, 1H), 2.33 (m, 1H), 2.24 – 2.01 (m, 4H), 1.78 (m, 1H), 1.65 (m, 1H), 1.06 – 0.98 (m, 6H); LC-MS: 399.2 $[M+H]^+$.

[00727] Example 117: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (117)

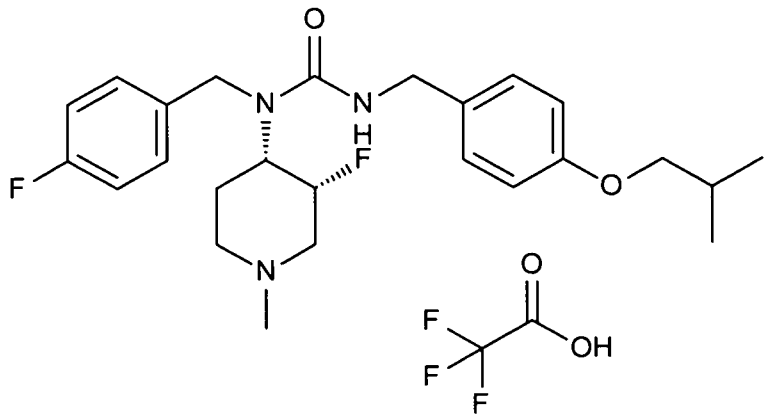
[00728] tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate



[00729] 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (7.7 mg, 38 μmol) in dichloromethane (0.5 ml) was added to tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)-methyl]amino}piperidine-1-carboxylate (8.2 mg, 25 μmol). After 100 minutes of stirring at ambient temperature the mixture was concentrated. The crude material was purified by

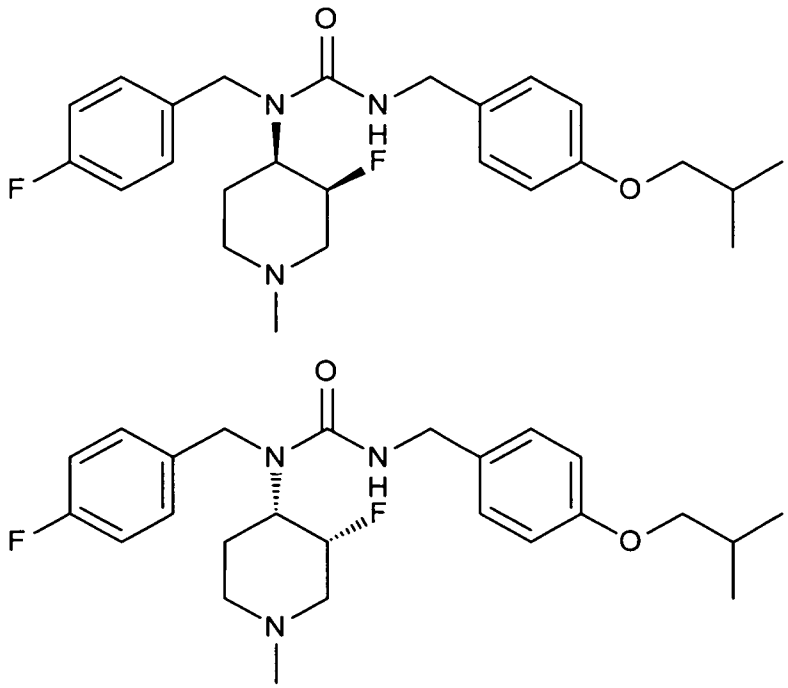
column chromatography using silicon dioxide gel, eluting with 50% ethyl acetate in petroleum ether to afford the desired urea (8 mg).

[00730] 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid



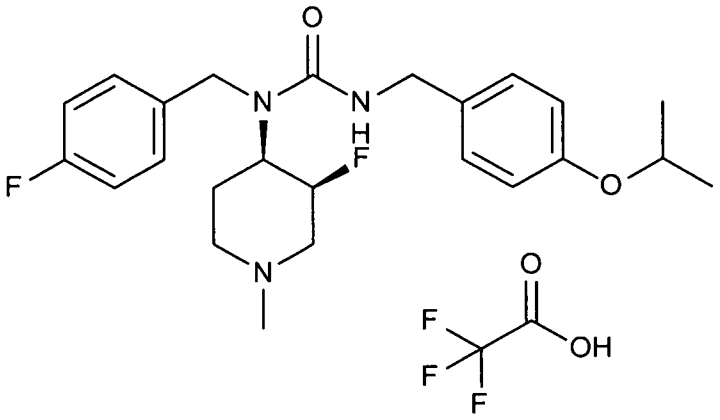
[00731] tert-Butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate (8 mg) was dissolved in dichloromethane (3 ml) and trifluoroacetic acid (1 ml) was added. After 20 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofuran (0.5 ml). Formaldehyde (37% aqueous, 1.7 µl, 23 µmol) and sodium cyanoborohydride (1.9 mg, 30 µmol) were added. After 20 minutes the mixture was concentrated and re-dissolved in methanol (1 ml). The resulting mixture was heated to reflux for 80 minutes before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with 30-70% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (9.1 mg): ^{1}H NMR (400 MHz, Methanol-d4) δ 7.27 – 7.17 (m, 2H), 7.10 – 6.99 (m, 4H), 6.84 – 6.74 (m, 2H), 5.12 (d, 1H), 4.83 – 4.64 (m, 2H), 4.57 (d, 1H), 4.29 (d, 1H), 4.22 (d, 1H), 3.85 – 3.73 (m, 1H), 3.70 (d, 2H), 3.58 – 3.39 (m, 2H), 3.26 (t, 1H), 2.89 (s, 3H), 2.39 – 2.21 (m, 1H), 2.03 (dp, 1H), 1.86 (d, 1H), 1.02 (d, 6H); LC-MS: 446.3 $[M+H]^+$.

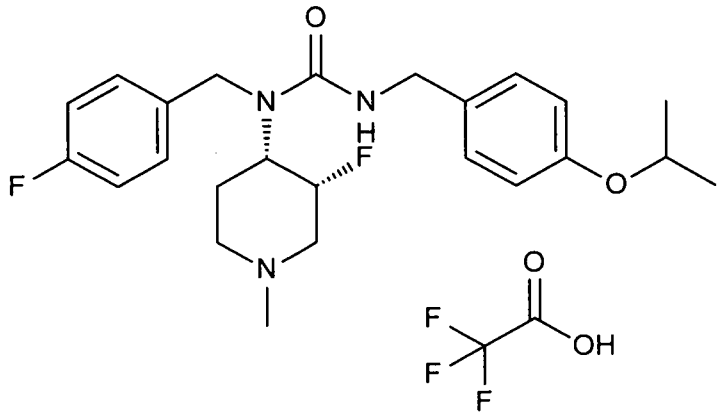
[00732] Example 118: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea (118a) and 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea (118b)



[00733] The compounds were prepared in analogy with example 117 using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 5% methanol in dichloromethane to afford the title compounds free bases. The compounds were isolated as a racemic mixture. Yield: 55%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.22 – 7.13 (m, 2H), 7.05 – 6.92 (m, 4H), 6.77 (d, J = 8.5 Hz, 2H), 4.92 (d, J = 50.2 Hz, 1H), 4.67 – 4.41 (m, 4H), 4.32 – 4.17 (m, 2H), 3.68 (d, J = 6.5 Hz, 2H), 3.15 (t, J = 12.1 Hz, 1H), 2.94 (d, J = 7.6 Hz, 1H), 2.36 – 2.12 (m, 6H), 2.06 (dq, J = 13.1, 6.6 Hz, 1H), 1.67 – 1.54 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 446.3 $[M+H]^+$.

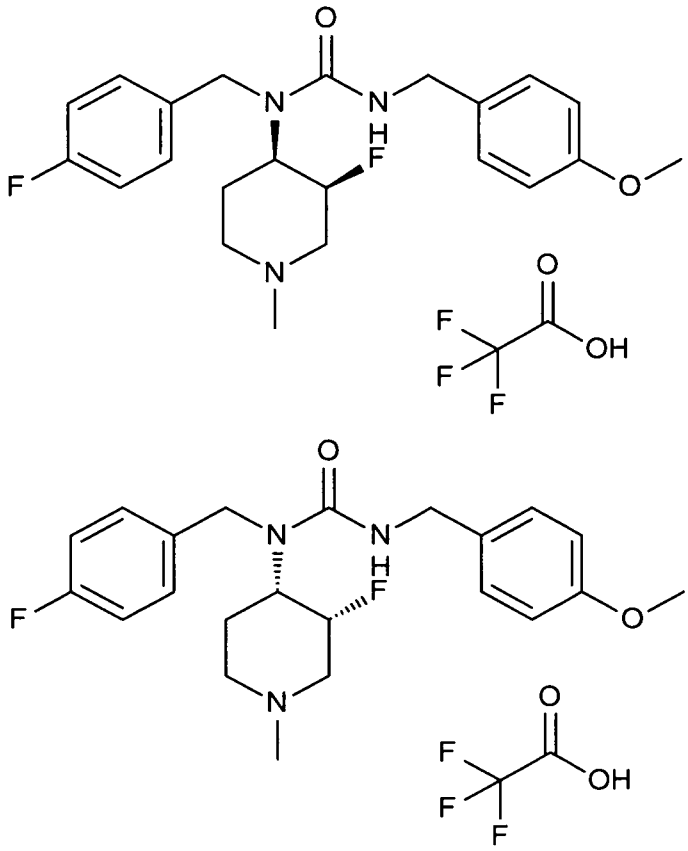
[00734] Example 119: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (119a) and 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (119b)





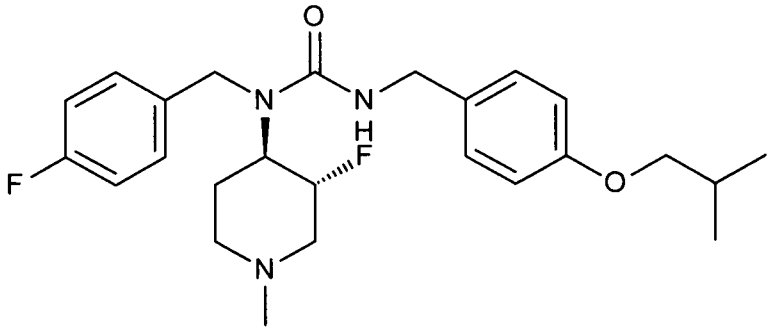
[00735] The compounds were prepared in analogy with example 1 using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene. The compounds were isolated as a racemic mixture. Yield: 48%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.15 (s, 2H), 7.02 (t, J = 8.5 Hz, 2H), 6.93 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 5.10 (d, J = 48.2 Hz, 1H), 4.95 – 4.75 (m, 1H), 4.72 (s, 1H), 4.59 – 4.40 (m, 3H), 4.32 – 4.15 (m, 2H), 3.95 – 3.76 (m, 2H), 3.03 (dd, J = 36.9, 13.3 Hz, 1H), 2.95 – 2.78 (m, 4H), 2.68 – 2.47 (m, 1H), 1.83 (d, J = 12.1 Hz, 1H), 1.32 (d, J = 6.0 Hz, 6H); LC-MS: 432.3 $[M+H]^+$.

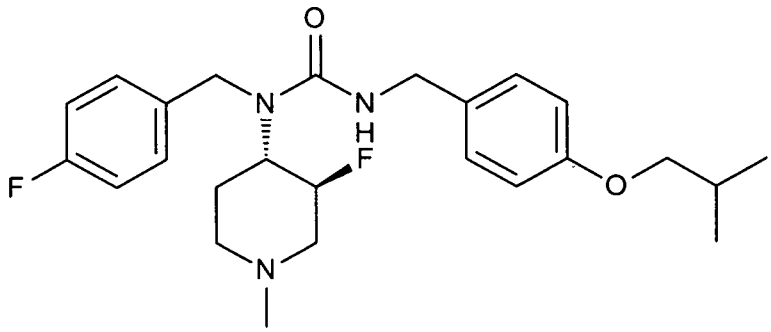
[00736] Example 120: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]urea; trifluoroacetic acid (120a) and 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]urea; trifluoroacetic acid (120b)



[00737] The compounds were prepared in analogy with example 117 using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-methoxybenzene. The compounds were isolated as a racemic mixture. Yield: 49%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.20 – 7.09 (m, 2H), 7.02 (t, J = 8.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.10 (d, J = 48.2 Hz, 1H), 4.85 (dd, J = 32.5, 11.6 Hz, 1H), 4.74 (s, 1H), 4.54 (d, J = 18.4 Hz, 1H), 4.46 (d, J = 18.4 Hz, 1H), 4.32 – 4.12 (m, 2H), 3.99 – 3.79 (m, 2H), 3.78 (s, 3H), 3.04 (dd, J = 37.4, 13.7 Hz, 1H), 2.96 – 2.81 (m, 4H), 2.72 – 2.50 (m, 1H), 1.83 (d, J = 13.3 Hz, 1H); LC-MS: 404.1 $[M+H]^+$.

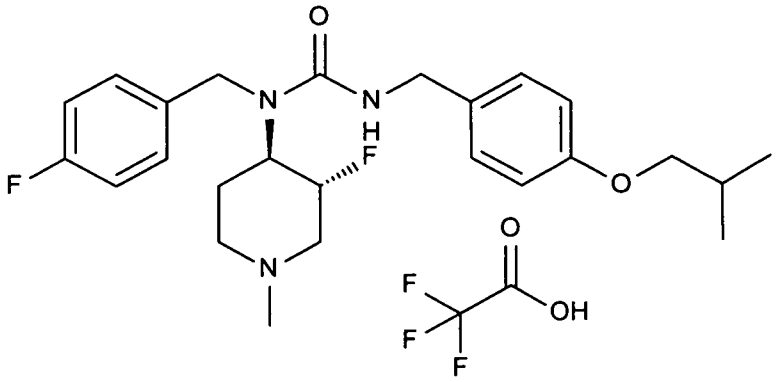
[00738] Example 121: 3-[(3R,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea (121a) and 3-[(3S,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea (121b)





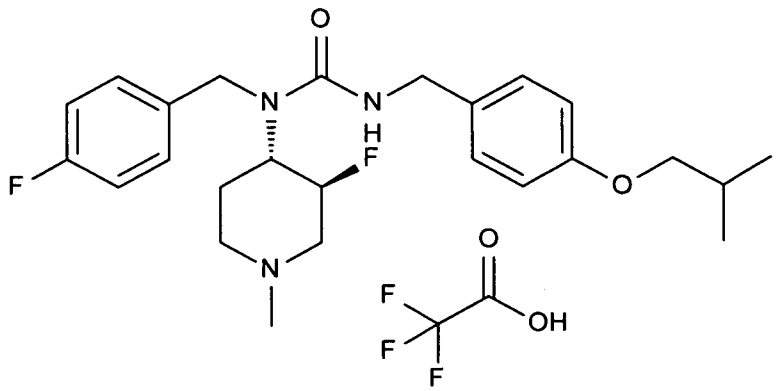
[00739] The compounds were prepared in analogy with example 117 using tert-butyl (3R,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. The title compounds were purified by column chromatography using silicon dioxide gel, eluting with 0-10% methanol in dichloromethane. The compounds were isolated as a racemic mixture. Yield: 36%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.30 – 7.22 (m, 2H), 7.08 – 6.95 (m, 4H), 6.79 (d, J = 8.6 Hz, 2H), 4.64 – 4.34 (m, 5H), 4.29 (d, J = 5.3 Hz, 2H), 3.69 (d, J = 6.6 Hz, 2H), 3.25 – 3.14 (m, 1H), 2.78 (d, J = 10.2 Hz, 1H), 2.31 (s, 3H), 2.19 – 2.01 (m, 3H), 1.90 – 1.62 (m, 2H), 1.02 (d, J = 6.7 Hz, 6H).; LC-MS: 446.3 $[M+H]^+$.

[00740] Example 122: 3-[(3R,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (122)



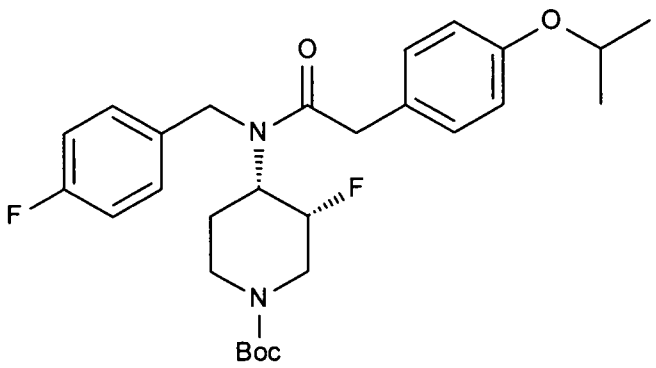
and

[00741] Example 123: 3-[(3S,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (123)



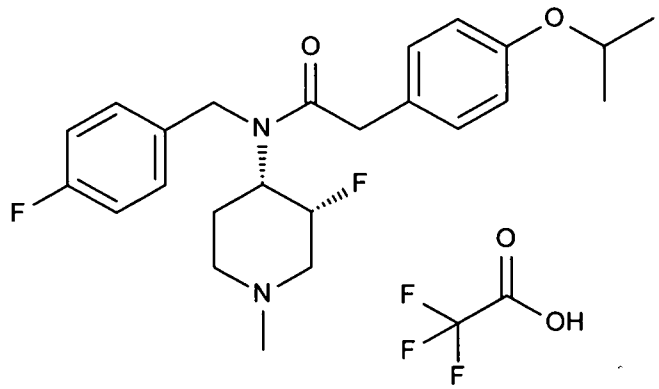
[00742] The compounds (122) and (123) were purified from example 121 by chiral chromatography using a Daicel IA column eluting with 15% methanol in 2-methoxy-2-methylpropane to afford the faster eluting enantiomer (5.4 mg, 40%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.17 (m, 2H), 7.07 – 6.99 (m, 2H), 6.97 – 6.90 (m, 2H), 6.81 – 6.71 (m, 2H), 5.16 – 4.94 (m, 2H), 4.73 (bs, 1H), 4.41 (q, 2H), 4.26 (d, 2H), 3.85 – 3.77 (m, 1H), 3.68 (d, 2H), 3.61 – 3.51 (m, 1H), 2.98 – 2.82 (m, 5H), 2.35 – 2.18 (m, 1H), 2.13 – 1.97 (m, 2H), 1.01 (d, 6H). LC-MS: 446.3 $[M+H]^+$ and the slower eluting enantiomer (5.5 mg, 41%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.24 – 7.18 (m, 2H), 7.06 – 6.98 (m, 2H), 6.97 – 6.89 (m, 2H), 6.80 – 6.73 (m, 2H), 5.24 – 4.98 (m, 2H), 4.71 (bs, 1H), 4.53 – 4.33 (m, 2H), 4.26 (d, 2H), 3.84 – 3.75 (m, 1H), 3.68 (d, 2H), 3.60 – 3.51 (m, 1H), 2.99 – 2.83 (m, 5H), 2.43 – 2.25 (m, 1H), 2.12 – 1.99 (m, 2H), 1.01 (d, 6H). LC-MS: 446.3 $[M+H]^+$.Example 124: N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (124)

[00743] tert-Butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}piperidine-1-carboxylate



[00744] 2-[4-(Propan-2-yloxy)phenyl]acetyl chloride (22.7 mg, 107 μmol) in dichloromethane (0.5 ml) was added to tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (29.0 mg, 88.9 μmol) and diisopropylethylamine (23 μl, 133 μmol) in dichloromethane (0.5 ml). After 2 hours of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 10-50% ethyl acetate in petroleum ether to afford the desired amide (39.8 mg, 89%).

[00745] N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid

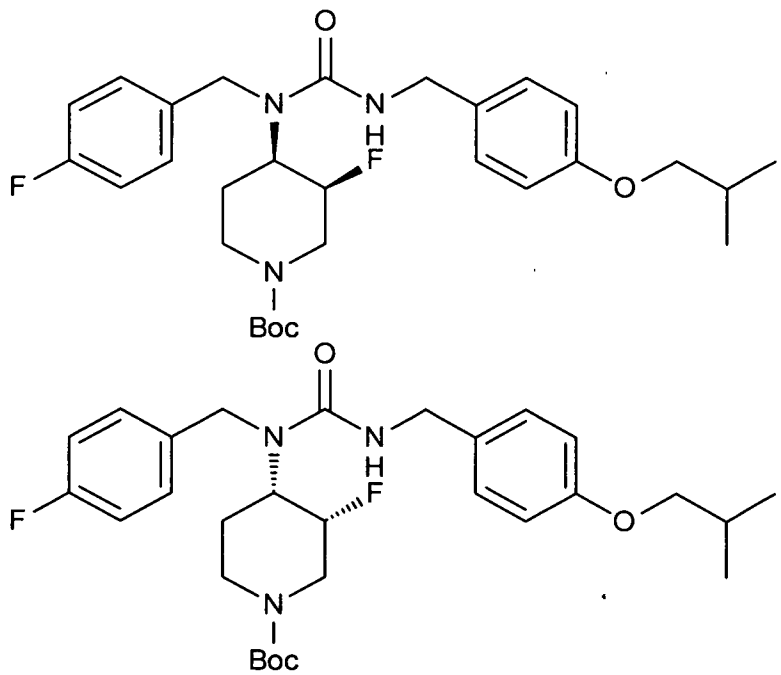


[00746] tert-Butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}piperidine-1-carboxylate (39.8 mg) was dissolved in dichloromethane (1.5 ml) and trifluoroacetic acid (0.5 ml) was added. After 45 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofuran (1.5 ml). Formaldehyde (37% aqueous, 8.8 μl, 119 μmol) and sodium cyanoborohydride (10.0 mg, 158 μmol) were added. After 15 hours, the mixture was

concentrated and re-dissolved in methanol (1 ml). The resulting mixture was heated to reflux for 2 hours before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with 30-55% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (23 mg 55%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.18 – 7.11 (m, 2H), 7.07 (t, J = 8.5 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.04 (d, J = 48.0 Hz, 1H), 4.88 (dd, J = 32.2, 11.2 Hz, 1H), 4.77 (d, J = 18.5 Hz, 1H), 4.61 (d, J = 18.4 Hz, 1H), 4.51 (hept, J = 6.2 Hz, 1H), 3.93 – 3.74 (m, 1H), 3.74 – 3.62 (m, 1H), 3.59 (s, 2H), 3.17 – 2.92 (m, 1H), 2.92 – 2.65 (m, 4H), 2.60 – 2.41 (m, 1H), 1.66 (d, J = 12.8 Hz, 1H), 1.32 (d, J = 6.1 Hz, 6H); LC-MS: 417.2 $[M+H]^+$.

[00747] Example 125a: 3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (125a) and 3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (125b)

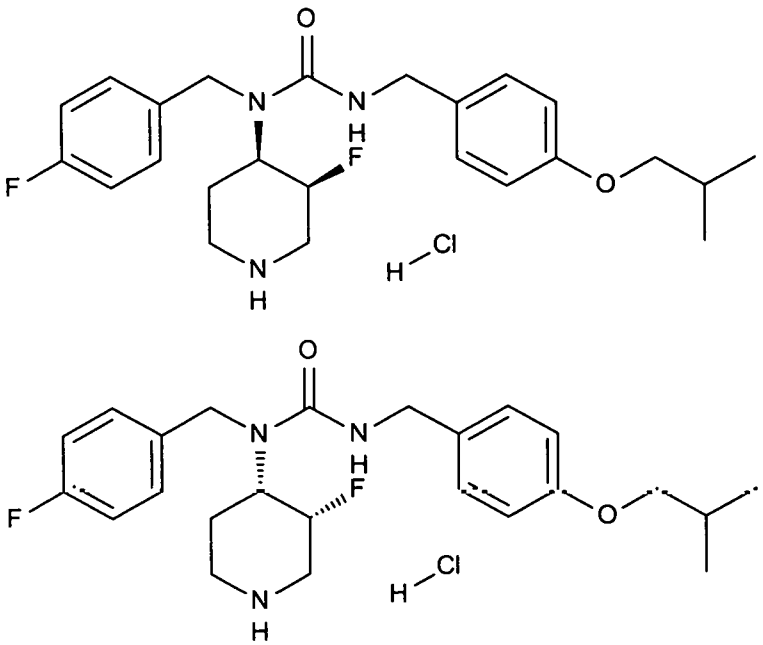
[00748] tert-Butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate



[00749] 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (377 mg, 1.84 mmol) in dichloromethane (5 ml) was added to tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-

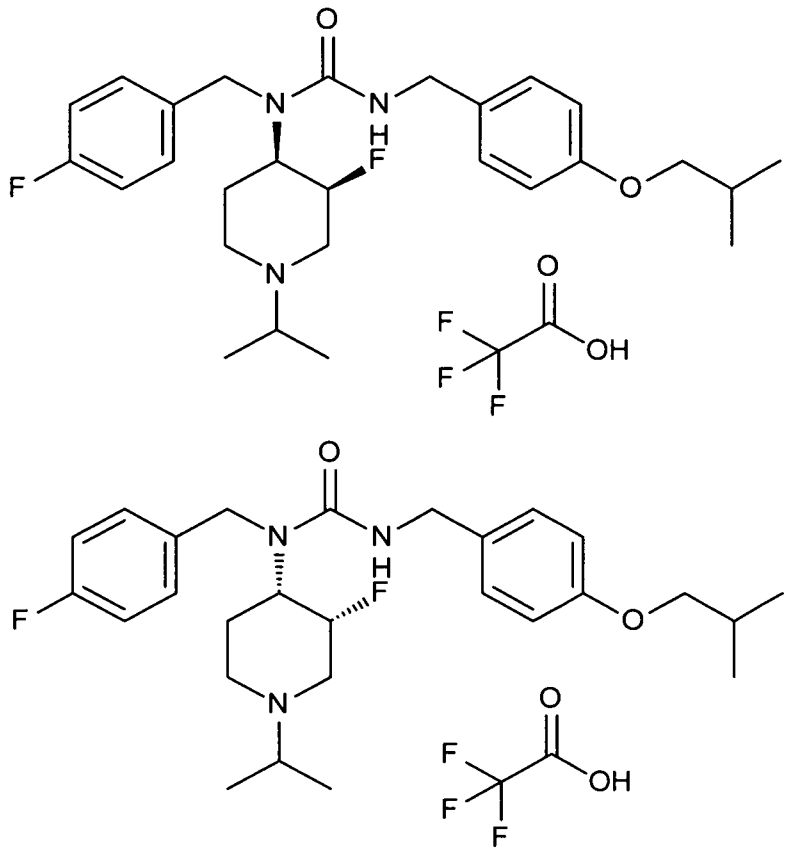
fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1, 500 mg, 1.53 mmol). After 90 minutes of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 25-50% ethyl acetate in petroleum ether to afford the desired urea (834 mg), as a racemic mixture.

[00750] 3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride and 3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride



[00751] Hydrochloric acid (2M, 2 ml, 4 mmol) was added to tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate (1:1, 834 mg). After 18 hours of stirring at ambient temperature additional hydrochloric acid (2M, 1 ml, 2 mmol) was added and the mixture was stirred for 8 hours before it was concentrated to give the desired ammonium salt (654 mg), as a racemic mixture.

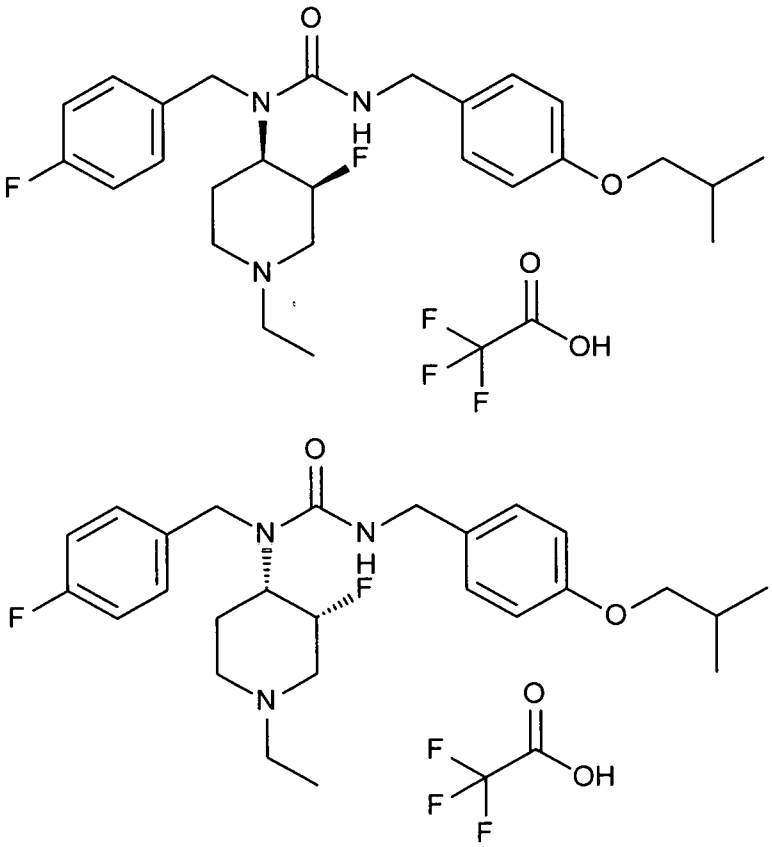
[00752] Example 125b: 3-[(3R,4S)-3-fluoro-1-(propan-2-yl)piperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (125c) and 3-[(3S,4R)-3-fluoro-1-(propan-2-yl)piperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (125d)



[00753] Acetone (15.7 µl, 214 µmol) and sodium triacetoxyborohydride (45.3 mg, 214 µmol) were added to 3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride and 3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (1:1, 50 mg, 107 µmol) in tetrahydrofuran (1 ml). The resulting suspension was diluted with ethanol (1 ml). After 6 hours of stirring at ambient temperature, more sodium triacetoxyborohydride (45.3 mg, 214 µmol) was added. After additionally 17 hours, sodium cyanoborohydride (13.4 mg, 214 µmol) was added and the resulting mixture was stirred for 23 hours and then concentrated. Sodium hydroxide (aqueous, 1M, 1 ml) was added and the mixture was extracted with dichloromethane (3 x 1 ml). The organic phase was dried (phase-separator) and concentrated. The crude material was purified by HPLC, eluting with 20-40% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compounds (44.4 mg 71%), as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.20 – 7.10 (m, 2H), 7.01 (t, J = 8.5 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 5.14 (d, J = 47.8 Hz, 1H), 4.87 – 4.65 (m, 2H), 4.55 (d, J = 18.4 Hz, 1H), 4.45 (d, J = 18.3 Hz, 1H), 4.26 (tt, J = 14.6, 7.5 Hz, 2H), 3.76 – 3.64 (m, 5H), 3.02 (dd, J = 38.1, 13.6 Hz, 1H), 2.89 (t, J = 11.9

Hz, 1H), 2.79 – 2.62 (m, 1H), 2.07 (dp, J = 13.0, 6.6 Hz, 1H), 1.82 (d, J = 12.5 Hz, 1H), 1.36 (t, J = 6.0 Hz, 6H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 474.3 $[M+H]^+$.

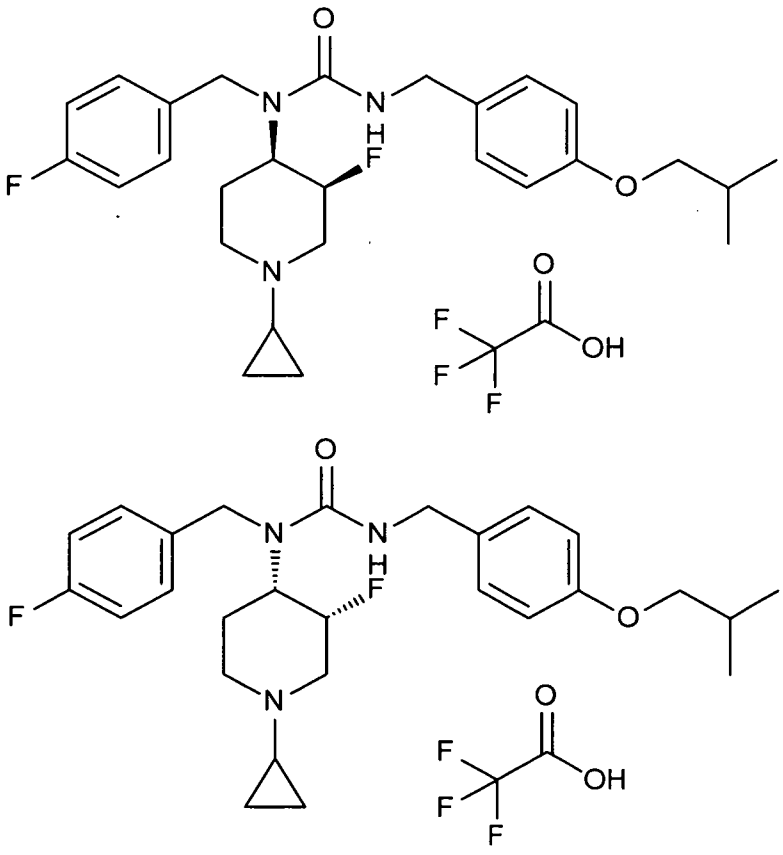
[00754] Example 126: 3-[(3R,4S)-1-ethyl-3-fluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (126a) and 3-[(3S,4R)-1-ethyl-3-fluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (126b)



[00755] Ethanol (1 ml) was added to Dess-Martin periodinane (90.6 mg, 214 μmol). After 30 minutes of stirring at ambient temperature, sodium triacetoxyborohydride (45.3 mg, 214 μmol) and 3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride and 3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (1:1, 50 mg, 107 μmol) were added. The mixture was stirred for 45 minutes, then it was diluted with ethyl acetate, filtered through a plug of Celite and concentrated. The crude material was purified by HPLC, eluting with 20-50% acetonitrile in water (containing 0.1% trifluoroacetic acid). Fractions containing product were concentrated. The material was suspended in sodium hydroxide (aqueous, 1M, 5 ml), extracted with dichloromethane (3 x 5 ml) and dried (phase-separator). Trifluoroacetic acid (50 μl) was added and the mixture was

concentrated to afford the title compounds (46.1 mg 75%), as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-d) δ 9.58 (bs, 1H), 7.22 – 7.10 (m, 2H), 7.02 (t, J = 8.3 Hz, 2H), 6.93 (d, J = 8.2 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.11 (d, J = 47.9 Hz, 1H), 4.99 – 4.74 (m, 2H), 4.53 (d, J = 18.4 Hz, 1H), 4.46 (d, J = 18.3 Hz, 1H), 4.33 – 4.16 (m, 2H), 3.99 – 3.82 (m, 2H), 3.69 (d, J = 6.5 Hz, 2H), 3.22 (tq, J = 13.0, 6.8 Hz, 2H), 3.04 (dd, J =37.5, 13.5 Hz, 1H), 2.87 (t, J = 12.0 Hz, 1H), 2.71 – 2.54 (m, 1H), 2.07 (dp, J = 13.6, 6.7 Hz, 1H), 1.85 (d, J = 13.2 Hz, 1H), 1.38 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 460.3 $[M+H]^+$.

[00756] Example 127: 3-[(3R,4S)-1-cyclopropyl-3-fluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (127a) and 3-[(3S,4R)-1-cyclopropyl-3-fluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (127b)

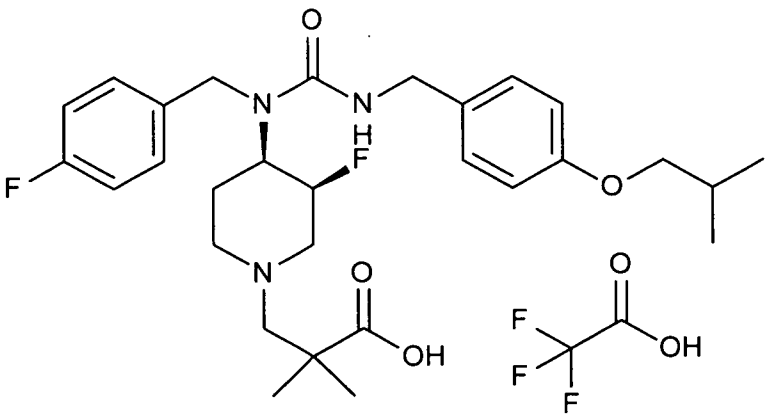


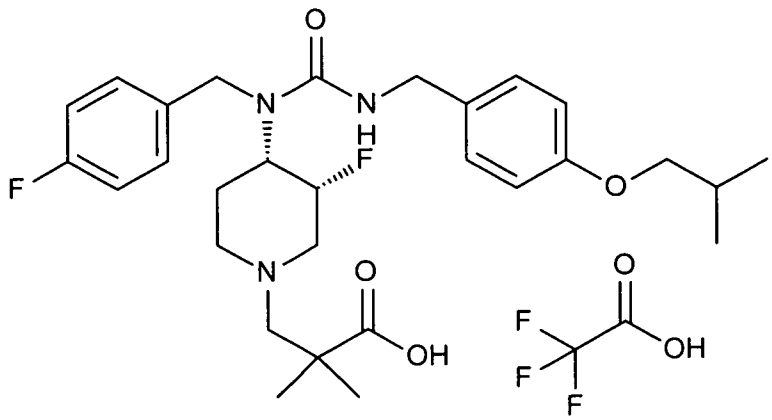
[00757] (1-Ethoxycyclopropoxy)trimethylsilane (35 µl, 174 µmol) and sodium cyanoborohydride (14.5 mg, 232 µmol) were added to 3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride and 3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (1:1, 50 mg, 107 µmol) in methanol (0.5 ml) and acetic acid (7.5 µl). The mixture was stirred at ambient temperature for 45 minutes

and then heated to 50 °C. After 8 hours, the mixture was cooled to ambient temperature and diluted with sodium hydrogen carbonate (aqueous, saturated, 10 ml). The mixture was extracted with dichloromethane (3 x 10 ml). The organic phase was dried (phase-separator) and concentrated. The crude material was purified by HPLC, eluting with 25-85% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compounds (56 mg 80%), as a racemic mixture.: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 – 7.08 (m, 2H), 7.01 (t, J = 8.5 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 5.10 (d, J = 48.4 Hz, 1H), 4.93 – 4.68 (m, 2H), 4.56 – 4.38 (m, 2H), 4.32 – 4.15 (m, 2H), 3.91 – 3.70 (m, 2H), 3.68 (d, J = 6.5 Hz, 2H), 3.45 – 3.05 (m, 2H), 2.70 – 2.54 (m, 1H), 2.06 (dp, J = 13.3, 6.6 Hz, 1H), 1.80 (d, J = 13.5 Hz, 1H), 1.44 – 1.23 (m, 2H), 1.01 (d, J = 6.7 Hz, 6H), 0.83 (d, J = 7.1 Hz, 2H); LC-MS: 472.3 $[M+H]^+$.

[00758]

[00759] Example 128: 3-[(3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methyl-propoxy)phenyl]methyl}carbamoyl)amino}piperidin-1-yl]-2,2-dimethylpropanoic acid; trifluoroacetic acid (128a) and 3-[(3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidin-1-yl]-2,2-dimethylpropanoic acid; trifluoroacetic acid (128b)

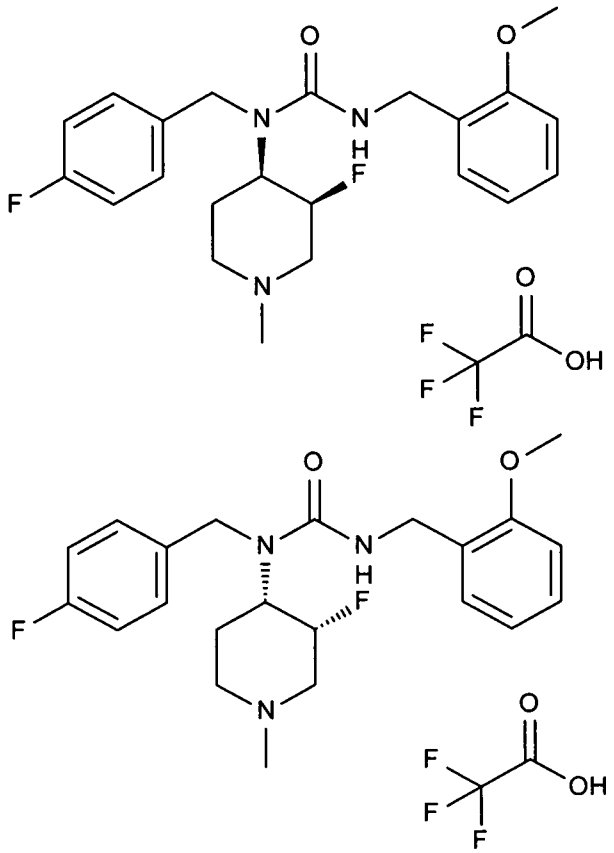




[00760] Mixture A: Methyl 2,2-dimethyl-3-oxopropanoate (9.0 mg, 69.5 μmol) and sodium triacetoxyborohydride (14.7 mg, 69.5 μmol) were added to 3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride and 3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (1:1, 50 mg, 107 μmol) in tetrahydrofuran.

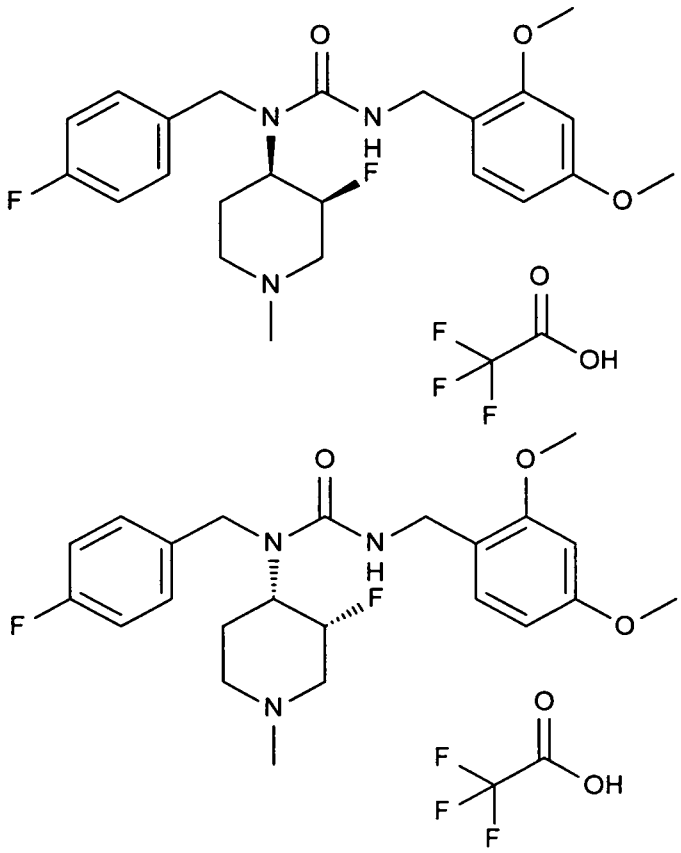
[00761] Mixture B: Methyl 2,2-dimethyl-3-oxopropanoate (9.0 mg, 69.5 μmol) and sodium triacetoxyborohydride (14.7 mg, 69.5 μmol) were added to 3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride and 3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (1:1, 50 mg, 107 μmol) in dichloromethane. After 4 hours, mixture A and B were pooled and water (5 ml) was added. The resulting mixture was extracted with dichloromethane (3 x 5 ml), dried (phase-separator) and concentrated. The crude material was filtered through a plug of silicon dioxide gel, eluting with 50% ethyl acetate in petroleum ether to afford the desired intermediate (24.1 mg, 95%). Methanol (4 ml), water (4 ml) and lithium hydroxide (19.6 mg, 833μmol) were added. After 80 minutes, tetrahydrofuran (4 ml) was added. The resulting solution was stirred at ambient temperature for 24 hours and then neutralized with hydrochloric acid (1M, 1 ml, 1 mmol) and concentrated. The crude material was purified by HPLC, eluting with 20-85% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compounds (14.9 mg 52%), as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.16 (dd, J = 8.6, 5.2 Hz, 2H), 7.02 (t, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 5.14 – 4.92 (m, 2H), 4.79 (s, 1H), 4.56 (d, J = 18.4 Hz, 1H), 4.47 (d, J = 18.2 Hz, 1H), 4.31 – 4.18 (m, 2H), 3.68 (d, J = 6.5 Hz, 2H), 3.66 – 3.54 (m, 2H), 3.44 – 3.18 (m, 3H), 3.17 – 3.00 (m, 1H), 2.64 – 2.41 (m, 1H), 2.07 (dp, J = 13.4, 6.7 Hz, 1H), 1.77 (d, J = 13.6 Hz, 1H), 1.37 (s, 3H), 1.33 (s, 3H), 1.02 (d, J = 6.7 Hz, 6H); LC-MS: 532.3 $[M+H]^+$.

[00762] Example 129: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluoro-phenyl)methyl]-1-[(2-methoxyphenyl)methyl]urea; trifluoroacetic acid (129a) and 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl)methyl]urea; trifluoroacetic acid (129b)



[00763] (2-Methoxyphenyl)methanamine (13.6 µl, 104 µmol) and triethylamine (35 µl, 250 µmol) in dichloromethane were added to diphosgene (6 µl, 50 µmol) in dichloromethane (0.5 ml), using a syringe pump (0.5 ml/hour). The mixture was stirred for additionally 1 hour at ambient temperature before (3R,4S)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (1:1, 20 mg, 83 µmol) in dichloromethane (0.5) ml was added. After 24 hours, the mixture was washed with water (1.5 ml). The aqueous phase was extracted with dichloromethane (1.5 ml). The combined organic phase was dried (phase-separator) and concentrated. The crude material was purified by HPLC, eluting with 20-85% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compounds (24.6 mg 46%), as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.23 (td, J = 8.1, 1.7 Hz, 1H), 7.16 – 7.05 (m, 3H), 7.00 (t, J = 8.5 Hz, 2H), 6.91 – 6.82 (m, 1H), 6.75 (d, J = 8.1 Hz, 1H), 5.21 (s, 1H), 5.06 (d, J = 47.4 Hz, 1H), 4.80 (dd, J = 33.5, 10.5 Hz, 1H), 4.52 (d, J = 18.4 Hz, 1H), 4.45 (d, J = 18.5 Hz, 1H), 4.28 (qd, J = 14.3, 5.6 Hz, 2H), 3.91 – 3.71 (m, 2H), 3.49 (s, 3H), 3.03 (dd, J = 37.5, 13.8 Hz, 1H), 2.94 – 2.76 (m, 4H), 2.63 – 2.44 (m, 1H), 1.78 (d, J = 14.1 Hz, 1H); LC-MS: 404.3 $[M+H]^+$.

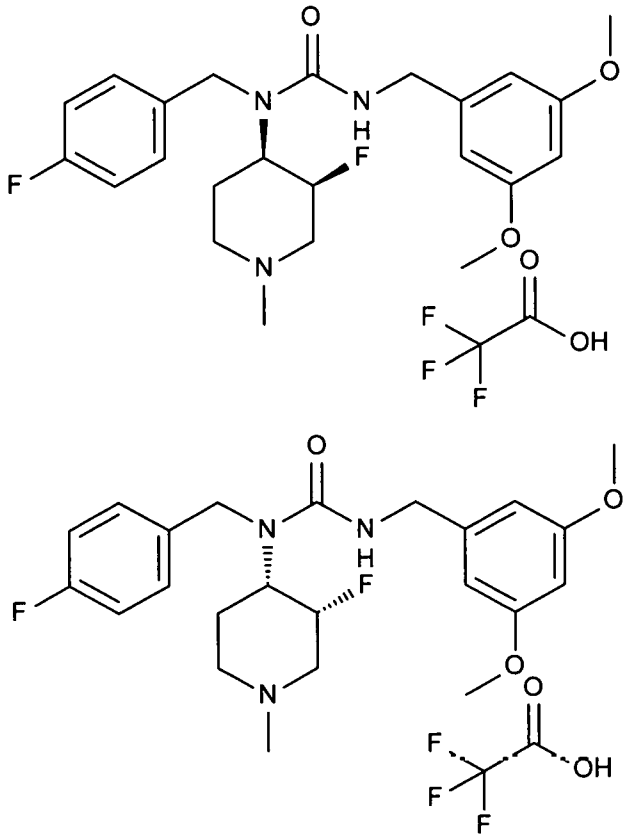
[00764] Example 130: 1-[(2,4-dimethoxyphenyl)methyl]-3-[(3R,4S)-3-fluoro-1-methyl-piperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (130a) and 1-[(2,4-dimethoxyphenyl)methyl]-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (130b)



[00765] The compounds were prepared in analogy with example 129 using (3R,4S)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (1:1) and (2,4-dimethoxyphenyl)methanamine. The compounds were isolated as a racemic mixture. Yield: 31.3 mg, 55%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.18 – 7.08 (m, 2H), 7.05 (d, J = 8.2 Hz, 1H), 7.00 (t, J = 8.5 Hz, 2H), 6.38 (dd, J = 8.2, 2.3 Hz, 1H), 6.32 (d, J = 2.3 Hz, 1H), 5.17 – 4.95 (m, 2H), 4.79 (dd, J = 33.1, 11.0 Hz, 1H), 4.51 (d, J = 18.3 Hz, 1H), 4.43 (d, J = 18.5 Hz, 1H), 4.20 (qd, J = 14.2, 5.5 Hz, 2H), 3.91 – 3.72 (m, 5H), 3.45 (s, 3H), 3.03 (dd, J = 37.4, 13.4 Hz, 1H), 2.94 – 2.75 (m, 4H), 2.63 – 2.45 (m, 1H), 1.77 (d, J = 12.9 Hz, 1H); LC-MS: 434.3 $[M+H]^+$.

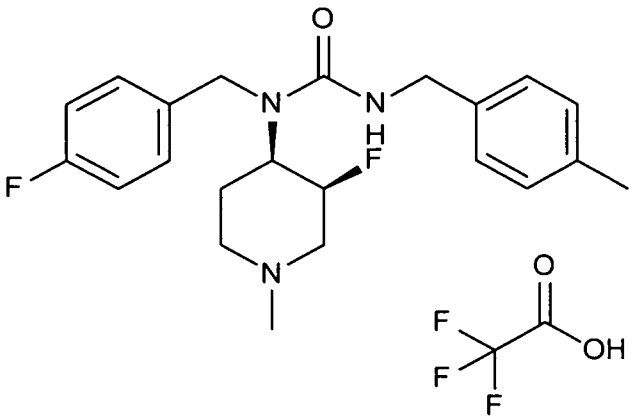
[00766] Example 131: 1-[(3,5-dimethoxyphenyl)methyl]-3-[(3R,4S)-3-fluoro-1-methyl-piperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (131a) and 1-[(3,5-

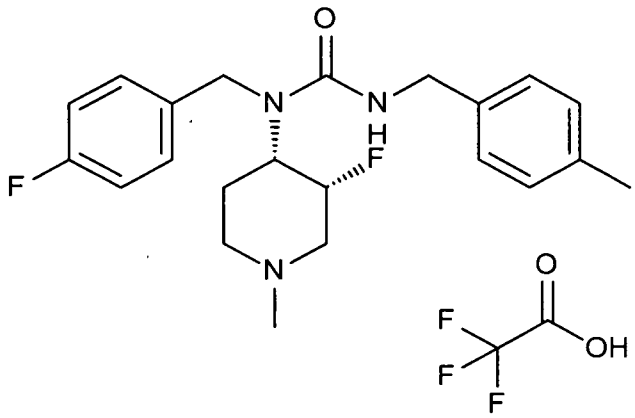
dimethoxyphenyl)methyl]-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (131b)



[00767] The compounds were prepared in analogy with example 129 using (3R,4S)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (1:1) and (3,5-dimethoxyphenyl)methanamine. The compounds were isolated as a racemic mixture. Yield: 12.1 mg, 21%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.18 (dd, J = 8.3, 5.3 Hz, 2H), 7.03 (t, J = 8.5 Hz, 2H), 6.32 (t, J = 2.2 Hz, 1H), 6.18 (d, J = 2.1 Hz, 2H), 5.09 (d, J = 47.7 Hz, 1H), 4.91 – 4.72 (m, 2H), 4.56 (d, J = 18.3 Hz, 1H), 4.48 (d, J = 18.3 Hz, 1H), 4.35 – 4.17 (m, 2H), 3.90 – 3.75 (m, 1H), 3.73 (s, 6H), 3.04 (dd, J = 38.0, 13.7 Hz, 1H), 2.96 – 2.71 (m, 4H), 2.71 – 2.47 (m, 1H), 1.83 (d, J = 12.6 Hz, 1H); LC-MS: 434.3 $[M+H]^+$.

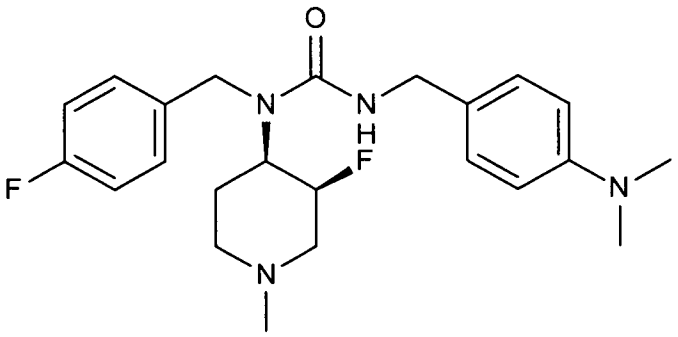
[00768] Example 132: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-[(4-methylphenyl)methyl]urea; trifluoroacetic acid (132a) and 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(4-methylphenyl)methyl]urea; trifluoroacetic acid (132b)

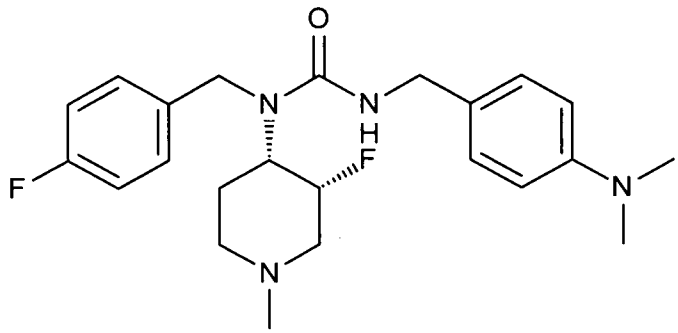




[00769] The compounds were prepared in analogy with example 129 using (3R,4S)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (1:1) and (4-methylphenyl)methanamine. The compounds were isolated as a racemic mixture. Yield: 32.0 mg, 61%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.16 (dd, J = 8.2, 5.3 Hz, 2H), 7.10 – 6.98 (m, 4H), 6.91 (d, J = 7.9 Hz, 2H), 5.08 (d, J = 47.8 Hz, 1H), 4.94 – 4.74 (m, 2H), 4.53 (d, J = 18.3 Hz, 1H), 4.47 (d, J = 18.5 Hz, 1H), 4.35 – 4.17 (m, 2H), 3.93 – 3.82 (m, 1H), 3.81 – 3.70 (m, 1H), 3.09 (dd, J = 37.8, 13.4 Hz, 1H), 2.94 (t, J = 11.6 Hz, 1H), 2.85 (s, 3H), 2.67 – 2.48 (m, 1H), 2.31 (s, 3H), 1.82 (d, J = 13.1 Hz, 1H); LC-MS: 388.3 $[M+H]^+$.

[00770] Example 133: 1-{[4-(dimethylamino)phenyl]methyl}-3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea (133a) and 1-{[4-(dimethyl-amino)phenyl]methyl}-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]urea (133b)

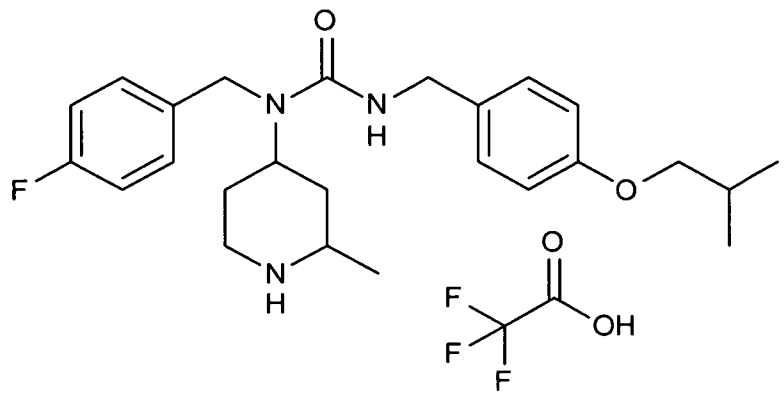




[00771] 4-(Aminomethyl)-N,N-dimethylaniline dihydrochloride (202 mg, 1 mmol) was suspended in dichloromethane (5 ml). The suspension was washed with sodium hydroxide (aqueous, 1M, 5 ml) and dried (phase-separator). Triethylamine (278 µl, 2 mmol) was added and the resulting mixture was added to diphosgene (121 µl, 1 mmol) in dichloromethane (5 ml). After stirring at ambient temperature for 1 hour the mixture was washed with water (10 ml), dried (phase-separator) and concentrated to afford the intermediate isocyanate (139 mg, 73%).

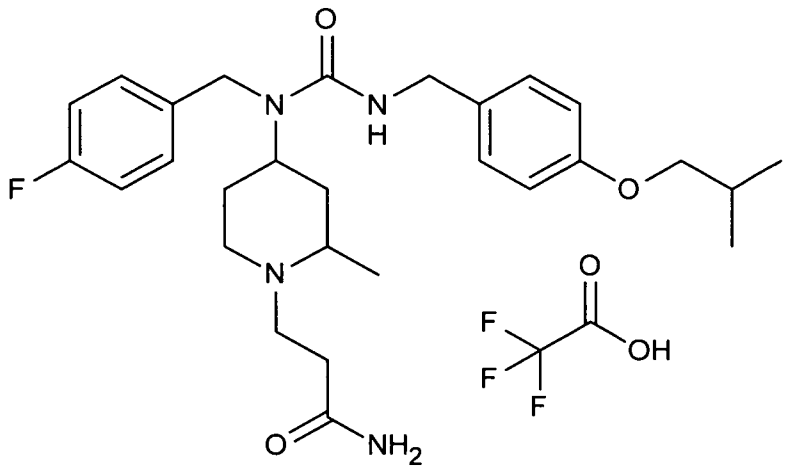
[00772] (3R,4S)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (1:1, 20 mg, 83 µmol) in dichloromethane (0.5) ml was added to 17.6 mg of the intermediate isocyanate. After 1 hour, the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 0-10% methanol in dichloromethane to afford the title compounds (20.6 mg, 50%), as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 (dd, J = 8.6, 5.3 Hz, 2H), 6.99 (t, J = 8.6 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 4.92 (d, J = 51.2 Hz, 1H), 4.65 – 4.39 (m, 4H), 4.23 (d, J = 5.2 Hz, 2H), 3.22 – 3.09 (m, 1H), 2.91 (s, 7H), 2.37 – 2.08 (m, 6H), 1.64 – 1.54 (m, 1H); LC-MS: 417.2 $[M+H]^+$.

[00773] Example 134: 3-[(4-fluorophenyl)methyl]-3-(2-methylpiperidin-4-yl)-1-{[4-(2-methylpropoxy)phenyl]-methyl}urea; trifluoroacetic acid (134)



[00774] The compound was prepared in analogy with example 124 using tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-2-methylpiperidine-1-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Yield: 46%. ^{1}H NMR (400 MHz, Methanol-d_3) δ 7.25 – 7.18 (m, 2H), 7.08 – 6.95 (m, 4H), 6.82 – 6.77 (m, 2H), 4.48 (s, 2H), 4.35 – 4.27 (m, 1H), 4.25 (s, 2H), 3.73 (d, 2H), 3.40 – 3.30 (m, 1H), 3.27 – 3.20 (m, 1H), 3.08 – 2.98 (m, 1H), 2.07 – 2.00 (m, 1H), 2.00 – 1.82 (m, 3H), 1.75 – 1.65 (m, 1H), 1.30 (d, 3H), 1.02 (d, 6H). LC-MS: 428.3 $[M+H]^+$.

[00775] Example 135: 3-(4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}-2-methylpiperidin-1-yl)propanamide; trifluoroacetic acid (135)

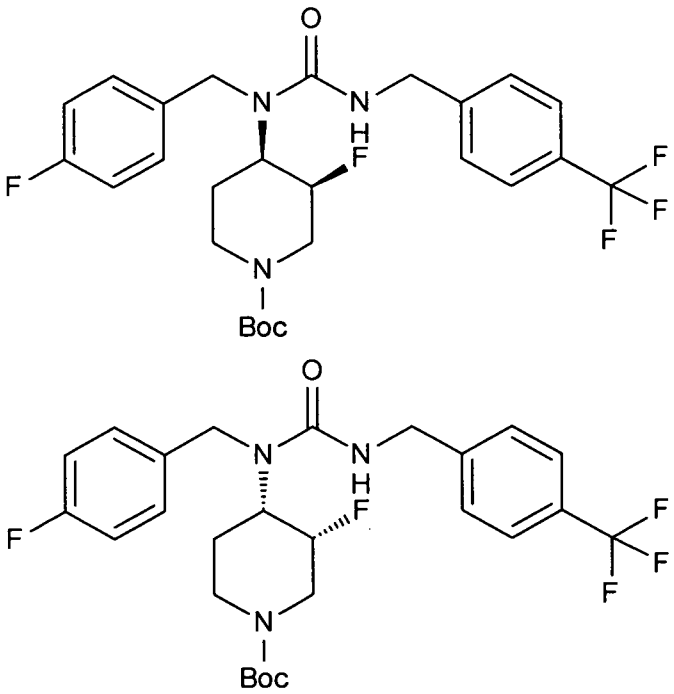


[00776] 3-[(4-fluorophenyl)methyl]-3-(2-methylpiperidin-4-yl)-1-{[4-(2-methylpropoxy)-phenyl]-methyl}urea; trifluoroacetic acid (31.5 mg, 0.058 mmol), acrylamide (5.5 mg, 0.77 mmol) and silicon dioxide (36 mg) were mixed in dry acetonitrile (1.5 ml). The reaction was heated to reflux overnight. The acetonitrile was evaporated and the crude was purified by

column chromatography using silicon dioxide gel, eluting with 5-11% methanol in dichloromethane. The collected fractions were further purified by HPLC, eluting with 40-90% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (9.4 mg, 26%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.20 – 7.10 (m, 2H), 7.08 – 6.95 (m, 4H), 6.9 (bs, 1H),6.80 – 6.72 (m, 2H), 5.65 (bs, 1H), 4.80 – 4.70 (m, 1H), 4.62 (bs, 1H), 4.32 (s, 2H), 4.23 (s, 2H), 3.73 (d, 2H), 3.70 – 3.62 (m, 2H), 3.20 – 3.10 (m, 2H), 2.95 – 2.85 (m, 1H), 2.83 – 2.71 (m, 2H), 2.20 – 2.02 (m, 3H), 2.00 – 2.92 (m, 1H), 2.92 – 2.84 (m, 1H), 1.48 (d, 3H), 1.02 (d, 6H). LC-MS: 499.4 $[M+H]^+$.

[00777] Example 136: 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-{[4-(trifluoromethyl)phenyl]methyl}urea; trifluoroacetic acid (136a) and 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(trifluoromethyl)phenyl]methyl}urea; trifluoroacetic acid (136b)

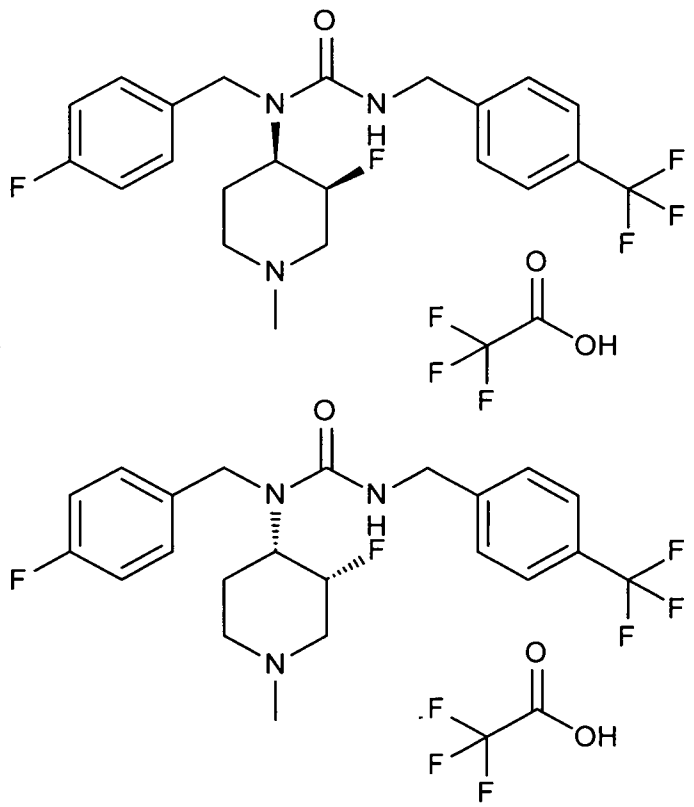
[00778] tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(trifluoromethyl)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(trifluoromethyl)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate



[00779] A mixture of [4-(trifluoromethyl)phenyl]methanamine (54.5 µl, 383 µmol) and triethylamine (128 µl) in dry dichloromethane (2 ml) was slowly injected via the syringe pump directly into a solution of diphosgene (24 µl, 199 µmol) in dry dichloromethane (1 ml) over the period of 1 hour. The resulting mixture was stirred at ambient temperature for 1 hour

before a solution of 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, 100 mg, 306 μmol) in dry dichloromethane (1 ml) was added dropwise over 5 minutes. The mixture was left stirring overnight, washed with water (5 ml) and the aqueous phase was extracted with dichloromethane (3 x 5 ml). Combined organic extracts were passed through the phase separator, concentrated and purified by column chromatography using silicon dioxide gel, eluting with 30% ethyl acetate in petroleum ether to afford of the desired ureas (0.13g, 72%) as the racemic mixture.

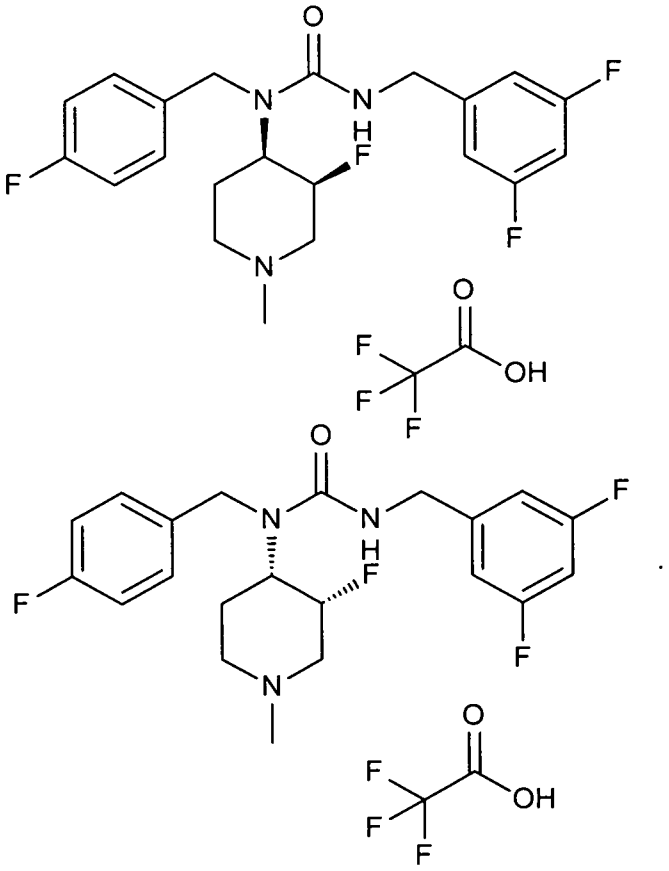
[00780] 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(trifluoromethyl)phenyl]methyl}urea; trifluoroacetic acid and 3-[(3R,4S)-3-fluoro-1-methyl-piperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(trifluoromethyl)phenyl]methyl}urea; trifluoroacetic acid



[00781] tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(trifluoromethyl)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(trifluoromethyl)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate (1:1, 130.0 mg, 222 μmol) was dissolved in dichloromethane (10 ml) and trifluoroacetic acid (1 ml) was added. After stirring for 3 hours at ambient temperature the

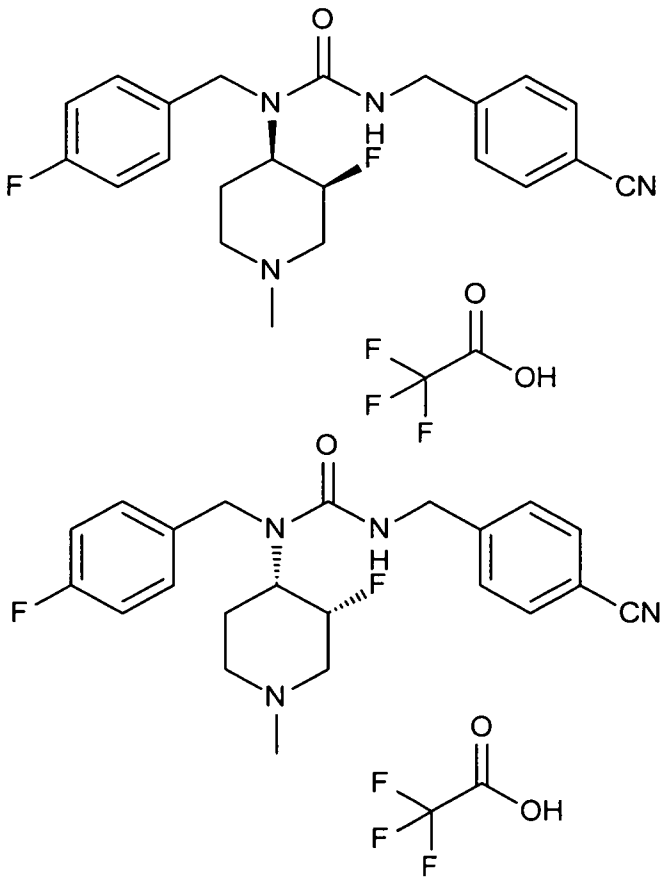
mixture was concentrated and re-dissolved in tetrahydrofuran (1 ml). Formaldehyde (37% aqueous, 31.5 µl, 423.0 µmol) and sodium cyanoborohydride (42 mg, 634 µmol) were added. The resulting mixture was stirred for 3 hours before it was diluted with sodium hydrogen carbonate (aq. sat. 5 ml) and extracted with dichloromethane (2 x 15 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 30-75% acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds as a racemic mixture. Yield: 65 mg, 70%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.53 (d, J = 8.0 Hz, 2H), 7.22 – 7.12 (m, 4H), 7.06 (t, J = 8.4 Hz, 2H), 5.09 (d, J = 48.4 Hz, 1H), 4.80 (d, J = 45.5 Hz, 2H), 4.56 (q, J = 18.2 Hz, 2H), 4.44 – 4.28 (m, 2H), 3.80 (s, 2H), 3.01 (s, 2H), 2.84 (s, 3H), 2.69 (s, 1H), 1.86 (s, 1H); LC-MS: 442.4 $[M+H]^+$.

[00782] Example 137: 1-[(3,5-difluorophenyl)methyl]-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (137a) and 1-[(3,5-difluorophenyl)methyl]-3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (137b)



[00783] The compounds were prepared in analogy with example 136, using 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) and (3,5-difluorophenyl)methanamine. Isolated as a racemic mixture. Yield: 40 mg, 69%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 (d, J = 5.3 Hz, 2H), 7.08 (t, J = 8.5 Hz, 2H), 6.71 – 6.62 (m, 1H), 6.55 (d, J = 6.7 Hz, 2H), 5.10 (d, J = 47.6 Hz, 1H), 4.82 (d, J = 22.6 Hz, 2H), 4.56 (q, J = 18.4 Hz, 2H), 4.43 – 4.18 (m, 2H), 3.83 (s, 2H), 3.12 – 2.79 (m, 5H), 2.71 (d, J = 10.2 Hz, 1H), 1.87 (d, J = 10.6 Hz, 1H); LC-MS: 410.4 $[M+H]^+$.

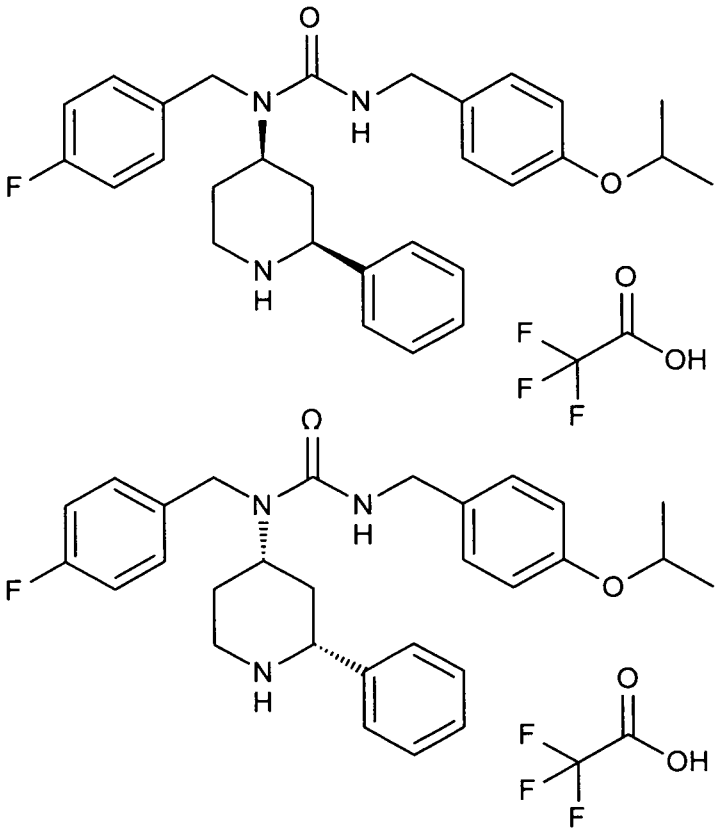
[00784] Example 138: 1-[(4-cyanophenyl)methyl]-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (138a) and 1-[(4-cyanophenyl)methyl]-3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (138b)



[00785] The compounds were prepared in analogy with example 136, using 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) and 4-(aminomethyl)benzonitrile. Isolated as a racemic mixture. Yield: 35 mg, 88%. ^{1}H NMR (400

MHz, Chloroform-d) δ 7.56 (d, J = 8.2 Hz, 2H), 7.22 – 7.13 (m, 4H), 7.07 (t, J = 8.5 Hz, 2H), 5.09 (d, J = 47.8 Hz, 1H), 4.95 (s, 1H), 4.80 (dd, J = 32.8, 10.3 Hz, 1H), 4.65 – 4.47 (m, 2H), 4.46 – 4.27 (m, 2H), 3.98 – 3.74 (m, 2H), 3.14 – 2.91 (m, 2H), 2.87 (s, 3H), 2.73 – 2.55 (m, 1H), 1.86 (d, J = 13.0 Hz, 1H); LC-MS: 399.4 $[M+H]^+$.

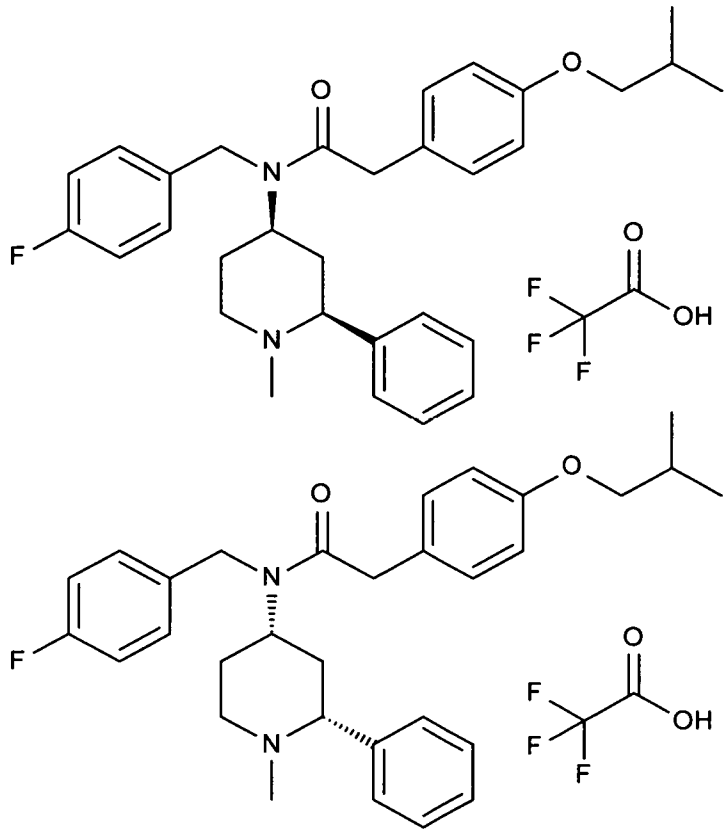
[00786] Example 139: 3-[(4-fluorophenyl)methyl]-3-[(2S,4R)-2-phenylpiperidin-4-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (139a) and 3-[(4-fluorophenyl)methyl]-3-[(2R,4S)-2-phenylpiperidin-4-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (139b)



[00787] The compounds were prepared in analogy with example 124, using tert-butyl 4-oxo-2-phenylpiperidine-1-carboxylate and 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene. Isolated as a racemic mixture. Yield: 117 mg, 63%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.28 (d, J = 11.6 Hz, 5H), 7.20 – 7.13 (m, 2H), 6.99 (dd, J = 19.6, 8.5 Hz, 4H), 6.76 (d, J = 8.5 Hz, 2H), 4.81 (t, J = 11.9 Hz, 1H), 4.62 – 4.44 (m, 2H), 4.40 (d, J = 3.5 Hz, 2H), 4.25 (d, J = 4.4 Hz, 2H), 4.02 (d, J = 11.5 Hz, 1H), 2.89 (d, J = 7.5 Hz, 2H), 2.31 (q, J = 12.7 Hz, 1H), 2.05 (s, 3H), 1.75 (d, J = 12.1 Hz, 1H), 1.31 (d, J = 6.0 Hz, 6H); LC-MS: 476.6 $[M+H]^+$.

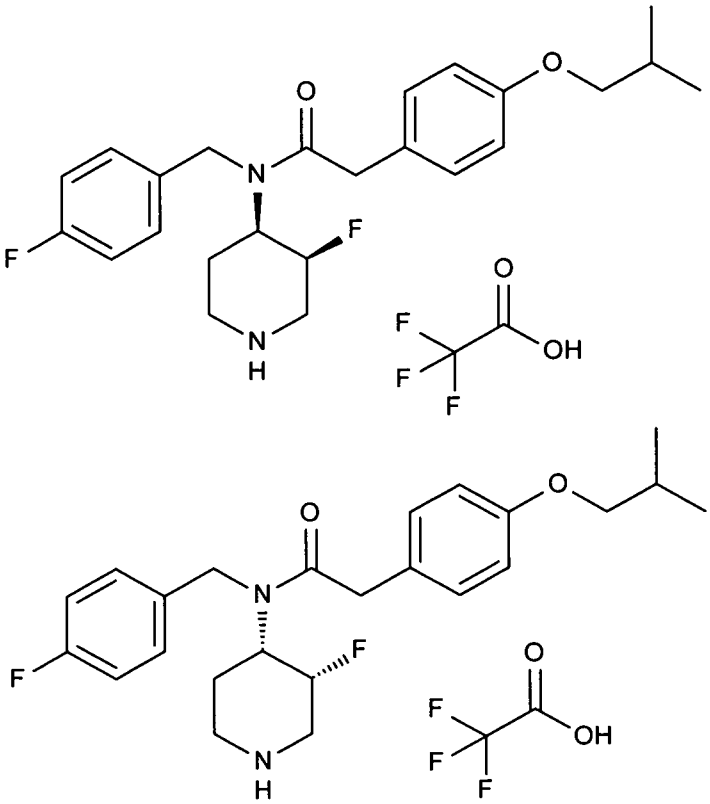
[00788] Example 140: N-[(4-fluorophenyl)methyl]-N-[(2S,4R)-1-methyl-2-phenylpiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (140a)

and N-[(4-fluorophenyl)methyl]-N-[(2R,4S)-1-methyl-2-phenylpiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (140b)



[00789] The compounds were prepared in analogy with example 124, using tert-butyl 4-oxo-2-phenylpiperidine-1-carboxylate and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Isolated as a racemic mixture. Yield: 41 mg, 72%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.42 (s, 5H), 7.22 – 7.13 (m, 2H), 7.04 (dd, J = 15.9, 8.3 Hz, 4H), 6.81 (d, J = 8.4 Hz, 2H), 5.08 (t, J = 12.3 Hz, 1H), 4.63 (s, 2H), 3.82 – 3.49 (m, 7H), 2.92 (t, J = 11.7 Hz, 1H), 2.63 (q, J = 12.5 Hz, 1H), 2.48 (s, 4H), 2.18 – 1.59 (m, 2H), 1.01 (d, J = 6.7 Hz, 6H); LC-MS: 489.6 $[M+H]^+$.

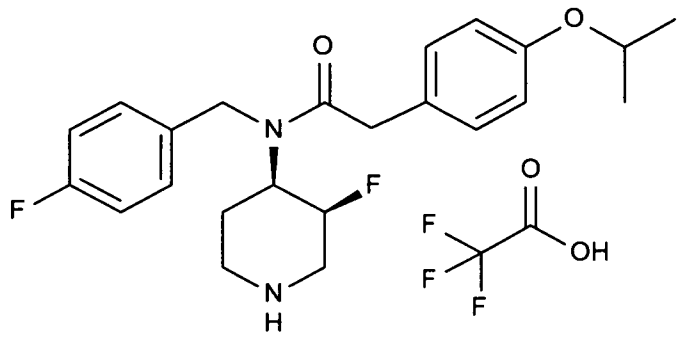
[00790] Example 141: N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (141a) and N-[(4-fluorophenyl)-methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (141b)

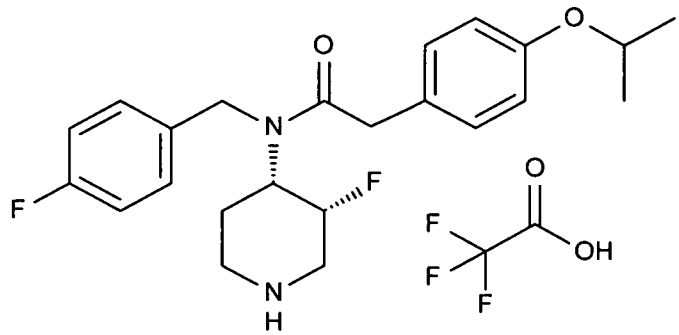


[00791] 2-[4-(2-methylpropoxy)phenyl]acetic acid (571 mg, 2.74 mmol) was added to 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (1.144 g, 3.01 mmol) and diisopropylethylamine (1.06 g, 8.22 mmol) in dry dimethylformamide (3.0 ml). The mixture was stirred for 30 minutes before tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1, 984 mg, 3.01 mmol) in dry dimethylformamide (3.0 ml) were added. After 18 hours, the mixture was diluted with brine (40 ml) and extracted with diethyl ether (2 x 250 ml). The combined organic phases were dried over sodium sulfate, filtered and concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 30% ethyl acetate in petroleum ether to afford tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate as an yellow foam (620 mg, 40%). This material was treated with a mixture of dichloromethane (5 ml) and trifluoroacetic acid (1.5ml) for 1 hour. Evaporation of the reaction mixture and freeze drying in 1,4-dioxane gave the title compounds as a racemic mixture (550 mg, 86%): ^{1}H NMR (400

MHz, Chloroform-d) δ 7.16 – 6.99 (m, 6H), 6.83 (d, 2H), 5.02 (d, 1H), 4.95 – 4.80 (m, 1H), 4.75 (d, 1H), 4.59 (d, 1H), 3.74 – 3.66 (m, 2H), 3.60 (s, 2H), 3.41 (d, 1H), 3.22 (d, 1H), 3.12 (d, 1H), 2.97 (t, 1H), 2.27 (q, 1H), 2.07 (m, 1H), 1.64 (d, 1H), 1.02 (d, 6H), LC-MS: 417.2 $[M+H]^+$.

[00792] Example 142: N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (142a) and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (142b)

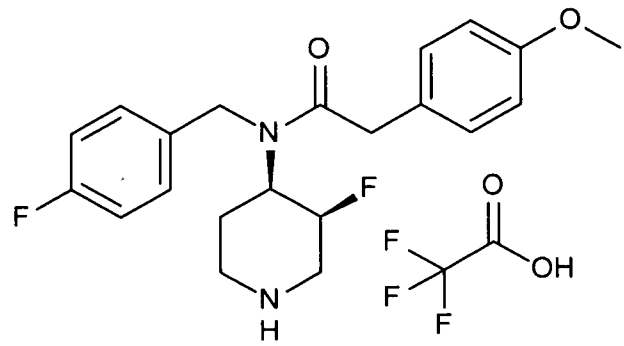


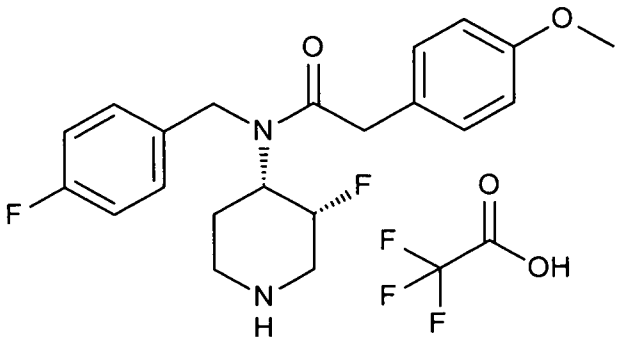


[00793] The compounds were prepared in analogy with example 141, using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 2-[4-(propan-2-yloxy)phenyl]acetic acid. Isolated as a racemic mixture. Yield: 44%: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 – 7.00 (m, 6H), 6.82 (d, 2H), 5.03 (d, 1H), 4.96 – 4.81 (m, 1H), 4.76 (d, 1H), 4.60 (d, 1H), 4.51 (m, 1H), 3.60 (s, 3H), 3.42 (d, 1H), 3.16 (dd, 1H), 2.97 (t, 1H), 2.30 (d, 1H), 1.64 (d, 1H), 1.33 (d, 6H), LC-MS: 403.3 $[M+H]^+$.

[00794] Example 143: N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)-methyl]-2-(4-methoxyphenyl)acetamide; hydrochloride (143a) and N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)acetamide; hydrochloride (143b)

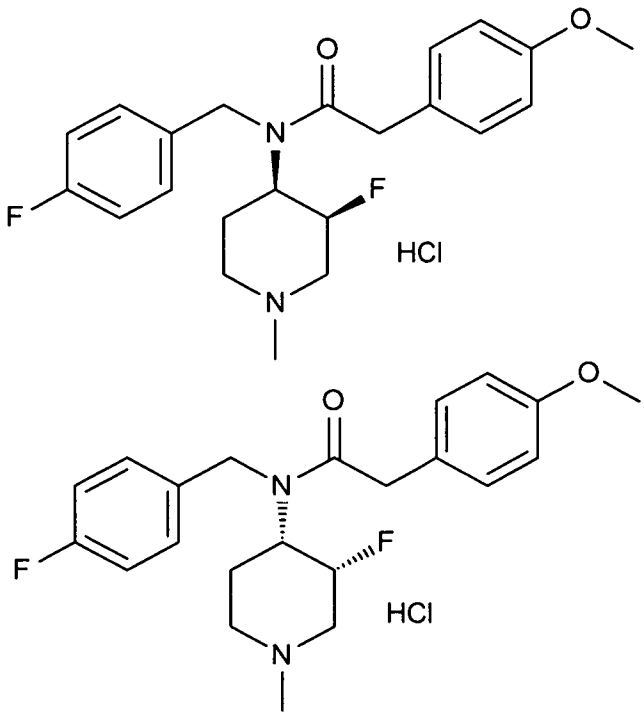
[00795] N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-2-(4-methoxyphenyl)acetamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-2-(4-methoxyphenyl)acetamide; trifluoroacetic acid





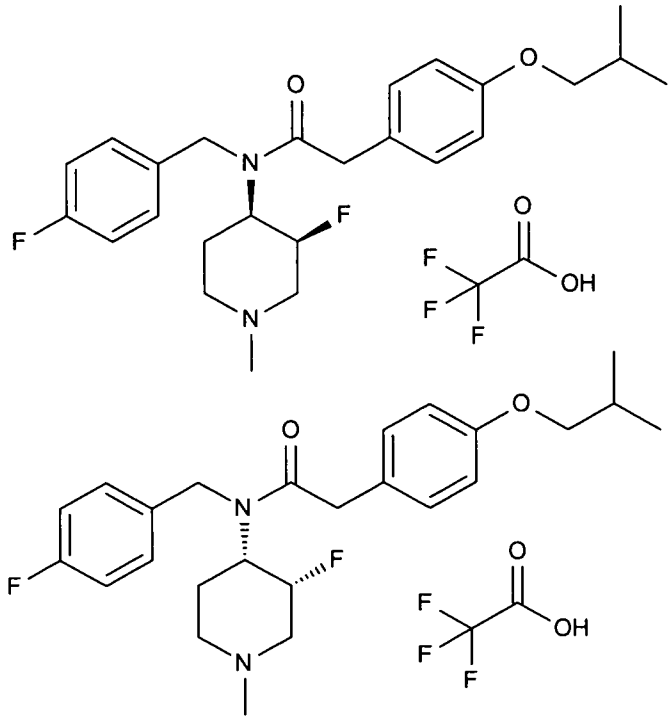
[00796] The compounds were prepared in analogy with example 26, using tert-butyl (3S,4R)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamido}piperidine-1-carboxylate (1:1) and 2-(4-methoxyphenyl)acetic acid. Isolated as a racemic mixture. Yield: 26%.

[00797] N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)acetamide; hydrochloride and N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)acetamide; hydrochloride



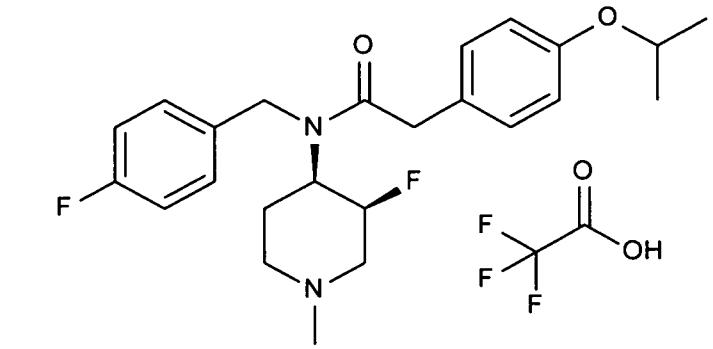
[00798] N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-2-(4-methoxyphenyl)acetamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-2-(4-methoxyphenyl)acetamide; trifluoroacetic acid (1:1, 54 mg, 110 μmmol) were dissolved in tetrahydrofuran (1 ml) and mixed with formaldehyde (aqueous, 37%, 13 μl) and sodium cyanoborohydride (14 mg, 220 μmmol). After stirring overnight the reaction mixture was evaporated and the residue was dissolved in methanol (8 ml). The solution was refluxed for 3 hours. After evaporating the solvent, the crude material was purified by column chromatography using silicon dioxide gel, eluting with 5% methanol in dichloromethane to afford the corresponding free bases of the title compounds. Freeze drying from a mixture of acetonitrile and aqueous hydrogen chloride solution gave the title compounds as a racemic mixture (4.9 mg, 10%): ^{1}H NMR (400 MHz, Methanol-d4) δ 7.25 (t, 2H), 7.10 (m, 4H), 6.85 (dd, 2H), 5.15 (d, 1H), 5.05 – 4.78 (m, 2H), 4.69 (d, 1H), 3.86 – 3.40 (m, 8H), 3.30 – 3.16 (m, 1H), 2.89 (s, 3H), 2.37 – 2.22 (m, 1H), 1.86 (d, 1H), LC-MS: 389.1 $[M+H]^+$.

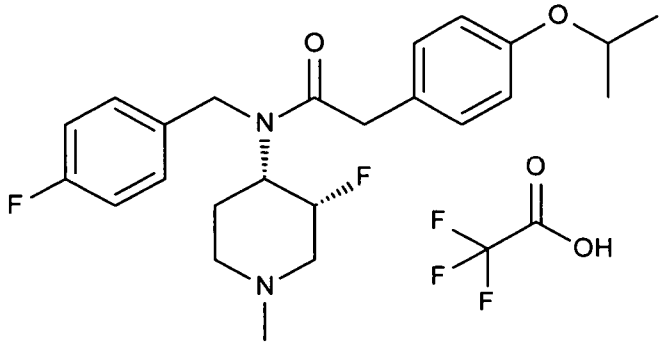
[00799] Example 144: N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)-methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (144a) and N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (144b)



[00800] The compounds were prepared in analogy with example 143, using N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]-acetamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (1:1). The material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Isolated as a racemic mixture. Yield: 14%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 – 6.97 (m, 6H), 6.89 – 6.77 (m, 2H), 5.15 – 4.80 (m, 2H), 4.80 – 4.54 (m, 2H), 3.92 – 3.66 (m, 4H), 3.59 (s, 3H), 3.07 – 2.70 (m, 4H), 2.61 – 2.43 (m, 1H), 2.07 (hept, 1H), 1.65 (d, Hz, 1H), 1.01 (d, 6H). LC-MS: 431.3 $[M+H]^+$.

[00801] Example 145: N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)-methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (145a) and N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-acetamide; trifluoroacetic acid (145b)

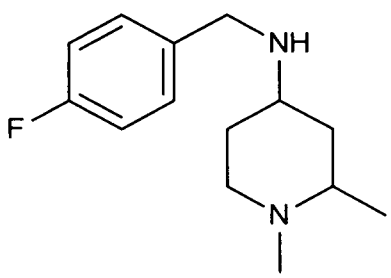




[00802] The compounds were prepared in analogy with example 143, using N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-2-[4-(propan-2-yloxy)phenyl]-acetamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (1:1). The material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Isolated as a racemic mixture. Yield: 14%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.20 – 6.94 (m, 6H), 6.90 – 6.74 (m, 2H), 5.17 – 4.56 (m, 4H), 4.50 (p, 1H), 3.94 – 3.64 (m, 2H), 3.59 (s, 2H), 3.01 (dd, 1H), 2.90 – 2.69 (m, 4H), 2.48 (d, 1H), 1.66 (d, 1H), 1.32 (d, 6H). LC-MS: 417.2 $[M+H]^+$.

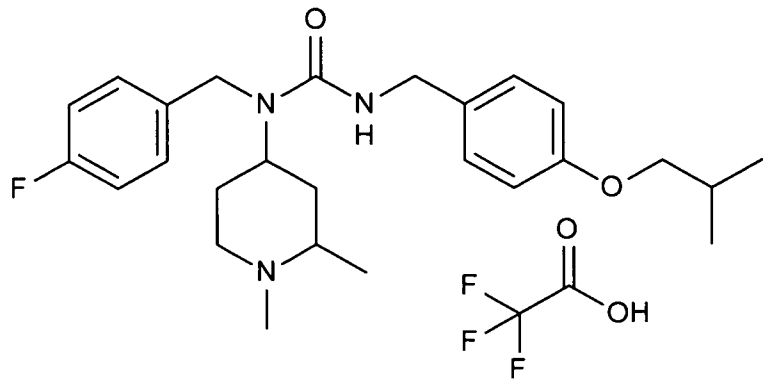
[00803] Example 146: 3-(1,2-dimethylpiperidin-4-yl)-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (146)

[00804] N-[(4-fluorophenyl)methyl]-1,2-dimethylpiperidin-4-amine



[00805] The compound was prepared in analogy with intermediate 41 using 1,2-dimethylpiperidin-4-one and 4-fluorobenzylamine. Methanol was used as solvent.

[00806] 3-(1,2-dimethylpiperidin-4-yl)-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid

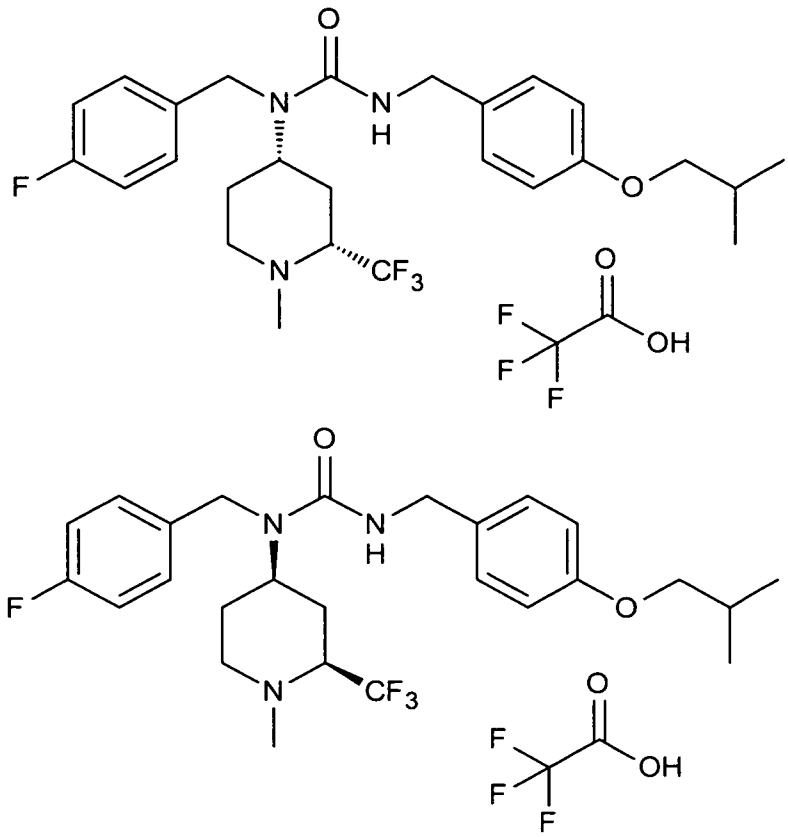


[00807] N-[(4-fluorophenyl)methyl]-1,2-dimethylpiperidin-4-amine (87 mg, 368 μmol) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (188 mg, 920 μmol) were mixed in dichloromethane (5 ml) and stirred for 1 hour at room temperature. After evaporation of the solvent the residue was purified by HPLC, eluting with 30-90% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compound (25 mg, 12 %). Isolated as a mixture of stereoisomers. Major isomer: ^{1}H NMR (500 MHz, Chloroform-d) δ 7.17 (dd, 2H), 7.02 (m, 2H), 6.95 (d, 2H), 6.78 (d, 2H), 4.99 (m, 1H), 4.66 (s, 1H), 4.43 – 4.35 (m, 2H), 4.25 (d, 2H), 3.75 (m, 1H), 3.69 (d, 2H), 3.28 (m, 1H), 3.09 (m, 1H), 2.70 (d, 3H), 2.60 (m, 1H), 2.39 (m, 1H), 2.07 (m, 1H), 1.89 (d, 1H), 1.78 (d, 1H), 1.46 (d, 3H), 1.02 (d, 6H), minor isomer: ^{1}H NMR (500 MHz, Chloroform-d) δ 7.17 (dd, 2H), 7.02 (m, 2H), 6.95 (d, 2H), 6.78 (d, 2H), 4.84 (m, 1H), 4.66 (s, 1H), 4.43 – 4.35 (m, 2H), 4.25 (d, 2H), 3.69 (m, 2H), 3.55 (d, 1H), 3.04 (m, 1H), 2.91 (m, 1H), 2.78 (d, 3H), 2.52 – 2.42 (m, 1H), 2.28 (m, 1H), 2.07 (m, 1H), 1.96 (d, 1H), 1.89 (m, 1H), 1.49 (d, 3H), 1.02 (d, 6H), LC-MS: 442.3 $[M+H]^+$.

[00808] Example 147: 3-[(4-fluorophenyl)methyl]-3-[(2R,4S)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (147a) and 3-[(4-fluorophenyl)methyl]-3-[(2S,4R)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (147b)

[00809] 3-[(4-fluorophenyl)methyl]-3-[(2R,4S)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 3-[(4-

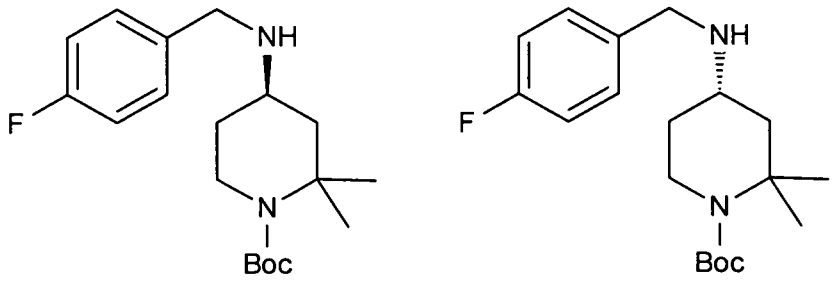
fluorophenyl)methyl]-3-[(2S,4R)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid



[00810] The compounds were prepared in analogy with example 117, using 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene and tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-2-(trifluoromethyl)piperidine-1-carboxylate. Isolated as a racemic mixture. Yield: 2.5%. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.19 (dd, 2H), 7.08 – 6.97 (m, 4H), 6.80 (d, 2H), 4.69 (t, 1H), 4.53 (s, 1H), 4.44 – 4.33 (m, 2H), 4.31 – 4.21 (m, 2H), 3.68 (d, 2H), 3.61 (s, 1H), 3.48 (d, 1H), 3.09 (t, 1H), 2.88 (s, 3H), 2.35 (s, 1H), 2.23 (d, 2H), 2.05 (tq, 1H), 1.91 (d, 1H), 1.01 (d, 6H).; LC-MS: 496.3 $[M+H]^+$

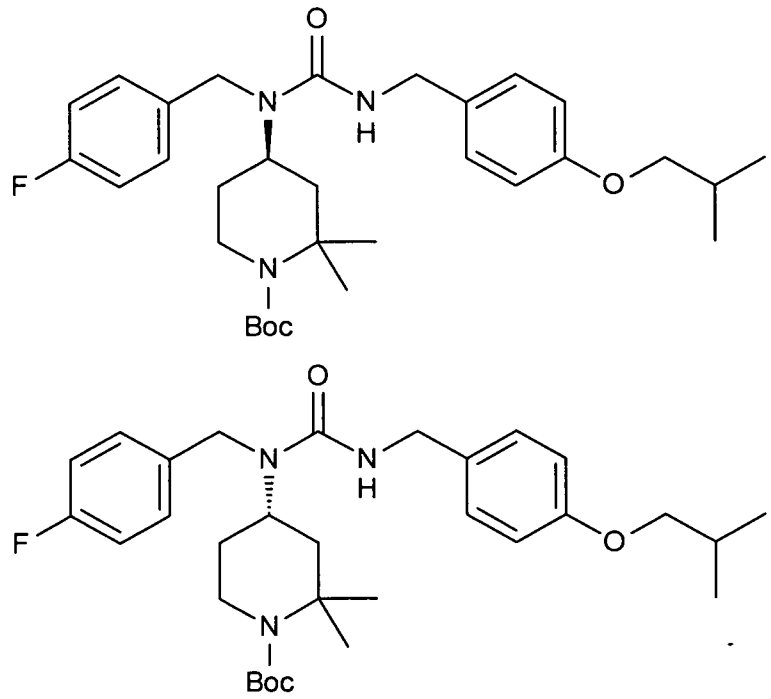
[00811] Example 148: 3-[(4R)-2,2-dimethylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (148a) and 3-[(4S)-2,2-dimethylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (148b)

[00812] tert-butyl (4R)-4-{[(4-fluorophenyl)methyl]amino}-2,2-dimethylpiperidine-1-carboxylate and tert-butyl (4S)-4-{[(4-fluorophenyl)methyl]amino}-2,2-dimethylpiperidine-1-carboxylate



[00813] The compounds were prepared in analogy with intermediate 41 using tert-butyl 2,2-dimethyl-4-oxopiperidine-1-carboxylate and 4-fluorobenzylamine. Methanol was used as solvent. Isolated as a racemic mixture.

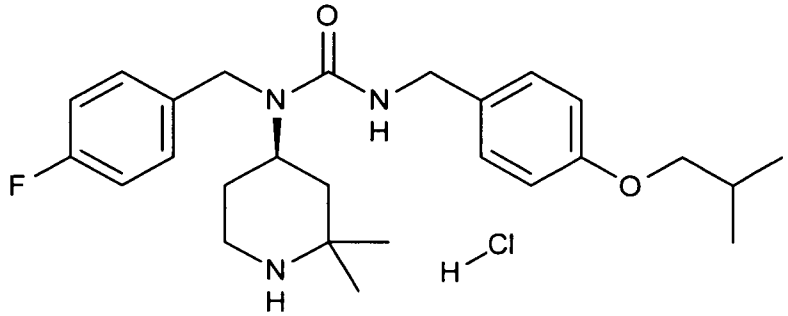
[00814] tert-butyl (4R)-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}-2,2-dimethylpiperidine-1-carboxylate and tert-butyl (4S)-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}-2,2-dimethylpiperidine-1-carboxylate

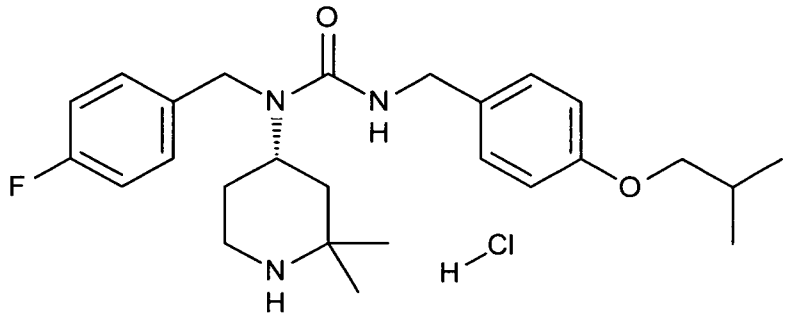


[00815] tert-butyl (4R)-4-{[(4-fluorophenyl)methyl]amino}-2,2-dimethylpiperidine-1-carboxylate and tert-butyl (4S)-4-{[(4-fluorophenyl)methyl]amino}-2,2-dimethylpiperidine-1-carboxylate (1:1, 170 mg, 0.50 mmol) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (205 mg, 1.00 mmol) were mixed in dichloromethane (3 ml) and stirred overnight. The solvent was evaporated and the crude material was purified by column

chromatography using silicon dioxide gel, eluting with 50% ethyl acetate in petroleum ether to afford the desired urea (240 mg, 88%). Isolated as a racemic mixture.

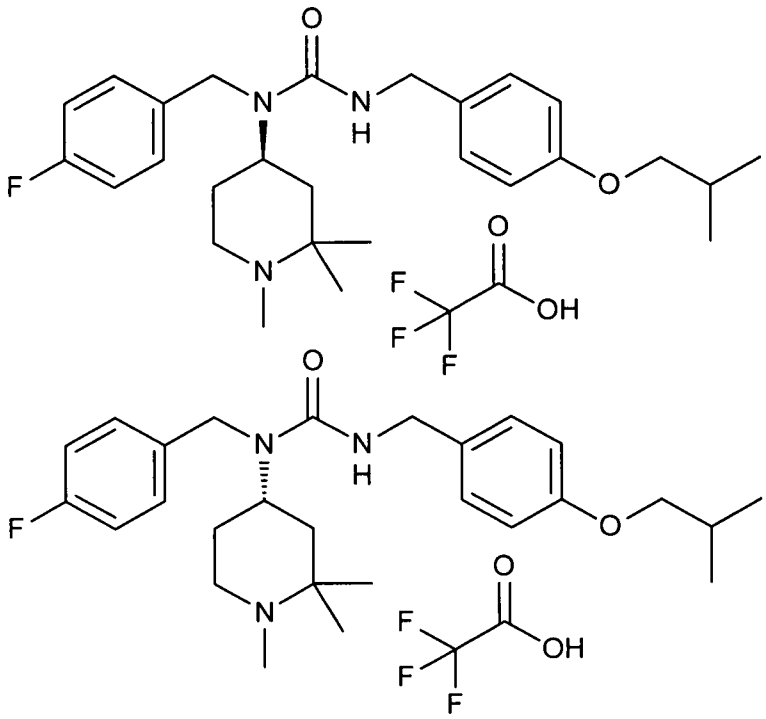
[00816] 3-[(4R)-2,2-dimethylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride and 3-[(4S)-2,2-dimethylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride





[00817] tert-Butyl (4R)-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}-2,2-dimethylpiperidine-1-carboxylate and tert-butyl (4S)-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}-2,2-dimethylpiperidine-1-carboxylate (1:1, 240 mg, 0.44 mmol) were stirred in a mixture of dichloromethane (10 ml) and trifluoroacetic acid (4 ml). After stirring for 1 hour the solvent was evaporated and the residue was freeze dried from an acetonitrile and hydrochloric acid solution to give the title compounds (200 mg, 93%). Isolated as a racemic mixture. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.28 – 7.21 (m, 2H), 7.11 – 7.02 (m, 4H), 6.80 (d, 2H), 4.60 – 4.52 (m, 1H), 4.48 (d, 2H), 4.26 (s, 2H), 3.71 (d, 2H), 3.28 – 3.22 (m, 2H), 2.03 (dt, 1H), 1.91 – 1.74 (m, 4H), 1.42 (s, 3H), 1.37 (s, 3H), 1.02 (d, 6H), LC-MS: 442.3 $[M+H]^+$.

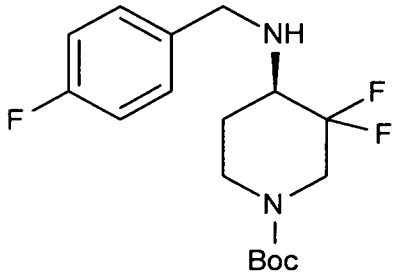
[00818] Example 149: 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(4R)-1,2,2-trimethylpiperidin-4-yl]urea; trifluoroacetic acid (149a) and 3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(4S)-1,2,2-trimethylpiperidin-4-yl]urea; trifluoroacetic (149b) acid

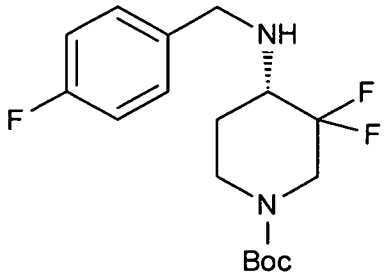


[00819] 3-[(4R)-2,2-dimethylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride and 3-[(4S)-2,2-dimethylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; hydrochloride (1:1, 80 mg, 0.18 mmol) was dissolved in methanol (dry, degassed, 1.5 ml). To this solution, chloro(cyclopentadienyl)bis(triphenylphosphine)ruthenium (8 mg, 11 μmol) was added and the solution was heated in a pressure tube at 90 °C for 2 days. After evaporation of the solvent the crude material was purified by HPLC, eluting with 30-90% acetonitrile in water (containing 0.1% trifluoroacetic acid) to afford the title compounds (10 mg, 9%), as a racemic mixture: ^{1}H NMR (500 MHz, Methanol-d4) δ 7.24 (dd, 2H), 7.11 – 7.02 (m, 4H), 6.84 – 6.77 (m, 2H), 4.56 – 4.40 (m, 3H), 4.26 (s, 2H), 3.71 (d, 2H), 3.30 (m, 2H), 2.75 (s, 3H), 2.03 (m, 1H), 2.00 – 1.83 (m, 4H), 1.40 (s, 3H), 1.39 (s, 3H), 1.02 (d, 6H), LC-MS: 456.4 $[M+H]^+$.

[00820] Example 150: 3-[(4R)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (150a) and 3-[(4S)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)-phenyl]methyl}urea; trifluoroacetic acid (150b)

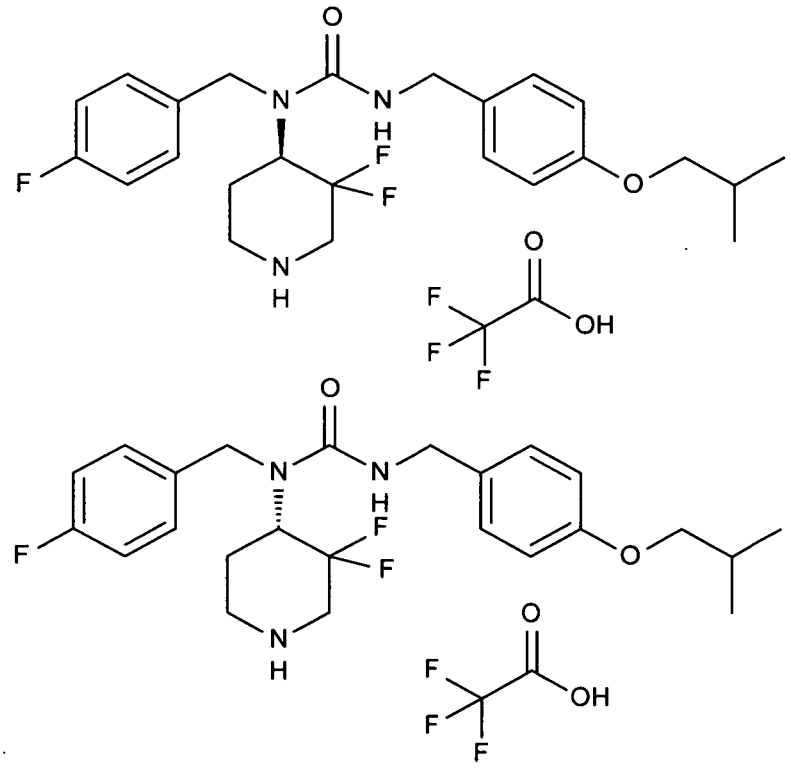
[00821] tert-butyl (4R)-3,3-difluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (4S)-3,3-difluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate





[00822] The compounds were prepared in analogy with intermediate 41 using tert-butyl 2,2-difluoro-4-oxopiperidine-1-carboxylate and 4-fluorobenzylamine. Methanol was used as solvent. Isolated as a racemic mixture.

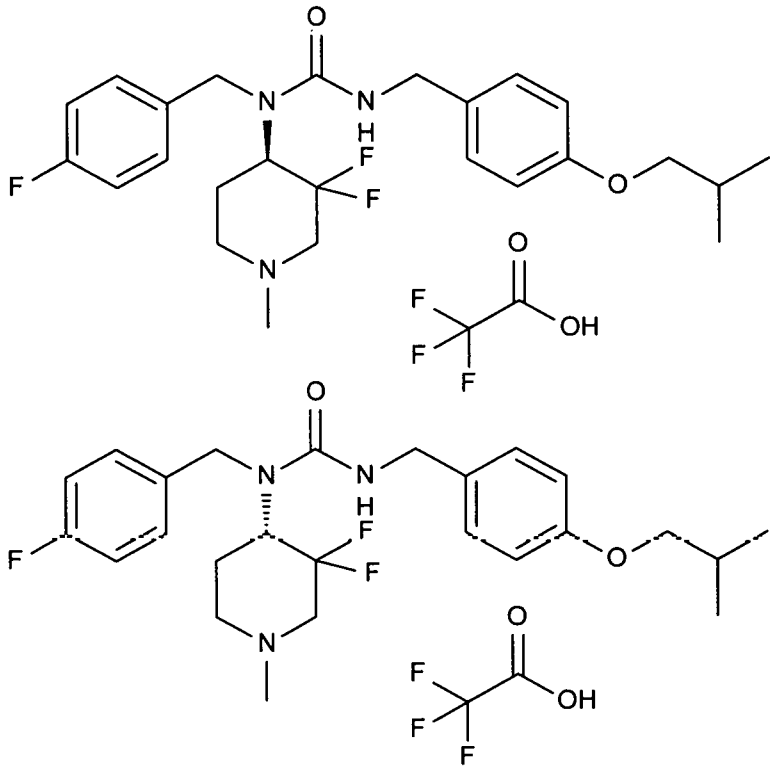
[00823] 3-[(4R)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 3-[(4S)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid



[00824] The compounds were prepared in analogy with example 148, using tert-butyl (4R)-3,3-difluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (4S)-3,3-difluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Isolated as a racemic mixture. The compounds were not freeze dried from hydrochloric acid. Yield: 47%: ^{1}H NMR (500 MHz, Chloroform-d) δ 7.17 (dd, 2H), 7.02 (t, 2H), 6.90 – 6.84 (m, 2H), 6.78 – 6.73 (m, 2H), 5.39 –

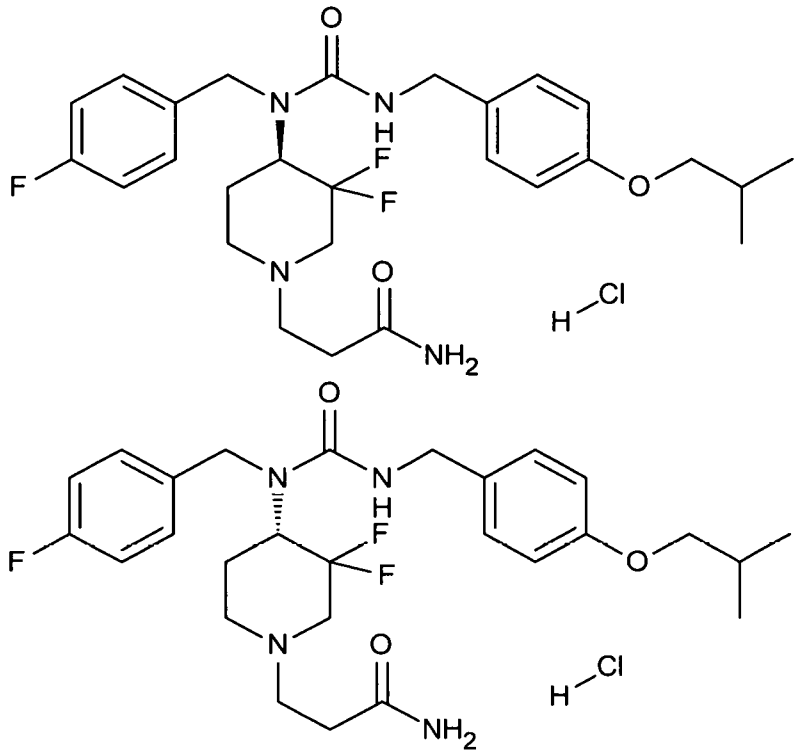
5.26 (m, 1H), 4.77 (t, 1H), 4.56 – 4.43 (m, 2H), 4.23 (t, 2H), 3.68 (m, 3H), 3.56 (d, 1H), 3.36 (dd, 1H), 3.19 (m, 1H), 2.36 (m, 1H), 2.07 (m, 2H), 1.02 (d, 6H), LC-MS: 450.4 $[M+H]^+$.

[00825] Example 151: 3-[(4R)-3,3-difluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (151a) and 3-[(4S)-3,3-difluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (151b)



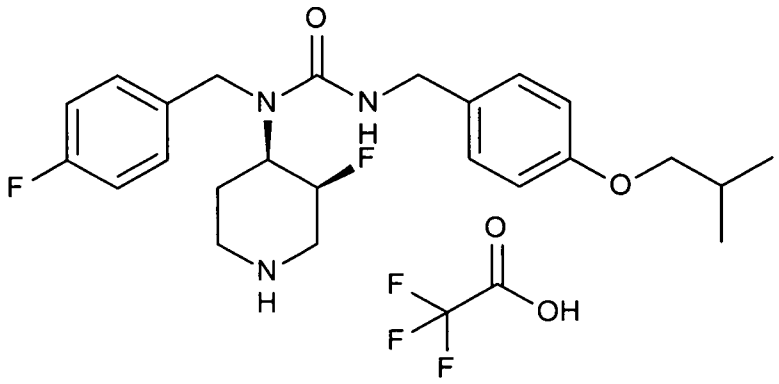
[00826] The compounds were prepared in analogy with example 149, using 3-[(4R)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-urea; trifluoroacetic acid and 3-[(4S)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (1:1). Isolated as a racemic mixture. Yield: 10%. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.19 (dd, 2H), 7.03 (t, 2H), 6.87 (d, 2H), 6.76 (d, 2H), 5.37 (dd, 1H), 4.77 (t, 1H), 4.59 – 4.46 (m, 2H), 4.26 – 4.20 (m, 2H), 3.82 (t, 1H), 3.73 (d, 1H), 3.68 (d, 2H), 3.26 (m, 1H), 3.12 (s, 1H), 2.91 (s, 3H), 2.60 (d, 1H), 2.07 (m, 2H), 1.02 (d, 6H), LC-MS: 464.3 $[M+H]^+$.

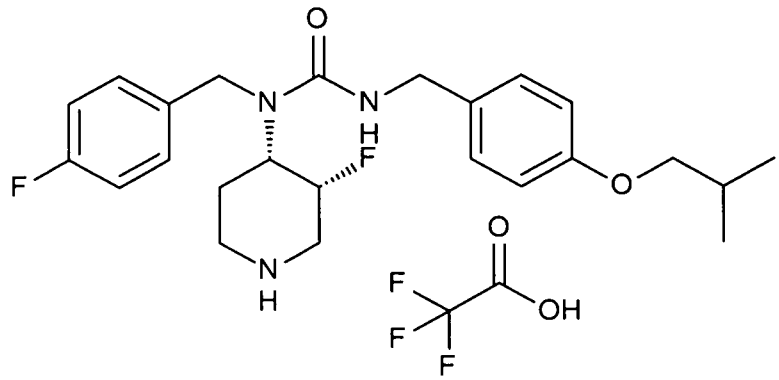
[00827] Example 152: 3-[(4R)-3,3-difluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methyl-propoxy)phenyl]methyl}carbamoyl)amino}piperidin-1-yl]propanamide; hydrochloride (152a) and 3-[(4S)-3,3-difluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}piperidin-1-yl]propanamide; hydrochloride (152b)



[00828] 3-[(4R)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 3-[(4S)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (1:1, 63 mg, 0.14 mmol) were dissolved in acetonitrile (1.5 ml) and prop-2-enamide (10 mg, 0.14 mmol) was added. Silicon dioxide gel (70 mg) was added and the reaction was heated to 95 °C over night. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 5% methanol in dichloromethane to afford the corresponding trifluoroacetic acid salt, which was converted to the title compounds (28 mg, 36%) using hydrochloric acid. Isolated as a racemic mixture: ^{1}H NMR (500 MHz, Methanol-d4) δ 7.22 (dd, 2H), 7.06 – 6.95 (m, 4H), 6.76 (d, 2H), 5.23 (m, 1H), 4.75 (d, 1H), 4.59 (d, 1H), 4.30 (d, 1H), 4.19 (d, 1H), 4.05 (m, 1H), 3.76 – 3.63 (m, 4H), 3.54 (t, 2H), 3.36 (m, 1H), 2.78 (t, 2H), 2.30 (m, 1H), 2.14 (dd, 1H), 2.03 (m, 1H), 1.02 (d, 6H), LC-MS: 521.3 $[M+H]^+$.

[00829] Example 153: 3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (153a) and 3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}urea; trifluoroacetic acid (153b)

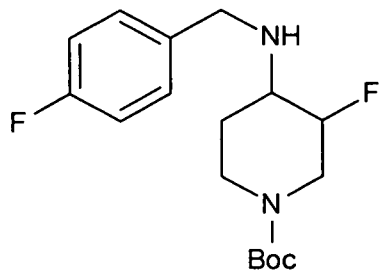




[00830] The compounds were prepared in analogy with example 148, using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate, tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. The compounds were not freeze dried from hydrochloric acid. Isolated as a racemic mixture. Yield: 4%: ^{1}H NMR (400 MHz, Methanol-d4) δ 7.22 (dd, 2H), 7.08 – 6.99 (m, 4H), 6.78 (d, 2H), 5.10 (d, 1H), 4.81 – 4.69 (m, 1H), 4.67 (d, 1H), 4.58 (d, 1H), 4.25 (q, 2H), 3.70 (d, 2H), 3.64 (t, 1H), 3.50 – 3.33 (m, 2H), 3.26 – 3.15 (m, 1H), 2.25 (m, 1H), 2.03 (m, 1H), 1.82 (d, 1H), 1.02 (d, 6H), LC-MS: 432.2 $[M+H]^+$.

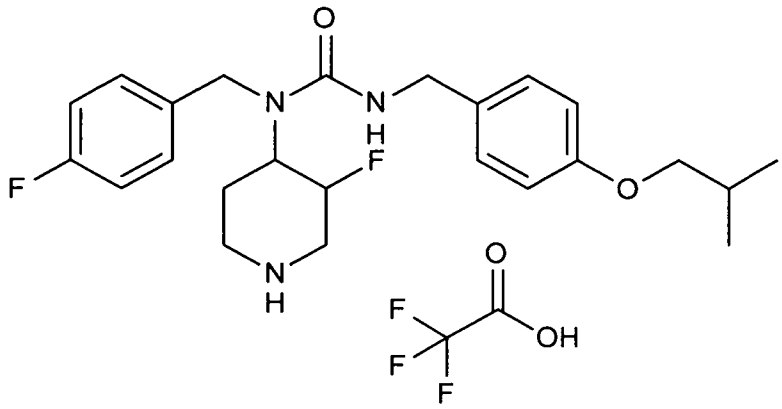
[00831] Example 154: 3-[(4-fluorophenyl)methyl]-3-(3-fluoropiperidin-4-yl)-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (154)

[00832] tert-butyl 3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate



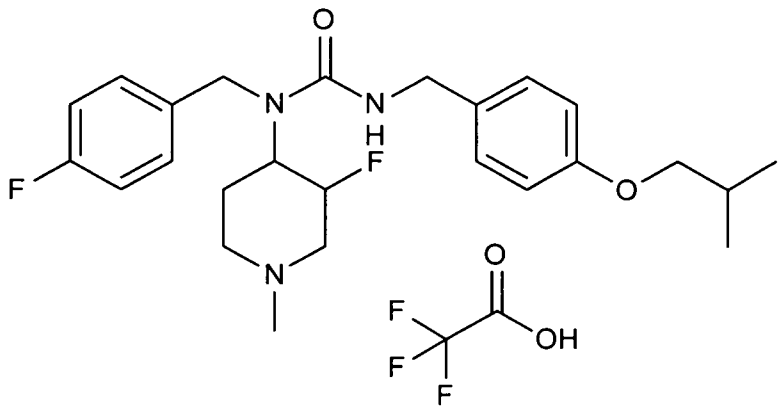
[00833] The compound was prepared in analogy with intermediate 41, using tert-butyl 3-fluoro-4-oxopiperidine-1-carboxylate and 4-fluorobenzylamine. Methanol was used as solvent.

[00834] 3-[(4-fluorophenyl)methyl]-3-(3-fluoropiperidin-4-yl)-1-{[4-(2-methylpropoxy)-phenyl]methyl}urea; trifluoroacetic acid



[00835] The compound was prepared in analogy with example 33, using tert-butyl 3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. The compound was not freeze dried from hydrochloric acid. Yield: 1%. LC-MS: 432.2 $[M+H]^+$.

[00836] Example 155: 3-(3-fluoro-1-methylpiperidin-4-yl)-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (155)

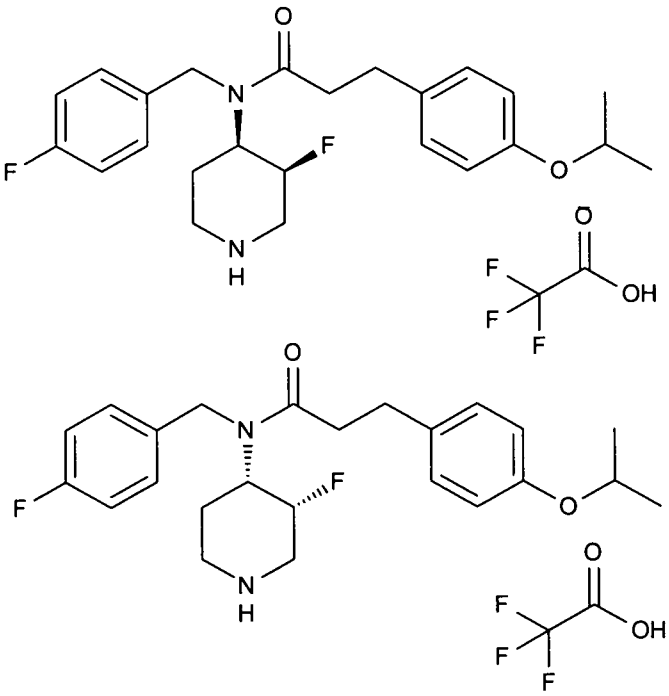


[00837] The compounds were prepared in analogy with example 143, using 1-(isocyanato-methyl)-4-(2-methylpropoxy)benzene and 3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine. The compounds were purified by HPLC, eluting with acetonitrile in water (containing 0.1% trifluoroacetic acid). The material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Isolated as a racemic and

diastereomeric mixture. Yield: 10%. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.26 – 7.17 (m, 2H), 7.09 – 6.98 (m, 4H), 6.83 – 6.74 (m, 2H), 5.12 (d, 1H), 4.73 – 4.50 (m, 2H), 4.25 (q, 2H), 3.84 – 3.73 (m, 1H), 3.70 (d, 2H), 3.58 – 3.46 (m, 2H), 3.42 (d, 1H), 3.24 (d, 1H), 2.89 (s, 3H), 2.38 – 2.20 (m, 1H), 2.03 (dt, 1H), 1.86 (d, 1H), 1.02 (d, 6H). LC-MS: 446.3 $[M+H]^+$.

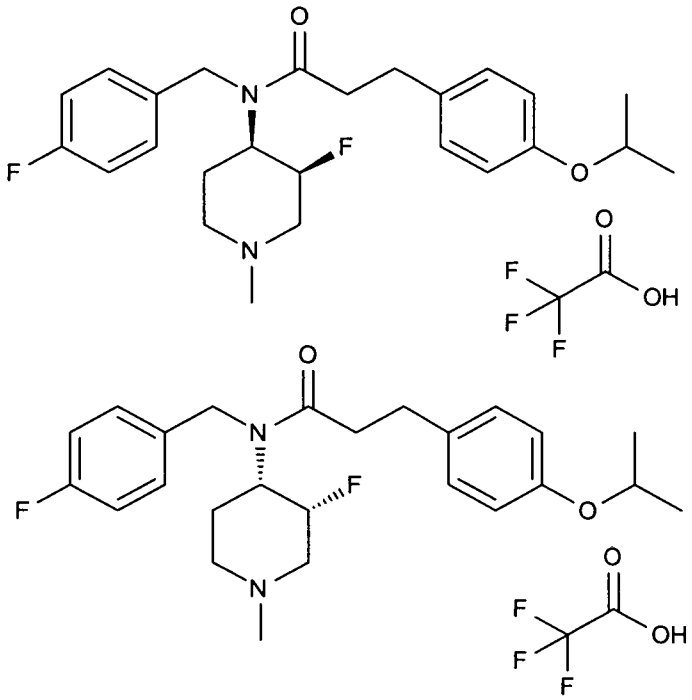
[00838] Example 156: N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)-methyl]-3-[4-(propan-2-yloxy)phenyl]propanamide;trifluoroacetic acid (156a) and N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(propan-2-yloxy)phenyl]propanamide; trifluoroacetic acid (156b)

[00839] N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide; trifluoroacetic acid



[00840] The compounds were prepared in analogy with example 141, using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 3-[4-(propan-2-yloxy)phenyl]propanoic acid. Isolated as a racemic mixture. Yield: 49%.

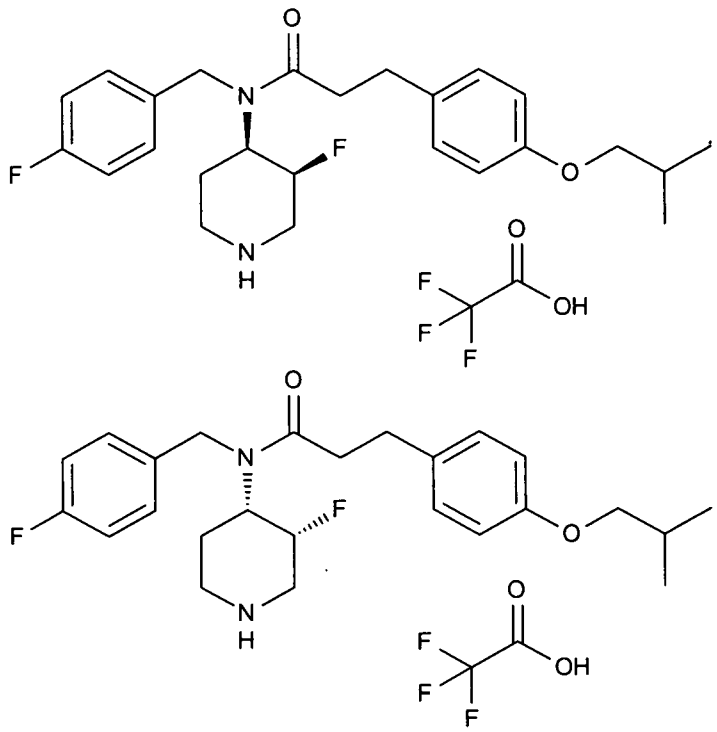
[00841] N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(propan-2-yloxy)phenyl]propanamide and N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(propan-2-yloxy)phenyl]propanamide; trifluoroacetic acid



[00842] The compounds were prepared in analogy with example 143, using N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]-propanamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide; trifluoroacetic acid (1:1). The compounds were not freeze dried from hydrochloric acid. The material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Isolated as a racemic mixture. Yield: 45%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.07 – 6.93 (m, 6H), 6.83 – 6.73 (m, 2H), 5.09 – 4.76 (m, 2H), 4.65 – 4.43 (m, 3H), 3.89 – 3.63 (m, 2H), 3.08 – 2.71 (m, 6H), 2.69 – 2.47 (m, 4H), 1.58 (d, 1H), 1.32 (d, 6H). LC-MS: 431.3 $[M+H]^+$.

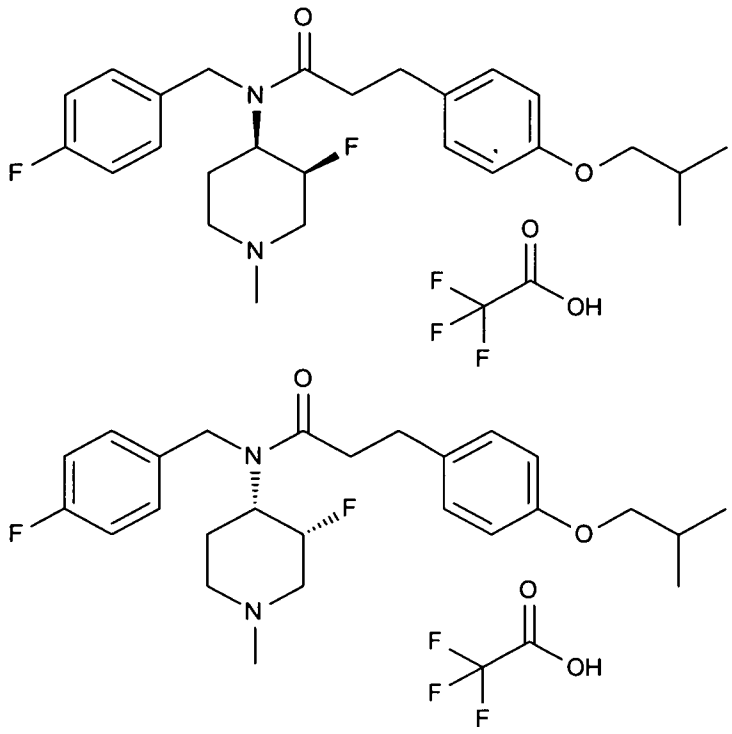
[00843] Example 157: N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)-methyl]-3-[4-(2-methylpropoxy)phenyl]propanamide; trifluoroacetic acid (157a) and N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(2-methyl-propoxy)phenyl]propanamide; trifluoroacetic acid (157b)

[00844] N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide; trifluoroacetic acid



[00845] The compounds were prepared in analogy with example 141, using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 3-[4-(2-methylpropoxy)phenyl]propanoic acid. Isolated as a racemic mixture. Yield: 42%.

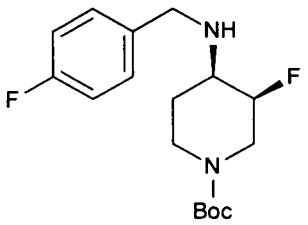
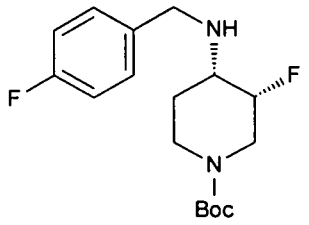
[00846] N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(2-methylpropoxy)phenyl]propanamide and N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(2-methylpropoxy)phenyl]propanamide; trifluoroacetic acid



[00847] The compounds were prepared in analogy with example 143, using N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide; trifluoroacetic acid and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide; trifluoroacetic acid (1:1). The compounds were not freeze dried from hydrochloric acid. The material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Isolated as a racemic mixture. Yield: 43%. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.06 – 6.93 (m, 6H), 6.83 – 6.73 (m, 2H), 5.08 – 4.76 (m, 2H), 4.57 (q, 2H), 3.83 (d, 1H), 3.68 (d, 2H), 3.09 – 2.72 (m, 8H), 2.69 – 2.48 (m, 3H), 2.06 (dt, 1H), 1.58 (d, 1H), 1.01 (d, 6H). LC-MS: 445.3 $[M+H]^+$.

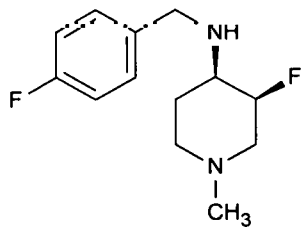
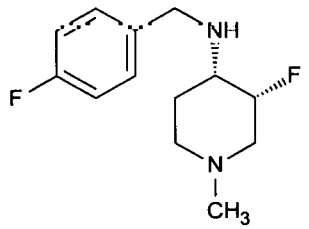
[00848] Example 158: 1-[(3S,4R)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[(1R)-1-(4-methoxyphenyl)ethyl]urea; trifluoroacetic acid (158a) and 1-[(3R,4S)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[(1R)-1-(4-methoxyphenyl)ethyl]urea; trifluoroacetic acid (158b)

[00849] tert-butyl (3R,4S)-3-Fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-Fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate

[00850] Sodium triacetoxyborohydride (100 mmol, 21.2 g) was added to a solution of tert-butyl 3-fluoro-4-oxopiperidine-1-carboxylate (10.86 g, 50 mmol) and 4-fluorobenzylamine (6.286 ml, 55 mmol) in ethanol (100 ml). After 4 hours of stirring at ambient temperature saturated sodium bicarbonate (100 ml) was added. The mixture was extracted with dichloromethane (3 x 100 ml), dried using a phase separator and concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting with 25-100% ethyl acetate in petroleum ether to afford the title compounds as a 1:1 mixture of enantiomers (8.90 g, 55%).

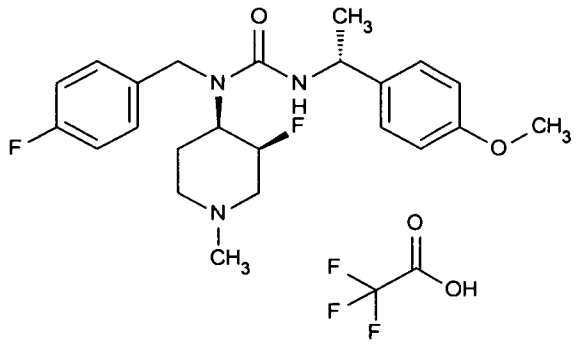
[00851] (3S,4R)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3R,4S)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine

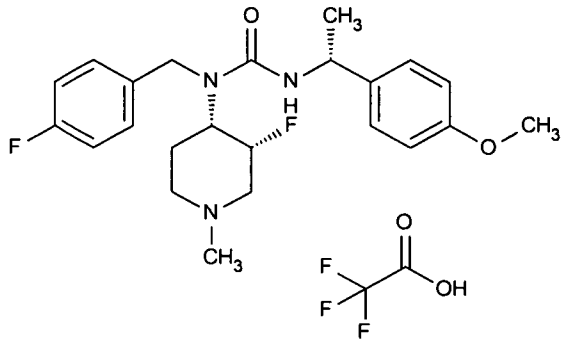



[00852] Trifluoroacetic acid (5 ml) was added to a 1:1 mixture of tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1.73 g, 5.31 mmol) in dichloromethane (15 ml). After 50 minutes the mixture was concentrated and redissolved in ethanol (53 ml). Formaldehyde (37% aqueous, 198 µl, 2.66 mmol) and sodium triacetoxyborohydride (1.13 g, 5.31 mmol) were added. After 30 minutes of stirring at ambient temperature additional formaldehyde (37% aqueous, 99 µl, 1.33 mmol) and sodium triacetoxyborohydride (565 mg, 2.66 mmol) were added. After additionally 45 minutes of stirring the mixture was concentrated. Sodium bicarbonate (saturated, 100 ml) was added and the resulting mixture was extracted with dichloromethane (3 x 100 ml). The organic phase was dried using a phase separator and concentrated. The crude material was purified by column chromatography using silicone dioxide gel, eluting with 5-15% methanol in

dichloromethane to afford the title compounds as a 1:1 mixture of enantiomers (545 mg, 43%).

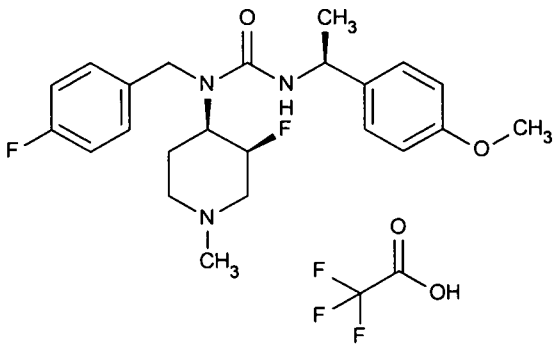
[00853] 1-[(3S,4R)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[(1R)-1-(4-methoxyphenyl)ethyl]urea; trifluoroacetic acid and 1-[(3R,4S)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[(1R)-1-(4-methoxyphenyl)ethyl]urea; trifluoroacetic acid

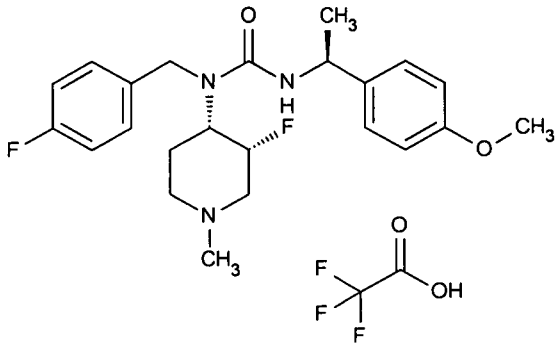




[00854] (R)-(+)-4-Methoxy-α-methylbenzylamine (15.4 µl, 104 µmol) and trimethylamine (34.7 µl, 250 µmol) in dichloromethane (0.5 ml) were added to diphosgene (6.0 µl, 50 µmol) in dichloromethane (0.5 ml), over 1 hour, using a syringe pump. A 1:1 mixture of (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (20 mg, 83.2 µmol) in dichloromethane (0.5 ml) was added. The mixture was stirred at ambient temperature for 19.5 hours before it was quenched with Water (1.5 ml). The organic phase was separated. The aqueous phase was extracted with dichloromethane (1.5 ml). The combine organic phase was dried using a phase separator and concentrated. The crude material was purified by HPLC, eluting with 20-85% acetonitrile in water (containing 0.1 % TFA) to afford the title compounds as a 1:1 mixture of diastereomers (31 mg, 70%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 (dt, 2H), 7.05 (q, 2H), 6.96 (d, 1H), 6.89 (d, 1H), 6.78 (dd, 2H), 5.04 (dd, 1H), 4.90 – 4.67 (m, 2H), 4.63 (dd, 1H), 4.58 – 4.37 (m, 2H), 3.94 – 3.64 (m, 5H), 3.09 – 2.91 (m, 2H), 2.82 (s, 3H), 2.70 – 2.41 (m, 1H), 1.80 (dd, 1H), 1.26 (dd, 3H); LC-MS: 418.2 $[M+H]^+$.

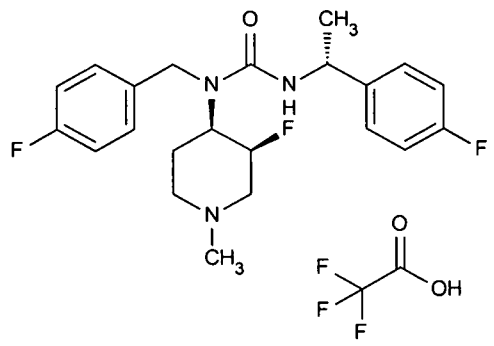
[00855] Example 159_1: 1-[(3S,4R)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[(1S)-1-(4-methoxyphenyl)ethyl]urea; trifluoroacetic acid (159a) and 1-[(3R,4S)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[(1S)-1-(4-methoxyphenyl)ethyl]urea; trifluoroacetic acid (159b)

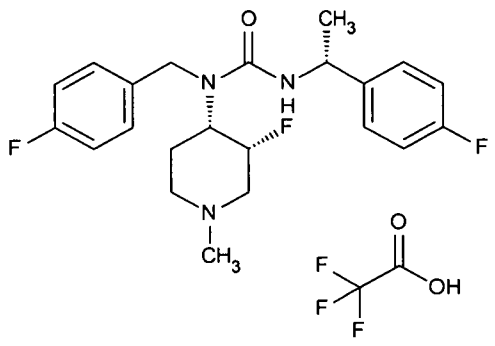




[00856] The compounds were prepared in analogy with example 158 using (S)-(-)-4-Methoxy-α-methylbenzylamine instead of (R)-(+)-4-Methoxy-α-methylbenzylamine. Yield: 25 mg, 57%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.12 (m, 2H), 7.05 (q, 2H), 6.97 (d, 1H), 6.90 (d, 1H), 6.78 (dd, 2H), 5.05 (dd, 1H), 4.90 – 4.68 (m, 2H), 4.63 (dd, 1H), 4.58 – 4.37 (m, 2H), 3.94 – 3.64 (m, 5H), 3.14 – 2.89 (m, 2H), 2.83 (s, 3H), 2.70 – 2.41 (m, 1H), 1.80 (dd, 1H), 1.27 (dd, 3H); LC-MS: 418.2 $[M+H]^+$.

[00857] Example 159_2: 1-[(3S,4R)-3-Fluoro-1-methylpiperidin-4-yl]-3-[(1R)-1-(4-fluorophenyl)ethyl]-1-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (159c) and 1-[(3R,4S)-3-Fluoro-1-methylpiperidin-4-yl]-3-[(1R)-1-(4-fluorophenyl)ethyl]-1-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (159d)

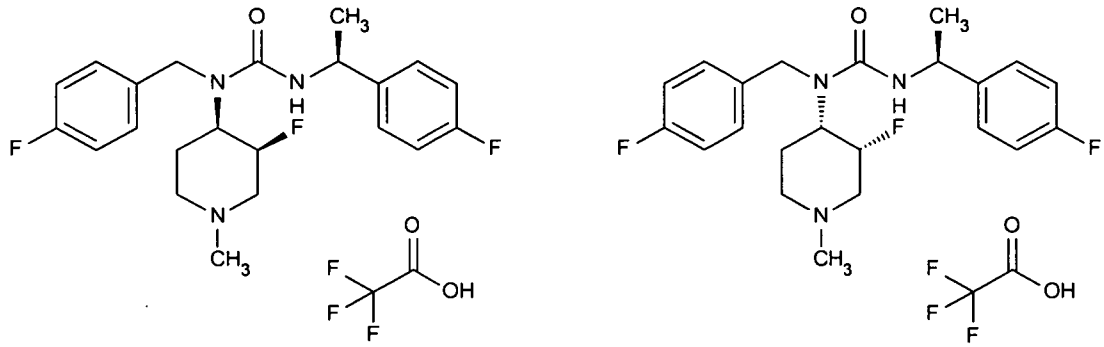




[00858] The compounds were prepared in analogy with example 158 using (1R)-1-(4-fluorophenyl)ethan-1-amine instead of (R)-(+)-4-Methoxy-α-methylbenzylamine. Yield: 33 mg, 76%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.12 (m, 2H), 7.12 – 7.05 (m, 2H), 7.04 – 6.90 (m, 4H), 5.21 – 4.92 (m, 1H), 4.90 – 4.68 (m, 2H), 4.70 – 4.57 (m, 1H), 4.57 – 4.37 (m, 2H), 3.94 – 3.64 (m, 2H), 3.10 – 2.90 (m, 2H), 2.83 (s, 3H), 2.70 – 2.41 (m, 1H), 1.92 – 1.68 (m, 1H), 1.26 (dd, 3H); LC-MS: 406.2 $[M+H]^+$.

[00859] Example 160_1: 1-[(3S,4R)-3-Fluoro-1-methylpiperidin-4-yl]-3-[(1S)-1-(4-fluorophenyl)ethyl]-1-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (160a) and 1-

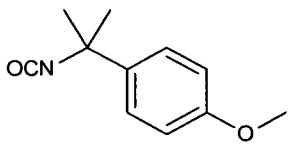
[(3R,4S)-3-Fluoro-1-methylpiperidin-4-yl]-3-[(1S)-1-(4-fluorophenyl)ethyl]-1-[(4-fluorophenyl)methyl]urea; trifluoroacetic acid (160b)



[00860] The compounds were prepared in analogy with example 158 using (1R)-1-(4-fluorophenyl)ethan-1-amine instead of (R)-(+)-4-Methoxy-α-methylbenzylamine. Yield: 29 mg, 67%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.13 (m, 2H), 7.07 (q, 2H), 7.04 – 6.90 (m, 4H), 5.05 (dd, 1H), 4.90 – 4.73 (m, 2H), 4.73 – 4.61 (m, 1H), 4.59 – 4.37 (m, 2H), 3.94 – 3.64 (m, 2H), 3.02 (dd, 2H), 2.86 (s, 3H), 2.70 – 2.41 (m, 1H), 1.92 – 1.68 (m, 1H), 1.26 (dd, 3H); LC-MS: 406.2 $[M+H]^+$.

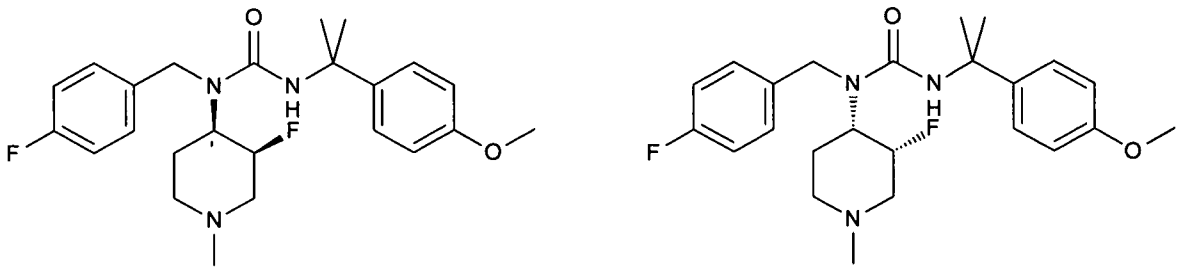
[00861] Example 159_3: 1-[(3S,4R)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[2-(4-methoxyphenyl)propan-2-yl]urea (159e) and 1-[(3R,4S)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[2-(4-methoxyphenyl)propan-2-yl]urea (159f)

[00862] 1-(2-Isocyanatopropan-2-yl)-4-methoxybenzene



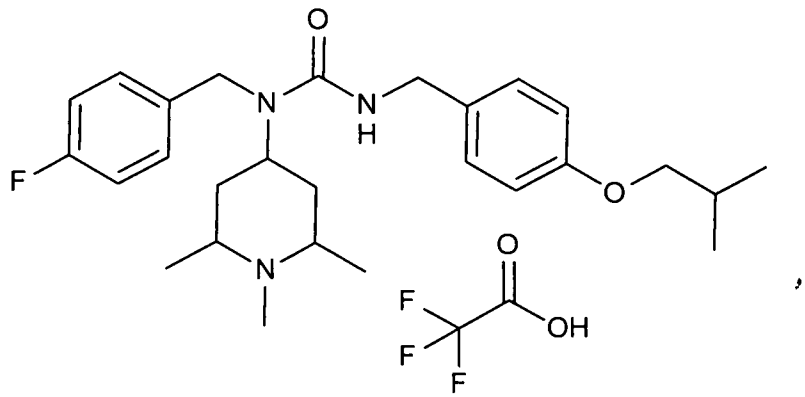
[00863] 2-(4-methoxyphenyl)propan-2-amine hydrochloride (202 mg, 1 mmol) was suspended in dichloromethane (5 ml). The mixture was washed with sodium hydroxide (1 M, 5 ml) and dried using a phase separator. Triethylamine (278 µl, 2 mmol) was added and the resulting mixture was added to diphosgene (121 µl, 1 mmol) in dichloromethane (5 ml). After 2 hours the mixture was washed with water (10 ml), dried using a phase separator and concentrated to afford the title compound (139 mg, 73%).

[00864] 1-[(3S,4R)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[2-(4-methoxyphenyl)propan-2-yl]urea and 1-[(3R,4S)-3-Fluoro-1-methylpiperidin-4-yl]-1-[(4-fluorophenyl)methyl]-3-[2-(4-methoxyphenyl)propan-2-yl]urea



[00865] A 1:1 mixture of (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (20 mg, 83.2 μmol) in dichloromethane (0.5 ml) was added 1-(2-isocyanatopropan-2-yl)-4-methoxybenzene (19.1 mg, 99.8 μmol). The mixture was stirred at ambient temperature for 1.5 hours before it was cooled to -20 °C. After 20 hours at -20 °C the mixture was heated to ambient temperature and stirred at this temperature for additionally 1 hour. The mixture was purified by column chromatography using silicone dioxide gel, eluting with 0-10% methanol in dichloromethane to afford the title compounds as a 1:1 mixture of enantiomers (27.6 mg, 64%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.21 (m, 2H), 7.13 – 7.06 (m, 2H), 7.06 – 7.00 (m, 2H), 6.84 – 6.70 (m, 2H), 4.84 (d, 1H), 4.67 (s, 1H), 4.62 – 4.36 (m, 3H), 3.77 (s, 3H), 3.17 – 3.05 (m, 1H), 2.98 – 2.87 (m, 1H), 2.28 (s, 3H), 2.23 – 2.10 (m, 3H), 1.68 – 1.56 (m, 1H), 1.48 (d, 6H); LC-MS: 432.2 $[M+H]^+$.

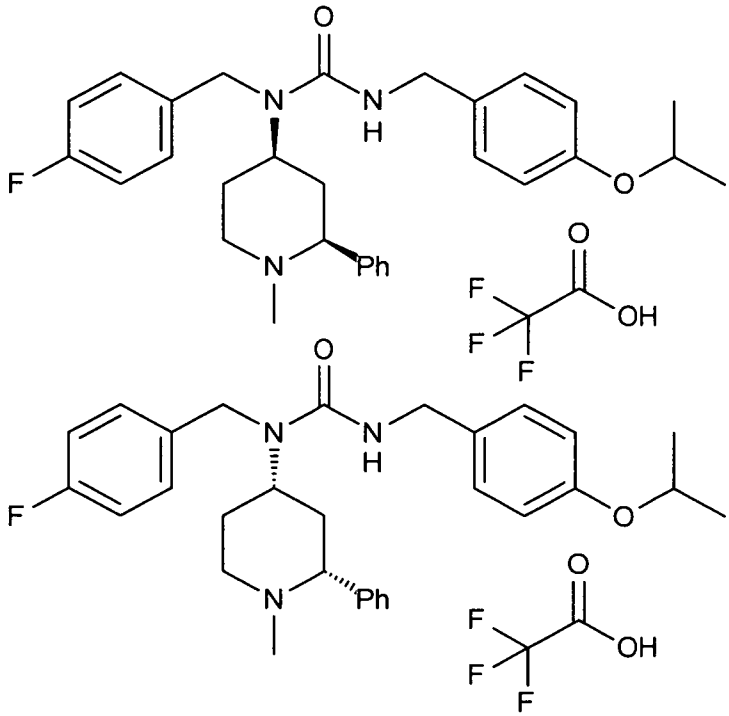
[00866] Example 160_2: 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}-1-(1,2,6-trimethylpiperidin-4-yl)urea; trifluoroacetic acid (160_2)



[00867] N-[(4-fluorophenyl)methyl]-1,2,6-trimethylpiperidin-4-amine (1 equivalent) in dichloromethane was added to 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (2 equivalents) in dichloromethane. The solution was stirred for 1 hour and then partitioned between dichloromethane and sodium hydroxide (aqueous, 0.5 M). The organic phase was separated, dried (sodium sulfate), filtered and evaporated. The crude product was purified by

column chromatography using silicon dioxide gel. Yield: 14 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.00 – 11.51 (m, 1H), 7.22 – 7.13 (m, 2H), 7.10 – 6.94 (m, 4H), 6.85 – 6.75 (m, 2H), 5.10 – 4.51 (m, 2H), 4.46 –4.31 (m, 2H), 4.26 (s, 2H), 3.89 –2.95 (m, 4H), 2.80 (d, 2H), 2.74 – 2.60 (m, 1H), 2.47 – 2.00 (m, 3H), 1.96 – 1.69 (m, 2H), 1.50 – 1.30 (m, 6H), 1.02 (d, 6H); LC-MS: 456.4 $[M+H]^+$.

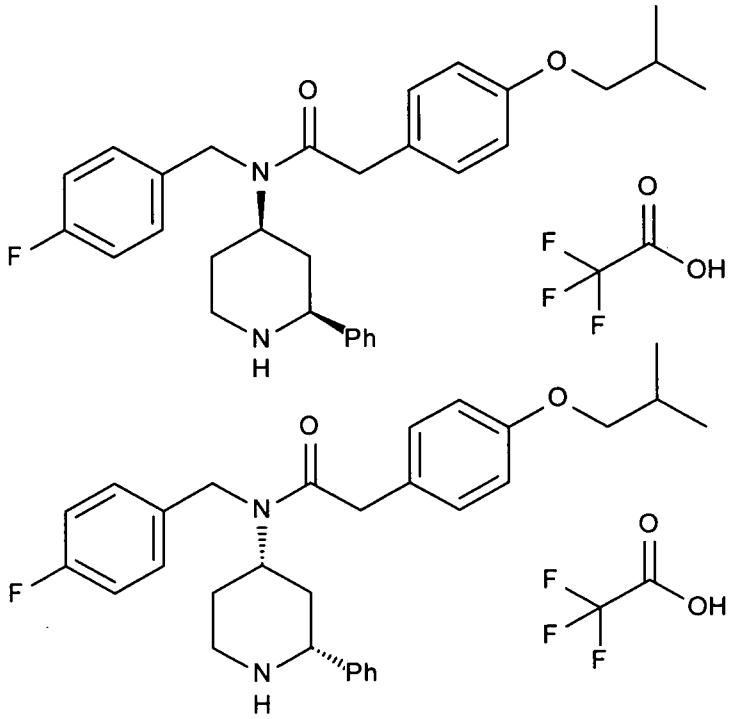
[00868] Example 161: 1-[(4-fluorophenyl)methyl]-1-[(2R,4S)-1-methyl-2-phenylpiperidin-4-yl]-3-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (161a) and 1-[(4-fluorophenyl)methyl]-1-[(2S,4R)-1-methyl-2-phenylpiperidin-4-yl]-3-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (161b)



[00869] The title compounds were prepared in analogy with example 124, using tert-butyl (2R,4S)-4-{[(4-fluorophenyl)methyl]amino}-2-phenylpiperidine-1-carboxylate and tert-butyl (2S,4R)-4-{[(4-fluorophenyl)methyl]amino}-2-phenylpiperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene. Isolated as a racemic mixture. Yield: 92 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (s, 5H), 7.18 (dd, 2H), 6.98 (dd, 4H), 6.76 (d, 2H), 5.03 – 4.88 (m, 1H), 4.64 (s, 1H), 4.60 – 4.34 (m, 3H), 4.25 (d, 2H), 3.81 (t, 2H), 3.08 – 2.60 (m, 2H), 2.51 (s, 3H), 2.41 (qd, 1H), 2.03 (dd, 2H), 1.31 (d, 6H); LC-MS: 490.6 $[M+H]^+$.

[00870] Example 162: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(2R,4S)-2-phenylpiperidin-4-yl]acetamide; trifluoroacetic acid (162a) and N-[(4-

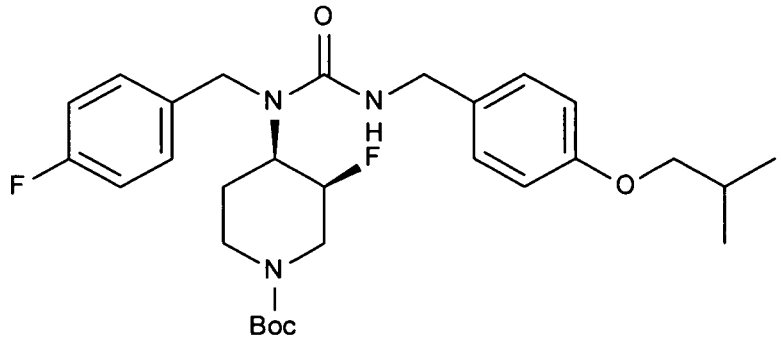
fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(2S,4R)-2-phenylpiperidin-4-yl]acetamide; trifluoroacetic acid (162b);



[00871] To a stirred solution of tert-butyl (2R,4S)-4-{[(4-fluorophenyl)methyl]amino}-2-phenylpiperidine-1-carboxylate and tert-butyl (2S,4R)-4-{[(4-fluorophenyl)methyl]amino}-2-phenylpiperidine-1-carboxylate (1:1, 150 mg, 390 μmol) and diisopropylethylamine (136 μl, 780 μmol) in dichloromethane (15 ml) was slowly added 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (102 mg, 429 μmol) as a solution in dichloromethane (0.5 ml). After stirring at room temperature for 2 hours the mixture was washed with water, extracted with dichloromethane (3 x 5 ml), dried and concentrated. The residue was re-dissolved in dichloromethane (10 ml) and treated with trifluoroacetic acid (1 ml) at room temperature for 3 hours and then concentrated and purified by HPLC, eluting with 30-75 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title product as a racemic mixture (124.4 mg, 67 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 6.90 (m, 11H), 6.82 (t, 2H), 4.98 – 4.35 (m, 2H), 4.18 – 3.42 (m, 4H), 2.83 (d, 1H), 2.27 (q, 1H), 2.06 (dt, 2H), 1.64 – 1.48 (m, 6H), 1.01 (d, 6H); LC-MS: 475.6 $[M+H]^+$.

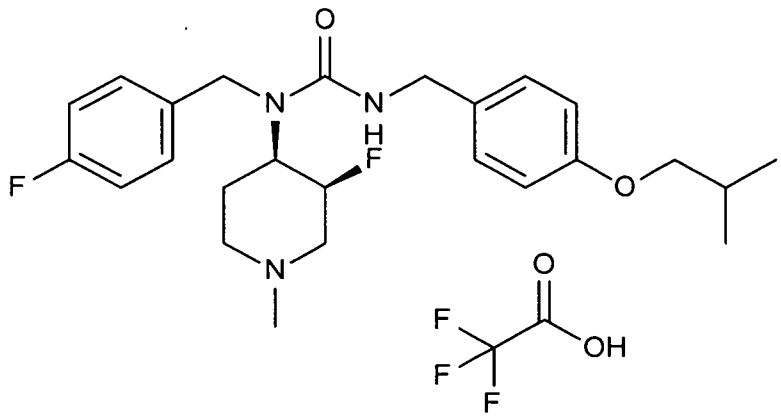
[00872] Example 163: 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (163)

[00873] tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate



[00874] 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (7.9 mg, 37 μmol) in dichloromethane (0.5 ml) was added to tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)-methyl]amino}piperidine-1-carboxylate (8.4 mg, 26 μmol). After 85 minutes of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 50 % ethyl acetate in petroleum ether to afford the desired urea (13 mg, 95 %).

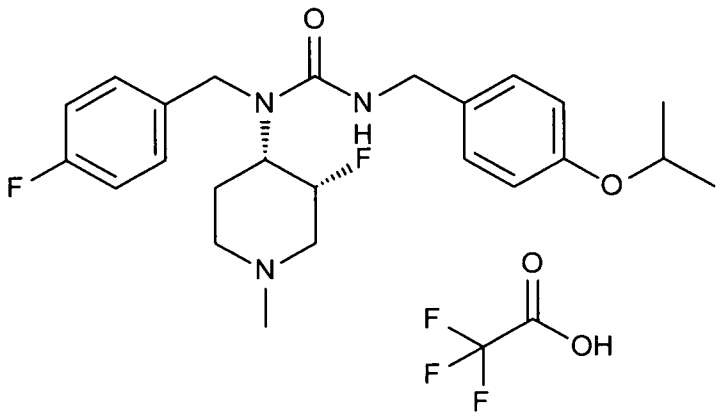
[00875] 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid



[00876] tert-Butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate (13 mg, 24 μmol) was dissolved in dichloromethane (3 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 (0.5 ml). Formaldehyde (37 % aqueous, 2.7 μl, 37 μmol) and sodium cyanoborohydride (3.1 mg, 49 μmol) were added. After 20 minutes the mixture was concentrated and re-dissolved in methanol (1 ml). The resulting mixture was heated to reflux for 80 minutes before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with 30-70 % acetonitrile in water (containing 0.1 %

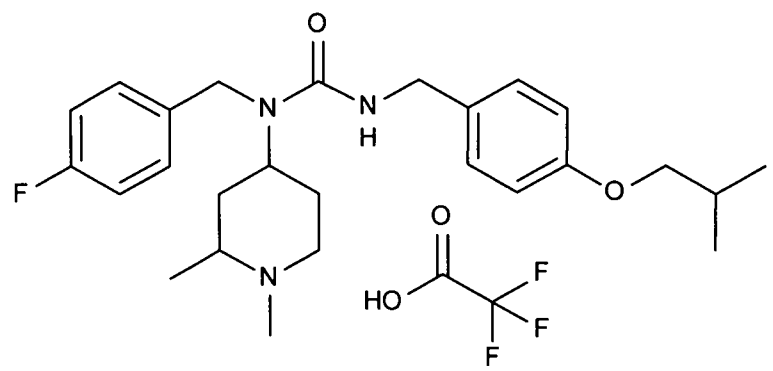
trifluoroacetic acid) to afford the title compound (10.5 mg, 75 %). ^{1}H NMR (400 MHz, Methanol-d4) δ 7.28 – 7.16 (m, 2H), 7.10 – 6.99 (m, 4H), 6.83 – 6.74 (m, 2H), 5.11 (d, 1H), 4.82 – 4.63 (m, 2H), 4.57 (d, 1H), 4.29 (d, 1H), 4.22 (d, 1H), 3.79 (t, 1H), 3.70 (d, 2H), 3.60 – 3.38 (m, 2H), 3.26 (t, 1H), 2.89 (s, 3H), 2.38 – 2.22 (m, 1H), 2.03 (dp, 1H), 1.86 (d, 1H), 1.02 (d, 6H); LC-MS: 446.3 $[M+H]^+$.

[00877] Example 164: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea; trifluoroacetic acid (164)



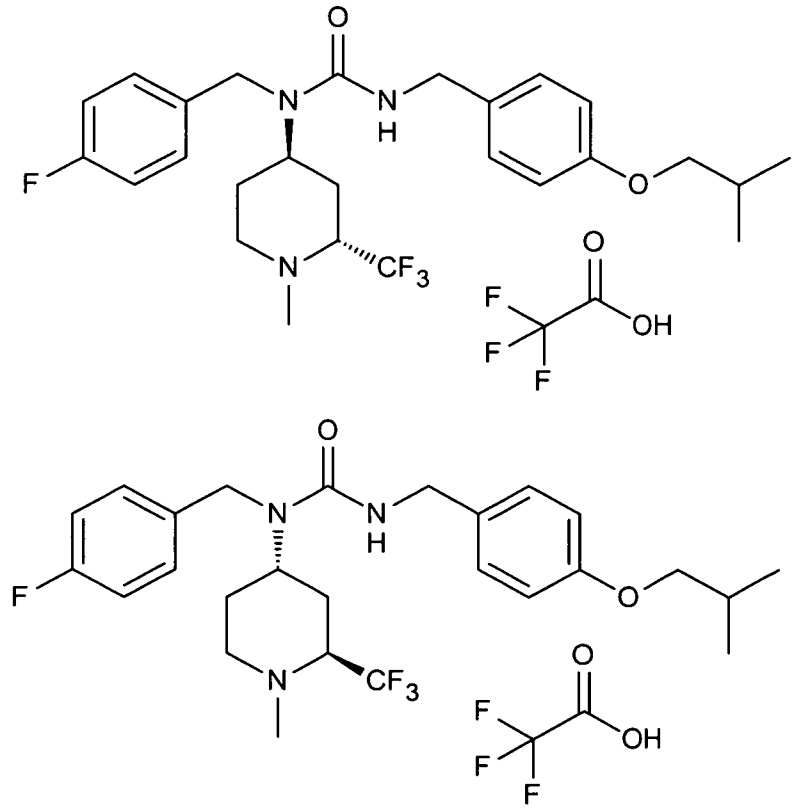
[00878] The compound was prepared in analogy with example 163 using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 1-(isocyanatomethyl)-4-(propan-2-yloxy)benzene. Yield: 55 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.10 (m, 2H), 7.02 (t, 2H), 6.93 (d, 2H), 6.82 – 6.71 (m, 2H), 5.10 (d, 1H), 4.84 (dd, 1H), 4.73 (s, 1H), 4.60 – 4.39 (m, 3H), 4.35 – 4.15 (m, 2H), 3.97 – 3.72 (m, 2H), 3.05 (dd, 1H), 2.97 – 2.78 (m, 4H), 2.71 – 2.48 (m, 1H), 1.83 (d, 1H), 1.32 (d, 6H); LC-MS: 432.1 $[M+H]^+$.

[00879] Example 165: 1-(1,2-dimethylpiperidin-4-yl)-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (165)



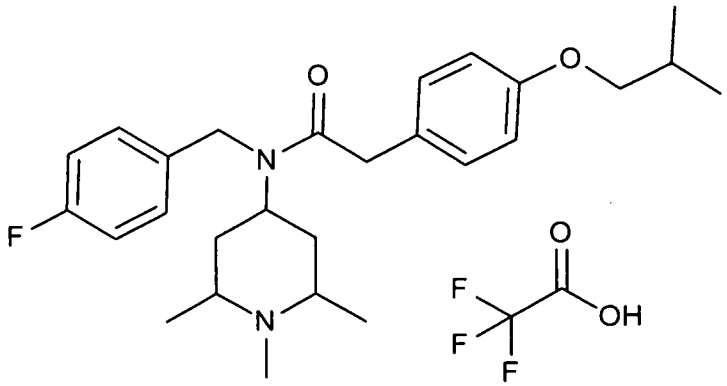
[00880] The compound was prepared in analogy with example 163 using tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-2-methylpiperidine-1-carboxylate and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Sodium triacetoxyborohydride was used instead of sodium cyanoborohydride in the methylation step. Yield: 56 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.15 (m, 2H), 7.05 – 6.95 (m, 4H), 6.78 (d, 2H), 4.84 – 4.72 (m, 1H), 4.61 (s, 1H), 4.38 (s, 2H), 4.26 (d, 2H), 3.68 (d, 2H), 3.59 (d, 1H), 2.97 (s, 1H), 2.77 (s, 4H), 2.31 – 1.81 (m, 5H), 1.44 (d, 3H), 1.02 (d, 6H); LC-MS: 442.3 $[M+H]^+$.

[00881] Example 166: 3-[(4-fluorophenyl)methyl]-3-[(2R,4R)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (166a) and 3-[(4-fluorophenyl)methyl]-3-[(2S,4S)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (166b)



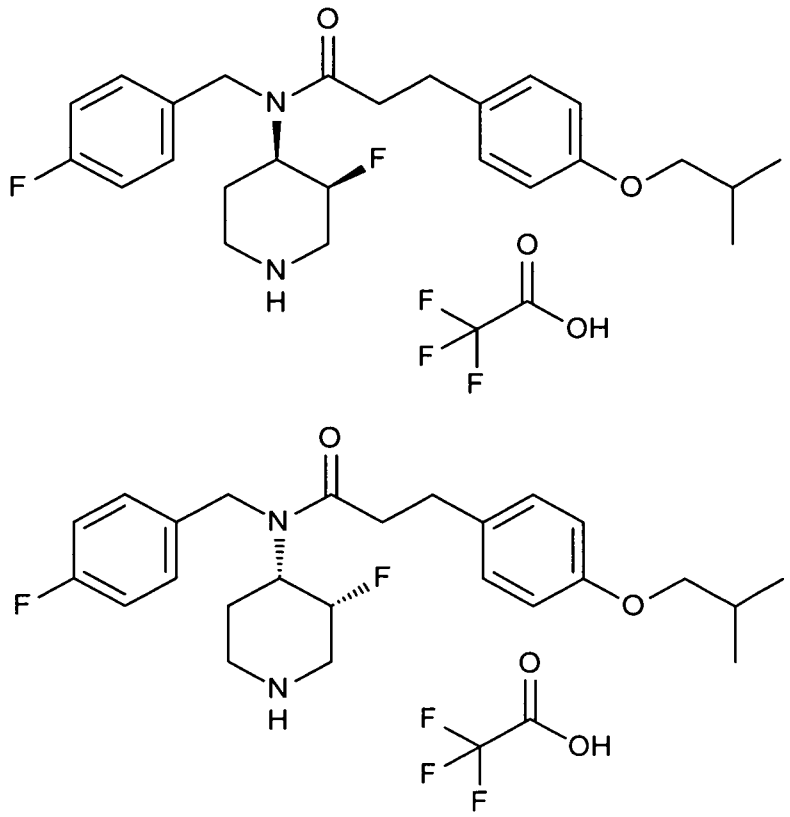
[00882] The compounds were prepared in analogy with example 163, using 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene and tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-2-(trifluoromethyl)piperidine-1-carboxylate. Isolated as a racemic mixture. Yield 3 %. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.23 – 7.14 (m, 2H), 7.03 (dd, 4H), 6.79 (d, 2H), 4.79 (s, 1H), 4.54 (s, 1H), 4.34 (s, 2H), 4.35 – 4.20 (m, 2H), 3.76 (s, 1H), 3.69 (d, 2H), 3.21 (d, 1H), 3.06 (s, 1H), 2.75 (s, 3H), 2.13 – 1.85 (m, 5H), 1.02 (d, 6H); LC-MS: 496.3 $[M+H]^+$.

[00883] Example 167: N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-(1,2,6-trimethylpiperidin-4-yl)acetamide; trifluoroacetic acid (167)



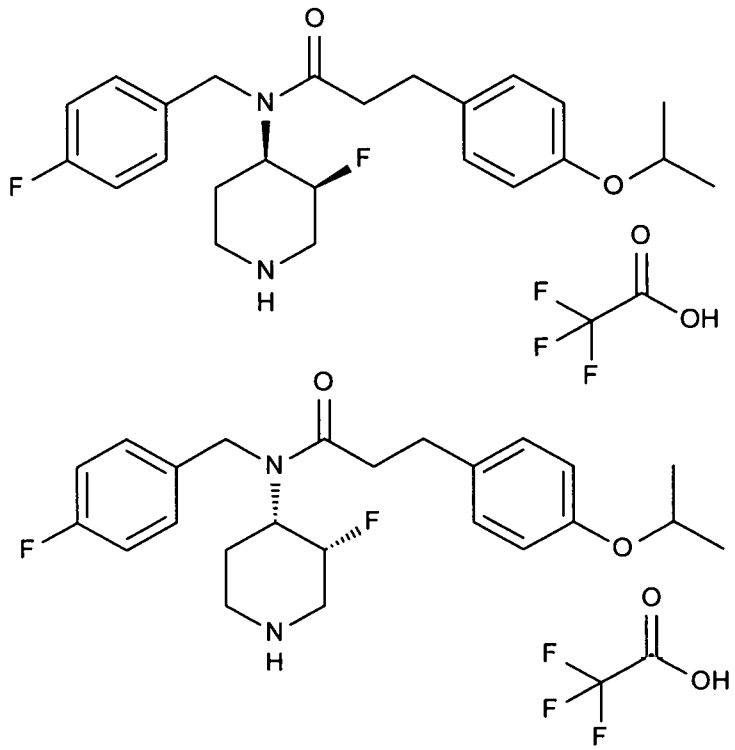
[00884] N-[(4-fluorophenyl)methyl]-1,2,6-trimethylpiperidin-4-amine (1 equivalent) was dissolved in dichloromethane. Pyridine (3 equivalents) was added followed by 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (1.2 equivalents) dissolved in dichloromethane. The mixture was stirred for 20 hours and then partitioned between dichloromethane and sodium hydroxide (aqueous, 0.5 M). The organic phase was dried and evaporated. The material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid) Yield: 31 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.81 – 11.97 (m, 1H), 7.25 – 6.99 (m, 6H), 6.92 – 6.79 (m, 2H), 5.22 – 4.86 (m, 1H), 4.64 – 4.39 (m, 2H), 3.85 – 3.48 (m, 4H), 3.39 – 2.89 (m, 1H), 2.81 -1.99 (m, 8H), 1.82 – 1.46 (m, 1H), 1.45 – 1.19 (m, 6H), 1.02 (d, 6H); LC-MS: 441.4 $[M+H]^+$.

[00885] Example 168: N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide; trifluoroacetic acid (168a) and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide; trifluoroacetic acid (168b)



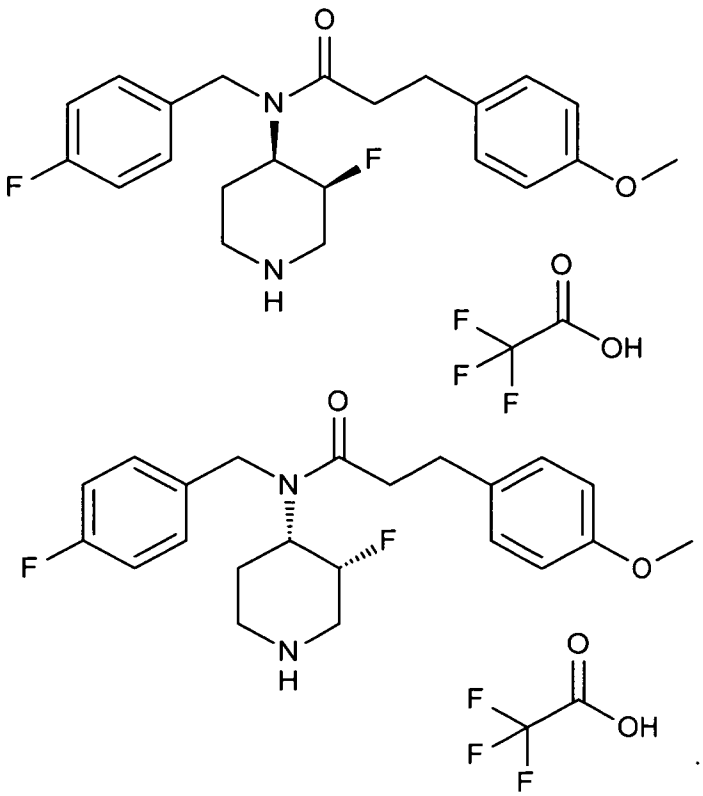
[00886] tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) (1 equivalent) in dimethylformamide was added to a solution of 3-[4-(2-methylpropoxy)phenyl]propanoic acid (1 equivalent), diisopropylethylamine (3 equivalents) and *N*-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate *N*-oxide (1.1 equivalent) in dimethylformamide. The mixture was stirred at room temperature overnight, then diluted with brine and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography using silicon dioxide gel. The material was dissolved in dichloromethane and trifluoroacetic acid was added. After 20 minutes the reaction mixture was concentrated. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid), and isolated as a racemic mixture. Yield: 44 %. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.04 – 6.92 (m, 6H), 6.84 – 6.76 (m, 2H), 5.07 – 4.77 (m, 2H), 4.52 (q, 2H), 3.68 (d, 2H), 3.57 (t, 1H), 3.40 (d, 1H), 3.17 (dd, 1H), 3.01 – 2.83 (m, 3H), 2.70 – 2.46 (m, 2H), 2.34 – 2.17 (m, 1H), 2.06 (dt, 1H), 1.55 (d, 1H), 1.43 (s, 1H), 1.01 (d, 6H); LC-MS: 431.3 $[M+H]^+$.

[00887] Example 169: N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide; trifluoroacetic acid (169a) and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide; trifluoroacetic acid (169b)



[00888] The compounds were prepared in analogy with example 168, using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 3-[4-(propan-2-yloxy)phenyl]propanoic acid. Dichloromethane was used as solvent. Isolated as a racemic mixture. Yield: 49 %. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.04 – 6.93 (m, 6H), 6.78 (d, 2H), 5.08 – 4.77 (m, 2H), 4.65 – 4.42 (m, 3H), 3.57 (t, 1H), 3.40 (d, 1H), 3.16 (dd, 1H), 3.02 – 2.83 (m, 3H), 2.69 – 2.46 (m, 2H), 2.33 – 2.16 (m, 1H), 1.55 (d, 1H), 1.43 (s, 1H), 1.31 (d, 6H); LC-MS: 417.2 $[M+H]^+$.

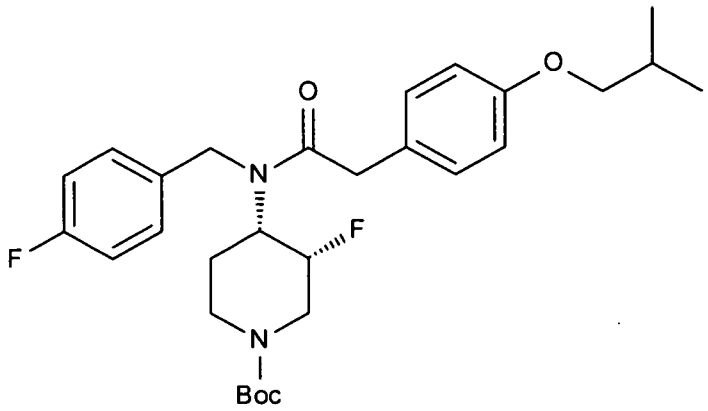
[00889] Example 170: N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-(4-methoxyphenyl)propanamide (170a) and N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-(4-methoxyphenyl)propanamide; trifluoroacetic acid (170b)



[00890] The compounds were prepared in analogy with example 168, using tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 3-[4-(propan-2-yloxy)phenyl]propanoic acid. Isolated as a racemic mixture. Yield: 48 %. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.09 – 6.90 (m, 6H), 6.89 – 6.72 (m, 2H), 5.10 – 4.74 (m, 2H), 4.54 (q, 2H), 3.78 (s, 3H), 3.70 (s, 1H), 3.66 – 3.51 (m, 1H), 3.40 (d, 1H), 3.17 (dd, 1H), 3.04 – 2.81 (m, 3H), 2.70 – 2.45 (m, 2H), 2.33 – 2.16 (m, 1H), 1.55 (d, 1H); LC-MS: 389.1 $[M+H]^+$.

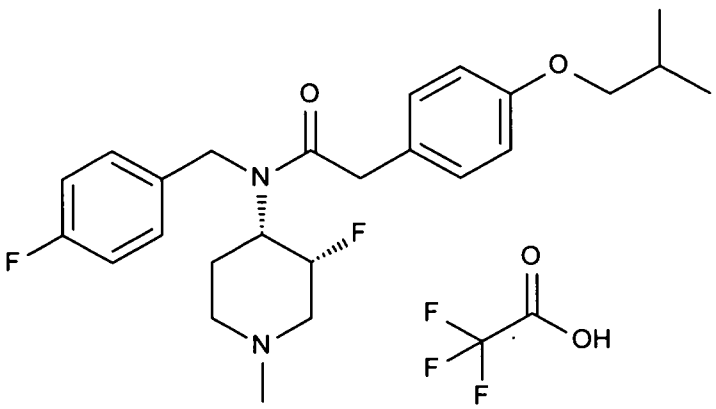
[00891] Example 171: N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluoro-phenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (171)

[00892] tert-butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamido}piperidine-1-carboxylate



[00893] 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (24.2 mg, 107 μmol) in dichloromethane (0.5 ml) was added to tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)-methyl]amino}piperidine-1-carboxylate (29.0 mg, 88.9 μmol) and diisopropylethylamine (23 μl, 133 μmol) in dichloromethane (0.5 ml). After 2.5 hours of stirring at ambient temperature, additional 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (10 mg, 44 μmol) was added. After 1 hour, the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 10-50 % ethyl acetate in petroleum ether to afford the desired amide (41.8 mg, 91 %).

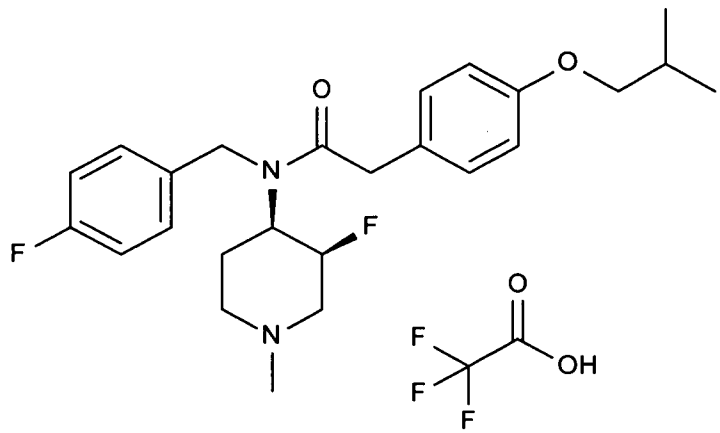
[00894] N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid



[00895] tert-butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamido}piperidine-1-carboxylate (41.8 mg) was dissolved in dichloromethane (1.5 ml) and trifluoroacetic acid (0.5 ml) was added. After 10 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofuran (1.5 ml). Formaldehyde (37 % aqueous, 9.0 μl, 121 μmol) and sodium

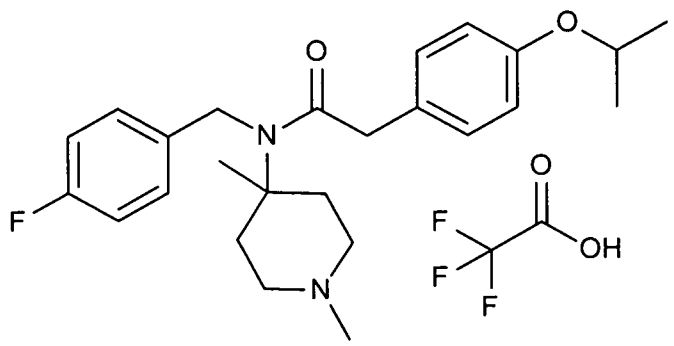
cyanoborohydride (10.2 mg, 162 μmol) were added. After 3 hours, the mixture was concentrated and re-dissolved in methanol (1 ml). The resulting mixture was heated to reflux for 2 hours before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with 40-70 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (23 mg 52 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 – 7.11 (m, 2H), 7.11 – 6.97 (m, 4H), 6.83 (d, 2H), 5.03 (d, 1H), 4.87 (dd, 1H), 4.76 (d, 1H), 4.60 (d, 1H), 3.90 – 3.73 (m, 1H), 3.73 – 3.62 (m, 3H), 3.59 (s, 2H), 3.13 – 2.87 (m, 1H), 2.78 (s, 4H), 2.60 – 2.36 (m, 1H), 2.07 (dp, 1H), 1.65 (d, 1H), 1.02 (d, 6H); LC-MS: 431.2 $[M+H]^+$.

[00896] Example 172: N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)-methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide; trifluoroacetic acid (172)



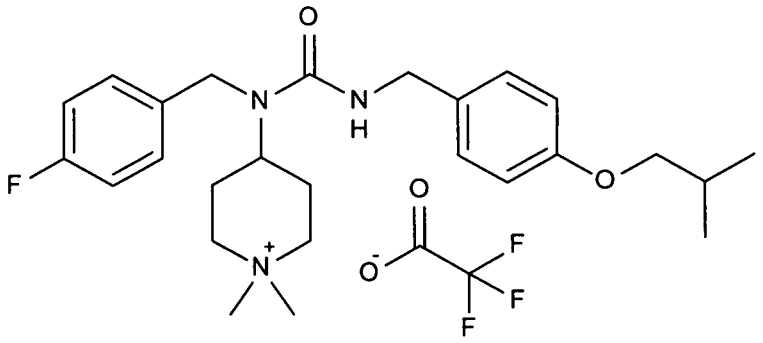
[00897] The compound was prepared in analogy with example 171 using tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and 2-[4-(2-methylpropoxy)phenyl]acetyl chloride. Yield: 50 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 7.04 (m, 4H), 7.01 (d, 2H), 6.84 (d, 2H), 5.05 (d, 1H), 4.99 – 4.84 (m, 1H), 4.79 (d, 1H), 4.61 (d, 1H), 3.93 (t, 1H), 3.74(d, 1H), 3.70 (d, 2H), 3.63 (s, 2H), 3.13 (dd, 1H), 2.99 – 2.79 (m, 4H), 2.59 –2.43 (m, 1H), 2.08 (dp, 1H), 1.70 (d, 1H), 1.02 (d, 6H); LC-MS: 431.3 $[M+H]^+$.

[00898] Example 173: (N-(1,4-dimethylpiperidin-4-yl)-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide; trifluoroacetic acid (173)



[00899] The title compound was prepared in analogy with example 171 from tert-butyl 4-{[(4-fluorophenyl)methyl]amino}-4-methylpiperidine-1-carboxylate and 2-[4-(propan-2-yloxy)phenyl]acetyl chloride. Yield: 67 %. Major conformer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.01 (m, 6H), 6.83 (d, 2H), 4.57 (s, 2H), 4.51 (p, 1H), 3.59 (s, 2H), 3.50 (d, 2H), 2.78 (d, 5H), 2.56 (d, 2H), 2.28 (dt, 2H), 1.63 (s, 3H), 1.33 (d, 6H). Minor conformer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.01 (m, 6H), 6.86 (d, 2H), 4.59 (s, 2H), 4.51 (p, 1H), 3.66 (s, 2H), 3.43 – 3.33 (m, 2H), 3.11 (d, 2H), 2.78 (s, 3H), 2.72 – 2.63 (m, 2H), 1.83 – 1.73 (m, 2H), 1.33 (d, 9H). LC-MS: 413.3 $[M+H]^+$.

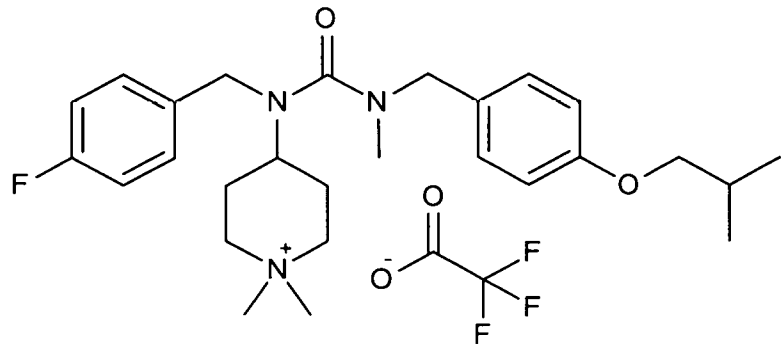
[00900] Example 171: 4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}-1,1-dimethylpiperidin-1-ium trifluoroacetate (174)



[00901] To a stirred solution of 1-[(4-fluorophenyl)methyl]-1-(1-methylpiperidin-4-yl)-3-{[4-(2-methylpropoxy)phenyl]methyl}urea (85.5 mg, 0.2 mmol) in tetrahydrofuran (3 ml) at 0 °C was added sodium hydride (14.4 mg, 0.3 mmol) in one portion. After 30 minutes, a solution of methyl iodide (24.8 µl, 0.4 mmol) in tetrahydrofuran (250 µl) was added dropwise. The reaction mixture was stirred for 1 hour at 0 °C then warmed to room temperature. After 12 hours, the reaction mixture was cooled to 0 °C and water (100 µl) was added. The mixture was concentrated under reduced pressure and partitioned between ethyl acetate (15 ml) and brine (15 ml). The organic phase was separated and concentrated under

reduced pressure. The crude material was purified by HPLC, eluting with 35-70 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (20 mg, 18 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 (dd, 2H), 7.08 (d, 2H), 7.00 (t, 2H), 6.79 (d, 2H), 5.38 (bs, 1H), 4.43 (s, 2H), 4.26 (s, 2H), 4.16 – 4.09 (m, 1H), 3.72 – 3.67 (m, 3H), 3.45 (d, 2H), 3.21 (s, 3H), 3.13 (s, 3H), 2.44 (q, 2H), 2.05 (m, 2H), 1.85 (d, 2H), 1.01 (d, 6H); LC-MS: 442.3 $[M]^+$.

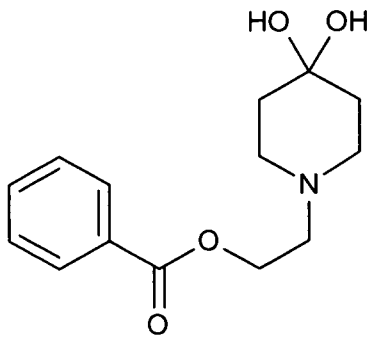
[00902] Example 175: 4-{[(4-fluorophenyl)methyl][methyl({[4-(2-methylpropoxy)-phenyl]methyl})carbamoyl]amino}-1,1-dimethylpiperidin-1-ium; trifluoroacetate (175)



[00903] To a stirred solution of 1-[(4-fluorophenyl)methyl]-1-(1-methylpiperidin-4-yl)-3-{[4-(2-methylpropoxy)phenyl]methyl}urea (85.5 mg, 0.2 mmol) in tetrahydrofuran (3 ml) at -65 °C was added a solution of lithium bis(trimethylsilyl)amide, (260 µl, 1 M in tetrahydrofuran, 0.26 mmol) in one portion. After 30 minutes, a solution of methyl iodide (24.8 µl, 0.4 mmol) in tetrahydrofuran (250 µl) was added dropwise. The reaction mixture was stirred for 1 hour at -65 °C, warmed to -10 °C and stirred at this temperature for 1 hour. The reaction was allowed to reach room temperature. After 1 hour, more methyl iodide (24.8 µl, 0.4 mmol) in tetrahydrofuran (250 µl) was added. After 12 hours, the reaction mixture was cooled to 0 °C and water (100 µl) was added. The mixture was concentrated under reduced pressure and partitioned between dichloromethane (15 ml) and water (15 ml). The water phase was extracted with dichloromethane (2 x 20 ml) and the combined organic phases were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by HPLC, eluting with 35-70 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (55 mg, 48 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 – 7.14 (m, 2H), 7.10 – 6.98 (m, 4H), 6.85 (d, 2H), 4.38 (s, 2H), 4.29 (s, 2H), 3.70 (d, 2H), 3.47 (dt, 4H), 3.35 – 3.25 (m, 1H), 3.20 (d, 6H), 2.83 (q, 2H), 2.73 (s, 3H), 2.08 (m, 1H), 1.83 (d, 2H), 1.02 (d, 6H); LC-MS: 456.3 $[M+H]^+$.

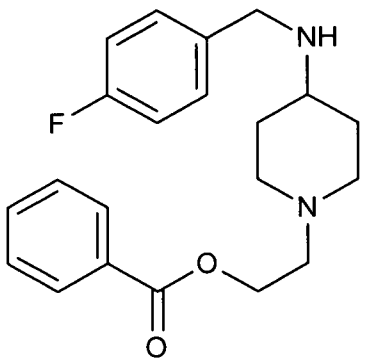
[00904] Example 176: N-[(4-fluorophenyl)methyl]-N-[1-(2-hydroxyethyl)-1-oxo-1λ^5-piperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide (176)

[00905] 2-(4,4-dihydroxypiperidin-1-yl)ethyl benzoate



[00906] 2-Chloroethanol (682 µl, 10.2 mmol) was added to benzoyl chloride (590 µl, 5.08 mmol) and dimethylaminopyridine (62.1 mg, 508 µmol) in dichloromethane (20 ml). After 1 hour of stirring at ambient temperature the mixture was washed with hydrochloric acid (aqueous, 1M, 20 ml), dried (phase-separator) and concentrated. The crude was dissolved in dimethylformamide (20 ml) and sodium iodide (76 mg, 508 µmol), potassium carbonate (2.11 g, 15.2 mmol) and piperidine-4,4-diol hydrochloride (1.56 g, 10.2 mmol) were added. The mixture was heated to 140 °C and stirred at that temperature for 2 hours before it was cooled to ambient temperature and diluted with ethyl acetate (200 ml). The mixture was washed with water (5 x 200 ml), dried (phase separator) and concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 25-50 % ethyl acetate in petroleum ether to give the desired ether (267 mg, 20 %).

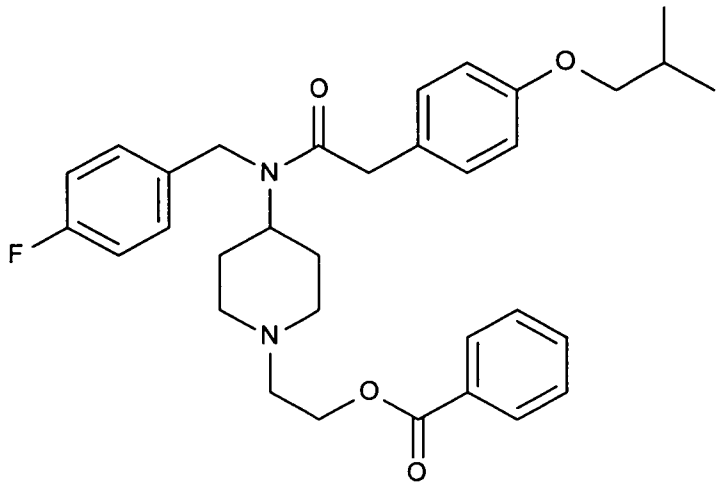
[00907] 2-(4-{[(4-fluorophenyl)methyl]amino}piperidin-1-yl)ethyl benzoate



[00908] Sodium triacetoxyborohydride (427 mg, 2.01 mmol) was added to 4-fluoro-benzylamine (127 µl, 1.11 mmol) and 2-(4,4-dihydroxypiperidin-1-yl)ethyl benzoate (267 mg, 1.01 mmol) in ethanol (5 ml). The mixture was stirred at ambient temperature for 1.5

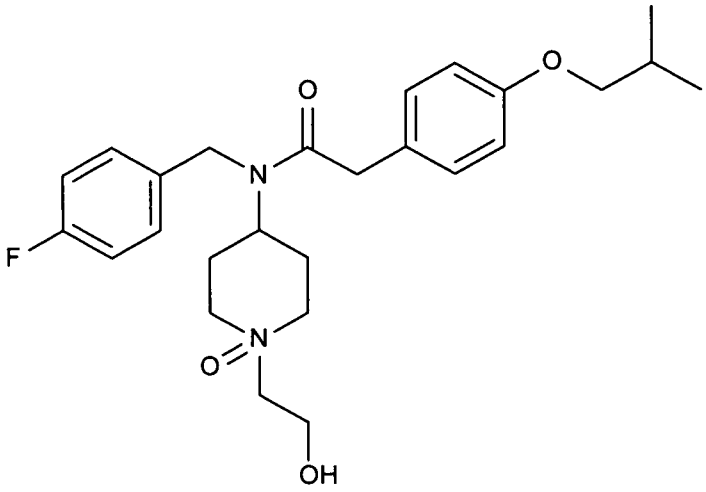
hours before it was concentrated. Sodium hydroxide (aqueous, 1 M, 5 ml) was added and the mixture was extracted with dichloromethane (3 x 5 ml). The organic phase was dried (phase-separator) and concentrated to yield the desired amine (379 mg), which was used without further purification.

[00909] 2-(4-{N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-acetamido}piperidin-1-yl)ethyl benzoate



[00910] 2-[4-(2-Methylpropoxy)phenyl]acetyl chloride (289 mg, 1.28 mmol) was added to 2-(4-{[(4-fluorophenyl)methyl]amino}piperidin-1-yl)ethyl benzoate (379 mg) and triethylamine (296 µl, 2.13 mmol) in dichloromethane (5 ml). After 1 hour of stirring at ambient temperature, additional 2-[4-(2-methylpropoxy)phenyl]acetyl chloride (145 mg, 640 µmol) was added. The resulting mixture was stirred for 30 minutes before it was diluted with water (10 ml). The organic phase was separated. The aqueous phase was extracted with dichloromethane (2 x 5 ml). The combined organic phase was dried (phase-separator) and concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 50-100 % ethyl acetate in petroleum ether to give the desired amide (524 mg, 90 %).

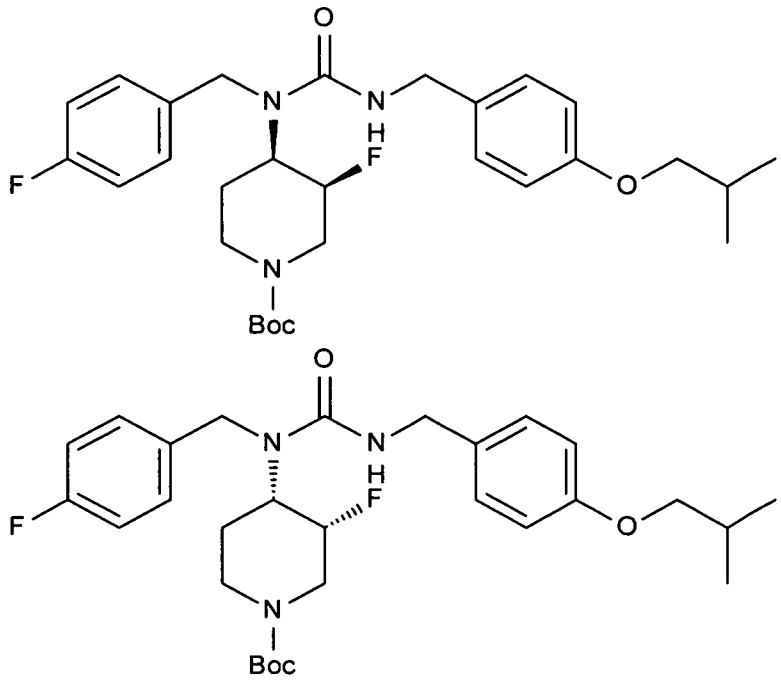
[00911] N-[(4-fluorophenyl)methyl]-N-[1-(2-hydroxyethyl)-1-oxo-1λ^5-piperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide



[00912] Sodium hydroxide (aqueous, 50 %, 29 µl, 549 µmol) was added to 2-(4-{N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamido}piperidin-1-yl)ethyl benzoate (200 mg, 366 µmol) in methanol (2 ml). After 30 minutes of stirring at ambient temperature the mixture was concentrated. Sodium hydroxide (aqueous, 1M, 1 ml) was added and the resulting mixture was extracted with dichloromethane (3 x 1 ml). The combined organic phase was washed with brine (1 ml), dried (phase-separator) and concentrated. The crude was dissolved in dichloromethane (1 ml) and cooled to 0 °C. 3-Chloroperoxybenzoic acid (50 %, 189 mg, 549 µmol) in dichloromethane (1 ml) was added and the mixture was stirred for 30 minutes before it was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 0-20 % methanol in dichloromethane to afford the title compound (132.5 mg, 79 %). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 – 7.14 (m, 2H), 7.05 (t, 4H), 6.83 (d, 2H), 4.81 (t, 1H), 4.58 (d, 2H), 4.05 (s, 2H), 3.69 (d, 2H), 3.55 (s, 2H), 3.49 (d, 2H), 3.35 (s, 2H), 3.12 (t, 2H), 2.47 (q, 2H), 2.07 (dp, 1H), 1.59 (d, 2H), 1.02 (d, 6H); LC-MS: 459.3 $[M+H]^+$.

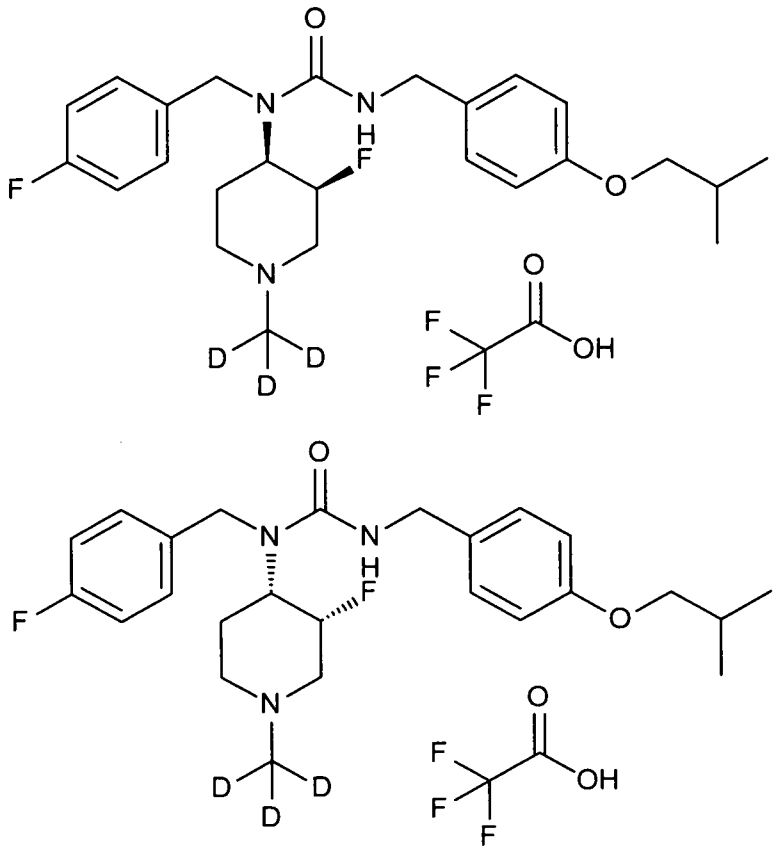
[00913] Example 177: 3-[(3R,4S)-3-fluoro-1-($^2H_3$)methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (177a) and 3-[(3S,4R)-3-fluoro-1-($^2H_3$)methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (177b)

[00914] tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate



[00915] 1-(Isocyanatomethyl)-4-(2-methylpropoxy)benzene (1.38 g, 6.74 mmol) was added to 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, 2.00 g, 6.13 mmol) in dichloromethane (20 ml). After 90 minutes of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel, eluting with 10-20 % ethyl acetate in dichloromethane to afford the desired ureas (2.55 g, 78 %), as a racemic mixture.

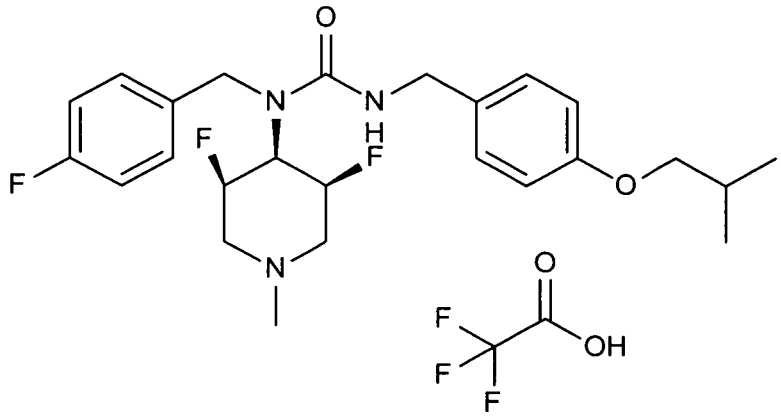
[00916] 3-[(3R,4S)-3-fluoro-1-($^2H_3$)methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid and 3-[(3S,4R)-3-fluoro-1-($^2H_3$)methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]-methyl}urea; trifluoroacetic acid



[00917] tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidine-1-carboxylate (1:1, 2.55 g, 4.79 mmol) was dissolved in dichloromethane (20 ml) and trifluoroacetic acid (1 ml) was added. After 1 hour of stirring at ambient temperature additional trifluoroacetic acid (1 ml) was added. The mixture was stirred for 15 hours before additional trifluoroacetic acid (1 ml) was added. After 1.5 hours, the mixture was concentrated, re-dissolved in dichloromethane (20 ml) and washed with sodium hydrogen carbonate (aqueous, saturated, 20 ml). The aqueous phase was extracted with dichloromethane (20 ml). The combined organic phase was dried (phase-separator) and concentrated. The crude was filtered through a plug of silicon dioxide gel, eluting with 10 % methanol in dichloromethane to afford the deprotected amine (1.40 g, 68 %). The deprotected amine (100 mg) was dissolved in acetone (5 ml). Potassium carbonate (64.1 mg, 463 µmol) and deuterated iodomethane (14.4 µl, 232 µmol) were added. After stirring at ambient temperature for 2 hours the mixture was diluted with water (10 ml) and extracted with dichloromethane (3 x 10 ml). the organic phase was dried (phase-separator) and concentrated. The crude material was purified by column chromatography

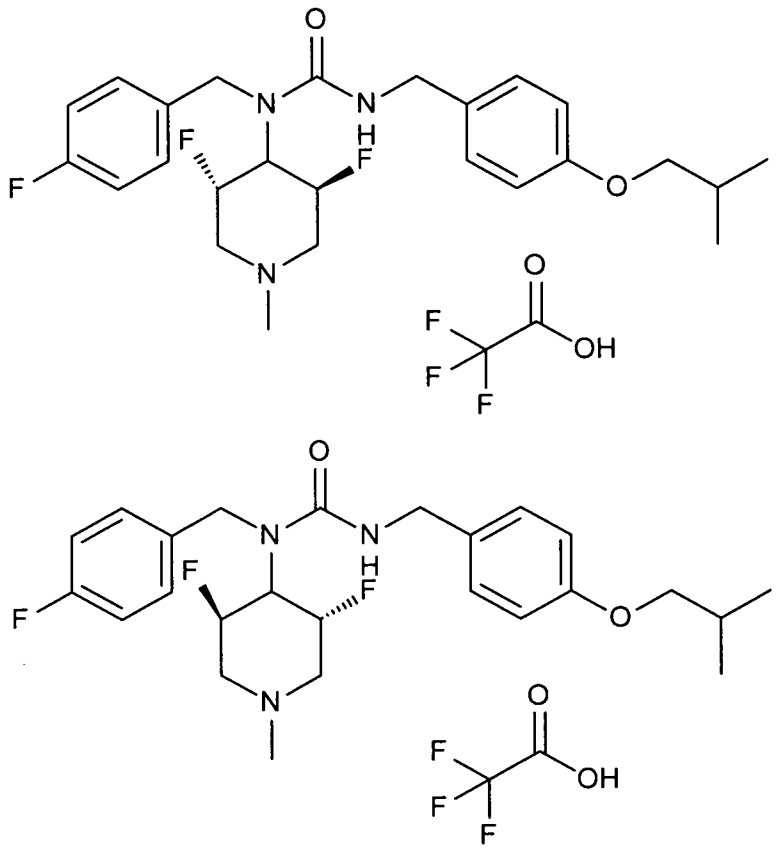
using silicon dioxide gel, eluting with 5-20 % methanol. Fractions containing product were pooled, concentrated and re-purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds (28 mg, 27 %), as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.09 (m, 2H), 7.03 (t, 2H), 6.94 (d, 2H), 6.78 (d, 2H), 5.10 (d, 1H), 4.94 – 4.76 (m, 1H), 4.76 – 4.66 (m, 1H), 4.54 (d, 1H), 4.45 (d, 1H), 4.34 – 4.15 (m, 2H), 3.98 – 3.76 (m, 2H), 3.69 (d, 2H), 3.03 (dd, 1H), 2.90 (t, 1H), 2.60 (d, 1H), 2.07 (dt, 1H), 1.83 (d, 1H), 1.02 (d, 6H); LC-MS: 449.3 $[M+H]^+$.

[00918] Example 178: 1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R,4s,5S)-3,5-difluoro-1-methylpiperidin-4-yl]urea; trifluoroacetic acid (178)



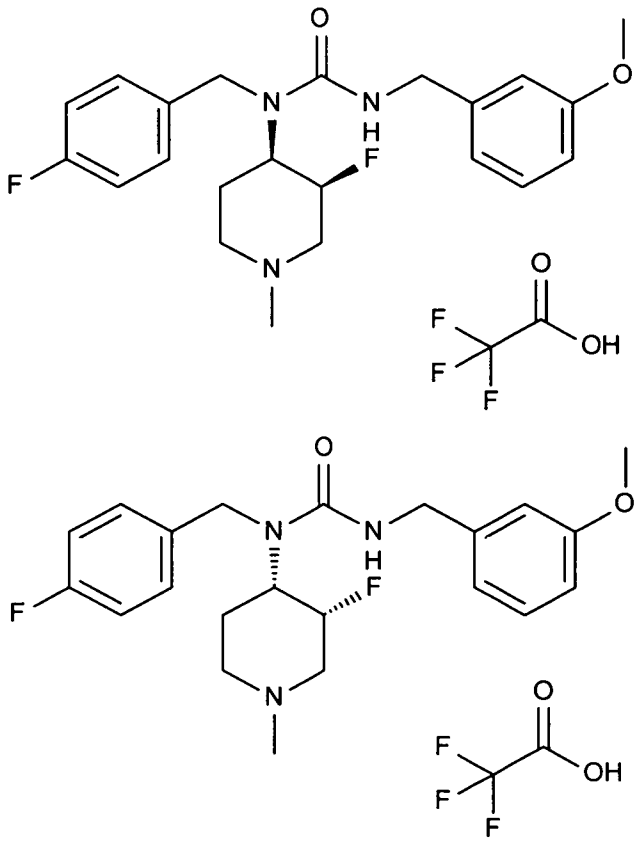
[00919] 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (1.4 equivalents) in dichloromethane was added to tert-butyl (3R,5S)-3,5-difluoro-4-{[(4-fluorophenyl)-methyl]amino}piperidine-1-carboxylate (1 equivalent). After 85 minutes of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel to afford the intermediate urea. The material was dissolved in dichloromethane and trifluoroacetic acid was added. After 20 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofuran. Formaldehyde (37 % aqueous, 1.5 equivalents) and sodium cyanoborohydride (2 equivalents) were added. After 20 minutes the mixture was concentrated and re-dissolved in methanol. The resulting mixture was heated to reflux for 80 minutes before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Yield: 45 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.18 (m, 2H), 7.11 (t, 2H), 7.00 (d, 2H), 6.86 (d, 2H), 5.32 – 4.94 (m, 4H), 4.84 (s, 2H), 4.31 (s, 2H), 3.88 (s, 2H), 3.77 (d, 2H), 3.72 – 3.37 (m, 2H), 3.03 (s, 3H), 2.15 (dp, 1H), 1.11 (d, 6H); LC-MS: 464.3 $[M+H]^+$.

[00920] Example 179: 3-[(3R,5R)-3,5-difluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (179a) and 3-[(3S,5S)-3,5-difluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (179b)



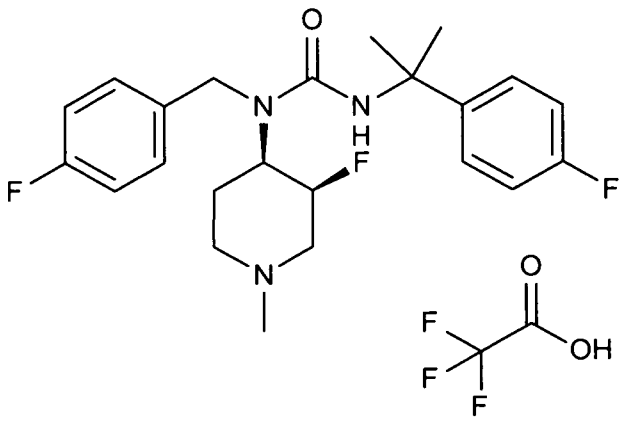
[00921] The compounds were prepared in analogy with example 178 using tert-butyl (3R,5R)-3,5-difluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate and tert-butyl (3S,5S)-3,5-difluoro-4-{[(4-fluorophenyl)methyl]amino}piperidine-1-carboxylate (1:1) and 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene. Isolated as a racemic mixture. Yield: 50 %. ^{1}H NMR (400 MHz, Methanol-d4) δ 7.33 – 7.24 (m, 2H), 7.02 (t, 2H), 6.97 (d, 2H), 6.76 (d, 2H), 5.40 – 5.11 (m, 2H), 5.01 (dt, 1H), 4.70 (s, 2H), 4.27 (d, 1H), 4.22 (d, 1H), 3.91 (d, 1H), 3.82 (t, 1H), 3.70 (d, 2H), 3.52 (dd, 1H), 3.42 – 3.32 (m, 1H), 2.99 (s, 3H), 2.03 (dp, 1H), 1.02 (d, 6H); LC-MS: 464.3 $[M+H]^+$.

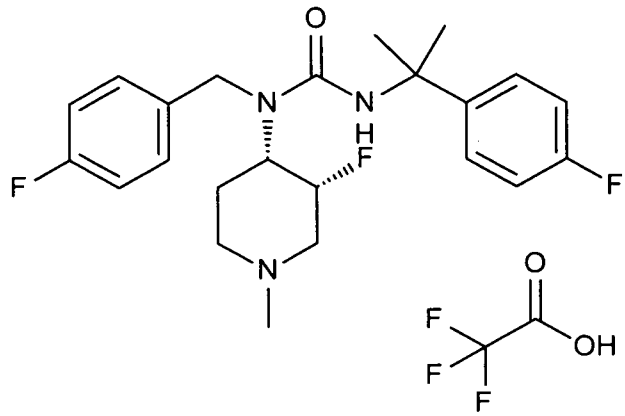
[00922] Example 180: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-[(3-methoxyphenyl)methyl]urea; trifluoroacetic acid (180a) and 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(3-methoxyphenyl)methyl]urea; trifluoroacetic acid (180b)



[00923] (3-Methoxyphenyl)methanamine (13.3 µl, 104 µmol) and triethylamine (35 µl, 250 µmol) in dichloromethane (0.5 ml) were added to diphosgene (6 µl, 50 µmol) in dichloromethane (0.5 ml), using a syringe pump (0.5 ml/hour). The mixture was stirred for additionally 1 hour at ambient temperature before (3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (1:1, 20 mg, 83 µmol) in dichloromethane (0.5) ml were added. After 2 hours, the mixture was concentrated. The crude material was purified by HPLC, eluting with 20-85 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compounds (24 mg 45 %), as a racemic mixture: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (t, 3H), 7.12 (t, 2H), 6.86 (dd, 1H), 6.75 – 6.60 (m, 2H), 5.18 (d, 1H), 5.01 – 4.80 (m, 2H), 4.64 (d, 2H), 4.47 – 4.29 (m, 2H), 4.02 – 3.70 (m, 5H), 3.32 – 2.96 (m, 2H), 2.92 (s, 3H), 2.80 – 2.51 (m, 1H), 1.91 (d, 1H).; LC-MS: 404.1 $[M+H]^+$.

[00924] Example 181: 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)-methyl]-1-[2-(4-fluorophenyl)propan-2-yl]urea; trifluoroacetic acid (181a) and 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[2-(4-fluorophenyl)propan-2-yl]urea; trifluoroacetic acid (181b)

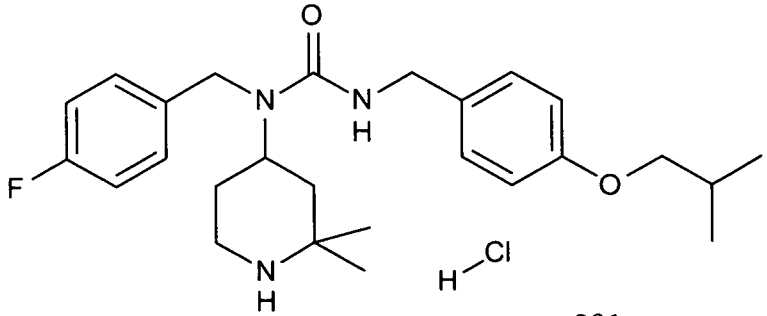




[00925] The compounds were prepared in analogy with example 180 using (3R,4S)-3-Fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine and (3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methylpiperidin-4-amine (1:1) and 2-(4-fluorophenyl)propan-2-amine. Isolated as a racemic mixture. Yield: 61 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 – 7.24 (m, 2H), 7.13 (t, 2H), 7.08 (dd, 2H), 6.94 (t, 2H), 5.00 (d, 1H), 4.81 (s, 1H), 4.72 (dd, 1H), 4.54 (d, 1H), 4.48 (d, 1H), 3.93 – 3.71 (m, 2H), 3.06 – 2.75 (m, 5H), 2.71 – 2.53 (m, 1H), 1.83 (d, 1H), 1.48 (s, 3H), 1.45 (s, 3H); LC-MS: 420.2 $[M+H]^+$.

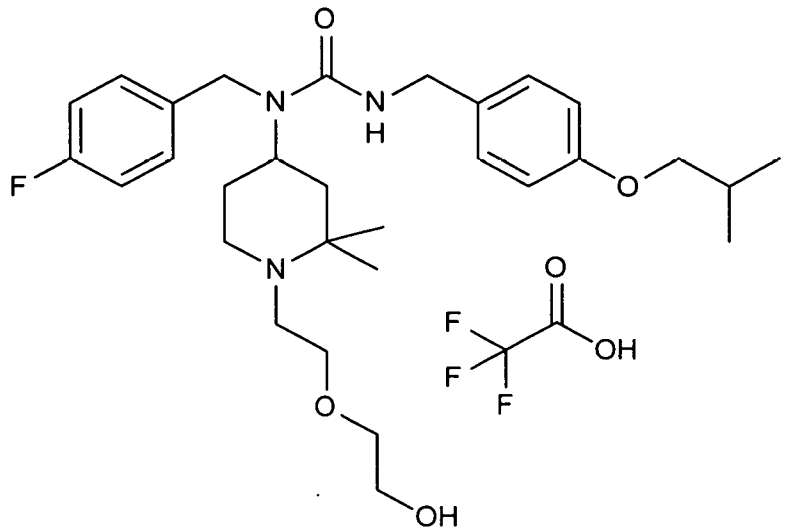
[00926] Example 182:3-[(4-fluorophenyl)methyl]-3-{1-[2-(2-hydroxyethoxy)ethyl]-2,2-dimethylpiperidin-4-yl}-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid (182)

[00927] 3-(2,2-dimethylpiperidin-4-yl)-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea hydrochloride



[00928] The compound was prepared in analogy with example 125 using 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene and tert-butyl 4-{[(4-fluorophenyl)-methyl]amino}-2,2-dimethylpiperidine-1-carboxylate. The compound was freeze dried from hydrochloric acid.

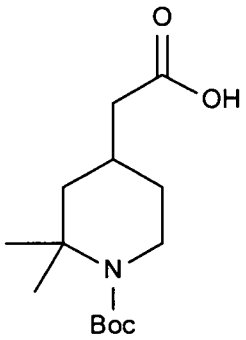
[00929] 3-[(4-fluorophenyl)methyl]-3-{1-[2-(2-hydroxyethoxy)ethyl]-2,2-dimethylpiperidin-4-yl}-1-{[4-(2-methylpropoxy)phenyl]methyl}urea; trifluoroacetic acid



[00930] 3-(2,2-dimethylpiperidin-4-yl)-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methyl-propoxy)phenyl]methyl}urea hydrochloride (30 mg, 63 μmol), 2-(2-chloroethoxy)ethan-1-ol (8.6 mg, 69 μmol), potassium carbonate (52 mg, 0.38 mmol), tetrabutylammonium iodide (2.3 mg, 6.3 μmol) were mixed in toluene and heated to 110 °C for 15 hours. The solvent was evaporated and resulting solid was dissolved in diethyl ether and water. The water phase was extracted with diethyl ether and the combined organic phases dried with magnesium sulfate and evaporated. The crude material was purified by HPLC, eluting with 30-90 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (4.5 mg, 13 %) LC-MS: 530.3 $[M+H]^+$.

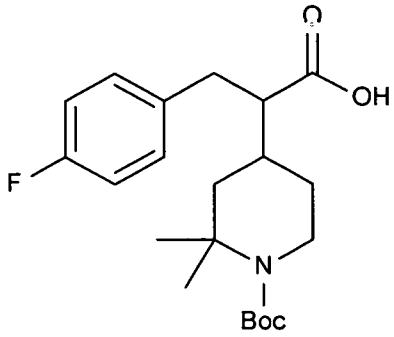
[00931] Example 183: 3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(1,2,2-trimethylpiperidin-4-yl)propanamide; trifluoroacetic acid (183)

[00932] 2-{1-[(tert-butoxy)carbonyl]-2,2-dimethylpiperidin-4-yl}acetic acid



[00933] To a stirred solution of tert-butyl 4-(2-ethoxy-2-oxoethyl)-2,2-dimethylpiperidine-1-carboxylate (243 mg, 0.81 mmol) in tetrahydrofuran was added LiOH (58 mg, 2.4 mmol), followed by water. The mixture was stirred for 2 hours then concentrated, acidified with HCl (1 M aqueous) the water phase was extracted with diethyl ether. The combined organic phases were dried and concentrated to give the desired intermediate (177 mg, 80%).

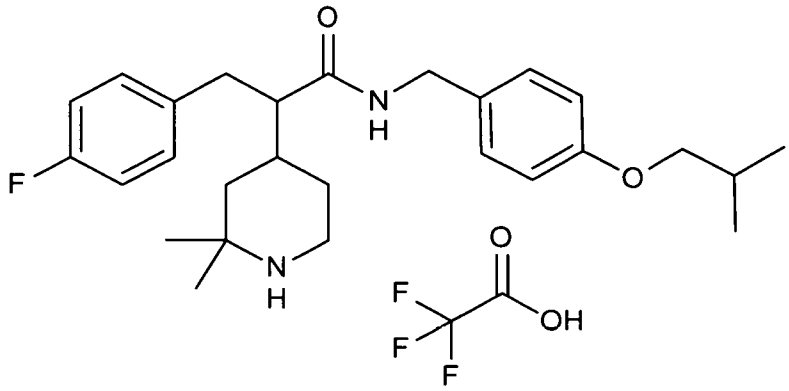
[00934] 2-{1-[(tert-butoxy)carbonyl]-2,2-dimethylpiperidin-4-yl}-3-(4-fluorophenyl)-propanoic acid



To a stirred solution of 2-{1-[(tert-butoxy)carbonyl]-2,2-dimethylpiperidin-4-yl}acetic acid (175 mg, 0.64 mmol) in tetrahydrofuran (8 ml) at -40 °C was added lithium diisopropylamine (1.44 ml, 1 M in tetrahydrofuran, 1.44 mmol) dropwise. The reaction mixture was allowed to reach room temperature over 3 hours. The mixture was cooled to -20 °C and 1-(bromomethyl)-4-fluorobenzene (85 µl, 0.68 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and stirred overnight. The mixture was diluted with ethyl acetate (20 ml), citric acid (8 ml, 2 M aqueous) was added, the phases separated and the water phase was extracted with ethyl acetate (2x40 ml). The combined organic phases were washed with brine (40 ml), dried over sodium sulfate, filtered, and concentrated. The crude (495 mg) was purified by column chromatography using silicon

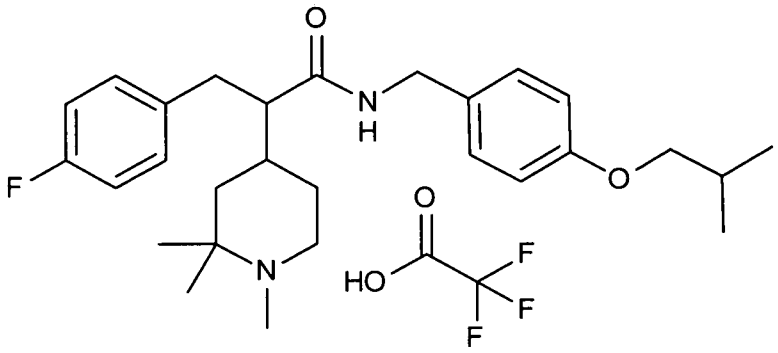
dioxide gel, eluting with 50% ethyl acetate in petroleum ether to afford the desired intermediate (43 mg, 17%).

[00935] 2-(2,2-dimethylpiperidin-4-yl)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)-phenyl]methyl}propanamide; trifluoroacetic acid



[00936] [4-(2-methylpropoxy)phenyl]methanamine (1 equivalent) in dimethylformamide was added to a solution of 2-{1-[(tert-butoxy)carbonyl]-2,2-dimethylpiperidin-4-yl}-3-(4-fluorophenyl)propanoic acid (1 equivalent), diisopropylethylamine (3 equivalents) and *N*-[(dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate *N*-oxide (1.1 equivalent) in dimethylformamide. The mixture was stirred at room temperature overnight, then diluted with brine and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. The crude material was purified by column chromatography using silicon dioxide gel. The material was dissolved in dichloromethane and trifluoroacetic acid was added. After 20 minutes the reaction mixture was concentrated. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Yield: 65 %.

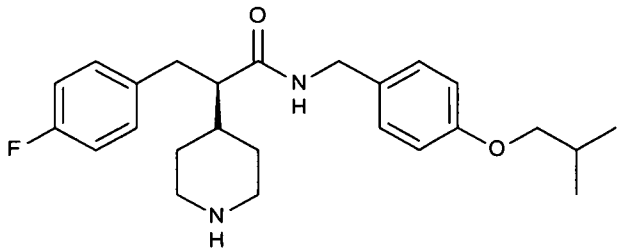
[00937] 3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(1,2,2-trimethylpiperidin-4-yl)propanamide; trifluoroacetic acid

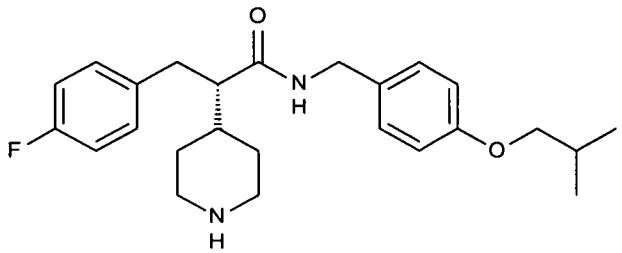


[00938] To a stirred solution of 2-(2,2-dimethylpiperidin-4-yl)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide; trifluoroacetic acid (1 equivalent) in tetrahydrofuran at room temperature was added formaldehyde (30 % in water, 5 equivalents). The mixture was stirred for 5 minutes, then sodium triacetoxyborohydride (2 equivalents) was added. The mixture was stirred for 3 hours, then additional formaldehyde (5 equivalents) and sodium triacetoxyborohydride (2 equivalents) were added. The reaction was stirred overnight, then sodium hydrogen carbonate (saturated, aqueous) was added. The mixture was concentrated, diluted with sodium hydrogen carbonate (saturated aqueous) and extracted with dichloromethane. The combined organic phases were washed with water and brine, dried over sodium sulfate, filtered and concentrated. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid). Yield: 32 %. Major diastereoisomer: ^{1}H NMR (500 MHz, Chloroform-d) δ 11.19 (s, 1H), 7.06 (m, 2H), 6.90 (m 2H), 6.80 – 6.71 (m, 4H), 5.86 (dt, 1H), 4.27 – 4.16 (m, 1H), 4.08 – 3.93 (m, 1H), 3.68 (d, 2H), 3.30 (d, 1H), 2.98 – 2.90 (m, 1H), 2.90 – 2.83 (m, 1H), 2.70 (m, 4H), 2.19 – 1.88 (m, 5H), 1.80 – 1.77 (m, 1H), 1.61 – 1.59 (m, 1H), 1.55 (s, 3H), 1.33 (s, 3H), 1.01 (d, 6H). Minor diastereoisomer ^{1}H NMR (500 MHz, Chloroform-d) δ 11.19 (s, 1H), 7.06 (m, 2H), 6.90 (m, 2H), 6.80 – 6.71 (m, 4H),5.86 (dt, 1H), 4.27 – 4.16 (m, 1H), 4.08 – 3.93 (m, 1H), 3.68 (d, 2H), 3.41 (d, 1H), 2.98 – 2.90 (m, 1H), 2.90 – 2.83 (m, 1H), 2.70 (dd, 4H), 2.19 – 1.88 (m, 5H), 1.80 – 1.77 (m, 1H), 1.61 – 1.59 (m, 1H), 1.42 (s, 3H), 1.28 (s, 3H), 1.01 (d, 6H); LC-MS: 455.3 $[M+H]^+$.

[00939] Example 184: (2R)-3-(4-fluorophenyl)-2-(1-methylpiperidin-4-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide (184a) and (2S)-3-(4-fluorophenyl)-2-(1-methylpiperidin-4-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide (184b)

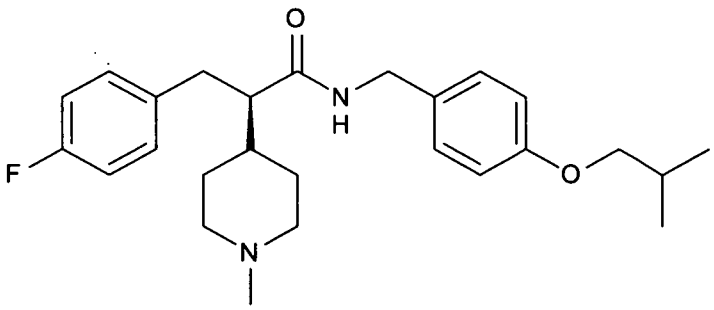
[00940] (2R)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide and (2S)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propenamide

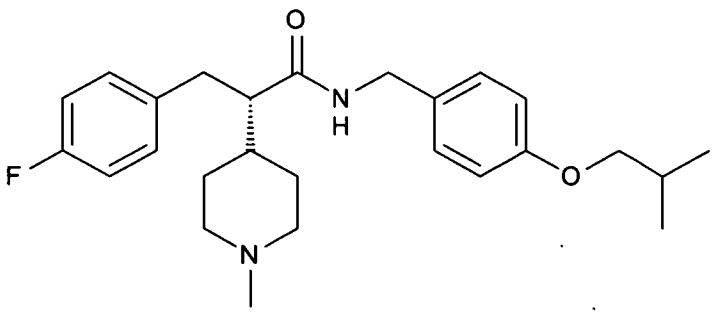




[00941] The compound was prepared in analogy with example 183 using 1-(bromomethyl)-4-fluorobenzene, 2-{1-[(tert-butoxy)carbonyl]piperidin-4-yl}acetic acid and [4-(2-methylpropoxy)phenyl]methanamine.

[00942] (2R)-3-(4-fluorophenyl)-2-(1-methylpiperidin-4-yl)-N-{[4-(2-methylpropoxy)-phenyl]methyl}propanamide and (2S)-3-(4-fluorophenyl)-2-(1-methylpiperidin-4-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide

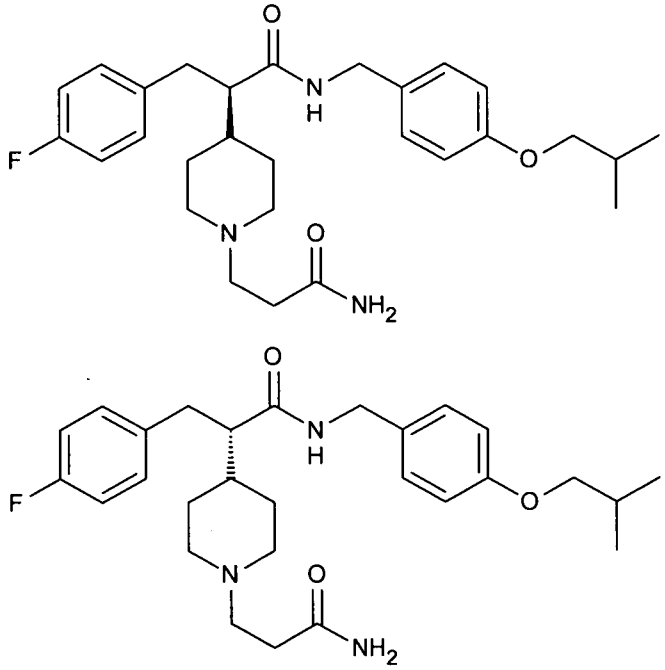




[00943] (2R)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide and (2S)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide (1:1, 90 mg, 218 μmol) was dissolved in methanol (dry, degassed, 1.5 ml). To this solution a catalytic amount of

chloro(cyclopentadienyl)bis(triphenylphosphine)ruthenium (8 mg, 11 μmol) was added and the solution was heated in a pressure tube at 90 °C for 1 day. The solvent was evaporated and the crude material was purified by HPLC, eluting with 40-70 % acetonitrile in water (containing 25 mM ammonia) to afford the title compound (62 mg, 66 %), as a racemic mixture. ^{1}H NMR (500 MHz, Chloroform-d) δ 7.10 – 7.02 (m, 2H), 6.96 – 6.88 (m, 2H), 6.81 – 6.71 (m, 4H), 5.37 (s, 1H), 4.18 (dd, 1H), 4.04 (dd, 1H), 3.68 (d, 2H), 3.46 (dd, 2H), 2.88 (dd, 1H), 2.81 – 2.56 (m, 6H), 2.21 – 1.80 (m, 7H), 1.02 (d, 6H); LC-MS: 427.2 $[M+H]^+$.

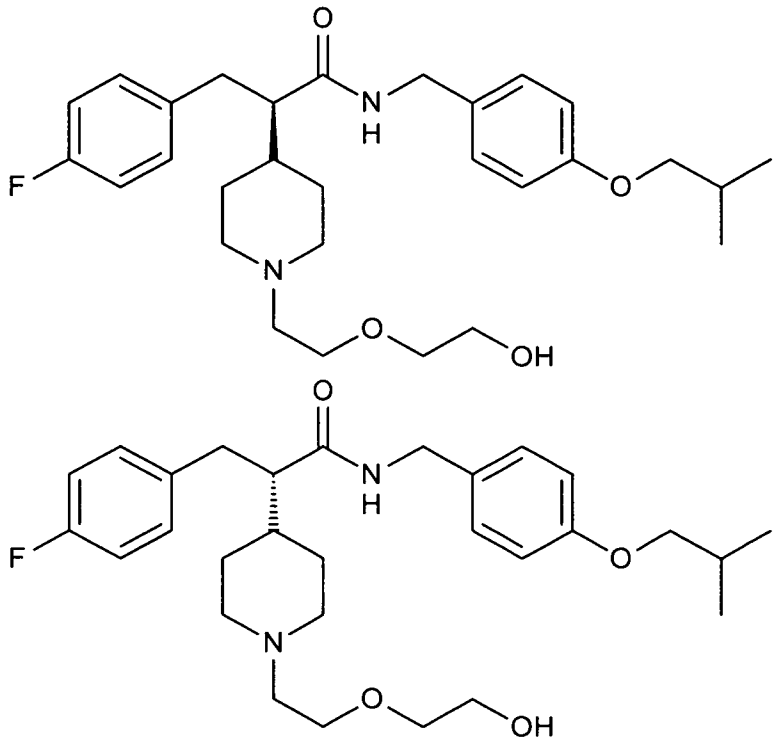
[00944] Example 185: (2R)-2-[1-(2-carbamoylethyl)piperidin-4-yl]-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide (185a) and (2S)-2-[1-(2-carbamoylethyl)piperidin-4-yl]-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)-phenyl]methyl}propanamide (185b)



[00945] The compounds were prepared in analogy with example 135 using (2R)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide and (2S)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide (1:1). The material was purified by column chromatography using silicon dioxide gel, eluting with dichloromethane:methanol:triethylamine (100:15:5). Isolated as a racemic mixture. Yield 39 %: ^{1}H NMR (500 MHz, DMSO-d6) δ 8.23 – 8.14 (m, 1H), 7.59 (s, 1H), 7.25 – 6.98 (m, 5H), 6.82 – 6.67 (m, 4H), 4.31 – 4.17 (m, 1H), 3.93 – 3.80 (m, 1H), 3.68 (d, 2H), 3.46 (t, 2H), 3.31 – 3.14 (m, 2H), 2.99 – 2.61 (m, 4H), 2.55 (t, 1H), 2.41 – 2.32 (m,

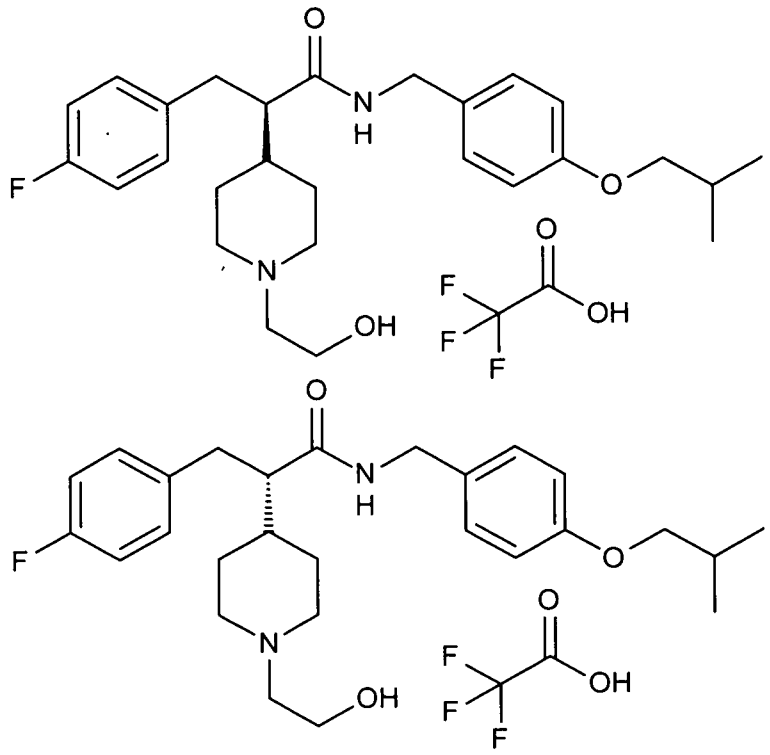
1H), 2.09 – 1.91 (m, 2H), 1.84 – 1.65 (m, 2H), 1.64 – 1.38 (m, 2H), 1.29 – 1.12 (m, 1H), 0.96 (d, 6H); LC-MS: 484.3 $[M+H]^+$.

[00946] Example 186: (2R)-3-(4-fluorophenyl)-2-{1-[2-(2-hydroxyethoxy)ethyl]piperidin-4-yl}-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide (186a) and (2S)-3-(4-fluorophenyl)-2-{1-[2-(2-hydroxyethoxy)ethyl]piperidin-4-yl}-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide (186b)



[00947] The compounds were prepared in analogy with example 187 using (2R)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide and (2S)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide (1:1). Purified by HPLC, eluting with acetonitrile in water (containing ammonia). Yield: 56 % LC-MS: 501.4 $[M+H]^+$.

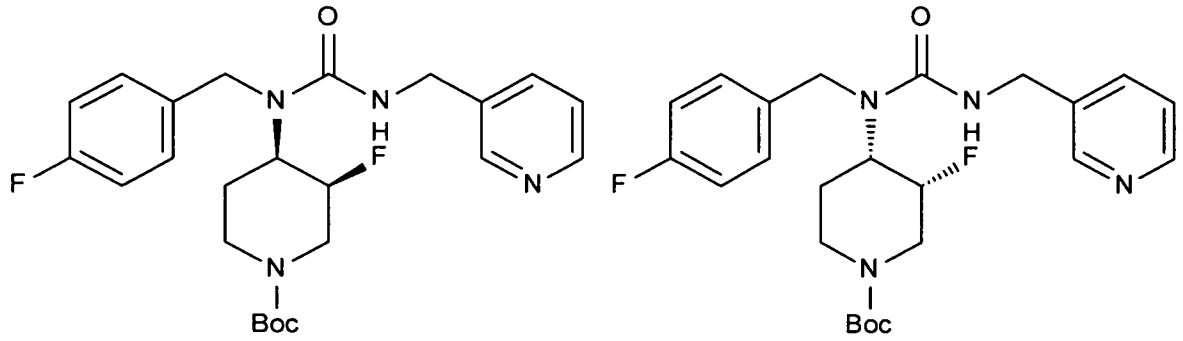
[00948] Example 187: (2R)-3-(4-fluorophenyl)-2-[1-(2-hydroxyethyl)piperidin-4-yl]-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide; trifluoroacetic acid (187a) and (2S)-3-(4-fluorophenyl)-2-[1-(2-hydroxyethyl)piperidin-4-yl]-N-{[4-(2-methylpropoxy)-phenyl]methyl}propanamide; trifluoroacetic acid (187b)



[00949] (2R)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide and (2S)-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(piperidin-4-yl)propanamide (1:1, 36 mg, 87 μmol), 2-chloroethan-1-ol (7.7 mg, 96 μmol), potassium carbonate (60 mg, 0.44 mmol), tetrabutylammonium iodide (3.2 mg, 8.7 μmol) were mixed in toluene and heated to 110°C for 19 hours. The reaction mixture was filtered and the filtrate washed with toluene. The solid was dissolved in diethyl ether and water. The water phase was extracted with diethyl ether and the combined organic phases dried with magnesium sulfate and evaporated. The crude material was purified by HPLC, eluting with 30-90 % acetonitrile in water (containing 0.1 % trifluoroacetic acid) to afford the title compound (15 mg, 31 %), as a racemic mixture. LC-MS: 457.3 $[M+H]^+$.

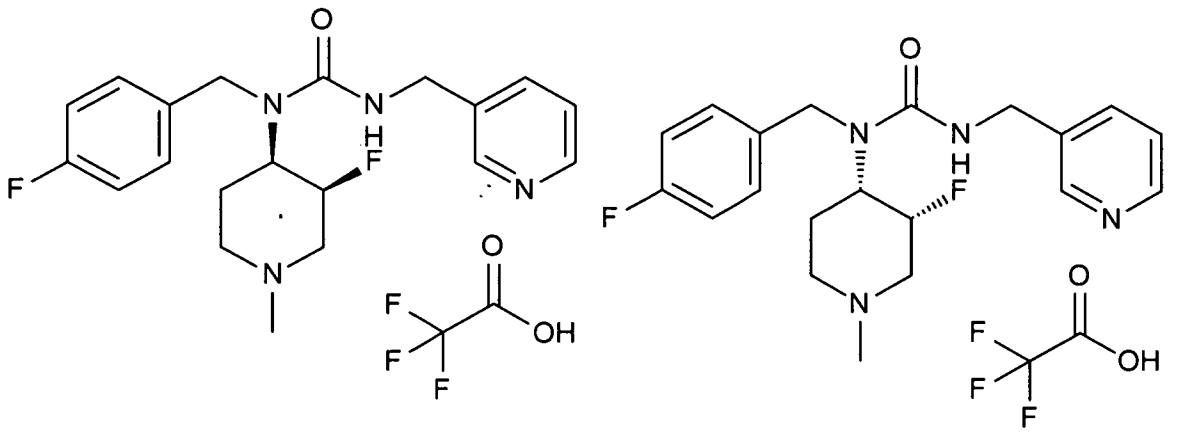
[00950] Example 188: 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(pyridin-3-yl)methyl]urea; trifluoroacetic acid (188a) and 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(pyridin-3-yl)methyl]urea; trifluoroacetic acid (188b)

[00951] tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[(pyridin-3-yl)methyl]carbamoyl})amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[(pyridin-3-yl)methyl]carbamoyl})amino}piperidine-1-carboxylate



[00952] A mixture of (pyridin-3-yl)methanamine (38.9 µl, 383 µmol) and triethylamine (128 µl) in dry dichloromethane (2 ml) was slowly injected via the syringe pump directly into a solution of diphosgene (24 µl, 199 µmol) in dry dichloromethane (1 ml) over the period of 1 hour. The resulting mixture was stirred at ambient temperature for 1 hour before a solution of 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, 100 mg, 306 µmol) in dry dichloromethane (1 ml) was added dropwise over 5 minutes. The mixture was left stirring overnight, washed with water (5 ml) and the aqueous phase was extracted with dichloromethane (3 x 5 ml). Combined organic extracts were passed through the phase separator, concentrated and purified by column chromatography using silicon dioxide gel, eluting with 30 % ethyl acetate in petroleum ether to afford of the desired ureas (26.7 mg, 61 %) as the racemic mixture.

[00953] 3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(pyridin-3-yl)methyl]urea; trifluoroacetic acid and 3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(pyridin-3-yl)methyl]urea; trifluoroacetic acid

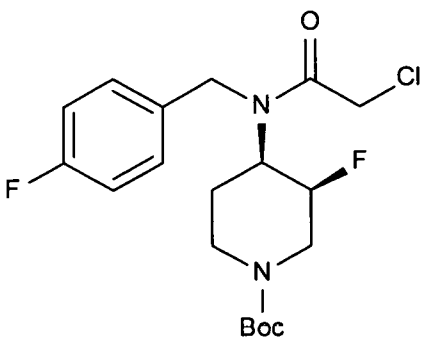


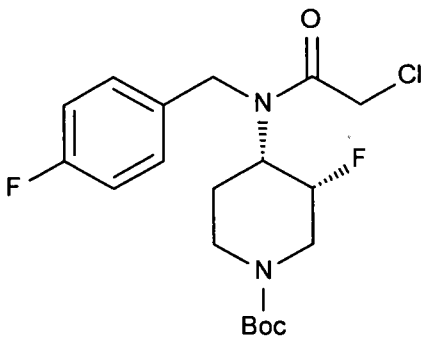
[00954] To a stirred solution of tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]-({[(pyridin-3-yl)methyl]carbamoyl})amino}piperidine-1-carboxylate and tert-butyl (3S,4R)-

3-fluoro-4-{[(4-fluorophenyl)methyl]({[(pyridin-3-yl)methyl]carbamoyl})amino}piperidine-1-carboxylate (1:1) (1 equivalent) in dichloromethane at room temperature was added trifluoroacetic acid. The reaction mixture was stirred for 20 minutes before it was concentrated and re-dissolved in tetrahydrofuran. Formaldehyde (5 equivalents) was added and the reaction mixture was stirred for 15 minutes before sodium triacetoxyborohydride (2 equivalents) was added. The mixture was stirred overnight, then additional formaldehyde (2 equivalents) and sodium triacetoxyborohydride (1 equivalent) were added. The mixture was stirred for 2 hours, then diluted with sodium hydrogen carbonate and extracted with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid), and isolated as a racemic mixture, 61% yield (26.7 mg): ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.65 (d, 1H), 8.61 (s, 1H), 8.20 (d, 1H), 7.83 (dd, 1H), 7.25 (dd, 2H), 7.08 (t, 2H), 5.13 (d, 1H), 4.79 – 4.59 (m, 3H), 4.48 (d, 2H), 3.89 – 3.71 (m, 1H), 3.62 – 3.49 (m, 2H), 3.25 (d, 1H), 2.90 (s, 4H), 2.45 – 2.15 (m, 1H), 1.88 (d, 1H); LC-MS: 375.4 $[M+H]^+$.

[00955] Example 189: N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)-methyl]-2-[methyl({[4-(2-methylpropoxy)phenyl]methyl})amino]acetamide; bis(trifluoroacetic acid) (189a) and N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[methyl({[4-(2-methylpropoxy)phenyl]methyl})amino]acetamide; bis(trifluoroacetic acid) (189b)

[00956] tert-butyl (3S,4R)-4-{2-chloro-N-[(4-fluorophenyl)methyl]acetamido}-3-fluoropiperidine-1-carboxylate and tert-butyl (3R,4S)-4-{2-chloro-N-[(4-fluorophenyl)-methyl]acetamido}-3-fluoropiperidine-1-carboxylate

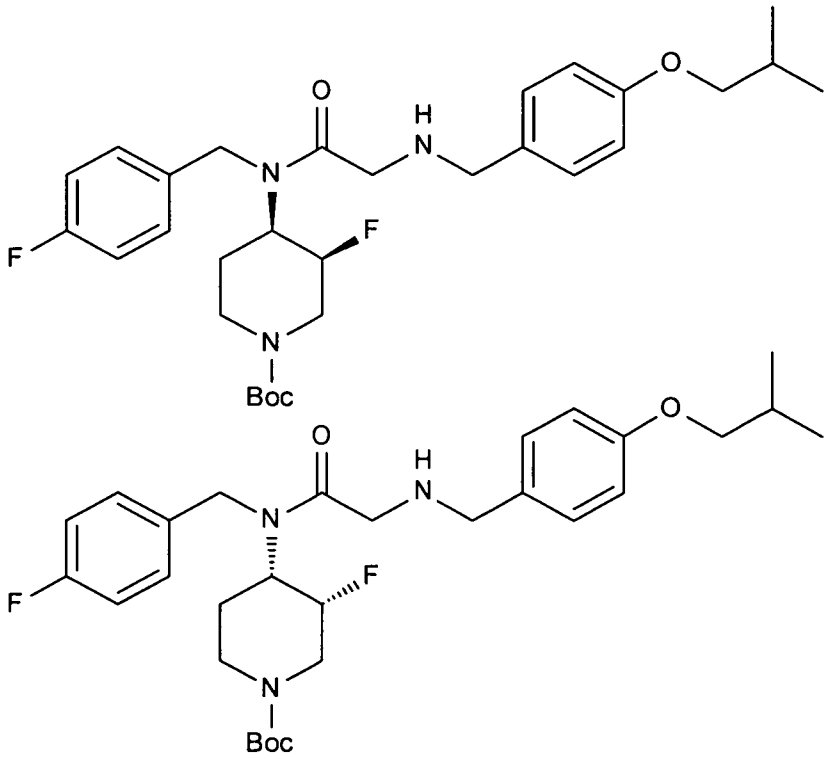




[00957] To a stirred solution of tert-butyl (3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]-amino}piperidine-1-carboxylate and tert-butyl (3R,4S)-3-fluoro-4-{[(4-fluorophenyl)-methyl]amino}piperidine-1-carboxylate (80 mg, 245 μmol) and diisopropylethylamine (55.5

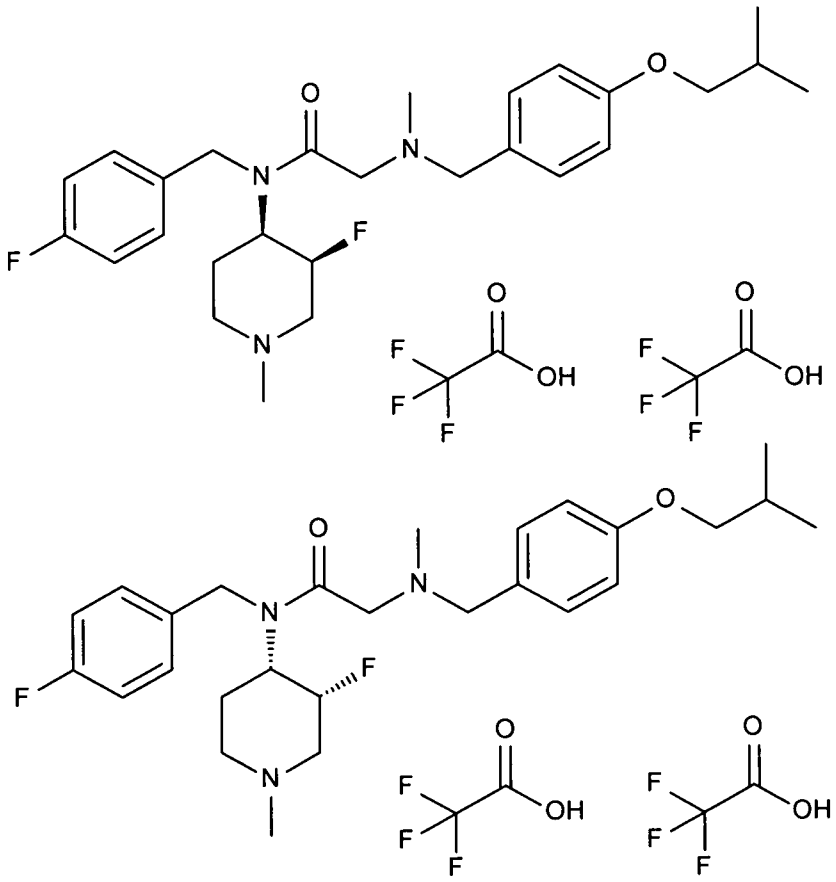
μL, 319 μmol) in dichloromethane (5 mL) was slowly added 2-chloroacetyl chloride (21.4 μL, 270 μmol) as a solution in dichloromethane (0.5 mL). After stirring at room temperature for 2 hours the mixture was concentrated and purified by column chromatography using silicon dioxide gel, eluting with 50 % ethyl acetate in petroleum ether to afford the title product as a racemic mixture (95 mg, 96.2 %).

[00958] tert-butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-({[4-(2-methylpropoxy)phenyl]methyl}amino)acetamido}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-({[4-(2-methylpropoxy)phenyl]methyl}amino)-acetamido}piperidine-1-carboxylate



[00959] To a mixture of tert-butyl (3S,4R)-4-{2-chloro-N-[(4-fluorophenyl)methyl]-acetamido}-3-fluoropiperidine-1-carboxylate and tert-butyl (3R,4S)-4-{2-chloro-N-[(4-fluorophenyl)methyl]acetamido}-3-fluoropiperidine-1-carboxylate (65 mg, 169 μmol) and [4-(2-methylpropoxy)phenyl]methanamine (37.5 mg, 186 μmol) in acetonitrile (5 mL) was added potassium carbonate (70 mg, 507 μmol) and diisopropylethylamine (88.5 μL, 507 μmol). The resulting mixture was stirred at reflux for 48 hours, diluted with water, extracted with dichloromethane (3 x 5 mL), dried and purified by column chromatography using silicon dioxide gel, eluting with 30 % ethyl acetate in petroleum ether to afford the title product as a racemic mixture (69 mg, 79.5 %).

[00960] N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[methyl({[4-(2-methylpropoxy)phenyl]methyl})amino]acetamide; bis(trifluoroacetic acid) and N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[methyl({[4-(2-methylpropoxy)phenyl]methyl})amino]acetamide; bis(trifluoroacetic acid)

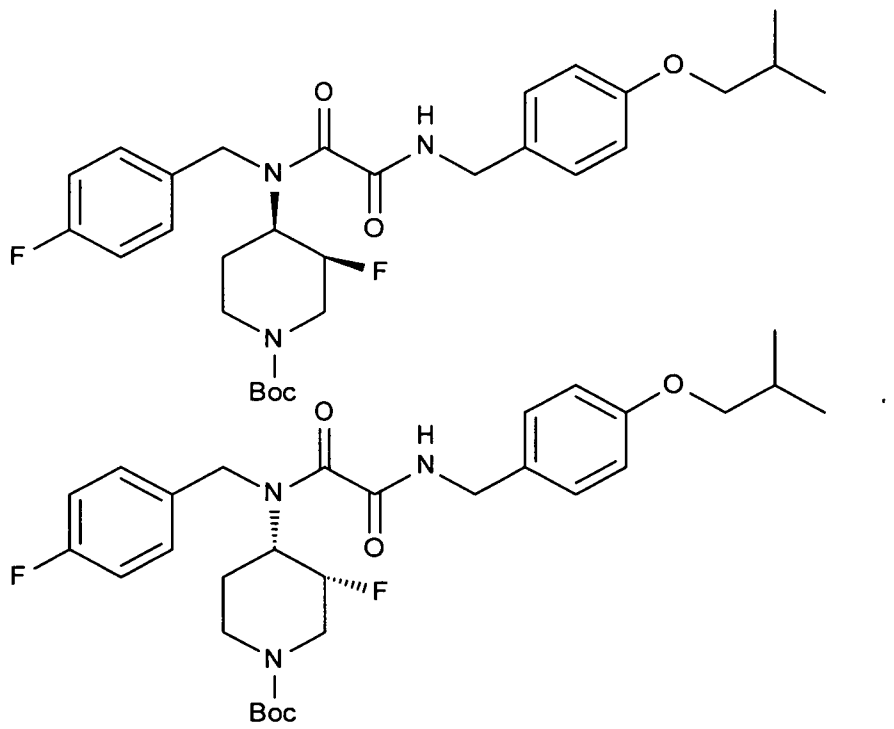


[00961] To a stirred solution of tert-butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-({[4-(2-methylpropoxy)phenyl]methyl}amino)acetamido}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-2-({[4-(2-methylpropoxy)phenyl]methyl}amino)acetamido}piperidine-1-carboxylate (1:1) (1 equivalent) in dichloromethane at room temperature was added trifluoroacetic acid. The reaction mixture was stirred for 20 minutes before it was concentrated and re-dissolved in tetrahydrofuran. Formaldehyde (5 equivalents) was added and the reaction mixture was stirred for 15 minutes before sodium triacetoxyborohydride (2 equivalents) was added. The mixture was stirred overnight, then additional formaldehyde (2 equivalents) and sodium triacetoxyborohydride (1 equivalent) were added. The mixture was stirred for 2 hours, then diluted with sodium hydrogen carbonate and extracted with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated. The

crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid), and isolated as a racemic mixture. Yield 16.7 mg, 74 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 (d, 2H), 7.04 – 6.82 (m, 6H), 5.14 – 4.77 (m, 2H), 4.62 – 4.23 (m, 4H), 4.00 – 3.43 (m, 6H), 3.16 (s, 1H), 3.04 – 2.71 (m, 7H), 2.55 (s, 1H), 2.11 (dt, 1H), 1.82 – 1.56 (m, 1H), 1.06 (d, 6H); LC-MS: 474.6 $[M+H]^+$

[00962] Example 190: N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)-methyl]-N'-{[4-(2-methylpropoxy)phenyl]methyl}ethanediamide; trifluoroacetic acid (190a) and N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-N'-{[4-(2-methylpropoxy)phenyl]methyl}ethanediamide; trifluoroacetic acid (190b)

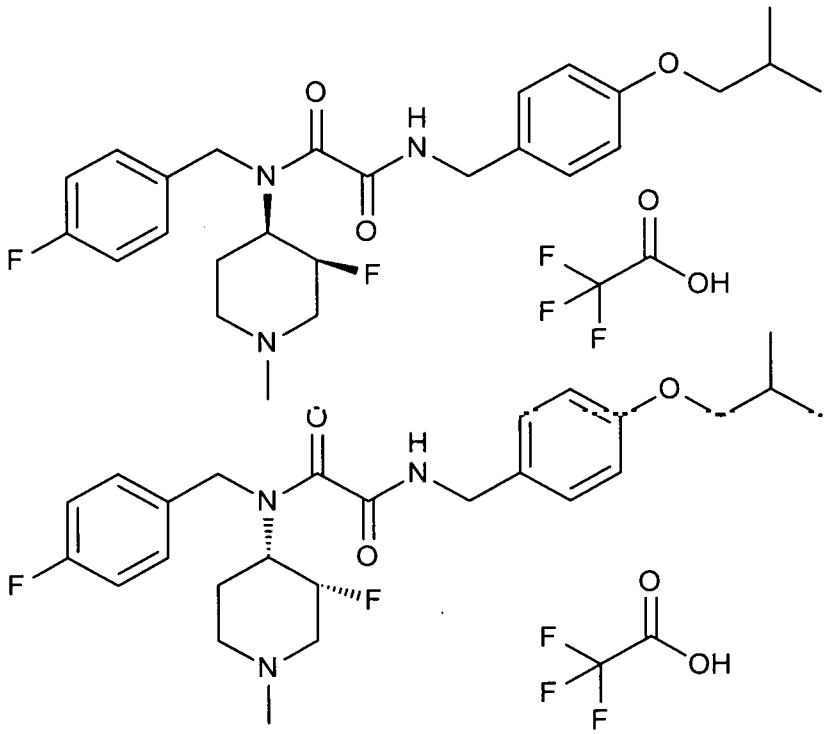
[00963] tert-butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-1-({[4-(2-methyl-propoxy)phenyl]methyl}carbamoyl)formamido}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-1-({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)formamido}piperidine-1-carboxylate



[00964] To a solution of oxalyl chloride (20.2 μL, 236 μmol) and diisopropylethylamine (45 μL, 257 μmol) in dichloromethane (3 mL), was added 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 (70 mg, 214 μmol). The resulting mixture was stirred for 2 hours and [4-(2-methylpropoxy)phenyl]methanamine (42.3 mg, 236 μmol) and diisopropylethylamine (74.9 μL, 429 μmol) was added. Stirring was continued for

2 hours before the reaction mixture was diluted with water, extracted with dichloromethane (3 x 5 mL), dried and purified by column chromatography using silicon dioxide gel, eluting with 30 % ethyl acetate in petroleum ether to afford the title product as a racemic mixture (86 mg, 72 %).

[00965] N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-N'-{[4-(2-methylpropoxy)phenyl]methyl}ethanediamide; trifluoroacetic acid and N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-N'-{[4-(2-methylpropoxy)phenyl]methyl}ethanediamide; trifluoroacetic acid

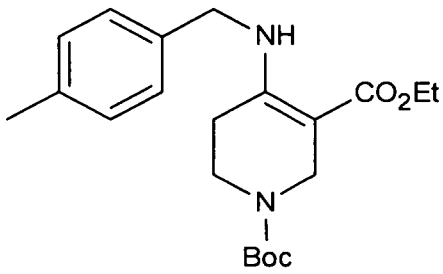


[00966] Tert-butyl (3R,4S)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-1-({[4-(2-methyl-propoxy)phenyl]methyl}carbamoyl)formamido}piperidine-1-carboxylate and tert-butyl (3S,4R)-3-fluoro-4-{N-[(4-fluorophenyl)methyl]-1-({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)formamido}piperidine-1-carboxylate (1:1) were dissolved in dichloromethane at room temperature and trifluoroacetic acid was added in one portion. The reaction mixture was stirred for 20 minutes before it was concentrated and re-dissolved in tetrahydrofuran. Formaldehyde (30 % in water) was added and the reaction mixture was stirred for 15 minutes before sodium triacetoxyborohydride was added. The mixture was stirred overnight, then diluted with sodium hydrogen carbonate (15 ml, saturated aqueous), and extracted with dichloromethane. The combined organic phases were washed with brine (15 ml), dried over

sodium sulfate, and concentrated. The crude material was purified by HPLC and the title compounds were isolated as a racemic mixture. Yield: 93 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.08 (m, 4H), 7.05 – 6.94 (m, 2H), 6.87 (dd, 2H), 5.62 – 4.93 (m, 3H), 4.77 – 4.55 (m, 1H), 4.54 – 4.27 (m, 3H), 3.94 – 3.46 (m, 5H), 2.76 (d, 5H), 2.08 (m, 1H), 1.77 – 1.39 (m, 1H), 1.03 (d, 6H); LC-MS: 474.6 $[M+H]^+$.

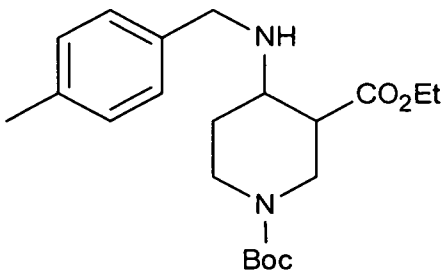
[00967] Example 191: ethyl 1-methyl-4-{[(4-methylphenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}piperidine-3-carboxylate; trifluoroacetic acid (191)

[00968] 1-tert-butyl 3-ethyl 4-{[(4-methylphenyl)methyl]amino}-1,2,5,6-tetrahydropyridine-1,3-dicarboxylate



[00969] A mixture of 1-tert-butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate (352 mg, 1.3 mmol), (4-methylphenyl)methanamine (157.5mg, 1.3 mmol) and ethanol (10 mL) was heated to reflux for 8 hours. The solvent was removed *in vacuo* to yield the desired intermediate (449 mg, 92 %) which was used in the next step without further purification.

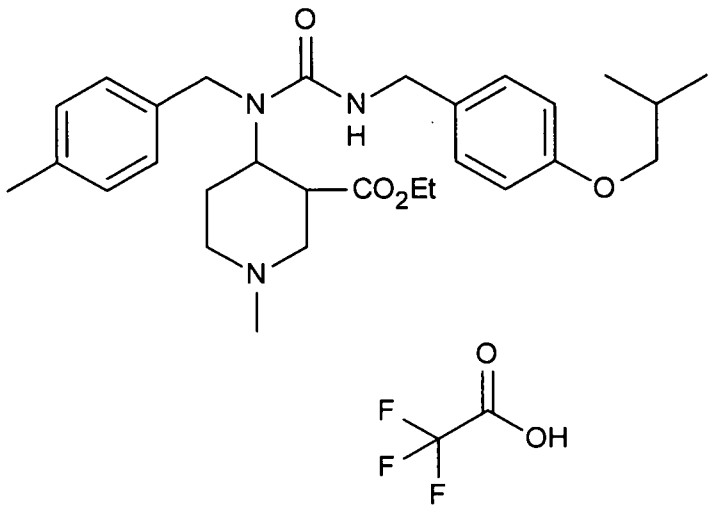
[00970] 1-tert-butyl 3-ethyl 4-{[(4-methylphenyl)methyl]amino}piperidine-1,3-dicarboxylate



[00971] 1-tert-butyl 3-ethyl 4-{[(4-methylphenyl)methyl]amino}-1,2,5,6-tetrahydropyridine-1,3-dicarboxylate (449 mg, 1.2 mmol) was dissolved in acetic acid (3 ml) and acetonitrile (3 ml). To the resulting solution, sodium triacetoxyborohydride (210 mg, 2.4 mmol) was added in portions at 0 °C. The mixture was allowed to warm up to ambient temperature and stirring was continued for 4 hours, followed by concentration. The residue

was dissolved in dichloromethane, washed with sodium hydrogen carbonate (aqueous, saturated, 5 ml), dried and concentrated to give pure product (412 mg, 1.09 mmol, 91 %) as an undefined mixture of stereoisomers.

[00972] ethyl 1-methyl-4-{[(4-methylphenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}piperidine-3-carboxylate; trifluoroacetic acid



[00973] 1-(isocyanatomethyl)-4-(2-methylpropoxy)benzene (1.4 equivalents) in dichloro-methane was added to 1-tert-butyl 3-ethyl 4-{[(4-methylphenyl)methyl]amino}piperidine-1,3-dicarboxylate (1 equivalent). After 85 minutes of stirring at ambient temperature the mixture was concentrated. The crude material was purified by column chromatography using silicon dioxide gel to afford the intermediate urea. The material was dissolved in dichloromethane and trifluoroacetic acid was added. After 20 minutes of stirring at ambient temperature the mixture was concentrated and re-dissolved in tetrahydrofuran. Formaldehyde (37 % aqueous, 1.5 equivalents) and sodium cyanoborohydride (2 equivalents) were added. After 20 minutes the mixture was concentrated and re-dissolved in methanol. The resulting mixture was heated to reflux for 80 minutes before it was cooled to ambient temperature and concentrated. The crude material was purified by HPLC, eluting with acetonitrile in water (containing 0.1 % trifluoroacetic acid; and isolated as an undefined mixture of stereoisomers. Yield 59 %. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 (d, 4H), 7.00 (d, 1H), 6.92 (d, 1H), 6.83 (d, 1H), 6.75 (d, 1H), 5.14 – 4.88 (m, 1H), 4.67 (d, 2H), 4.51 – 4.05 (m, 6H), 3.99 – 3.58 (m, 6H), 3.13 – 2.62 (m, 4H), 2.34 (d, 4H), 2.06 (dt, 1H), 1.81 (s, 1H), 1.29 (t, 2H), 1.02 (d, 6H); LC-MS: 496.7 $[M+H]^+$.

[00974] 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.

[00975] In vitro determination of receptor activity

[00976] 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-HT2A 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-HT2A 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-HT2A or other appropriate agonists for other receptors. With both methods, cells were then grown in a humidified atmosphere with 5% ambient CO_2 for five days. Media was then removed from the plates and marker gene activity was measured by the addition of the b-galactosidase substrate o-nitrophenyl b-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-HT2A). pIC_{50} is the negative of the $\log(IC_{50})$, where IC_{50} is the calculated concentration in molar that produces 50% maximal repression. The compounds as provided herein were assayed as described herein.

[00977] Compounds described herein, demonstrated high inhibition of the 5-HT2a 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 pKi ≥ 8.4

Moderate affinity pKi ≥ 7.7.

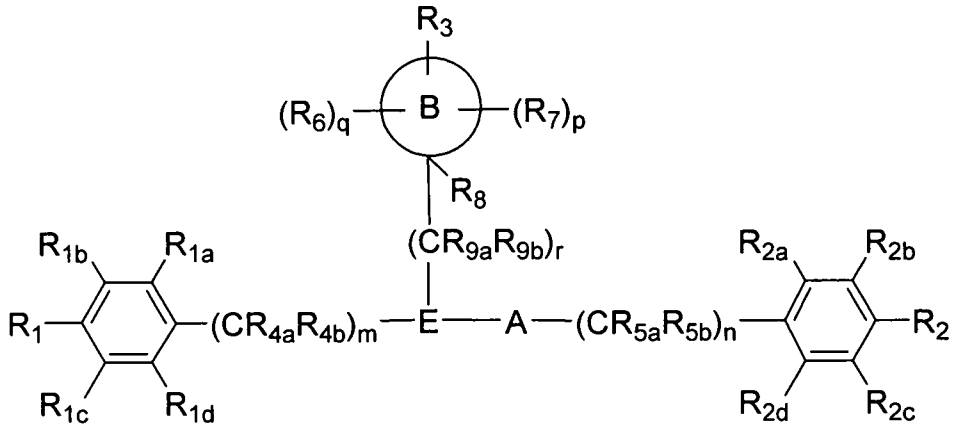
[00978] Table 1 – pKi values of exemplified compounds

Compound	5-HT2a pKi	Compound	5-HT2a pKi	Compound	5-HT2a pKi
1a	8.0	45a/45b	7.9	73	9.5
1c	7.9	38	7.4	74	8.4
2b	8.0	41a/41b	7.4	75	10.1
2c	7.5	33	7.4	76	8.4
3b	7.2	29	7.3	77	10.8
4c	7.6	37a/37b	7.3	78a/78b	7.6
4d	7.9	42	7.3	79a/79b	1
4e	6.9	46a/46b	7.1	80a/80b	8.2
4f	7.2	47	7.5	80c/80d	7.3
5b	7.1	30	6.9	81a/81b	7.9
5d	7.2	31	6.4	81c/81d	7.4
7	8.2	34	9.8	82a/82b	7.7
6	8.1	44a/44b	1	82c/82d	9.0
8	7.0	43	1	83a/83b	8.9
9	6.9	39a/39b		83c/83d	8.0
10	4.0	49	3.7	84a/84b	1
11	4.0	50	2.9	85a/85b	1
12	4.0	51		86a/86b	1
13	4.5	52	7.3	87a/87b	1
14	8.5	53	1	88a/88b	1
15	8.7	54	1	113a/113b	9.1
16	8.3	55	1	112a/112b	8.3
17	8.8	56	7.0	110a/110b	8.1
18	7.7	57	1	111a/111b	8.0
19a/19b	7.0	58	1	108a/108b	7.8
20	8.0	59	1	109a/109b	7.5
21	7.9	61	1.0	96a/96b	7.4
22	8.2	70	1	107a/107b	7.8
23	8.1	69a	1	94a/94b	8.1
24	8.3	69b	1	106a/106b	8.1
25	7.7	68	1	95a/95b	8.4
26	8.0	62	6.6	93a/93b	8.4
27	8.0	60	6.9	91	8.3
48	7.4	65	7.4	92	7.6
40a/40b	8.7	64	8.2	105	7.2

Compound	5-HT2a pKi	Compound	5-HT2a pKi	Compound	5-HT2a pKi
35	8.5	63	8.2	104	7.5
31	8.4	67	1	114a/114b	7.0
28	8.4	66	7.2	103	7.6
32	8.2	71	8.9	98	8.3
36a/36b	8.0	72	8.5	100	7.4
97	7.8	148a/148b	7.9	185a/185b	7.2
99	7.4	149a/149b	8.5	186a/186b	7.3
101	7.8	150a/150b	8.4	187a/187b	7.4
112	7.3	151a/151b	8.3	188a/188b	1
89	7.9	152a/152b	7.4	189a/189b	1
90	7.4	153	9.1	190a/190b	1
115	1	154	9.0	191	7.5
116a/116b	7.8	155	8.9		
116c/116d	7.4	156a/156b	8.1		
117	9.1	157a/158b	8.0		
118a/118b	8.7	158a	7.1		
119a/119b	9.3	159a	6.3		
120a/120b	9.0	159c	7.2		
121a/121b	7.8	160a	6.5		
122	7.5	159e/159f	6.3		
123	8.4	160_2	7.8		
124	9.4	161a/161b	1		
125c/125d	8.5	162a/162b	7.2		
126a/126b	8.8	163	7.7		
127a/127b	7.8	164	9.4		
128a/128b	8.5	166	1		
129a/129b	7.2	166a/166b	1		
130a/130b	7.6	167	6.5		
131a/131b	7.4	168a/168b	7.9		
132a/132b	8.7	169a/169b	7.9		
133a/133b	8.6	170a/170b	7.6		
134	8.4	171	8.9		
135	8.8	172	7.8		
136a/136b	8.3	173	7.7		
137a/137b	7.7	174	7.3		
138a/138b	7.8	175	1		
139a/139b	6.0	176	7.8		
140a/140b	7.0	177a/177b	9.3		
141a/141b	9.0	178	8.0		
142a/142b	9.4	179a/179b	6.3		
143a/143b	8.2	180a/180b	7.9		
144a/144b	9.1	181a/181b	4.0		
145a/145b	9.0	182	8.1		
146	9.0	183	7.3		
147a/147b	6.2	184a/184b	7.5		

WHAT IS CLAIMED IS:

1. A compound according to Formula (I)



(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;

p is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6;

q is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

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

R_1, R_{1a}, R_{1b}, R_{1c} and R_{1d} are independently selected from the group consisting of hydrogen, deuterium, hydroxyl, -OD, halogen, cyano, amino, $-SO_2R_{10}$, $-OC(=O)R_{11}$, $-C(=O)OR_{11}$, 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_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl,

R_2, 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 C_{1-6} alkyl, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} hydroxyalkyl, unsubstituted or substituted C_{1-6} alkenyl, unsubstituted or substituted C_{1-6} alkoxy, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl, or R_2 and R_{2b} or R_{2c}, taken together with the atoms to which they are attached form a ring system;

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_{1-6} alkenyl, unsubstituted or substituted C_{3-6}

cycloalkyl, unsubstituted or substituted C_{3-6} heteroalicyclyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

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;

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;

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;

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_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy;

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

A is selected from the group consisting of -C(=X)–$CR_{5c}R_{5d}$-, – C(=S)–($CR_{5c}R_{5d}$)NH-, -C(=S)-S-, -C(=X)-O-, -C(=X)–NH-, and substituted or unsubstituted heteroaryl;

E is N or CH;

B is a ring system selected from the group consisting of substituted or unsubstituted 4-12 membered heteroalicyclic ring systems; and

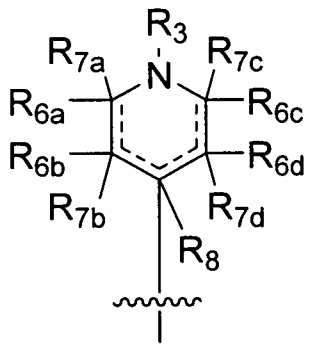
X is O or S.

2. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 1, wherein A is substituted or unsubstituted 5 or 6 membered heteroaryl.

3. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-2, wherein A is substituted or unsubstituted oxadiazolyl or substituted or unsubstituted triazolyl.

4. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-3, wherein A is substituted or unsubstituted 1,2,4-oxadiazol-5-yl, substituted or unsubstituted 1,2,4-oxadiazol-3-yl or substituted or unsubstituted triazolyl.

5. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-4, wherein ring system B has the formula:



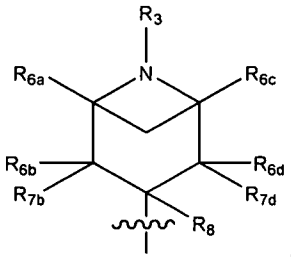
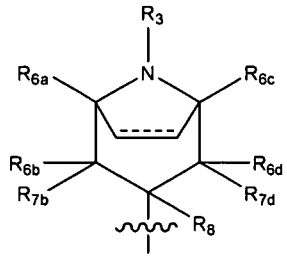
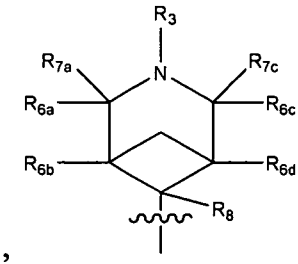
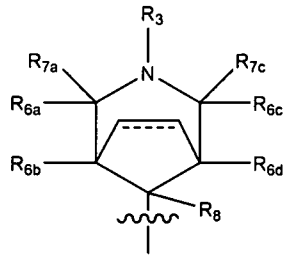
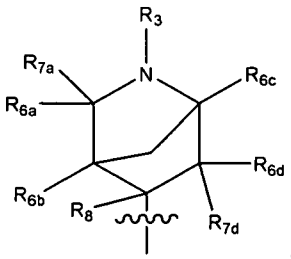
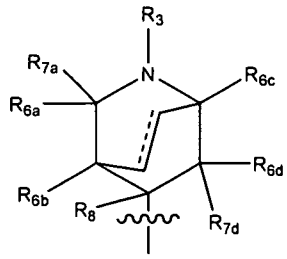
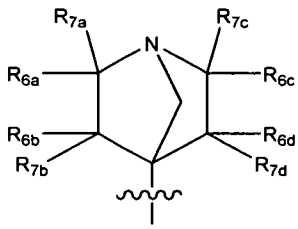
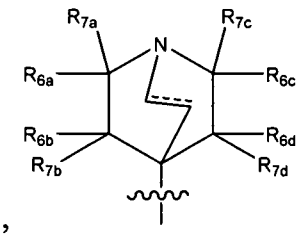
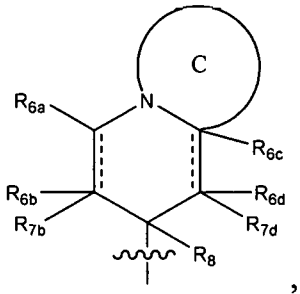
, or

R_{6a}, R_{6b}, R_{6c} and R_{6d} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

R_{7a}, R_{7b}, R_{7c} and R_{7d} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

R_8 is absent, or selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy;

or R_{7a}, and R_{7c}; or R_{7b} and R_{7d}; or R_{7a} and R_{7d}; or R_{7a} and R_{7d}; or R_3 and R_8 are combined and taken together with ring system B and to form:

, or ,

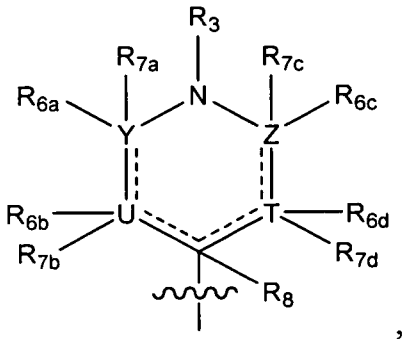
wherein

ring system C combined with the nitrogen and carbon atoms to which they are attached form a 5 or 6 membered heteroalicyclic ring

6. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 1, wherein r is an integer selected from the group consisting of 1, 2, and 3.

7. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 6, wherein the ring system B is selected from the group consisting of 4, 5, 6 or 7 membered ring comprising at least one nitrogen atom.

8. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claims 6 or 7, wherein the ring system B is selected from the group consisting of



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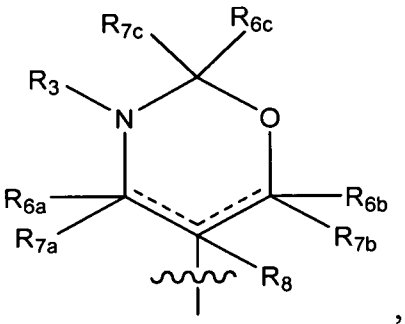

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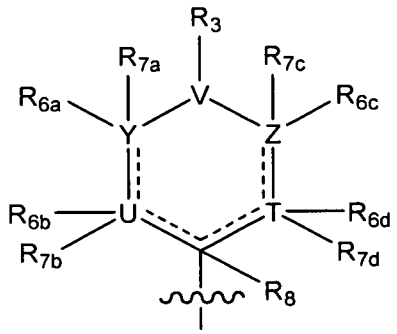

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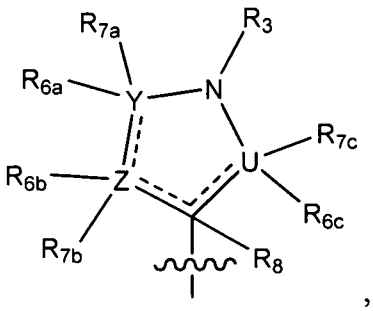

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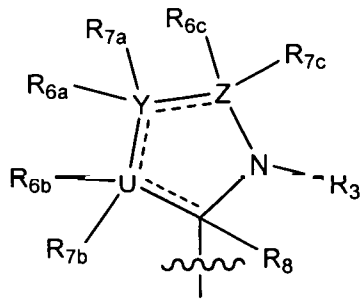

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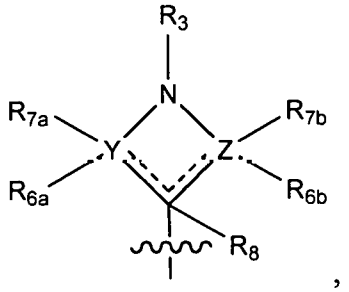
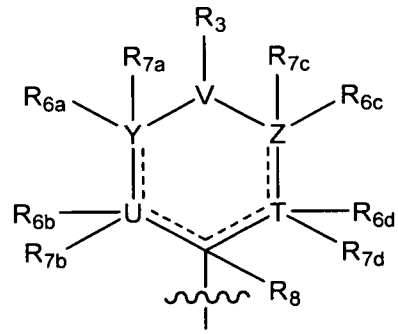


,

wherein

T, U, V, Y, Z are independently selected from the group consisting of –O-, -C-, and -N-; wherein when B is selected from



then at least one of T,U,V,Y,Z are –O- or –N-;

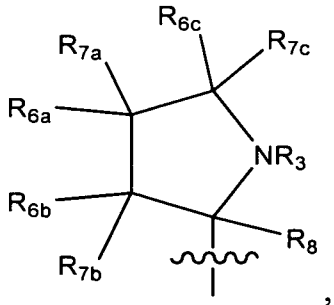
R_{6a}, R_{6b}, R_{6c} and R_{6d} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

R_{7a}, R_{7b}, R_{7c} and R_{7d} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

R_8 is absent, or selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy.

9. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 8, wherein T, U, Y, and Z are –C-.

10. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 6-9, wherein the ring system B is selected from the group consisting of



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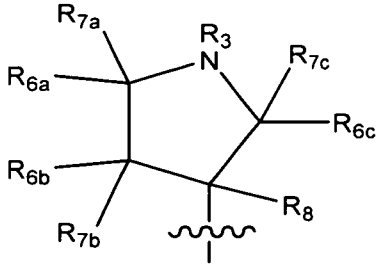

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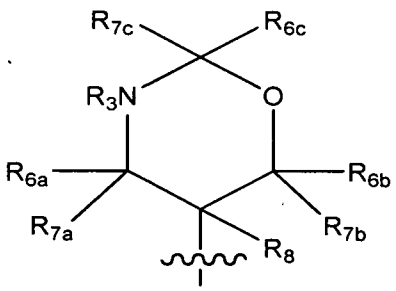
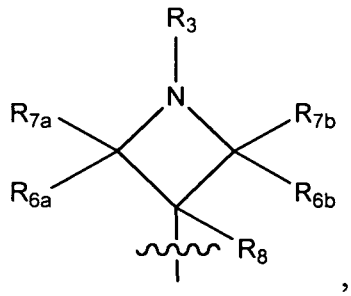




and ,

wherein

R_{6a}, R_{6b}, and R_{6c} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

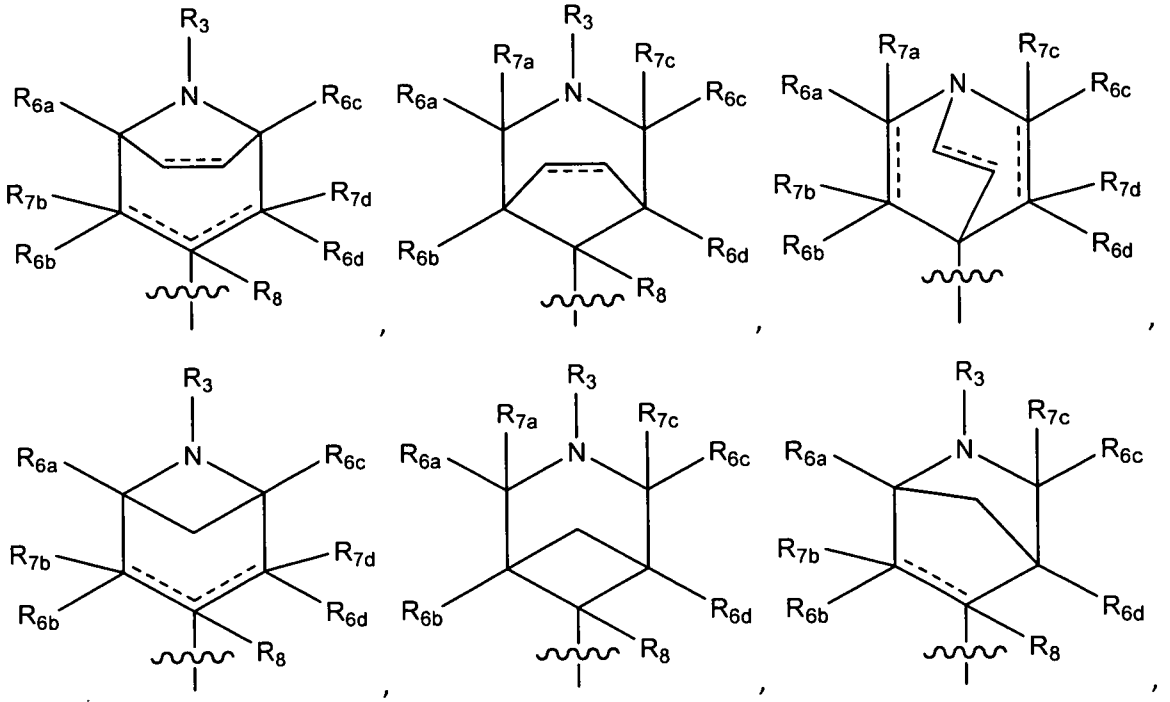
R_{7a}, R_{7b}, and R_{7c} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

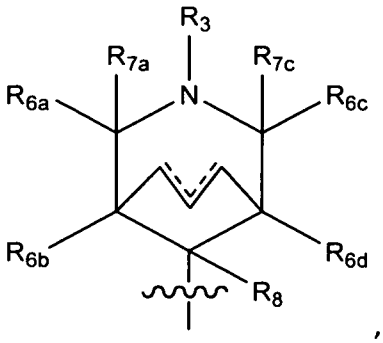
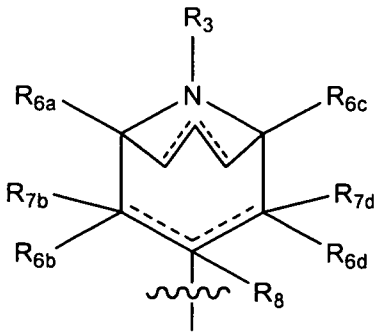
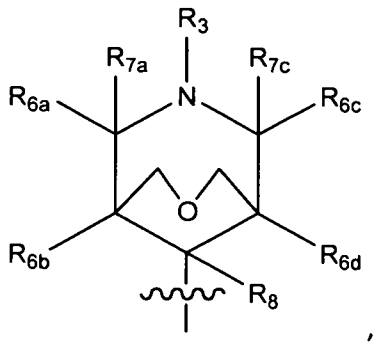
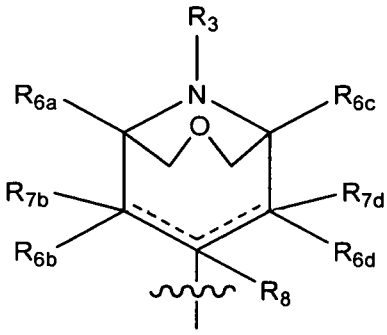
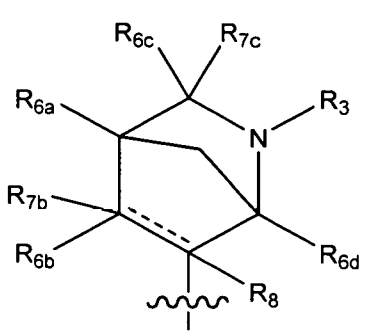
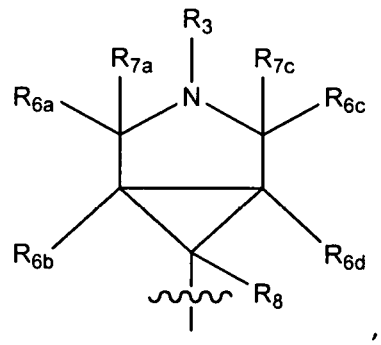
R_8 is selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy; and r is 1; R_{9a} and R_{9b} are hydrogen.

11. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to claim 1, wherein B is a bridged bicyclic ring system, wherein the two rings share three or more atoms, and ring system B is heteroalicyclic, such as bridged bicyclic ring system comprising at least one nitrogen atom.

12. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to claim 1, wherein the bridged bicyclic ring system is a 6-12 membered bicyclic ring system comprising at least one nitrogen atom, such as a ring system consisting of carbon atoms and one nitrogen atom only.

13. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 11-12, wherein the ring system B is selected from the group consisting of



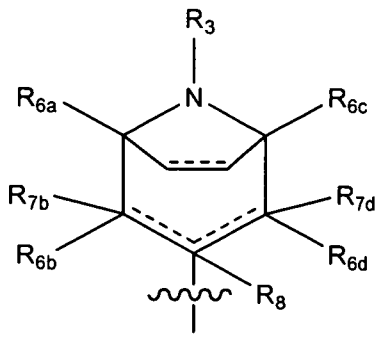







wherein

R_{6a}, R_{6b}, R_{6c} and R_{6d} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

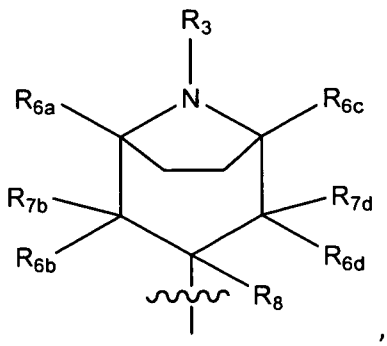
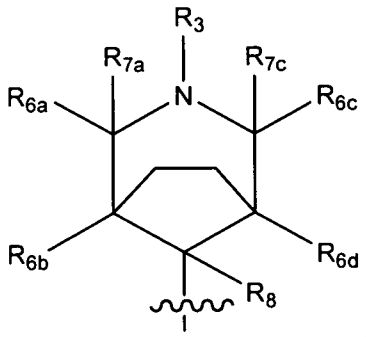
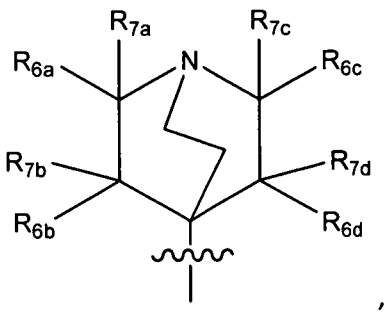
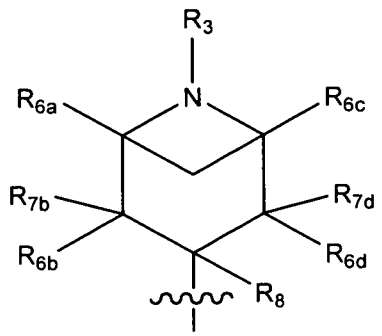
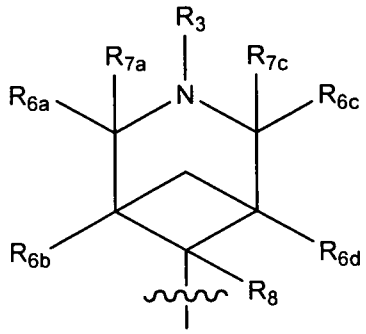
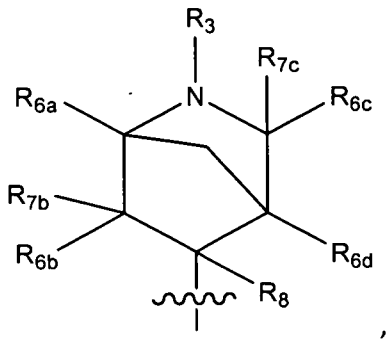
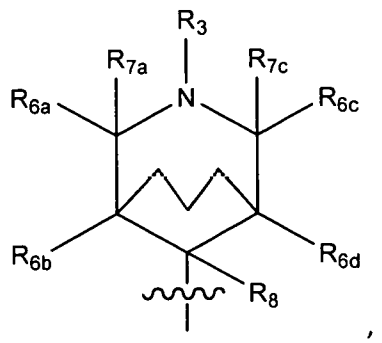
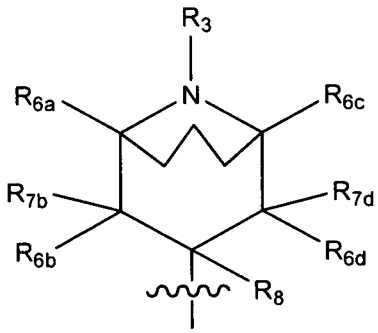
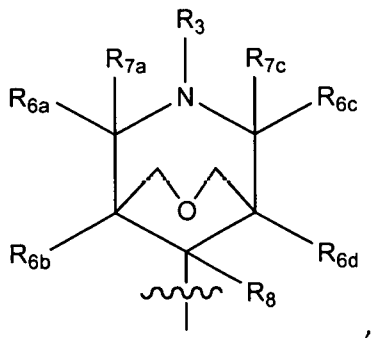
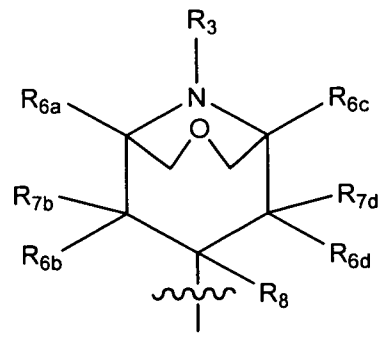
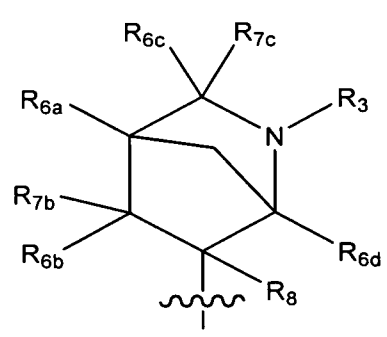
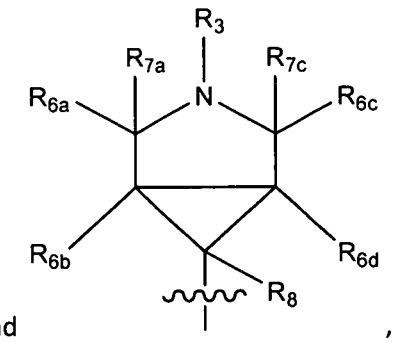
R_{7a}, R_{7b}, R_{7c} and R_{7d} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

R_8 is absent, or selected from the group consisting of hydrogen, cyano, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy; provided that whenever A is –



(CH_2)- and B is selected from , then R_1 cannot be methyl.

14. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 11-13, wherein the ring system B is selected from the group consisting of

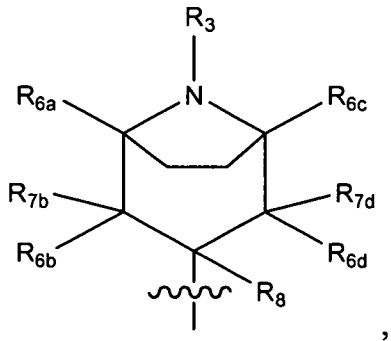













wherein

R_{6a}, R_{6b}, R_{6c} and R_{6d} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

R_{7a}, R_{7b}, R_{7c} and R_{7d} independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

R_8 is absent, or selected from the group consisting of hydrogen, cyano, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy; provided that whenever A is –

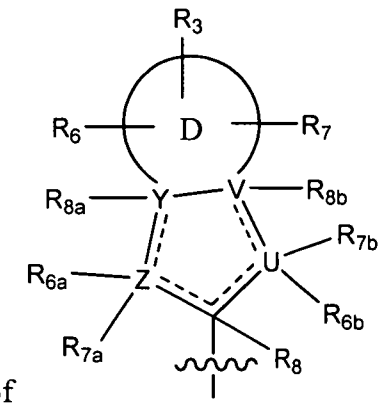


(CH_2)- and B is selected from , then R_1 cannot be methyl.

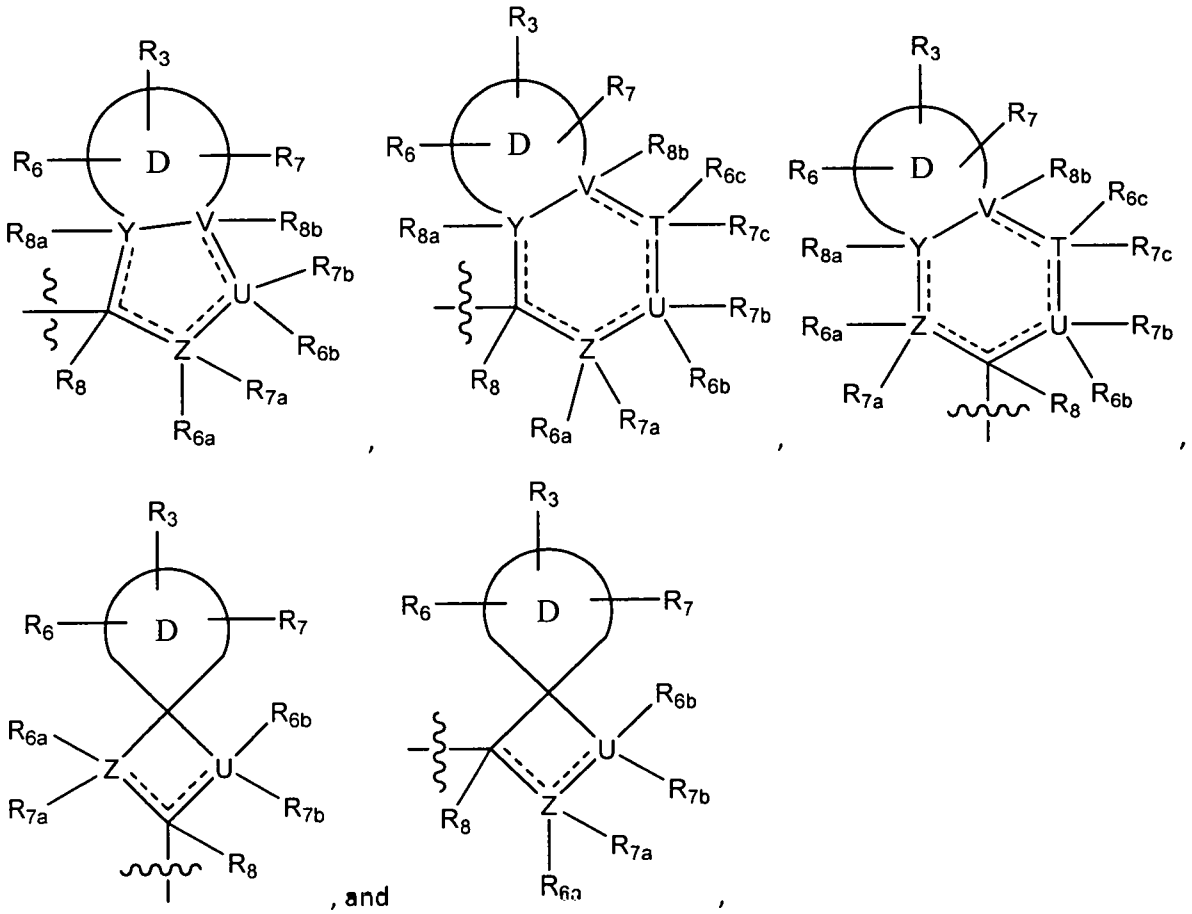
15. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to claim 1, wherein B is a fused bicyclic ring system, wherein the two rings share two adjacent atoms, or a spiro bicyclic ring system, wherein the two rings share one atom; and ring system B is heteroalicyclic, such as a 7-12 membered ring system comprising at least one nitrogen atom.

16. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 15, wherein at least one of the rings in ring system B is selected from the group consisting of a 4-membered ring, 5-membered ring or a 6-membered ring system, such as a 4-membered ring, 5-membered ring or a 6-membered ring system comprising carbon atoms and one nitrogen atom.

17. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 15-16, wherein the ring system B is selected from the group consisting of



,



wherein

T, U, V, Y, and Z are independently selected from the group consisting of –O-, -C-, and -N-;

R_6, R_{6a}, R_{6b}, R_{6c} and R_6 independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

R_7, R_{7a}, R_{7b}, R_{7c} and R_7 independently are absent or selected from the group consisting of, hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

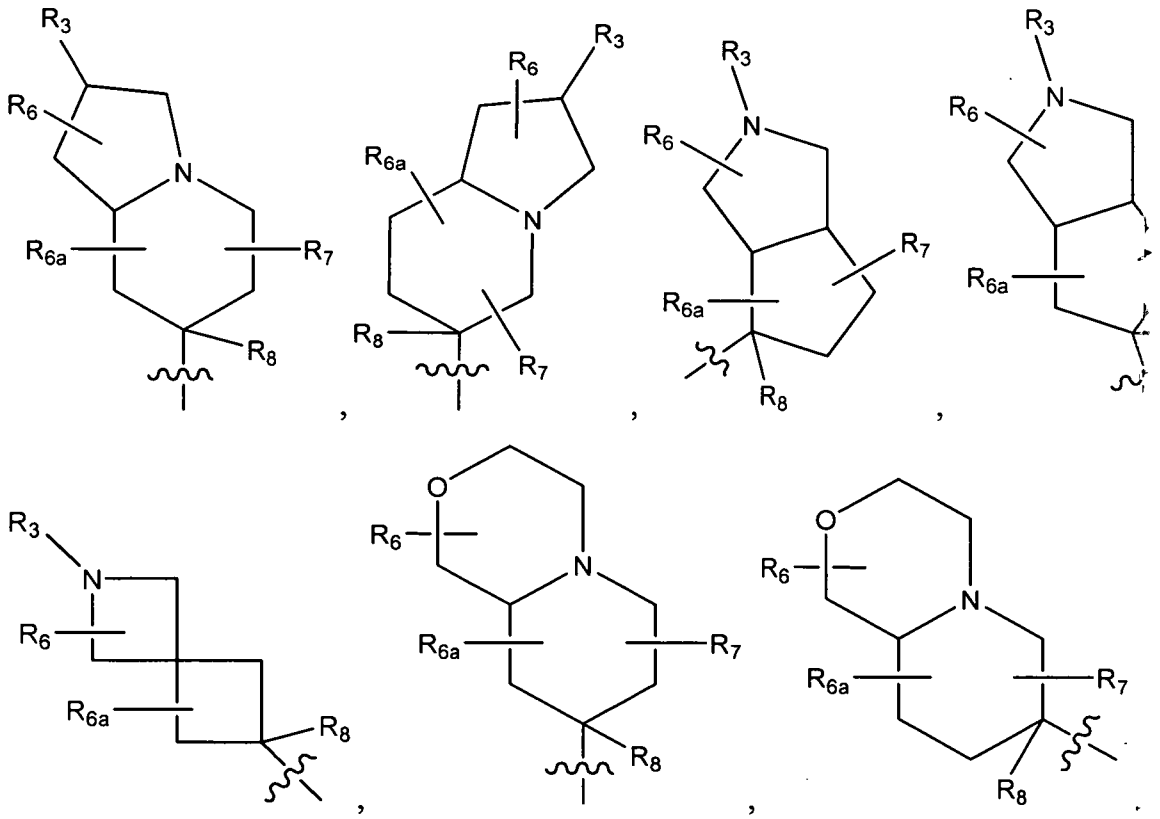
R_{8a}, R_{8b} and R_8 independently are absent, or selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

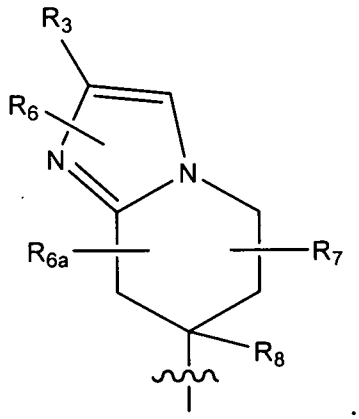
ring system D is a 4-7 membered heteroalicyclic or heteroaryl ring system comprising at least one nitrogen atom.

18. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 15-17, wherein ring system D i selected from the group consisting of a 4 membered heteroalicyclic ring system, a 5 membered heteroalicyclic ring system, and a 6 membered heteroalicyclic ring system, a heteroalicyclic ring system comprising one heteroatom only, and the heteroatom is a nitrogen atom.

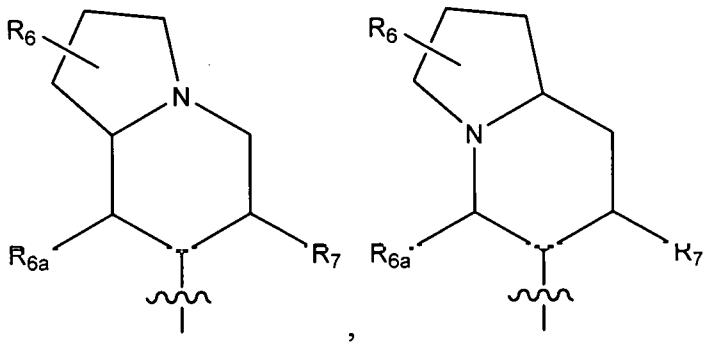
19. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 15-18, wherein T, U, V, Y, an independently selected from the group consisting of -C- and -N-; or
T, U, and Z are -C-; and V and Y are independently selected from the group consisting and -N-; or
T, U, V, Y, and Z are -C-.

20. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 1-9, wherein the ring system II selected from the group consisting of



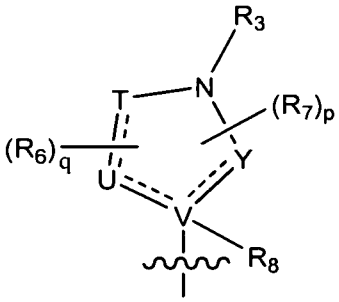
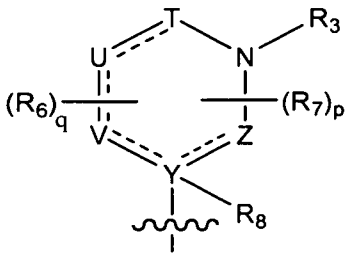
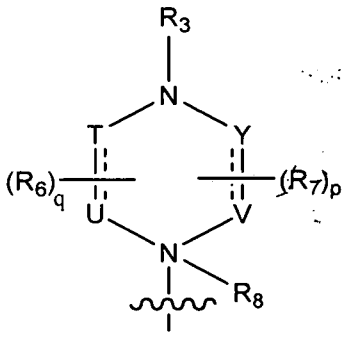


21. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 15-20, wherein the ring system B is selected from the group consisting of



22. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 1, wherein the ring system B is a monocyclic nitrogen containing heteroalicyclic ring system, such as a 4-7 membered ring system, and provided that B is not substituted or unsubstituted piperidyl-4-yl or unsubstituted 1-phenylmethyl pyrrolidin-3-yl.

23. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 22, wherein the ring system B is selected from the group consisting of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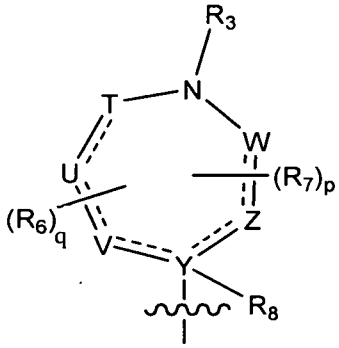

,

wherein

T, U, V, W, Y, and Z are independently selected from the group consisting of -O-, -C-, and -N-;

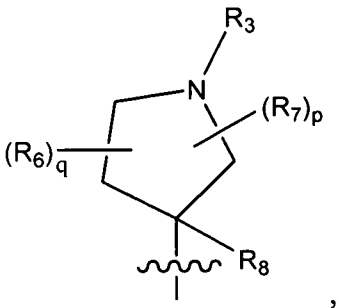
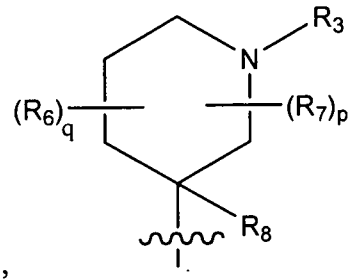
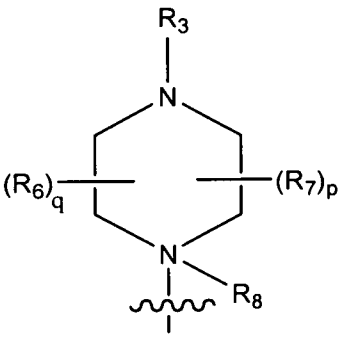
R_6 is absent or selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy;

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

R_8 is absent, or selected from the group consisting of hydrogen, cyano, -OH, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy.

24. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 22-23 wherein T, U, V, W, Y, and Z are independently selected from the group consisting of -C- and -N-.

25. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 22-24, wherein ring system B is selected from the group consisting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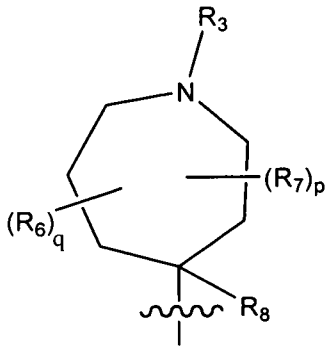
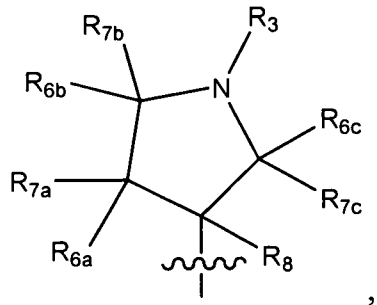
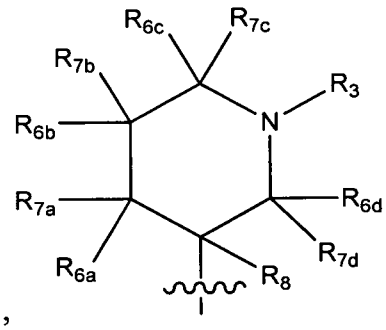
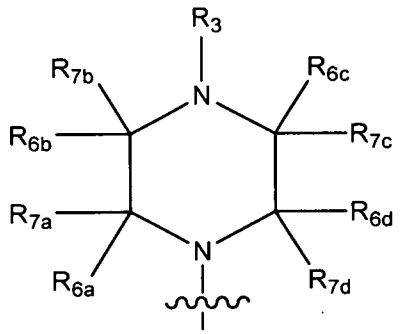

, wherein q and p, independently are 0 or 1.

26. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 22-25, wherein ring system B is selected from the group consisting of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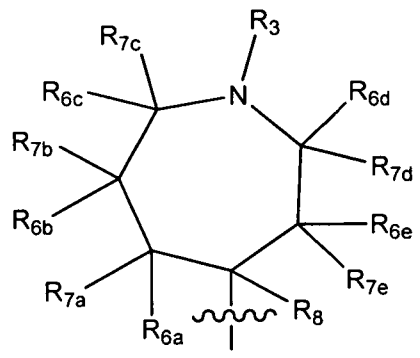

,

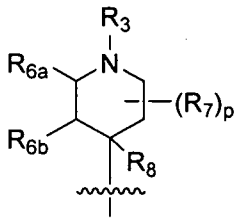
wherein

R_{6a}, R_{6b}, R_{6c}, R_{6d}, and R_{6e} are independently selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, oxo, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

R_{7a}, R_{7b}, R_{7c}, R_{7d} and R_{7e} are independently selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, -OD, substituted or unsubstituted C_{1-4} alkyl, and substituted or unsubstituted C_{1-4} alkoxy; and

R_8, is selected from the group consisting of hydrogen, cyano, hydroxyl, substituted or unsubstituted C_{1-4} alkyl, substituted or unsubstituted C_{1-4} alkenyl, substituted or unsubstituted C_{3-6} cycloalkyl, and substituted or unsubstituted C_{1-4} alkoxy.

27. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to claim 1, wherein ring system B has the following formula



, wherein

R_{6a}, and R_{6b} are independently 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;

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;

when p is 0 then at least one of R_{6a} and R_{6b} is not hydrogen.

28. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 27, wherein at least one of R_{6a} and R_{6b} is not hydrogen or deuterium; or one of R_{6a} and R_{6b} is selected from halogen, C_{1-4} alkyl and aryl.

29. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 27-28, wherein R_{6b} is halogen and R_{6a} is hydrogen.

30. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to any one of claims 27-28, wherein R_{6b} is fluoro and R_{6a} is hydrogen.

31. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-30, wherein R_1, R_{1a}, R_{1b}, R_{1c} and R_{1d} independently are selected from the group consisting of hydrogen, halogen, hydroxyl, amino, $-SO_2NH_2$, $-SO_2N(C_{1-4}\text{ alkyl})_2$, $-SO_2-C_{1-4}$ alkyl, $-OC(=O)-C_{1-4}$ alkyl, $-S(C_{1-6}$ alkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, C_{1-6} alkoxy, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-3} alkyl and deuterated analogues thereof.

32. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-31, wherein R_{1a}, R_{1b}, R_{1c} and R_{1d} independently are selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, $-SO_2NH_2$, $-SO_2CH_3$, $-OC(=O)CH_3$, methyl, $-CD_3$, methoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$.

33. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-32, wherein R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is hydrogen, deuterium, halogen, hydroxyl, methyl, $-CD_3$, methoxy, $-OCD_3$, $-OCF_3$ and $-CF_3$.

34. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-33, wherein R_{1a}, R_{1b}, and R_{1c} are hydrogen, and R_{1d} is selected from the group consisting of hydrogen, hydroxyl and fluoro.

35. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-34, wherein R_1 is selected from the group consisting of halogen, amino, 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.

36. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-35, wherein R_1 is selected from the group consisting of fluoro, chloro, methoxy,$-NMe_2$, $-OCF_3$, $-CF_3$ and methyl.

37. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-36, wherein R_1 is fluoro.

38. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-37, wherein R_1 and R_{1d} are fluoro, and R_{1a}, R_{1b} and R_{1c} are hydrogen.

39. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-38, 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_{1-6} haloalkoxy, C_{3-4} cycloalkyl, C_{3-4} cycloalkyl-C_{1-3} alkyl and deuterated analogues thereof; or R_2 and R_{2b}, taken together with the phenyl ring they attach to and the atoms to which they are attached form a bicyclic fused ring system.

40. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-39, wherein R_{2a}, R_{2c}, R_{2d}, and R_{2b}, provided R_{2b} is not forming a ring system with R_2, independently are selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, methyl, $-CD_3$, methoxy, $-OCD_3$,$-OCF_3$ and $-CF_3$.

41. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-40, wherein R_{2a}, R_{2c} and R_{2b} are hydrogen, and R_{2d} is hydrogen, fluoro or hydroxyl.

42. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-41, wherein R_2, provided R_2 is not forming a ring system with R_{2b}, 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, optionally deuterated methoxy, optionally deuterated ethoxy, optionally deuterated n-propoxy, optionally deuterated isopropoxy, optionally deuterated allyloxy, optionally deuterated prop-2-yn-1-yloxy, optionally deuterated n-butoxy, optionally deuterated iso-butoxy, optionally deuterated tert-butoxy, optionally deuterated pentyl-oxy, optionally deuterated 4-methyl-butoxy, optionally deuterated hexyl-oxy, optionally deuterated 4-methylpentoxy, optionally deuterated cyclopropyloxy, optionally deuterated cyclopropylmethoxy, optionally deuterated cyclopropylethoxy, optionally deuterated cyclobutyloxy, optionally deuterated cyclobutyloxy, optionally deuterated cyclobutylmethoxy, optionally deuterated cyclobutylethoxy, optionally deuterated C_{1-6} haloalkoxy, $-OCF_3$, $-OCF_2CF_3$, $-OCHF_2$, $-OCDF_2$, $-CF_3$, $-CF_2CF_3$, $-CHF_2$, CDF_2 $-CH_2CF_3$, $-CD_2CF_3$, $-CF_2$, 1,1,2,2-tetrafluorobutyl and 1,1,1,2,2-pentafluorobutyl.

43. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-42, wherein R_2, provided R_2 is not forming a ring system with R_{2b}, is selected from the group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, allyloxy, prop-2-yn-1-yloxy, n-butoxy, iso-butoxy, tert-butoxy, pentyl-oxy, 4-methyl-butoxy, hexyl-oxy, 4-methylpentoxy, cyclopropyloxy, cyclopropylmethoxy, cyclopropylethoxy, cyclobutyloxy, cyclobutylmethoxy, cyclobutylethoxy, 2-fluoroethoxy, 3-fluoropropoxy, 4-fluoroethoxy, $-OCF_3$ and (1,3-difluoropropan-2-yl)oxy.

44. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-43,

wherein R_1 and R_{1d} are fluoro, and R_{1a}, R_{1b} and R_{1c} are hydrogen; and R_2 is selected from the group consisting of ethoxy, isopropoxy, allyloxy, tert-butoxy, cyclopropyloxy, and 2-fluoroethoxy, and R_{2a}, R_{2b}, R_{2d} and R_{2d} are hydrogen.

45. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-44, 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} heteroalicyclyl, 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.

46. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-45, 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, cyclobutyl, -$CDCD_3CD_3$, –CH_2CH_3OH, –$(CR_{9c}R_{9d})_tC(=O)OR_{9e}$ and –$(CH_2)_tC(=O)NR_{9c}R_{9d}$, wherein R_{9c} ,R_{9d}, and R_{9e} independently are hydrogen or C_{1-4}-alkyl, wherein each t is selected from the group consisting of 0, 1, 2 and 3.

47. . The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-46, wherein R_3 is hydrogen or methyl.

48. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-47, wherein R_{4a}, R_{4b}, R_{5a}, R_{5b}, R_{5c} and R_{5d}, when present, are independently hydrogen or methyl.

49. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-48, wherein R_{4a}, R_{4b} and R_{5a} are hydrogen and R_{5b} is methyl or hydrogen.

50. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-49, wherein R_{4a}, R_{5a} and R_{5b} are hydrogen and R_{4b} is methyl or hydrogen.

51. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-50, wherein R_{4a}, R_{4b}, R_{5a}, R_{5b}, R_{5c} and R_{5d}, when present, are hydrogen.

52. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-51, wherein R_6, R_{6a}, R_{6b}, R_{6c}, R_{6d}, and R_{6e} independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, and substituted or unsubstituted C_{1-4} alkyl. 0

53. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-52, wherein R_6 is hydrogen or fluoro, or R_{6a}, R_{6b}, R_{6c}, R_{6d}, and R_{6e} independently are absent or selected from the group consisting of hydrogen, fluoro, methyl and methoxy.

54. The compound, pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug or stereoisomer according to claim 53, wherein at least one of R_{6a}, R_{6b}, R_{6c}, R_{6d}, and R_{6e} is selected from the group consisting of from fluoro, methyl and methoxy, and the others are hydrogen or absent.

55. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-54, wherein R_7, R_{7a}, R_{7b}, R_{7c}, R_{7d} and R_{7e}, independently are absent or selected from the group consisting of hydrogen, deuterium, halogen, methyl and methoxy.

56. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-55, wherein R_7, R_{7a}, R_{7b}, R_{7c}, R_{7d} and R_{7e} are absent.

57. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-56,

wherein R_8 R_{8a}, and R_{8b} independently are absent or selected from the group consisting of hydrogen, halogen, methyl, ethyl, propyl, methoxy, ethoxy, C_{1-2}- haloalkyl, and C_{1-2}- haloalkoxy.

58. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-57, wherein R_8 is selected from the group consisting of hydrogen, $-CF_3$, $-CHF_2$, $-CF_2CF_3$ $-OCF_3$, $-OCF_2CF_3$ and $-OCHF_2$.

59. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-58, wherein R_8 is hydrogen.

60. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-59, wherein X is O.

61. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-60, wherein E is N (nitrogen).

62. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1 and 6-60, wherein A is -C(=O)–NH- or -C(=O)-O-.

63. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to claim 62, wherein A is -C(=O)–NH-.

64. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1 and 6-60, wherein A is -C(=O)–NH- and E is N.

65. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-64, wherein r is 0 or 1.

66. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-5 and 11-64, wherein r is 0.

67. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-66, wherein m and n independently are selected from 0 and 1.

68. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-67, wherein m is 1 and n is 0 or 1.

69. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-68, wherein p and q independently are selected from 0 and 1.

70. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to claim 1, selected from the group consisting of:
(3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine;
(3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine;
(3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine;
(3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine;
Tert-butyl 4-{[(4-fluorophenyl)methyl](3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)amino}piperidine-1-carboxylate;

N-[(4-fluorophenyl)methyl]-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine;
N-[(4-fluorophenyl)methyl]-1-methyl-N-(3-{[4-(2-methylpropoxy)phenyl]methyl}-1,2,4-oxadiazol-5-yl)piperidin-4-amine;
Tert-Butyl 4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}-piperidine-1-carboxylate;
N-[(4-fluorophenyl)methyl]-N-{5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl}piperidin-4-amine;
N-[(4-fluorophenyl)methyl]-1-methyl-N-{5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl}piperidin-4-amine;
Tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl})amino}piperidine-1-carboxylate;
Tert-butyl 4-{[(4-fluorophenyl)methyl]({1-methyl-3-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-5-yl})amino}piperidine-1-carboxylate;
N-[(4-fluorophenyl)methyl]-N-{1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine;
N-[(4-fluorophenyl)methyl]-1-methyl-N-{1-methyl-5-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-3-yl}piperidin-4-amine;
N-[(4-fluorophenyl)methyl]-1-methyl-N-{1-methyl-3-[4-(2-methylpropoxy) phenyl]-1H-1,2,4-triazol-5-yl}piperidin-4-amine;
tert-Butyl 4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidine-1-carboxylate;
N-[(4-fluorophenyl)methyl]-N-(5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine;
N-[(4-fluorophenyl)methyl]-1-methyl-N-(5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)piperidin-4-amine;
3-(4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidin-1-yl)propanamide, and
(3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}piperidin-4-amine;
(3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}piperidin-4-amine;

(3S,4R)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}-1-methylpiperidin-4-amine;
(3R,4S)-3-fluoro-N-[(4-fluorophenyl)methyl]-N-{3-[(4-methoxyphenyl)methyl]-1,2,4-oxadiazol-5-yl}-1-methylpiperidin-4-amine;
3-(4-{[(4-fluorophenyl)methyl](5-{[4-(2-methylpropoxy)phenyl]methyl}-4H-1,2,4-triazol-3-yl)amino}piperidin-1-yl)propanoic acid;
N-[(4-fluorophenyl)methyl]-N-{1-methyl-3-[4-(2-methylpropoxy)phenyl]-1H-1,2,4-triazol-5-yl}piperidin-4-amine;
N-[(4-fluorophenyl)methyl]-N-{5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl}piperidin-4-amine;
methyl 3-(4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidin-1-yl)propanoate;
3-(4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidin-1-yl)propanoic acid;
3-(4-{[(4-fluorophenyl)methyl]({5-[4-(2-methylpropoxy)phenyl]-4H-1,2,4-triazol-3-yl})amino}piperidin-1-yl)propanamide;
N-[(4-fluorophenyl)methyl]-N-{[(3R)-1-methylpyrrolidin-3-yl]methyl}-2-[4-(propan-2-yloxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-{[(3S)-1-methylpyrrolidin-3-yl]methyl}-2-[4-(propan-2-yloxy)phenyl]acetamide;
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(3R)-1-methylpyrrolidin-3-yl]methyl}urea;
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(3S)-1-methylpyrrolidin-3-yl]methyl}urea;
N-[(4-fluorophenyl)methyl]-N-[(1-methylazetidin-3-yl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-{[(5R)-3-methyl-1,3-oxazinan-5-yl]methyl}-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-{[(5S)-3-methyl-1,3-oxazinan-5-yl]methyl}-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-2-[4-(propan-2-yloxy)phenyl]-acetamide;
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-acetamide;

N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-{[(2S)-1-methylpyrrolidin-2-yl]methyl}acetamide;
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-{[(2S)-1-methylpyrrolidin-2-yl]methyl}acetamide;
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2S)-pyrrolidin-2-yl]methyl}urea;
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2S)-1-methylpyrrolidin-2-yl]methyl}urea;
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-{[(2S)-pyrrolidin-2-yl]methyl}-urea;
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-{[(2S)-1-methylpyrrolidin-2-yl]methyl}-urea;
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2R)-pyrrolidin-2-yl]methyl}urea;
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-{[(2R)-1-methylpyrrolidin-2-yl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-{[(2R)-pyrrolidin-2-yl]methyl}-1-{[4-(propan-2-yloxy)phenyl]-methyl}urea;
3-[(4-fluorophenyl)methyl]-3-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-1-{[4-(propan-2-yloxy)phenyl]-methyl}urea;
N-[(4-fluorophenyl)methyl]-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]acetamide,
2-(4-methoxyphenyl)-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide,
2-(4-methoxyphenyl)-N-[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide,

N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
N-[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
1-[(4-fluorophenyl)methyl]-1-[(1R,4S,6S)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
1-[(4-fluorophenyl)methyl]-1-[(1S,4R,6R)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
N-[(4-fluorophenyl)methyl]-N-[(1R,4S,6S)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(1S,4R,6R)-2-methyl-2-azabicyclo[2.2.1]heptan-6-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide,
3-{1-azabicyclo[2.2.2]octan-4-yl}-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea,
2-(4-methoxyphenyl)-N-[(1R,3s,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide,
2-(4-methoxyphenyl)-N-[(1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl]-N-[(4-methylphenyl)methyl]acetamide,
N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,6r)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,6s)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide,
3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}-3-[(1R,5S,6r)-3-methyl-3-azabicyclo [3.1.1]heptan-6-yl]urea,
3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}-3-[(1R,5S,6s)-3-methyl-3-azabicyclo [3.1.1]heptan-6-yl]urea,
N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,9s)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]-N-[(1R,5S,9r)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]acetamide,
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9r)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]urea,

3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9s)-7-methyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl]urea,
N-[(4-fluorophenyl)methyl]-N-[(1R,4R,5R)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(1S,4S,5S)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
3-[(4-fluorophenyl)methyl]-3-[(1R,4R,5R)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-3-[(1S,4S,5S)-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl]-1-{[4-(2-methylpropoxy)phenyl] methyl}urea,
N-{[4-(dimethylamino)phenyl]methyl}-2-[4-(2-methylpropoxy)phenyl]-N-[(1R,5S,6r)-3-methyl-3-azabicyclo[3.1.1]heptan-6-yl]acetamide,
3-[(4-fluorophenyl)methyl]-3-[(1R,5S,6s)-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea,
1-[(4-fluorophenyl)methyl]-1-[(1R,5S,8r)-3-methyl-3-azabicyclo[3.2.1]octan-8-yl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
N-[(4-fluorophenyl)methyl]-N-[(1R,5S,8r)-3-methyl-3-azabicyclo[3.2.1]octan-8-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9s)-3-methyl-3-azabicyclo[3.3.1]nonan-9-yl]urea,
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(1R,5S,9s)-3-methyl-3-azabicyclo[3.3.1]nonan-9-yl]acetamide,
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(1R,5S,9r)-3-methyl-3-azabicyclo[3.3.1]nonan-9-yl]urea;
N-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide;
3-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
N-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
3-[(3aR,5s,6aS)-2-methyl-octahydrocyclopenta[c]pyrrol-5-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
N-[(4-fluorophenyl)methyl]-N-{2-methyl-2-azaspiro[3.3]heptan-6-yl}-2-[4-(2-methylpropoxy)phenyl]acetamide;

3-[(4-fluorophenyl)methyl]-3-{2-methyl-2-azaspiro[3.3]heptan-6-yl}-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-{2-methyl-octahydrocyclopenta[c]pyrrol-4-yl}-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-(2-methyl-octahydro-1H-isoindol-4-yl)urea;
3-[(4-fluorophenyl)methyl]-3-(2-methyl-octahydro-1H-isoindol-4-yl)-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-(octahydro-1H-isoindol-4-yl)acetamide;
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-(2-methyl-octahydro-1H-isoindol-4-yl)acetamide;
N-[(4-fluorophenyl)methyl]-N-(2-methyl-octahydro-1H-isoindol-4-yl)-2-[4-(2-methylpropoxy)phenyl]acetamide;
3-[(7S,8aR)-octahydroindolizin-7-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(7R,8aS)-octahydroindolizin-7-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(7R,8aR)-octahydroindolizin-7-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(7S,8aS)-octahydroindolizin-7-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
N-[(7S,8aS)-octahydroindolizin-7-yl]-2-[4-(cyclopropylmethoxy)phenyl]-N-[(4-fluorophenyl)methyl]acetamide;
N-[(7R,8aS)-octahydroindolizin-7-yl]-2-[4-(cyclopropylmethoxy)phenyl]-N-[(4-fluorophenyl)methyl]acetamide;
[4-(propan-2-yloxy)phenyl]methyl N-[(7S,8aS)-octahydroindolizin-7-yl]-N-[(4-fluorophenyl)methyl]carbamate;
N-[(8R,9aS)-octahydropyrido[2,1-c]morpholin-8-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(8S,9aR)-octahydropyrido[2,1-c]morpholin-8-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
3-[(8R,9aS)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;

3-[(8S,9aR)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
1-[(6S,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6R,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(7R,8R,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(7S,8S,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6R,7S,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6S,7R,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(7R,8R,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(7S,8S,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6R,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6S,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6R,7R,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6S,7S,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2 methylpropoxy)phenyl]methyl}urea;
1-[(7R,8S,8aS)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(7S,8R,8aR)-8-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6R,7R,8aS)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(6S,7S,8aR)-6-fluoro-octahydroindolizin-7-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;

3-[(4-fluorophenyl)methyl]-3-[(7R)-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-[(7S)-5H,6H,7H,8H-imidazo[1,2-a]pyridin-7-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-[(7R)-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-[(7S)-5H,6H,7H,8H-imidazo[1,5-a]pyridin-7-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
3-[(8S,9aR)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(8R,9aS)-octahydropyrido[2,1-c]morpholin-8-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(3S)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)-phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(3R)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(3S)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]acetamide,

N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(3R)-1-methylpiperidin-3-yl]-2-[4-(2-ethylpropoxy)phenyl]-acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]acetamide,
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(3R)-piperidin-3-yl]urea,
3-[(4-fluorophenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)-phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]urea,
3-[(4-fluorophenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)-phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]urea,
3-[(4-fluorophenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]urea,
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]urea,
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R)-pyrrolidin-3-yl]urea,
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3S)-pyrrolidin-3-yl]urea,
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R)-1-methylpyrrolidin-3-yl]urea,
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3S)-1-methylpyrrolidin-3-yl]urea,

1-[(3R)-1-cyclopropylpyrrolidin-3-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
1-[(3S)-1-cyclopropylpyrrolidin-3-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
1-[(4R)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}urea,
1-[(4S)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
1-[(4-fluorophenyl)methyl]-1-[(4R)-1-methylazepan-4-yl]-3-{[4-(2-methyl-propoxy)phenyl]methyl}urea,
1-[(4-fluorophenyl)methyl]-1-[(4S)-1-methylazepan-4-yl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}urea,
1-[(4R)-1-cyclopropylazepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea,
1-[(4S)-1-cyclopropylazepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea,
(2R)-3-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)-N-{[4-(2-methylpropoxy)phenyl]-methyl}propanamide,
(2S)-3-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)-N-{[4-(2-methylpropoxy)phenyl]-methyl}propanamide; and 1-(1-acetyl-1,3-diazinan-5-yl)-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea.;
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(3S)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)-phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3S)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]acetamide,

N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(3R)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(3S)-1-methylpiperidin-3-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3S)-1-methylpiperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(3R)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-N-[(3R)-1-methylpiperidin-3-yl]-2-[4-(2-ethylpropoxy)phenyl]-acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-piperidin-3-yl]acetamide,
N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)-N-[(3R)-1-methylpiperidin-3-yl]acetamide,
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(3R)-piperidin-3-yl]urea,
3-[(4-fluorophenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)-phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]urea,
3-[(4-fluorophenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)-phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]urea,
3-[(4-fluorophenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea,
3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3R)-1-methylpiperidin-3-yl]urea,

3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]-3-[(3S)-1-methylpiperidin-3-yl]urea,
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R)-pyrrolidin-3-yl]urea,
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3S)-pyrrolidin-3-yl]urea,
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R)-1-methylpyrrolidin-3-yl]urea,
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3S)-1-methylpyrrolidin-3-yl]urea,
1-[(3R)-1-cyclopropylpyrrolidin-3-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
1-[(3S)-1-cyclopropylpyrrolidin-3-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
1-[(4R)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}urea,
1-[(4S)-azepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea,
1-[(4-fluorophenyl)methyl]-1-[(4R)-1-methylazepan-4-yl]-3-{[4-(2-methyl-propoxy)phenyl]methyl}urea,
1-[(4-fluorophenyl)methyl]-1-[(4S)-1-methylazepan-4-yl]-3-{[4-(2-methylpropoxy)phenyl]-methyl}urea,
1-[(4R)-1-cyclopropylazepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea,
1-[(4S)-1-cyclopropylazepan-4-yl]-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)-phenyl]methyl}urea,
(2R)-3-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)-N-{[4-(2-methylpropoxy)phenyl]-methyl}propanamide,
(2S)-3-(4-fluorophenyl)-2-(4-methylpiperazin-1-yl)-N-{[4-(2-methylpropoxy)phenyl]-methyl}propanamide;
1-(1-acetyl-1,3-diazinan-5-yl)-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;

3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]urea;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(4-methoxyphenyl)methyl]urea;
3-[(3R,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3S,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3R,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3S,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide;
3-[(3R,4S)-3-fluoro-1-(propan-2-yl)piperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3S,4R)-3-fluoro-1-(propan-2-yl)piperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3R,4S)-1-ethyl-3-fluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3S,4R)-1-ethyl-3-fluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3R,4S)-1-cyclopropyl-3-fluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3S,4R)-1-cyclopropyl-3-fluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3R,4S)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}piperidin-1-yl]-2,2-dimethylpropanoic acid;

3-[(3S,4R)-3-fluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)amino}piperidin-1-yl]-2,2-dimethylpropanoic acid;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl)methyl]urea;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(2-methoxyphenyl)methyl]urea;
1-[(2,4-dimethoxyphenyl)methyl]-3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
1-[(2,4-dimethoxyphenyl)methyl]-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
1-[(3,5-dimethoxyphenyl)methyl]-3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
1-[(3,5-dimethoxyphenyl)methyl]-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(4-methylphenyl)methyl]urea;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(4-methylphenyl)methyl]urea;
1-{[4-(dimethylamino)phenyl]methyl}-3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
1-{[4-(dimethylamino)phenyl]methyl}-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
3-[(4-fluorophenyl)methyl]-3-(2-methylpiperidin-4-yl)-1-{[4-(2-methylpropoxy)phenyl]-methyl}urea;
3-(4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}-2-methylpiperidin-1-yl)propanamide;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(trifluoromethyl)phenyl]methyl}urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(trifluoromethyl)phenyl]methyl}urea;
1-[(3,5-difluorophenyl)methyl]-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
1-[(3,5-difluorophenyl)methyl]-3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;

1-[(4-cyanophenyl)methyl]-3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
1-[(4-cyanophenyl)methyl]-3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]urea;
3-[(4-fluorophenyl)methyl]-3-[(2S,4R)-2-phenylpiperidin-4-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-[(2R,4S)-2-phenylpiperidin-4-yl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
N-[(4-fluorophenyl)methyl]-N-[(2S,4R)-1-methyl-2-phenylpiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-[(2R,4S)-1-methyl-2-phenylpiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide;
N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-2-[4-(propan-2-yloxy)phenyl]acetamide;
N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)acetamide;
N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-(4-methoxyphenyl)acetamide;
N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide;
N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide;
N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide;
3-(1,2-dimethylpiperidin-4-yl)-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;

3-[(4-fluorophenyl)methyl]-3-[(2R,4S)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-[(2S,4R)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4R)-2,2-dimethylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4S)-2,2-dimethylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(4R)-1,2,2-trimethylpiperidin-4-yl]urea;
3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}-3-[(4S)-1,2,2-trimethylpiperidin-4-yl]urea;
3-[(4R)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4S)-3,3-difluoropiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4R)-3,3-difluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4S)-3,3-difluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4R)-3,3-difluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]-methyl}carbamoyl)amino}piperidin-1-yl]propenamide;
3-[(4S)-3,3-difluoro-4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}-carbamoyl)amino}piperidin-1-yl]propenamide;
3-[(4-fluorophenyl)methyl]-3-[(3R,4S)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-[(3S,4R)-3-fluoropiperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-(3-fluoro-1-methylpiperidin-4-yl)-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-(3-fluoro-1-methylpiperidin-4-yl)-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide;

N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide;
N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(propan-2-yloxy)phenyl]propenamide;
N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(propan-2-yloxy)phenyl]propanamide;
N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide;
N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide;
N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(2-methylpropoxy)phenyl]propenamide;
N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-3-[4-(2-methylpropoxy)phenyl]propanamide;
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-(1,2,6-trimethylpiperidin-4-yl)urea
1-[(4-fluorophenyl)methyl]-1-[(2R,4S)-1-methyl-2-phenylpiperidin-4-yl]-3-{[4-(propan-2-yloxy)phenyl]methyl}urea;
1-[(4-fluorophenyl)methyl]-1-[(2S,4R)-1-methyl-2-phenylpiperidin-4-yl]-3-{[4-(propan-2-yloxy)phenyl]methyl}urea;
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(2R,4S)-2-phenylpiperidin-4-yl]acetamide;
N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-[(2S,4R)-2-phenylpiperidin-4-yl]acetamide;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(propan-2-yloxy)phenyl]methyl}urea;
1-(1,2-dimethylpiperidin-4-yl)-1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-[(2R,4R)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(4-fluorophenyl)methyl]-3-[(2S,4S)-1-methyl-2-(trifluoromethyl)piperidin-4-yl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;

N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]-N-(1,2,6-trimethylpiperidin-4-yl)acetamide;

N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide;

N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide;

N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide;

N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(2-methylpropoxy)phenyl]propanamide;

N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide;

N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-[4-(propan-2-yloxy)phenyl]propanamide;

N-[(4-fluorophenyl)methyl]-N-[(3R,4S)-3-fluoropiperidin-4-yl]-3-(4-methoxyphenyl)propanamide;

N-[(4-fluorophenyl)methyl]-N-[(3S,4R)-3-fluoropiperidin-4-yl]-3-(4-methoxyphenyl)propanamide;

N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide;

N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[4-(2-methylpropoxy)phenyl]acetamide;

(N-(1,4-dimethylpiperidin-4-yl)-N-[(4-fluorophenyl)methyl]-2-[4-(propan-2-yloxy)phenyl]acetamide;

4-{[(4-fluorophenyl)methyl]({[4-(2-methylpropoxy)phenyl]methyl}carbamoyl)amino}-1,1-dimethylpiperidin-1-ium trifluoroacetate;

4-{[(4-fluorophenyl)methyl][methyl({[4-(2-methylpropoxy)-phenyl]methyl})carbamoyl]amino}-1,1-dimethylpiperidin-1-ium trifluoroacetate;

N-[(4-fluorophenyl)methyl]-N-[1-(2-hydroxyethyl)-1-oxo-1λ^5-piperidin-4-yl]-2-[4-(2-methylpropoxy)phenyl]acetamide;

3-[(3R,4S)-3-fluoro-1-($^2H_3$)methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;

3-[(3S,4R)-3-fluoro-1-($^2H_3$)methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
1-[(4-fluorophenyl)methyl]-3-{[4-(2-methylpropoxy)phenyl]methyl}-1-[(3R,4s,5S)-3,5-difluoro-1-methylpiperidin-4-yl]urea;
3-[(3R,5R)-3,5-difluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3S,5S)-3,5-difluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(3-methoxyphenyl)methyl]urea;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(3-methoxyphenyl)methyl]urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[2-(4-fluorophenyl)propan-2-yl]urea;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[2-(4-fluorophenyl)propan-2-yl]urea;
3-[(4-fluorophenyl)methyl]-3-{1-[2-(2-hydroxyethoxy)ethyl]-2,2-dimethylpiperidin-4-yl}-1-{[4-(2-methylpropoxy)phenyl]methyl}urea;
3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}-2-(1,2,2-trimethylpiperidin-4-yl)propanamide;
(2R)-3-(4-fluorophenyl)-2-(1-methylpiperidin-4-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide;
(2S)-3-(4-fluorophenyl)-2-(1-methylpiperidin-4-yl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide;
(2R)-2-[1-(2-carbamoylethyl)piperidin-4-yl]-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide;
(2S)-2-[1-(2-carbamoylethyl)piperidin-4-yl]-3-(4-fluorophenyl)-N-{[4-(2-methylpropoxy)-phenyl]methyl}propanamide;
(2R)-3-(4-fluorophenyl)-2-{1-[2-(2-hydroxyethoxy)ethyl]piperidin-4-yl}-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide;
(2S)-3-(4-fluorophenyl)-2-{1-[2-(2-hydroxyethoxy)ethyl]piperidin-4-yl}-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide;
(2R)-3-(4-fluorophenyl)-2-[1-(2-hydroxyethyl)piperidin-4-yl]-N-{[4-(2-methylpropoxy)phenyl]methyl}propanamide;

(2S)-3-(4-fluorophenyl)-2-[1-(2-hydroxyethyl)piperidin-4-yl]-N-{[4-(2-methylpropoxy)-phenyl]methyl}propanamide;
3-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(pyridin-3-yl)methyl]urea;
3-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-3-[(4-fluorophenyl)methyl]-1-[(pyridin-3-yl)methyl]urea;
N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[methyl({[4-(2-methylpropoxy)phenyl]methyl})amino]acetamide;
N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-2-[methyl({[4-(2-methylpropoxy)phenyl]methyl})amino]acetamide;
N-[(3S,4R)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-N'-{[4-(2-methylpropoxy)phenyl]methyl}ethanediamide;
N-[(3R,4S)-3-fluoro-1-methylpiperidin-4-yl]-N-[(4-fluorophenyl)methyl]-N'-{[4-(2-methylpropoxy)phenyl]methyl}ethanediamide; and
Ethyl 1-methyl-4-{[(4-methylphenyl)methyl]({[4-(2-methylpropoxy)-phenyl]methyl}carbamoyl)amino}piperidine-3-carboxylate.

71. A method for treating a disease in a patient comprising administering to the patient an effective amount of a compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-70, or a composition comprising an effective amount of a compound, pharmaceutically acceptable salt, polymorph or stereoisomer of a compound according to any one of claims 1-70,
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 familiar 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, Extrapyramidal 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, Pancreatis, 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 Supranucelar Palsy, Prion disease including Creutzfeld-Jakob disease (CJD), Gerstmann-Strausser-Schenker disease (GSSD) and fatal familiar 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.

72. The compound, or pharmaceutically acceptable salt, hydrate, solvate, polymorph, prodrug, stereoisomer, and deuterated analogue thereof according to any one of claims 1-70, or a composition comprising an effective amount of a compound, pharmaceutically acceptable salt, polymorph or stereoisomer of a compound according to any one of claims 1-70,

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 familiar 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, Extrapyramidal 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, Pancreatis, 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 Supranucelar Palsy, Prion disease including Creutzfeld-Jakob disease (CJD), Gerstmann-Strausser-Schenker disease (GSSD) and fatal familiar 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.