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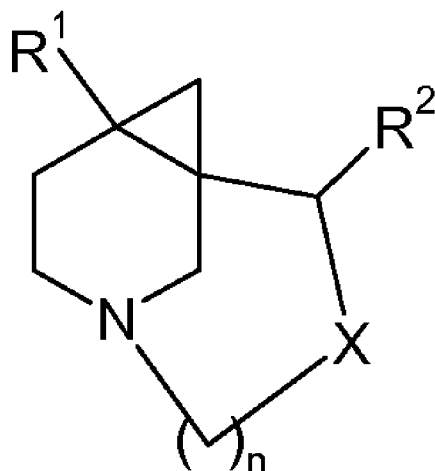
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(54) Title: TRICYCLIC AZABICYCLO [4.1.0] HEPTANE DERIVATIVES AS INHIBITORS OF SEROTONIN, DOPAMINE AND NOREPINEPHRINE RE-UP TAKE



(I)

(57) Abstract: The invention relates to compounds of formula (I), processes for their preparation, intermediates used in these processes, pharmaceutical compositions containing them and their use in therapy, as serotonin (5-HT), dopamine (DA) and norepinephrine (NE), re-uptake inhibitors.

TITLE

TRICYCLIC AZABICYCLO [4.1.0] HEPTANE DERIVATIVES AS INHIBITORS OF SEROTONIN, DOPAMINE AND NOREPINEPHRINE RE-UP TAKE

The present invention relates to novel compounds, processes for their preparation,
 5 intermediates used in these processes, pharmaceutical compositions containing the compounds and their use in therapy as inhibitors of serotonin (5-HT), dopamine (DA) and norepinephrine (NE) reuptake.

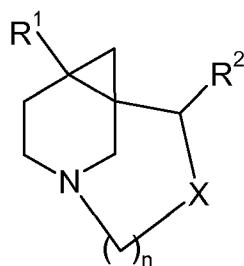
BACKGROUND

10 International patent publication WO 2008031772 discloses 1,6-disubstituted azabicyclo[4.1.0]heptane derivatives for use in therapy as inhibitors of 5-HT, DA and NE reuptake.

It is an object of the present invention to provide further inhibitors of 5-HT, DA and
 15 NE re-uptake.

SUMMARY OF THE INVENTION

According to a first aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof



(I)

20

wherein

R¹ is 3,4-dichlorophenyl or naphthyl;

R² is H or C₁₋₄alkoxy;

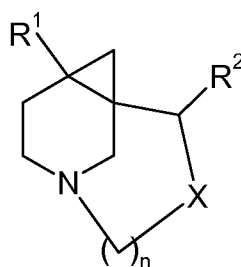
n is 0, 1 or 2; and

25 X is CH₂ or O;

wherein when n is 0 or 1, X is CH₂.

DESCRIPTION OF THE EMBODIMENTS

According to a first aspect, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof



(I)

5 wherein

R^1 is 3,4-dichlorophenyl or naphthyl;

R^2 is H or C_{1-4} alkoxy;

n is 0, 1 or 2; and

X is CH_2 or O;

10 wherein when n is 0 or 1, X is CH_2 .

As used herein, alkyl is a univalent radical derived by removal of a hydrogen atom from an acyclic alkane of formula C_nH_{2n+2} . For example, a C_{1-6} alkyl is alkyl comprising from 1 to 6 carbon atoms. Alkyl may be straight chain or branched chain.

15 Examples of alkyl are methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, iso-propyl, iso-butyl, sec-butyl, tert-butyl, iso-pentyl and neo-pentyl.

As used herein, alkoxy is a group of formula "R-O-" where R is alkyl (as defined hereinbefore). For example, C_{1-6} alkoxy is alkoxy consisting of 1 to 6 carbon atoms.

20 Examples of alkoxy are methoxy, ethoxy, n-propoxy, n-butoxy, n-pentoxy, n-hexyloxy, iso-propoxy, iso-butoxy, sec-butoxy, tert-butoxy, iso-pentoxy and neo-pentoxy.

The skilled chemist will appreciate from formula (I) that R^1 and the carbon attached to R^2 (i.e. the radicals attached to the two fused carbons) possess a cis relationship, i.e. both R^1 and the carbon attached to R^2 are on the same face of the bicyclic ring system. The skilled chemist will also appreciate from formula (I) that the carbon attached to R^2 is itself stereogenic. It will be appreciated therefore that compounds of formula (I) may exist in a variety of stereoisomers.

Mixtures of enantiomers, may be separated by appropriate optical resolution techniques (for example chiral HPLC).

- 5 In an embodiment, R¹ is 3,4-dichlorophenyl.

In an embodiment, X is CH₂ and R² is C₁₋₄alkoxy.

In an embodiment, the compound defined in the first aspect is selected from the list:

- 10 (1S,3R,8S or 1R,3S,8R)-3-(3,4-dichlorophenyl)-8-(methyloxy)-6-azatricyclo[4.2.1.0^{1,3}]nonane (single enantiomer) (Compound 1);
 (1S,3R or 1R,3S)-3-(3,4-dichlorophenyl)-8-(methyloxy)-6-azatricyclo[4.2.1.0^{1,3}]nonane (single diastereoisomer 2, single enantiomer) (Compound 2);
 15 (1S,3R,9S or 1R,3S,9R)-3-(3,4-dichlorophenyl)-9-(methyloxy)-6-azatricyclo[4.3.1.0^{1,3}]decane (single enantiomer) (Compound 3);
 (1S,3R,9S or 1R,3S,9R)-3-(3,4-dichlorophenyl)-9-(methyloxy)-6-azatricyclo[4.3.1.0^{1,3}]decane (single enantiomer) (Compound 4);
 (1S,3R or 1R,6S)-3-(3,4-dichlorophenyl)-9-oxa-6-azatricyclo[4.4.1.0^{1,3}]undecane
 20 (single enantiomer) (Compound 5); and
 (1R,3S/1S,3R)-3-(3,4-dichlorophenyl)-6-azatricyclo[4.2.1.0^{1,3}]-nonane (Racemate) (Compound 6);
 or a pharmaceutically acceptable salt thereof.

- 25 The compounds of formula (I) as defined in the first aspect contain a basic centre and may form non-toxic acid addition salts formed with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, with carboxylic acids or with organo-sulfonic acids. Examples include the HCl, HBr, HI, sulfate or bisulfate, nitrate, phosphate or hydrogen phosphate, acetate, benzoate, succinate,
 30 saccharate, fumarate, maleate, lactate, citrate, tartrate, gluconate, camsylate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate salts. For reviews on suitable pharmaceutical salts see Berge *et al*, J. Pharm, Sci., 66, 1-19, 1977; P L Gould, International Journal of Pharmaceutics, 33 (1986), 201-217; and Bighley *et al*, Encyclopedia of Pharmaceutical Technology,

Marcel Dekker Inc, New York 1996, Volume 13, page 453-497. In an embodiment, the salt is pharmaceutically acceptable.

It will be appreciated by those skilled in the art that certain protected derivatives of the compounds of formula (I) as defined in the first aspect, which may be made prior to a final deprotection stage, may not possess pharmacological activity as such, but may, in certain instances, be administered orally or parenterally and thereafter metabolised in the body to form compounds defined in the first aspect which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All protected derivatives and prodrugs of compounds defined in the first aspect are included within the scope of the invention. Examples of suitable pro-drugs for the compounds of the present invention are described in Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538 and in Topics in Chemistry, Chapter 31, pp 306 – 316 and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference). It will further be appreciated by those skilled in the art, that certain moieties, known to those skilled in the art as "pro-moieties", for example as described by H. Bundgaard in "Design of Prodrugs" (the disclosure in which document is incorporated herein by reference) may be placed on appropriate functionalities when such functionalities are present within the compounds defined in the first aspect. Therefore, in a further aspect, the invention provides a prodrug of a compound defined in the first aspect.

The compounds defined in the first aspect, their salts or prodrugs, may exist in solvated or hydrated form. Therefore, in a further aspect, the invention provides a solvate or hydrate of a compound defined in the first aspect or a salt thereof.

The compounds of formula (I) and their salts, as defined in the first aspect or solvates or hydrates of either, may exist in one or more polymorphic form. Therefore, in a further aspect, the invention provides a polymorph of a compound of formula (I) defined in the first aspect or their salts, or a polymorph of a solvate or hydrate of a compound of formula (I) defined in the first aspect, or a salt thereof.

Hereinafter, compounds of formula (I) as defined in the first aspect, their salts and prodrugs; any solvates or hydrates of any salt or prodrug; and any polymorph of any compound, salt, solvate or hydrate are referred to as "compounds of the invention".

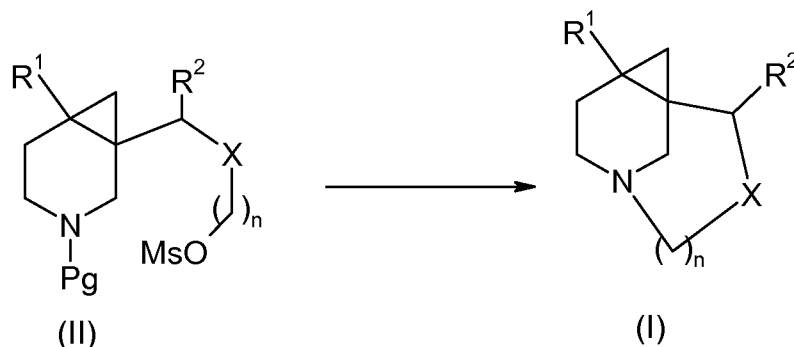
The term "compounds of the invention" also includes all embodiments of the first aspect.

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine and chlorine such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{35}S , ^{18}F and ^{36}Cl , respectively. Certain isotopic variations of the invention, for example, those in which a radioactive isotope such as ^3H or ^{14}C is incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium, i.e., ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of the compounds of the invention can generally be prepared by conventional procedures such as by the illustrative methods or by the preparations described in the Experimental section hereafter using appropriate isotopic variations of suitable reagents.

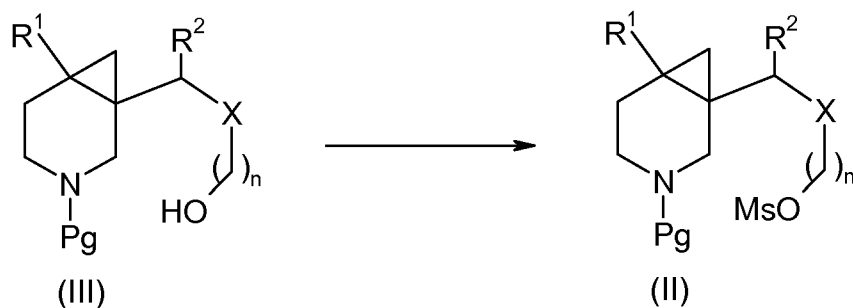
Compounds of the invention may be prepared in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated R^1 , R^5 , n and X are as defined in the first aspect.

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III), (IV) etc. Subsets of these general formulae are defined as (Ia), (Ib), (Ic) etc (IVa), (IVb), (IVc) etc.

Compounds of formula (I) may be obtained according to Scheme 1, by reacting compounds of formula (II), wherein Pg is a suitable N-protecting group (typically Boc), through deprotection of the N-Pg group. Typical deprotection conditions comprise treatment with sodium iodide in DMF at elevated temperature, such as heating in a microwave to 120 -130 °C.

Scheme 1

- 5 Compounds of formula (II), may be obtained according to Scheme 2, by reacting compounds of formula (III), wherein Pg is a suitable N-protecting group (typically Boc), with methane sulfonyl chloride and an appropriate base like DIPEA at room temperature.

10 Scheme 2

Compounds of formula (III) may be prepared using methods similar to the procedures discussed in the experimental section below.

15

A specific enantiomer or diastereoisomer of a compound of the invention may be obtained for example by optical resolution of a mixture of enantiomers or diastereoisomers using conventional methods, such as chiral chromatography.

- 20 The compounds of the invention may be used to treat diseases or conditions for which inhibition of 5-HT, DA and NE re-uptake is beneficial, i.e. inhibition of their respective monoamine transporter proteins referred to as SERT for 5-HT, DAT for DA and NET for NE. Therefore according to a further aspect, the invention provides a

compound of the invention for use in treating a disease or condition. In an embodiment the disease or condition is a human disease or condition. In an embodiment, the invention provides a compound of the invention for use in treating a disease or condition for which inhibition of monoamine neurotransmitter re-uptake is
5 beneficial, i.e. inhibition of one or more of SERT, NET and DAT.

In an embodiment the disease or condition which may benefit from inhibition of monoamine neurotransmitter re-uptake, i.e. inhibition of one or more of 5-HT, DA and NE re-uptake, is selected from the list consisting of: Parkinsonism, depression,
10 eating disorders, sleep disorders, substance related disorders, attention-deficit hyperactivity disorders, anxiety disorders, cognition impairment, sexual dysfunctions, obsessive compulsive spectrum disorders, Gilles de la Tourettes disease and senile dementia, as well as other disorders sensitive to the monoamine neurotransmitter re-uptake-inhibiting activity of the compounds.

15 The terms describing some indications used hereinabove are classified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, published by the American Psychiatric Association (DSM-IV) and/or the International Classification of Diseases, 10th Edition (ICD-10). The various subtypes of the disorders mentioned
20 hereinabove are contemplated as part of the present invention. Numbers in brackets after the listed diseases below refer to the classification code in DSM-IV.

The term "depression" includes:

25 Depression and mood disorders including Major Depressive Episode, Manic Episode, Mixed Episode and Hypomanic Episode; Depressive Disorders including Major Depressive Disorder, Dysthymic Disorder (300.4), Depressive Disorder Not Otherwise Specified (311); Other Mood Disorders including Mood Disorder Due to a General Medical Condition (293.83) which includes the subtypes With Depressive
30 Features, With Major Depressive-like Episode, With Manic Features and With Mixed Features), Substance-Induced Mood Disorder (including the subtypes With Depressive Features, With Manic Features and With Mixed Features) and Mood Disorder Not Otherwise Specified (296.90). Bipolar Disorders including Bipolar I Disorder, Bipolar II Disorder (Recurrent Major Depressive Episodes with Hypomanic

Episodes) (296.89), Cyclothymic Disorder (301.13) and Bipolar Disorder Not Otherwise Specified (296.80);

The term "anxiety disorders" includes:

5

Anxiety disorders including Panic Attack; Panic Disorder including Panic Disorder without Agoraphobia (300.01) and Panic Disorder with Agoraphobia (300.21); Agoraphobia; Agoraphobia Without History of Panic Disorder (300.22), Specific Phobia (300.29, formerly Simple Phobia) including the subtypes Animal Type,
 10 Natural Environment Type, Blood-Injection-Injury Type, Situational Type and Other Type), Social Phobia (Social Anxiety Disorder, 300.23), Obsessive-Compulsive Disorder (300.3), Posttraumatic Stress Disorder (309.81), Acute Stress Disorder (308.3), Generalized Anxiety Disorder (300.02), Anxiety Disorder Due to a General Medical Condition (293.84), Substance-Induced Anxiety Disorder, Separation Anxiety
 15 Disorder (309.21), Adjustment Disorders with Anxiety (309.24) and Anxiety Disorder Not Otherwise Specified (300.00):

The term "substance related disorder" includes:

20 Substance-related disorders including Substance Use Disorders such as Substance Dependence, Substance Craving and Substance Abuse; Substance-Induced Disorders such as Substance Intoxication, Substance Withdrawal, Substance-Induced Delirium, Substance-Induced Persisting Dementia, Substance-Induced Persisting Amnesic Disorder, Substance-Induced Psychotic Disorder, Substance-
 25 Induced Mood Disorder, Substance-Induced Anxiety Disorder, Substance-Induced Sexual Dysfunction, Substance-Induced Sleep Disorder and Hallucinogen Persisting Perception Disorder (Flashbacks); Alcohol-Related Disorders such as Alcohol Dependence (303.90), Alcohol Abuse (305.00), Alcohol Intoxication (303.00), Alcohol Withdrawal (291.81), Alcohol Intoxication Delirium, Alcohol Withdrawal Delirium,
 30 Alcohol-Induced Persisting Dementia, Alcohol-Induced Persisting Amnesic Disorder, Alcohol-Induced Psychotic Disorder, Alcohol-Induced Mood Disorder, Alcohol-Induced Anxiety Disorder, Alcohol-Induced Sexual Dysfunction, Alcohol-Induced Sleep Disorder and Alcohol-Related Disorder Not Otherwise Specified (291.9); Amphetamine (or Amphetamine-Like)-Related Disorders such as Amphetamine
 35 Dependence (304.40), Amphetamine Abuse (305.70), Amphetamine Intoxication

(292.89), Amphetamine Withdrawal (292.0), Amphetamine Intoxication Delirium, Amphetamine Induced Psychotic Disorder, Amphetamine-Induced Mood Disorder, Amphetamine-Induced Anxiety Disorder, Amphetamine-Induced Sexual Dysfunction, Amphetamine-Induced Sleep Disorder and Amphetamine-Related Disorder Not
5 Otherwise Specified (292.9); Caffeine Related Disorders such as Caffeine Intoxication (305.90), Caffeine-Induced Anxiety Disorder, Caffeine-Induced Sleep Disorder and Caffeine-Related Disorder Not Otherwise Specified (292.9); Cannabis-Related Disorders such as Cannabis Dependence (304.30), Cannabis Abuse (305.20), Cannabis Intoxication (292.89), Cannabis Intoxication Delirium, Cannabis-
10 Induced Psychotic Disorder, Cannabis-Induced Anxiety Disorder and Cannabis-Related Disorder Not Otherwise Specified (292.9); Cocaine-Related Disorders such as Cocaine Dependence (304.20), Cocaine Abuse (305.60), Cocaine Intoxication (292.89), Cocaine Withdrawal (292.0), Cocaine Intoxication Delirium, Cocaine-Induced Psychotic Disorder, Cocaine-Induced Mood Disorder, Cocaine-Induced
15 Anxiety Disorder, Cocaine-Induced Sexual Dysfunction, Cocaine-Induced Sleep Disorder and Cocaine-Related Disorder Not Otherwise Specified (292.9); Hallucinogen-Related Disorders such as Hallucinogen Dependence (304.50), Hallucinogen Abuse (305.30), Hallucinogen Intoxication (292.89), Hallucinogen Persisting Perception Disorder (Flashbacks) (292.89), Hallucinogen Intoxication
20 Delirium, Hallucinogen-Induced Psychotic Disorder, Hallucinogen-Induced Mood Disorder, Hallucinogen-Induced Anxiety Disorder and Hallucinogen-Related Disorder Not Otherwise Specified (292.9); Inhalant-Related Disorders such as Inhalant Dependence (304.60), Inhalant Abuse (305.90), Inhalant Intoxication (292.89), Inhalant Intoxication Delirium, Inhalant-Induced Persisting Dementia, Inhalant-
25 Induced Psychotic Disorder, Inhalant-Induced Mood Disorder, Inhalant-Induced Anxiety Disorder and Inhalant-Related Disorder Not Otherwise Specified (292.9); Nicotine-Related Disorders such as Nicotine Dependence (305.1), Nicotine Withdrawal (292.0) and Nicotine-Related Disorder Not Otherwise Specified (292.9); Opioid-Related Disorders such as Opioid Dependence (304.00), Opioid Abuse
30 (305.50), Opioid Intoxication (292.89), Opioid Withdrawal (292.0), Opioid Intoxication Delirium, Opioid-Induced Psychotic Disorder, Opioid-Induced Mood Disorder, Opioid-Induced Sexual Dysfunction, Opioid-Induced Sleep Disorder and Opioid-Related Disorder Not Otherwise Specified (292.9); Phencyclidine (or Phencyclidine-Like)-Related Disorders such as Phencyclidine Dependence (304.60), Phencyclidine
35 Abuse (305.90), Phencyclidine Intoxication (292.89), Phencyclidine Intoxication

Delirium, Phencyclidine-Induced Psychotic Disorder, Phencyclidine-Induced Mood Disorder, Phencyclidine-Induced Anxiety Disorder and Phencyclidine-Related Disorder Not Otherwise Specified (292.9); Sedative-, Hypnotic-, or Anxiolytic-Related Disorders such as Sedative, Hypnotic, or Anxiolytic Dependence (304.10), Sedative, 5 Hypnotic, or Anxiolytic Abuse (305.40), Sedative, Hypnotic, or Anxiolytic Intoxication (292.89), Sedative, Hypnotic, or Anxiolytic Withdrawal (292.0), Sedative, Hypnotic, or Anxiolytic Intoxication Delirium, Sedative, Hypnotic, or Anxiolytic Withdrawal Delirium, Sedative-, Hypnotic-, or Anxiolytic-Persisting Dementia, Sedative-, Hypnotic-, or Anxiolytic- Persisting Amnesic Disorder, Sedative-, Hypnotic-, or 10 Anxiolytic-Induced Psychotic Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Mood Disorder, Sedative-, Hypnotic-, or Anxiolytic-Induced Anxiety Disorder Sedative-, Hypnotic-, or Anxiolytic-Induced Sexual Dysfunction, Sedative-, Hypnotic-, or Anxiolytic-Induced Sleep Disorder and Sedative-, Hypnotic-, or Anxiolytic-Related Disorder Not Otherwise Specified (292.9); Polysubstance-Related Disorder such as 15 Polysubstance Dependence (304.80); and Other (or Unknown) Substance-Related Disorders such as Anabolic Steroids, Nitrate Inhalants and Nitrous Oxide;

The term "Sleep disorder" includes:

20 Sleep disorders including primary sleep disorders such as Dyssomnias such as Primary Insomnia (307.42), Primary Hypersomnia (307.44), Narcolepsy (347), Breathing-Related Sleep Disorders (780.59), Circadian Rhythm Sleep Disorder (307.45) and Dyssomnia Not Otherwise Specified (307.47); primary sleep disorders such as Parasomnias such as Nightmare Disorder (307.47), Sleep Terror Disorder 25 (307.46), Sleepwalking Disorder (307.46) and Parasomnia Not Otherwise Specified (307.47); Sleep Disorders Related to Another Mental Disorder such as Insomnia Related to Another Mental Disorder (307.42) and Hypersomnia Related to Another Mental Disorder (307.44); Sleep Disorder Due to a General Medical Condition; and Substance-Induced Sleep Disorder including the subtypes Insomnia Type, 30 Hypersomnia Type, Parasomnia Type and Mixed Type;

The term "eating disorder" includes:

Eating disorders such as Anorexia Nervosa (307.1) including the subtypes 35 Restricting Type and Binge-Eating/Purging Type; Bulimia Nervosa (307.51) including

the subtypes Purging Type and Nonpurging Type; Obesity; Compulsive Eating Disorder; Binge Eating Disorder; and Eating Disorder Not Otherwise Specified (307.50):

- 5 The term "Attention-Deficit/Hyperactivity Disorder" includes:

Attention-Deficit/Hyperactivity Disorder including the subtypes Attention-Deficit /Hyperactivity Disorder Combined Type (314.01), Attention-Deficit /Hyperactivity Disorder Predominantly Inattentive Type (314.00), Attention-Deficit /Hyperactivity
 10 Disorder Hyperactive-Impulse Type (314.01) and Attention-Deficit /Hyperactivity Disorder Not Otherwise Specified (314.9); Hyperkinetic Disorder; Disruptive Behaviour Disorders such as Conduct Disorder including the subtypes childhood-onset type (321.81), Adolescent-Onset Type (312.82) and Unspecified Onset (312.89), Oppositional Defiant Disorder (313.81) and Disruptive Behaviour Disorder
 15 Not Otherwise Specified; and Tic Disorders such as Tourette's Disorder (307.23);

The term "Cognition impairment" includes:

Cognition impairment including cognition impairment in other diseases such as
 20 schizophrenia, bipolar disorder, depression, other psychiatric disorders and psychotic conditions associated with cognitive impairment, e.g. Alzheimer's disease;

The term "Sexual dysfunctions" includes:

25 Sexual dysfunctions including Sexual Desire Disorders such as Hypoactive Sexual Desire Disorder (302.71), and Sexual Aversion Disorder (302.79); sexual arousal disorders such as Female Sexual Arousal Disorder (302.72) and Male Erectile Disorder (302.72); orgasmic disorders such as Female Orgasmic Disorder (302.73), Male Orgasmic Disorder (302.74) and Premature Ejaculation (302.75); sexual pain
 30 disorder such as Dyspareunia (302.76) and Vaginismus (306.51); Sexual Dysfunction Not Otherwise Specified (302.70); paraphilias such as Exhibitionism (302.4), Fetishism (302.81), Frotteurism (302.89), Pedophilia (302.2), Sexual Masochism (302.83), Sexual Sadism (302.84), Transvestic Fetishism (302.3), Voyeurism (302.82) and Paraphilia Not Otherwise Specified (302.9); gender identity
 35 disorders such as Gender Identity Disorder in Children (302.6) and Gender Identity

Disorder in Adolescents or Adults (302.85); and Sexual Disorder Not Otherwise Specified (302.9);

The term "Obsessive compulsive spectrum disorder" includes:

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Obsessive compulsive spectrum disorder including Obsessive compulsive disorders (300.3), somatoform disorders including body dysmorphic disorder (300.7) and hyperchondriasis (300.7), bulimia nervosa (307.51), anorexia nervosa (307.1), eating disorders not elsewhere classified (307.50) such as binge eating, impulse control disorders not elsewhere classified (including intermittent explosive disorder (312.34), compulsive buying or shopping, repetitive self-mutilation, onychophagia, psychogenic excoriation, kleptomania (312.32), pathological gambling (312.31), trichotillomania (312.39) and internet addiction), paraphilia (302.70) and nonparaphilic sexual addictions, Sydeham's chorea, torticollis, autistic disorders (299.0), compulsive hoarding, and movement disorders, including Tourette's syndrome (307.23).

All of the various forms and sub-forms of the disorders mentioned herein are contemplated as part of the present invention.

20 In an embodiment, compounds of the invention may be useful as analgesics. For example they may be useful in the treatment of chronic inflammatory pain (e.g. pain associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis); musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain
25 associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and
30 dysmenorrhea.

Compounds of the invention may be useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may persist for months or years, even after the original injury has healed.

35 Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or

certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; 5 trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, 10 burning pain. In addition, there is pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of 15 the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

Compounds of the invention may also be useful in the amelioration of inflammatory disorders, for example in the treatment of skin conditions (e.g. sunburn, burns, 20 eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, chronic obstructive pulmonary disease, (COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's 25 disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastroesophageal reflux disease); other conditions with an inflammatory component such as migraine, multiple sclerosis, myocardial ischemia.

30 In one embodiment, compounds of the invention are useful in the treatment of depression and anxiety disorders.

In another embodiment, compounds of the invention are useful in the treatment of depression.

"Treatment" includes prophylaxis, where this is appropriate for the relevant condition(s).

5 The compounds of the invention may also be used in combination with other therapeutic agents. The invention thus provides, in a further aspect, a combination comprising a compound of the invention together with a further therapeutic agent.

10 The compounds of the invention may be used in combination with the following agents to treat or prevent psychotic disorders: i) antipsychotics; ii) drugs for extrapyramidal side effects, for example anticholinergics (such as benztropine, biperiden, procyclidine and trihexyphenidyl), antihistamines (such as diphenhydramine) and dopaminergics (such as amantadine); iii) antidepressants; iv) anxiolytics; and v) cognitive enhancers for example cholinesterase inhibitors (such as tacrine, donepezil, rivastigmine and galantamine).

15 The compounds of the invention may be used in combination with antidepressants to treat or prevent depression and mood disorders.

20 The compounds of the invention may be used in combination with the following agents to treat or prevent bipolar disease: i) mood stabilisers; ii) antipsychotics; and iii) antidepressants.

25 The compounds of the invention may be used in combination with the following agents to treat or prevent anxiety disorders: i) anxiolytics; and ii) antidepressants.

30 The compounds of the invention may be used in combination with the following agents to improve nicotine withdrawal and reduce nicotine craving: i) nicotine replacement therapy for example a sublingual formulation of nicotine beta-cyclodextrin and nicotine patches; and ii) bupropion.

35 The compounds of the invention may be used in combination with the following agents to improve alcohol withdrawal and reduce alcohol craving: i) NMDA receptor antagonists for example acamprosate; ii) GABA receptor agonists for example tetrabamate; and iii) Opioid receptor antagonists for example naltrexone.

The compounds of the invention may be used in combination with the following agents to improve opiate withdrawal and reduce opiate craving: i) opioid mu receptor agonist/opioid kappa receptor antagonist for example buprenorphine; ii) opioid receptor antagonists for example naltrexone; and iii) vasodilatory antihypertensives
5 for example lofexidine.

The compounds of the invention may be used in combination with the following agents to treat or prevent sleeping disorders: i) benzodiazepines for example temazepam, lormetazepam, estazolam and triazolam; ii) non-benzodiazepine
10 hypnotics for example zolpidem, zopiclone, zaleplon and indiplon; iii) barbiturates for example aprobarbital, butabarbital, pentobarbital, secobarbital and phenobarbital; iv) antidepressants; v) other sedative-hypnotics for example chloral hydrate and chlormethiazole.

15 The compounds of the invention may be used in combination with the following agents to treat anorexia: i) appetite stimulants for example cyproheptidine; ii) antidepressants; iii) antipsychotics; iv) zinc; and v) premenstrual agents for example pyridoxine and progesterones.

20 The compounds of the invention may be used in combination with the following agents to treat or prevent bulimia: i) antidepressants; ii) opioid receptor antagonists; iii) antiemetics for example ondansetron; iv) testosterone receptor antagonists for example flutamide; v) mood stabilisers; vi) zinc; and vii) premenstrual agents.

25 The compounds of the invention may be used in combination with the following agents to treat or prevent autism: i) antipsychotics; ii) antidepressants; iii) anxiolytics; and iv) stimulants for example methylphenidate, amphetamine formulations and pemoline.

30 The compounds of the invention may be used in combination with the following agents to treat or prevent ADHD: i) stimulants for example methylphenidate, amphetamine formulations and pemoline; and ii) non-stimulants for example norepinephrine reuptake inhibitors (such as atomoxetine), alpha 2 adrenoceptor agonists (such as clonidine), antidepressants, modafinil, and cholinesterase
35 inhibitors (such as galantamine and donepezil).

The compounds of the invention may be used in combination with the following agents to treat personality disorders: i) antipsychotics; ii) antidepressants; iii) mood stabilisers; and iv) anxiolytics.

5

The compounds of the invention may be used in combination with the following agents to treat or prevent male sexual dysfunction: i) phosphodiesterase V inhibitors, for example vardenafil and sildenafil; ii) dopamine agonists/dopamine transport inhibitors for example apomorphine and bupropion; iii) alpha adrenoceptor antagonists for example phentolamine; iv) prostaglandin agonists for example alprostadil; v) testosterone agonists such as testosterone; vi) serotonin transport inhibitors for example serotonin reuptake inhibitors; vii) noradrenaline transport inhibitors for example reboxetine and viii) 5-HT_{1A} agonists, for example flibanserin.

10

15 The compounds of the invention may be used in combination with the same agents specified for male sexual dysfunction to treat or prevent female sexual dysfunction, and in addition an estrogen agonist such as estradiol.

Antipsychotic drugs include Typical Antipsychotics (for example chlorpromazine, thioridazine, mesoridazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, thiothixine, haloperidol, molindone and loxapine); and Atypical Antipsychotics (for example clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone and amisulpride).

20

25 Antidepressant drugs include serotonin reuptake inhibitors (such as citalopram, escitalopram, fluoxetine, paroxetine and sertraline); dual serotonin/noradrenaline reuptake inhibitors (such as venlafaxine, duloxetine and milnacipran); Noradrenaline reuptake inhibitors (such as reboxetine); tricyclic antidepressants (such as amitriptyline, clomipramine, imipramine, maprotiline, nortriptyline and trimipramine);
30 monoamine oxidase inhibitors (such as isocarboxazide, moclobemide, phenelzine and tranylcypromine); and others (such as bupropion, mianserin, mirtazapine, nefazodone and trazodone).

30

Mood stabiliser drugs include lithium, sodium valproate/valproic acid/divalproex, carbamazepine, lamotrigine, gabapentin, topiramate and tiagabine.

35

Anxiolytics include benzodiazepines such as alprazolam and lorazepam.

5 The compounds of the invention will normally, but not necessarily, be formulated into pharmaceutical compositions prior to administration to a patient by an appropriate route. Accordingly, in another aspect, the invention provides pharmaceutical compositions comprising a compound of the invention and one or more pharmaceutically-acceptable excipients.

10 As used herein, "pharmaceutically acceptable excipient" means any pharmaceutically acceptable material present in the pharmaceutical composition or dosage form other than the compound or compounds of the invention. Typically the material gives form, consistency and performance to the pharmaceutical composition.

15 The pharmaceutical compositions of the invention typically contain one compound of the invention. However, in certain embodiments, the pharmaceutical compositions of the invention contain more than one compound of the invention. In addition, the pharmaceutical compositions of the invention may comprise one or more additional
20 pharmaceutically active compounds.

Such pharmaceutical compositions of the invention may be prepared and packaged in bulk form wherein a safe and effective amount of a compound of the invention can be dispensed and then given to the patient such as with powders or syrups.

25 Alternatively, the pharmaceutical compositions of the invention may be prepared and packaged as dosage forms wherein each physically discrete dosage form contains a safe and effective amount of a compound of the invention. Accordingly, in another aspect, the invention provides dosage forms comprising pharmaceutical compositions of the invention. Each discrete dosage form typically contains from 1
30 mg to 500 mg of a compound of the invention.

The compositions of the invention will typically be formulated into dosage forms which are adapted for administration to the patient by the desired route of administration. For example, dosage forms include those adapted for (1) oral
35 administration such as tablets, capsules, caplets, pills, lozenges, powders, syrups,

elixirs, suspensions, solutions, emulsions, sachets and cachets; (2) parenteral administration such as sterile solutions, suspensions, implants and powders for reconstitution; (3) transdermal administration such as transdermal patches; (4) rectal and vaginal administration such as suppositories, pessaries and foams; (5) inhalation and intranasal such as dry powders, aerosols, suspensions and solutions (sprays and drops); (6) topical administration such as creams, ointments, lotions, solutions, pastes, drops, sprays, foams and gels; (7) ocular administration such as drops, ointment, sprays, suspensions and inserts; (8) buccal and sublingual administration such as lozenges, patches, sprays, drops, chewing gums and tablets.

Suitable pharmaceutically acceptable excipients will vary depending upon the particular dosage form chosen. In addition, suitable pharmaceutically acceptable excipients may be chosen for a particular function that they may serve in the composition. For example, certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of uniform dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the production of stable dosage forms. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the carrying or transporting of the compound or compounds of the invention once administered to the patient from one organ, or portion of the body, to another organ, or portion of the body. Certain pharmaceutically acceptable excipients may be chosen for their ability to enhance patient compliance. Certain pharmaceutically acceptable excipients may be chosen for their ability to facilitate the release of the compound of the invention at the appropriate rate to treat the condition.

Suitable pharmaceutically acceptable excipients include the following types of excipients: diluents, fillers, binders, disintegrants, lubricants, glidants, granulating agents, coating agents, wetting agents, solvents, co-solvents, suspending agents, emulsifiers, sweeteners, flavouring agents, flavour masking agents, colouring agents, anticaking agents, humectants, chelating agents, plasticizers, viscosity increasing agents, rate modifying agents, antioxidants, preservatives, stabilizers, surfactants and buffering agents. The skilled artisan will appreciate that certain pharmaceutically acceptable excipients may serve more than one function and may serve alternative functions depending on how much of the excipient is present in the formulation and what other ingredients are present in the formulation.

Skilled artisans possess the knowledge and skill in the art to enable them to determine suitable pharmaceutically acceptable excipients in appropriate amounts for use with the compounds of the invention. In addition, there are a number of resources that are available to the skilled artisan which describe pharmaceutically acceptable excipients and may be useful in selecting suitable pharmaceutically acceptable excipients. Examples include Remington's Pharmaceutical Sciences (Mack Publishing Company), The Handbook of Pharmaceutical Additives (Gower Publishing Limited), and The Handbook of Pharmaceutical Excipients (the American Pharmaceutical Association and the Pharmaceutical Press). The pharmaceutical compositions of the invention may be prepared using techniques and methods known to those skilled in the art. Some of the methods commonly used in the art are described in Remington's Pharmaceutical Sciences (Mack Publishing Company).

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

It will be appreciated that the invention includes the following further aspects. The diseases and conditions described above extend, where appropriate, to these further aspects.

i) The use of a compound of the invention in the manufacture of a medicament in treating a disease or condition for which inhibition of monoamine neurotransmitter re-uptake is beneficial, i.e. inhibition of one or more of SERT, NET and DAT. In an embodiment the disease or condition is depression or an anxiety disorder. In a further embodiment the disease or condition is an eating disorder

ii) A method of treating a disease or condition for which inhibition of monoamine neurotransmitter re-uptake is beneficial, i.e. inhibition of one or more of SERT, NET

and DAT in a mammal (preferably a human) comprising administering an effective amount of a compound of the invention. In an embodiment the disease or condition is a depression or an anxiety disorder. In a further embodiment the disease or condition is an eating disorder.

5

Supporting Compounds

The preparation of a number of the compounds of the invention are described below.

10 In the procedures that follow, after each starting material, reference to an intermediate is typically provided. This is provided merely for assistance to the skilled chemist. The starting material may not necessarily have been prepared from the batch referred to.

15 Compounds of the invention and intermediates are named using ACD/Name PRO 6.02 chemical naming software (Advanced Chemistry Development Inc., Toronto, Ontario, M5H2L3, Canada).

20 Where reference is made to the use of a "similar" or "analogous" procedure, as will be appreciated by those skilled in the art, such a procedure may involve minor variation, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

25 Flash silica gel chromatography was carried out on silica gel 230-400 mesh (supplied by Merck AG Darmstadt, Germany) or over Varian Mega Be-Si pre-packed cartridges or over pre-packed Biotage silica cartridges.

SPE-SCX cartridges are ion exchange solid phase extraction columns supplied by Varian. The eluent used with SPE-SCX cartridges is methanol followed by 2N ammonia solution in methanol.

30 In a number of preparations, purification was performed using either Biotage manual flash chromatography (Flash+) or automatic flash chromatography (Horizon, SP1) systems. All these instruments work with Biotage Silica cartridges.

SPE-Si cartridges are silica solid phase extraction columns supplied by Varian.

A number of the supporting compounds have been prepared as racemic mixtures and a number have been prepared as single enantiomers. The absolute stereochemistry of those compounds prepared as single enantiomers have not been assigned, but may be assigned using ab initio vibrational circular dichroism (VCD).

Chiral molecules exhibit VCD. VCD is the differential interaction of a chiral molecule with left and right circularly polarized infrared radiation during vibrational excitation.

The VCD spectrum of a chiral molecule is dependent on its three-dimensional structure. Most importantly, the VCD spectrum of a chiral molecule is a function of its absolute configuration and, in the case of flexible molecules, of its conformation. In principle, therefore, VCD permits the determination of the structure of a chiral molecule. VCD spectra were first measured in the 1970s. Subsequently, VCD instrumentation has developed enormously in spectral range and in sensitivity. Currently, VCD spectra of liquids and solutions can be measured over the majority of the fundamental infrared (IR) spectral range ($\nu \geq 650 \text{ cm}^{-1}$) with high sensitivity at acceptable resolution ($1\text{--}5 \text{ cm}^{-1}$) using both dispersive and Fourier Transform (FT) VCD instrumentation. Very recently, commercial FT VCD instrumentation has become available, greatly enhancing the accessibility of VCD spectra.

The use of VCD as a reliable method for the determination of absolute configuration of chiral molecules is now well established (see for example Shah RD, et al., *Curr Opin Drug Disc Dev* 2001;4:764–774; Freedman TB, et al., *Helv Chim Acta* 2002; 85:1160–1165; Dyatkin AB, et al. *Chirality* 2002;14:215–219; Solladie'-Cavallo A, Balaz Met al., *Tetrahedron Assym* 2001;12:2605–2611; Nafie LA, et al. *Circular dichroism, principles and applications*, 2nd ed. New York: John Wiley & Sons; 2000. p 97–131; Nafie LA, et al. in: Yan B, Gremlish H-U, editors. *Infrared and Raman spectroscopy of biological materials*. New York: Marcel Dekker; 2001. p 15–54; Polavarapu PL, et al., *J Anal Chem* 2000;366:727–734; Stephens PJ, et al., *Chirality* 2000;12:172–179; Solladie'-Cavallo A, et al., *Eur J Org Chem* 2002: 1788–1796). The method entails comparison of observed IR and VCD spectra with calculations of the spectra for a specific configuration and provides information both on the absolute configuration and on the solution conformation.

- Given an experimental spectrum of a chiral molecule whose absolute configuration and/or conformation are unknown and to be determined, the general procedure is as follows: 1) all possible structures are defined; 2) the spectra of these structures are predicted; and 3) predicted spectra are compared to the experimental spectrum. The correct structure will give a spectrum in agreement with experiment; incorrect structures will give spectra in disagreement with experiment.

- VCD spectra are always measured simultaneously with vibrational unpolarized absorption spectra ("infrared (IR) spectra") and the two vibrational spectra together provide more information than does the VCD spectrum alone. In addition, vibrational unpolarized absorption spectra are automatically predicted simultaneously with VCD spectra.

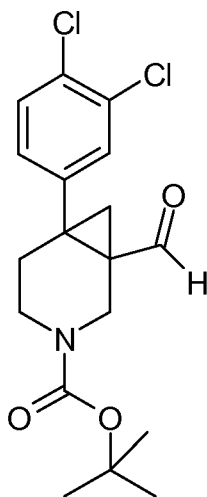
- For ab initio assignments, VCD and unpolarized IR spectra were calculated using the Gaussian 98 software package.

Abbreviations

EtOAc/EA	-	ethyl acetate
DCM	-	dichloromethane
Cy		cyclohexane
CV	-	column volume
Et ₂ O	-	diethyl ether
THF	-	tetrahydrofuran
TFA	-	trifluoroacetic acid
MeOH	-	Methanol
DMSO	-	dimethylsulfoxide
DMF	-	N,N-dimethylformamide
TEA	-	triethylamine
Boc ₂ O	-	di-t-butylidicarbonate
SCX	-	strong cation exchanger
dried	-	refers to a solution dried over anhydrous sodium sulphate
r.t./RT	-	room temperature
Rt	-	retention time

h	-	hour
FC	-	flash chromatography
NH column	-	secondary amine functionalised silica cartridge
CDI	-	carbonyldiimidazole
min	-	minutes
conc	-	concentrated
vol	-	volume
eq	-	equivalent
HOBT	-	1-hydroxybenzotriazole
EDC	-	N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide

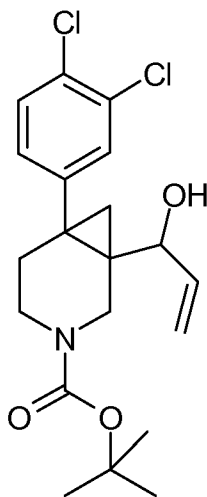
Intermediate 1: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-formyl-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)



- 5 In a round bottom flask, 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (500 mg, 1.343 mmol) (Intermediate 29) was dissolved in dry DCM (15 mL) and stirred under a nitrogen atmosphere at 0 °C. After 10 minutes, Dess-Martin periodinane (684 mg, 1.612 mmol) was added portionwise and the mixture slowly warmed to room temperature
- 10 and stirred for 1 h. It was then quenched by the addition of a saturated solution of NaHCO₃ (50 ml), followed by an aqueous solution of Na₂S₂O₃ 5H₂O (9.22 g dissolved in 40 ml of H₂O). The two phases were stirred for 30 minutes and then the organic layer was separated, dried over Na₂SO₄ and concentrated under reduced pressure to give the title compound (0.505 mg) as an oil; ¹H NMR (400 MHz,

CHLOROFORM-*d*) δ ppm 8.46 - 8.66 (1 H, m), 7.36 - 7.45 (2 H, m), 7.12 (1 H, dd), 4.25 - 4.42 (1 H, m), 3.16 - 3.93 (3 H, m), 2.04 - 2.20 (2 H, m), 2.00 (1 H, d), 1.47 - 1.64 (10 H, m); MS (*m/z*): 314 [MH-56]⁺.

- 5 Intermediate 2 and Intermediate 3: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-((R or S)-1-hydroxy-2-propen-1-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (single diastereoisomers, single enantiomers)



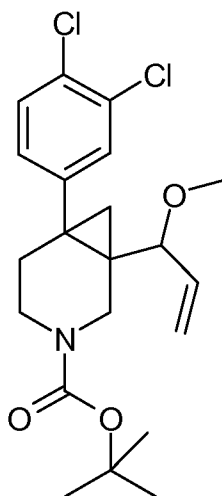
- 1,1-Dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-formyl-3-
 10 azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 1) (5mg, 1.364 mmol) was dissolved in dry THF (20 ml) and cooled to -20 °C under a nitrogen atmosphere. Vinyl magnesium bromide (4092 μ l, 4.09 mmol) was added dropwise keeping the internal temperature below -20 °C. The mixture was stirred at this temperature for 1 h. Additional vinyl magnesium bromide (4092 μ l, 4.09 mmol) was required to drive
 15 the reaction to completion. The solution was cooled to -78 °C and then slowly warmed to RT and stirred overnight. The reaction mixture was quenched with NH₄Cl saturated solution (20 ml), the organic phase was extracted with EtOAc (3 x 25 ml), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with a gradient from 10% to 50%
 20 ethyl acetate in cyclohexane.

- Intermediate 2: First eluting compound from chromatography purification system (353 mg) as white foam; ¹H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 7.48 - 7.56 (1 H, m), 7.34 - 7.43 (1 H, m), 7.27 (3 H, s), 5.84 - 5.98 (1 H, m), 5.11 - 5.35 (2 H, m),
 25 3.85 - 4.01 (1 H, m), 3.43 - 3.54 (1 H, m), 3.06 - 3.42 (2 H, m), 1.85 - 2.34 (2 H, m),

1.50 (9 H, s), 0.95 - 1.10 (2 H, m); MS (m/s) = 397 [MH⁺] LCMS: Rt 0.95 min (Acquity™ UPLC BEH C18 column (50 x 21 mm, 1.7 μm particle size), column temperature 40 °C. (LC/MS - ES (+): mobile phase: A-water + 0.1% HCOOH / B - CH₃CN + 0.06% HCOOH, Flow rate: 1.0 mL/min, Gradient: t = 0 min 3% B, t = 0.05 min 6% B, t = 0.57 min 70% B, t = 1.449 min 99% B, t = 1.45 min 3% B).

Intermediate 3: Second eluting compound from chromatography purification system (240 mg) as white foam; ¹H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 7.52 (d, *J*=2.02 Hz, 1 H) 7.39 (d, 1 H) 7.27 - 7.32 (m, 1 H) 5.92 (ddd, *J*=17.18, 10.61, 4.55 Hz, 1 H) 5.13 - 5.33 (m, 1 H) 3.93 (br. s., 1 H) 3.44 - 3.54 (m, 1 H) 3.31 - 3.41 (m, 1 H) 3.19 (br. s., 1 H) 2.32 (d, *J*=2.53 Hz, 1 H) 2.04 - 2.14 (m, 1 H) 1.96 (br. s., 1 H) 1.59 (s, 9 H) 1.49 - 1.54 (m, 3 H) 1.42 - 1.47 (m, 4 H) 1.10 (bs, 1H) 1.02 - 1.10 (m, 1 H) 0.95 - 1.00 (m, 1 H); MS (m/s) = 397 [MH⁺].

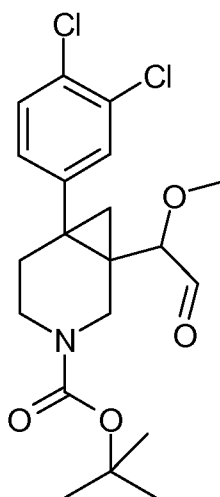
15 Intermediate 4: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methoxy)-2-propen-1-yl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)



To a solution of 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-hydroxy-2-propen-1-yl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 2) (348 mg, 0.874 mmol) in dry DMF (15 ml) under a nitrogen atmosphere was added NaH (60% in mineral oil, 41.9 mg, 1.048 mmol) portionwise at 0 °C. The colourless solution turned yellow, and was stirred for 30 minutes at 0 °C and then for 30 minutes at room temperature. Iodomethane (0.066 ml, 1.048 mmol) was then added and the solution was stirred at room temperature for 1 h. Additional quantities

of NaH 60% in mineral oil (10 mg) and of iodomethane (0.016 ml) were added and the solution was stirred for further 30 minutes. The reaction was quenched with saturated solution of NH_4Cl (10 ml). The organic phase was diluted with water (100 ml) and extracted with diethyl ether (3 x 40 ml). The organic phases were collected, dried on Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with a gradient from 10% to 50% ethyl acetate in cyclohexane. The title compound was obtained as a yellow oil (273 mg); ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 7.51 (1 H, d), 7.36 (1 H, d), 7.23 (1 H, dd), 5.64 - 5.84 (1 H, m), 5.13 - 5.27 (1 H, m), 5.07 (1 H, d), 3.51 - 4.02 (2 H, m), 3.13 - 3.48 (2 H, m), 2.90 (3 H, s), 2.47 (1 H, d), 1.86 - 2.12 (2 H, m), 1.45 (9 H, s), 0.85 (2 H, m).

Intermediate 5: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methyloxy)-2-oxoethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)

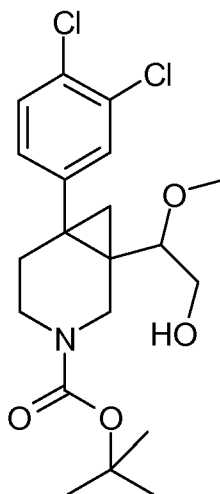


1,1-Dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methyloxy)-2-propen-1-yl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 4) (273 mg, 0.662 mmol) was dissolved in THF (11 ml) and water (5.50 ml). Under a nitrogen atmosphere, osmium tetroxide (4% in water, 0.182 ml, 0.023 mmol) was added dropwise. Sodium periodate (354 mg, 1.655 mmol) was subsequently added at 0 °C and then the solution was warmed to room temperature and stirred at this temperature for 3 h. Additional osmium tetroxide 4% in water (0.182 ml, 0.023 mmol) was required to drive the reaction to completion. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was collected, dried over

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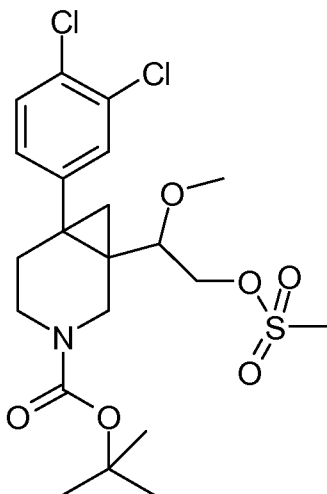
Na₂SO₄ and concentrated to dryness to give the title compound (322 mg) as a yellow oil; MS(m/z): 359 [MH-56]⁺.

Intermediate 6: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[2-hydroxy-(R or S)-1-(methyloxy)ethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)



To a solution of 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methyloxy)-2-oxoethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 5) (322 mg, 0.777 mmol) in dry methanol (15.500 ml) was added NaBH₄ (29.4 mg, 0.777 mmol) at 0 °C under a nitrogen atmosphere and the solution was stirred for 60 minutes. Additional NaBH₄ (29.4 mg, 0.777 mmol) was added at 0 °C and the mixture allowed to warm to room temperature and stirred for 30 minutes. The volatiles were removed under reduced pressure and the crude material was dissolved in DCM (50 ml), washed with NH₄Cl saturated solution (2 x 25 ml), water (2 x 25 ml) and brine (2 x 25 ml). The organic phase was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by chromatography on silica gel eluting with a gradient from 10% to 50% ethyl acetate in cyclohexane to give the title compound as a yellow oil (167 mg); UPLC: Rt = 0.86 min (Acquity™ UPLC BEH C18 column (50 x 21 mm, 1.7 μm particle size), column temperature 40 °C. (LC/MS - ES (+): mobile phase: A-water + 0.1% HCOOH / B - CH₃CN + 0.06% HCOOH, Flow rate: 1.0 mL/min, Gradient: t = 0 min 3% B, t = 0.05 min 6% B, t = 0.57 min 70% B, t = 1.449 min 99% B, t = 1.45 min 3% B); MS(m/z): 416 [MH]⁺ and 360 [MH-56]⁺.

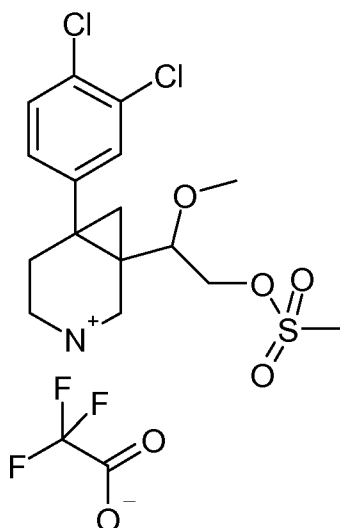
Intermediate 7: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methyloxy)-2-[(methylsulfonyl)oxy]ethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)



- 5 1,1-Dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[2-hydroxy-(R or S)-1-(methyloxy)ethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 6) (167 mg, 0.401 mmol) was dissolved in dry DCM (10 mL) and stirred under a nitrogen atmosphere. DIPEA (0.210 mL, 1.203 mmol) and mesyl chloride (0.094 mL, 1.203 mmol) were added and the solution was stirred at rt for 2 h. Additional quantities of
- 10 DIPEA (0.210 mL, 1.203 mmol) and mesyl chloride (0.094 mL, 1.203 mmol) were added to allow the reaction to proceed and the mixture was stirred at rt overnight. Water (100 ml) was added and the aqueous phase was extracted with diethyl ether (3 x 50 ml). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in dry DMF (5 ml)
- 15 and TEA (56 µl) was added followed by mesyl chloride (31 µl). The reaction mixture was stirred under a nitrogen atmosphere for 4 h and it was then quenched as previously described. The crude material thus obtained was dissolved in dry DCM (5 ml) and TEA (56 µl) was added followed by MsCl (31 µl). The reaction did not proceed to completion and further TEA (20 µl) and MsCl (20 µl) were added. The
- 20 solution was stirred for 2 h and then quenched with NH₄Cl saturated solution (5 ml). The organic phase was washed with water, dried over Na₂SO₄ and concentrated to dryness. The crude material was purified by chromatography on silica gel eluting with a gradient starting from 100% cyclohexane to 20% ethyl acetate in cyclohexane to give the title compound as a yellow oil (145 mg); ¹H NMR (400 MHz,
- 25 CHLOROFORM-*d*) δ ppm 7.40 (1 H, d), 7.32 (1 H, d), 7.09 - 7.16 (1 H, m), 4.31 (1 H,

d), 4.10 - 4.25 (1 H, m), 3.52 - 3.85 (2 H, m), 3.15 - 3.40 (2 H, m), 3.01 (3 H, s), 2.95 (3 H, s), 2.34 - 2.47 (1 H, m), 1.96 - 2.08 (1 H, m), 1.79 - 1.96 (1 H, m), 1.40 (9 H, br. s.), 0.96 (2 H, br. s.); MS(m/z): 438 [MH-56]⁺

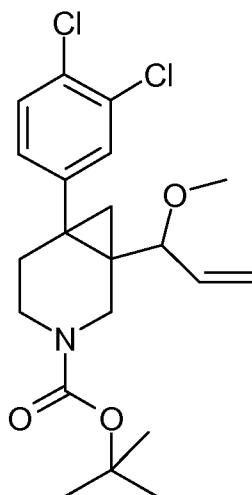
- 5 Intermediate 8: (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methyloxy)-2-[(methylsulfonyl)oxy]ethyl]-3-azoniabicyclo[4.1.0]heptane trifluoroacetate (single enantiomer)



- In a round bottom flask, 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-
 10 {[(R or S)-1-(methyloxy)-2-[(methylsulfonyl)oxy]ethyl]-3-azabicyclo[4.1.0]heptane-3-
 carboxylate (Intermediate 7) (145 mg, 0.293 mmol) was dissolved in dry DCM (6 ml)
 and cooled to 0 °C. TFA (0.226 ml, 2.93 mmol) was added dropwise and slowly
 warmed to rt. Additional TFA (67 µl) was required to drive the reaction to completion.
 Dry toluene (5 ml) was added to the solution and the volatiles were removed under
 15 reduced pressure. The residue was dried under reduced pressure to give the title
 compound as yellow-brown dense oil (155 mg); MS(m/z): 394 [MH]⁺.

- Intermediate 9: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or
 S)-1-(methyloxy)-2-propen-1-yl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single
 20 enantiomer)

30



To a solution of 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-((R or S)-1-hydroxy-2-propen-1-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 3) (345 mg, 0.866 mmol) in dry DMF (15 ml) under stirring and nitrogen was added

5 NaH (60% in mineral oil, 41.6 mg, 1.039 mmol) portionwise at 0 °C. The colourless solution became yellow immediately. It was stirred for 30 minutes at 0 °C and a further 30 minutes at room temperature before adding iodomethane (0.065 ml, 1.039 mmol). The solution was left at room temperature and stirred overnight. Further addition of NaH (60% in mineral oil, 41.6 mg, 1.039 mmol) was added at 0 °C and 30

10 minutes at room temperature before adding iodomethane (0.065 ml, 1.039 mmol) dropwise. After 3 h, further NaH (8 mg) was added to the solution and it was left to stir for 20 minutes and then iodomethane (10 µl) was added. The reaction was quenched with aqueous saturated NH₄Cl (10 ml) and water (15 ml) was added. The aqueous phase was extracted with diethyl ether (3 x 50 ml). The organic layers were collected and dried over Na₂SO₄, filtered and concentrated to dryness. The residue

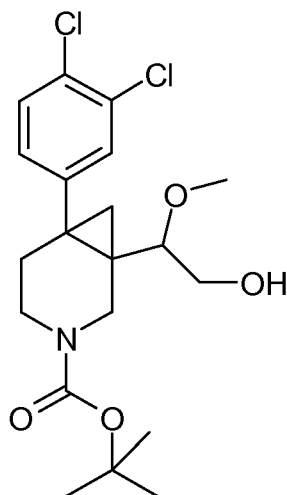
15 was purified by silica gel chromatography (SNAP 50 g) eluting with a gradient from pure cyclohexane to cyclohexane:ethyl acetate 6:4 to give the title compound (251 mg) as yellow oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.37 (m, 2 H) 7.11 (d, 1 H) 5.63 (m, 1 H) 5.21 (d, 1 H) 4.85 (d, 1 H) 3.75 (m, 1 H) 3.40 (m, 1 H) 3.25 (br. s., 1 H) 3.10 (br. s., 3 H) 2.75 (m, 1 H) 2.12 (m, 1 H) 2.20 (m, 1 H) 1.92 (br. s., 1 H)

20 1.05 (s, 9 H) 1.32 (d, 1 H) 1.07 (d, 1 H); MS (m/z) = 412 [MH⁺].

Intermediate 10: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[2-hydroxy-1-(methyloxy)ethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single

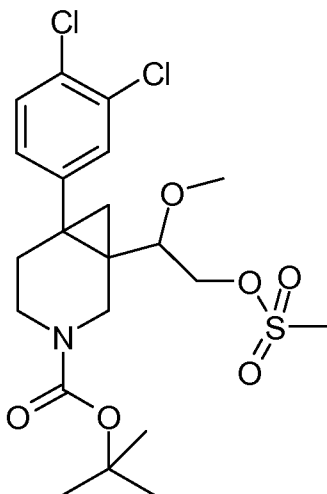
25 enantiomer)

31



1,1-Dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methoxy)-2-propen-1-yl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 9) (251 mg, 0.609 mmol) was dissolved in THF (8.116 ml) and water (4.06 ml). Osmium tetroxide (4% in water, 0.334 ml, 0.043 mmol) was added drop wise, the solution was cooled to 0 °C and sodium periodate (325 mg, 1.522 mmol) was added. After 3 h further osmium tetroxide (34 µl, 0.007 eq) was added followed by sodium periodate (195 mg, 1.5 eq). The solution was left stirring overnight. The reaction was quenched with water (5 ml) and diluted with ethyl acetate. The aqueous phase was extracted with ethyl acetate (2 x 15 ml). The organic layers were collected, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was dissolved in dry methanol (13.1 ml) and NaBH₄ (24.84 mg, 0.656 mmol) was added at 0 °C under nitrogen. The solution was stirred for 60 minutes. After this period, the reaction was concentrated to dryness and dissolved in DCM (50 ml). The organic phase was washed with saturated NH₄Cl solution (2 x 10 ml), water (2 x 10 ml) and brine (2 x 10 ml). The organic phase was dried over Na₂SO₄, filtered and the solvent was removed under reduced pressure to obtain a crude material that was purified by silica gel chromatography (SNAP, 10g) eluting with a gradient from pure cyclohexane to pure ethyl acetate to give the title compound (59 mg) as colourless oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.34 (d, 2 H) 7.14 (d, 1 H) 3.65 (m, 3 H) 3.35 (m, 6 H) 2.5 (dd, 1 H) 2.20 (m, 1 H) 1.90 (br. s., 1 H) 1.50 (s, 9 H) 1.45 (br. s., 2 H) 1.15 (d, 1 H); MS (m/z) = 416 [MH⁺].

Intermediate 11: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methyloxy)-2-[(methylsulfonyl)oxy]ethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)

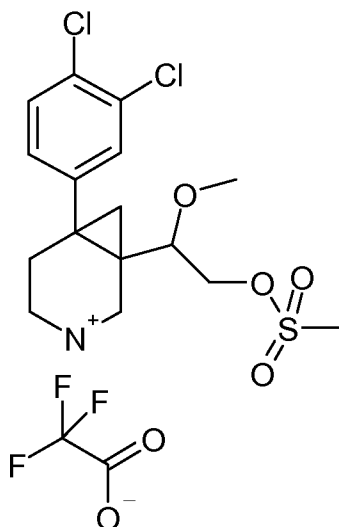


- 5 1,1-Dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[2-hydroxy-(R or S)-1-(methyloxy)ethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 10) (59 mg, 0.142 mmol) was dissolved in dry DCM (7 ml) under nitrogen at room temperature. DIPEA (0.074 ml, 0.425 mmol) was added followed by mesyl chloride (0.033 ml, 0.425 mmol) and the solution was stirred for 1 h. The reaction quenched
- 10 with a saturated solution of NH_4Cl (5 ml). The organic phase was washed with water, dried over Na_2SO_4 and concentrated to dryness. The residue was purified using a silica cartridge eluting with a gradient from pure cyclohexane to cyclohexane: ethyl acetate 8:2 to give the title compound (32.3 mg); ^1H NMR (400 MHz, CHCl_3) δ ppm 7.44 (d, 1 H) 7.38 (s, 1 H) 7.15 (dd, 1 H) 4.22 (m, 1 H) 4.15 (d, 1 H) 3.65 (m, 2 H) 3.40 (m, 5 H) 2.95 (s, 3 H) 2.65 (br. s., 1 H) 2.23 (m, 1 H) 1.95 (br. s., 1 H) 1.50 (s, 10 H) 1.15 (d, 1 H); MS (m/z) = 494 [MH^+].
- 15

Intermediate 12: (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(1-(methyloxy)-2-[(methylsulfonyl)oxy]ethyl)-3-azoniabicyclo[4.1.0]heptane trifluoroacetate (single enantiomer)

20

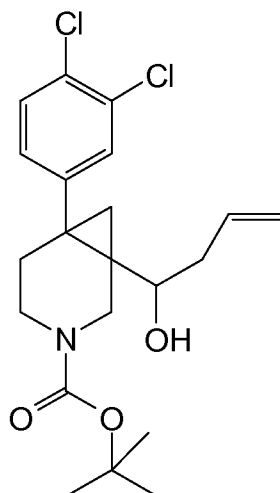
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To a stirred solution of 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-
 {(R or S)-1-(methoxy)-2-[(methylsulfonyl)oxy]ethyl}-3-azabicyclo[4.1.0]heptane-3-
 5 carboxylate (Intermediate 11) (32.3 mg, 0.065 mmol) in dry DCM (1.5 ml) under
 nitrogen, was added TFA (0.050 ml, 0.653 mmol) dropwise. A further portion of TFA
 (25 μ l) was added dropwise, followed by a further portion (50 μ l). Toluene (5 ml) was
 added and the solvent was removed under reduced pressure to obtain title
 compound (42.5 mg) as colourless oil; ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm
 7.60 (s, 1 H) 7.45 (br. s., 1 H) 4.3 (br. s., 2 H) 3.83 (m, 1 H) 3.43 (br. s., 1 H) 3.35 (s,
 10 3 H) 3.15 (br. s., 1H) 2.95 (s, 3 H) 2.55 (m, 2 H) 2.20 (d, 1 H) 1.73 (d, 1 H) 1.45 (m, 1
 H) 1.25 (m, 2 H) 0.96 (m, 2 H); MS (m/z) = 394 [MH^+].

Intermediate 13 and Intermediate 14: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-
 15 dichlorophenyl)-1-((R or S)-1-hydroxy-3-buten-1-yl)-3-azabicyclo[4.1.0]heptane-3-
 carboxylate (each a single diastereoisomer and a single enantiomers)

34



To a solution of 1,1-dimethylethyl (1R,6S or 1S,6R)-6-(3,4-dichlorophenyl)-1-formyl-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 1) (480 mg, 1.296 mmol) in dry THF at -20 °C was added allylmagnesium bromide (1M in diethyl ether, 2.59 mL) and the reaction mixture was stirred at -20°C for 30 min and then at RT for 3h.

Further allylmagnesium bromide (1M in diethyl ether, 2.59 mL) was added and the mixture was stirred at RT overnight. The reaction was quenched with NH₄Cl (sat. sol.) and diluted with ethyl acetate. The organic layer was then dried and concentrated under reduced pressure. The residue was purified by flash

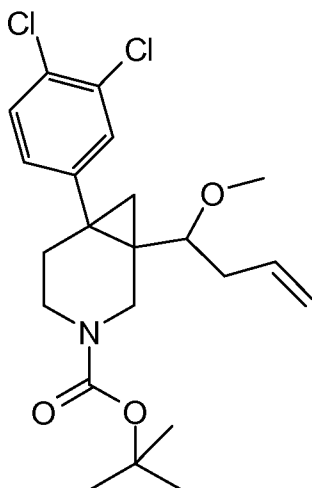
chromatography eluting with cyclohexane/ethyl acetate from 100% Cy to 4/6 to give:

Intermediate 13: First eluting compound (290 mg) as colorless oil; ¹H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 7.5 (s, 1 H), 7.4 (d, 1H), 7.3 (d, 1H), 5.65 (m, 1H), 5.1 (m, 2H), 3.95 (m, 1H), 3.65 (bs, 1H), 3.4 (bs, 1H), 3.3 (m, 1H), 2.65 (bs, 1H), 2.3 (bs, 2H), 2.05 (bs, 1H), 1.95 (bs, 1H), 1.6 (m, 1H), 1.5 (s, 9H), 0.95 (s, 2H); MS (m/z) = 412 [MH⁺]; and

Intermediate 14: Second eluting compound (150 mg) as colorless oil; ¹H NMR (400 MHz, CHLOROFORM-*d*): δ ppm 7.4 (d, 2 H), 7.1 (d, 1H), 5.5 (m, 1H), 5.0 (m, 2H), 3.8 (m, 2H), 3.4 (bs, 1H), 3.25 (m, 1H), 2.8 (bs, 1H), 2.25 (m, 2H), 2.20 (m, 1H), 1.95 (bs, 1H), 1.6 (bs, 1H), 1.5 (s, 9H), 1.3 (d, 1H), 1.1 (d, 2H); MS (m/z) = 412 [MH⁺].

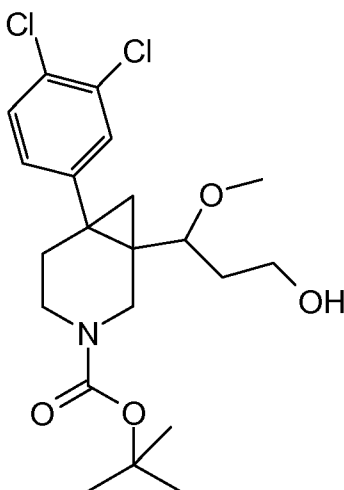
Intermediate 15: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(1S or 1R)-1-(methoxy)-3-buten-1-yl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)

35



The title compound was obtained (193 mg) as colourless oil starting from 1,1-dimethylethyl 6-(3,4-dichlorophenyl)-1-(1-hydroxy-3-buten-1-yl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 13) (290 mg) in a similar fashion to the preparation of Intermediate 4; ^1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.50 (s, 1 H) 7.37 (d, 1 H) 7.21 (d, 1 H) 5.75 (m, 1 H) 5.05 (m, 2 H) 3.95 (m, 1 H) 3.70 (m, 1 H) 3.40 (m, 1 H) 3.30 (m, 1 H) 2.95 (s, 3 H) 2.45 (m, 1 H) 2.35 (br. s., 1 H) 2.23 (br. s., 1 H) 2.07 (br. S., 1 H) 1.95 (br. S., 1 H) 1.50 (s, 9 H) 0.93 (m, 2 H); MS (m/s) = 426 [MH^+].

Intermediate 16: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(1S or 1R)-3-hydroxy-1-(methoxy)propyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)



To a solution of 1,1-dimethylethyl 6-(3,4-dichlorophenyl)-1-[(R or S)-1-(methoxy)-3-buten-1-yl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 15) (193 mg) in

THF/water (2:1) at RT was added osmium tetroxide (4% solution in water, 0.124 mL, 0.016 mmol) and the reaction mixture was stirred until the solution became dark.

Then the reaction was cooled to 0 °C and sodium periodate (242 mg) was added.

The mixture was allowed to reach RT and stirred for 2hrs. The reaction was

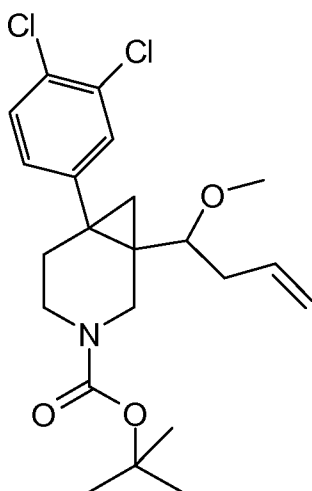
5 quenched with water, concentrated under reduced pressure and diluted with DCM.

The organic layer was then dried and concentrated under reduced pressure. The residue was dissolved in methanol at 0 °C and sodium borohydride (18.64 mg) was added. The reaction mixture was stirred for 1h. Saturated NH₄Cl solution was added and the mixture was concentrated under reduced pressure to remove the methanol.

10 The aqueous phase was extracted with DCM (x2) and then the combined organic layers were dried and concentrated. The residue was purified with cyclohexane/ ethyl acetate from 9:1 to 6:4 and N8106-30-1 to give title compound (128 mg) as colourless oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm δ ppm 7.49 (br. S., 1 H) 7.39 (d, 1 H) 7.25 (dd, 1 H) 3.60 - 4.00 (m, 4 H) 3.39 (m, 2 H) 2.97 (s, 3 H) 2.48 (t, 1 H) 2.17 (br. s., 1 H) 1.98 (m, 2 H) 1.70 (m, 2 H) 1.50 (s, 9 H) 0.99 (m, 2 H); MS (m/s) = 430 [MH⁺].

Intermediate 17: 1,1-dimethylethyl (1*S*,6*R* or 1*R*,6*S*)-6-(3,4-dichlorophenyl)-1-[(1*S* or 1*R*)-1-(methyloxy)-3-buten-1-yl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)

20

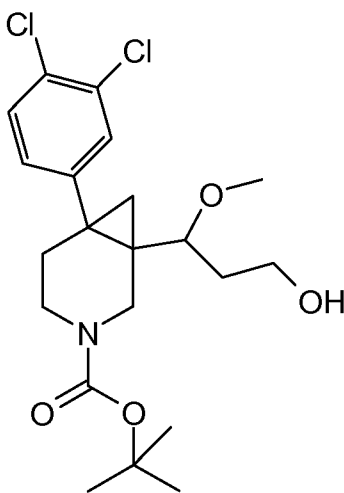


The title compound was obtained (103 mg) as a colourless oil starting from 1,1-dimethylethyl 6-(3,4-dichlorophenyl)-1-(1-hydroxy-3-buten-1-yl)-3-

25 azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 14) (150 mg, 0.364 mmol) in a similar fashion to the preparation of Intermediate 15; ¹H NMR (400 MHz,

CHLOROFORM-*d*) δ ppm 7.40 (m, 2 H) 7.15 (d, 1 H) 5.55 (m, 1 H) 4.85 (m, 2 H) 3.75 (m, 2 H) 3.30 (m, 5 H) 2.40 (m, 2 H) 2.20 (m, 2 H) 1.95 (br. s., 2 H) 1.50 (s, 10 H) 1.15 (d, 1 H); MS (m/s) = 426 [MH⁺].

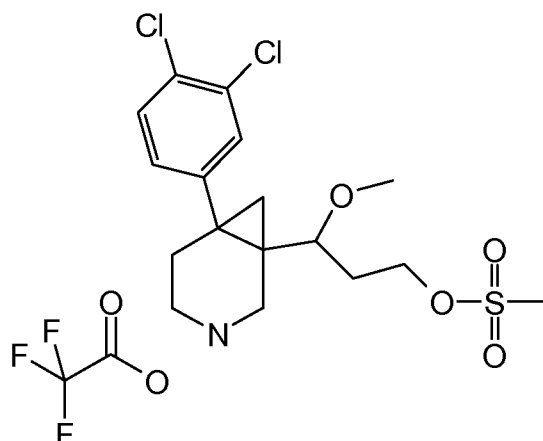
- 5 Intermediate 18: 1,1-dimethylethyl (1*S*,6*R* or 1*R*,6*S*)-6-(3,4-dichlorophenyl)-1-[(1*S* or 1*R*)-3-hydroxy-1-(methyloxy)propyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)



- To a solution of 1,1-dimethylethyl 6-(3,4-dichlorophenyl)-1-[(*R* or *S*)-1-(methyloxy)-3-oxopropyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 17) (68 mg, 0.159 mmol) in methanol at 0 °C was added sodium borohydride (6.01 mg, 0.159 mmol) and the reaction mixture was stirred for 1h. Saturated NH₄Cl was added and the mixture was concentrated under reduced pressure to remove the methanol. The aqueous phase was extracted with DCM (x2) and the combined organic layers were dried and concentrated under reduced pressure. The residue was purified by silica gel chromatography with cyclohexane/ ethyl acetate from 9:1 to 6:4 to give the title compound (36 mg) as colourless oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.31 (d, 1 H) 7.29 (s, 1 H) 7.06 (dd, 1 H) 3.62 (br. s., 1 H) 3.21 - 3.43 (m, 7 H) 2.51 (dd, 1 H) 2.14 (dt, 1 H) 2.06 (dd, 1 H) 1.75 - 1.93 (m, 2 H) 1.60 (m, 1 H) 1.38 - 1.49 (m, 11 H) 1.09 (d, 1 H); MS (m/z): 430 [MH⁺].

Intermediate 19: (3*S* or 3*R*)-3-[(1*S*,6*R* or 1*R*,6*S*)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-1-yl]-3-(methyloxy)propyl methanesulfonate trifluoroacetate (single enantiomer)

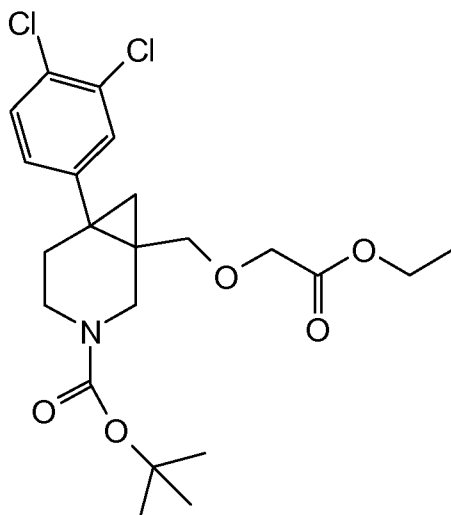
38



To a solution of 1,1-dimethylethyl 6-(3,4-dichlorophenyl)-1-[3-hydroxy-1-(methoxy)propyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 18) (36 mg, 0.084 mmol) in dry DCM at 0 °C were added MsCl (9.78 μ L, 0.125 mmol) and TEA (0.016 mL, 0.117 mmol) and the reaction mixture was stirred at RT. The reaction was quenched with NH_4Cl sat. solution and diluted with DCM. The organic layer was dried and concentrated under reduced pressure. To the residue was added DCM (1 mL) and TFA (0.229 mL, 2.97 mmol) and then the mixture was stirred at RT for 1h. The solution was concentrated under reduced pressure to give the title compound (57 mg) as a colourless oil; ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 9.23 (br. s., 1 H) 8.68 (br. s., 1 H) 7.46 (s, 1 H) 7.39 (d, 1 H) 7.02 (d, 1 H) 3.98 (br. s., 2 H) 3.70 (d, 1 H) 3.60 (d, 1 H) 3.45 (q, 2 H) 3.35 (br. s., 1 H) 3.37 (s, 2 H) 3.12 (m, 2 H) 3.07 (s, 3 H) 2.71 (s, 2 H) 1.25 (t, 2 H) 1.15 (t, 1 H); MS (m/s) = 408 [MH^+].

- 15 Intermediate 20: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-([2-(ethoxy)-2-oxoethyl]oxy)methyl-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)

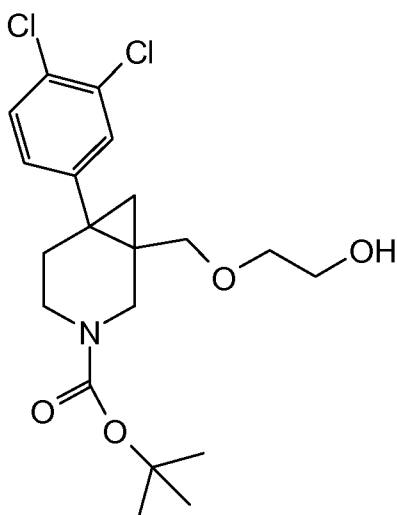
39



To a solution of 1,1-dimethylethyl (1R,6S or 1S,6R)dichlorophenyl)-1-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 29) (600 mg, 1.612 mmol) in dry DMF at 0 °C was added NaH (97 mg, 2.417 mmol) and the reaction mixture was stirred at RT for 30 min. Sodium iodide (242 mg, 1.612 mmol) and ethyl bromoacetate (0.269 mL, 2.417 mmol) were added and the solution was heated at 80 °C for 6h. On cooling, saturated NH₄Cl solution was added and the mixture was extracted with diethyl ether (x2). The combined organic layers were washed with saturated brine, dried and concentrated under reduced pressure. The residue was purified by chromatography eluting with Cy/EA from 100% to 7/3 to give title compound (150 mg) as colourless oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.31 (d, 1 H) 7.29 (s, 1 H) 7.06 (dd, 1 H) 3.62 (br. s., 1 H) 3.21 - 3.43 (m, 7 H) 2.51 (dd, 1 H) 2.14 (dt, 1 H) 2.06 (dd, 1 H) 1.75 - 1.93 (m, 2 H) 1.60 (m, 1 H) 1.38 - 1.49 (m, 11 H) 1.09 (d, 1 H); MS (m/z): 458 [MH⁺].

Intermediate 21: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-[(2-hydroxyethyl)oxy]methyl-3-azabicyclo[4.1.0]heptane-3-carboxylate (single enantiomer)

40



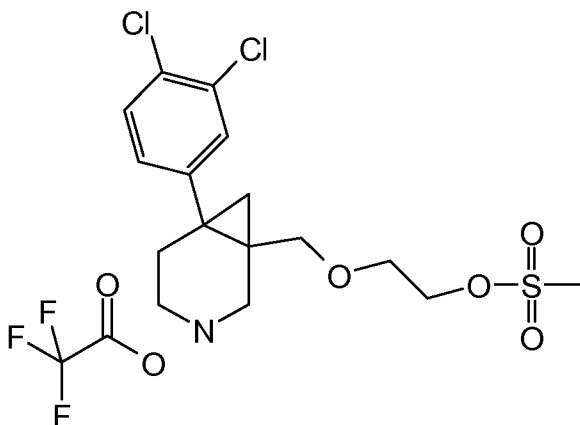
To a solution of 1,1-dimethylethyl-6-(3,4-dichlorophenyl)-1-([2-(ethoxy)-2-oxoethyl]oxy)methyl-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 20) (150 mg, 0.327 mmol) in dry toluene at -20 °C was added lithium aluminium hydride

5 (0.327 mL, 0.327 mmol) and the reaction mixture was stirred at -20 °C for 3h.

Saturated NH_4Cl solution was added and the mixture was extracted with ethyl acetate (x2). The combined organic layers were washed with saturated brine solution, dried and concentrated under reduced pressure to give title compound (65 mg); ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 7.46 (s, 1 H) 7.35 (d, 1 H) 7.17 (d, 1 H) 4.00 (br. s., 1 H) 3.80 (br. s., 1 H) 3.68 (br. s., 2 H) 3.40 (br. s., 2 H) 3.26 (br. s., 2 H) 2.90 (br. s., 1 H) 2.05 (m, 1 H) 1.95 (br. s., 1 H) 2.16 (m, 1 H) 1.60 (s, 9 H) 1.00 (s, 2 H); MS (m/s) = 416 $[\text{MH}^+]$.

Intermediate 22: 2-([(1S,6R or 1R,6S)-6-(3,4-Dichlorophenyl)-3-

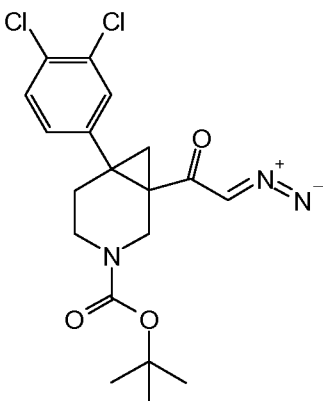
15 azabicyclo[4.1.0]hept-1-yl]methyl]oxy)ethyl methanesulfonate trifluoroacetate (single enantiomer)



To a solution of 1,1-dimethylethyl-6-(3,4-dichlorophenyl)-1-([2-(ethoxy)-2-oxoethyl]oxy)methyl-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 21) (150 mg, 0.327 mmol) in dry toluene at -20 °C was added lithium aluminium hydride (0.327 mL, 0.327 mmol) and the reaction mixture was stirred at -20°C for 3h.

- 5 Saturated NH_4Cl solution was added and the mixture was extracted with ethyl acetate (x2). The combined organic layers were washed with saturated brine, dried and concentrated under reduced pressure to give a residue containing 1,1-dimethylethyl (1R,6S or 1S,6R)-6-(3,4-dichlorophenyl)-1-[(2-hydroxyethyl)oxy]methyl-3-azabicyclo[4.1.0]heptane-3-carboxylate (65 mg, 0.156 mmol). This residue was dissolved in dry DCM and MsCl (0.018 mL, 0.234 mmol) and TEA (0.030 mL, 0.219 mmol) were added at 0 degC. The reaction mixture was then stirred at RT for 2h. The reaction was quenched with NH_4Cl saturated solution and diluted with DCM. The organic layer was then dried and concentrated under reduced pressure. To the residue was added DCM (1 mL) and TFA (0.120 mL, 1.561 mmol) and then the mixture was stirred at RT for 1h. The solution was concentrated under reduced pressure to give title compound (96 mg) as colourless oil; ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.59 (d, 1 H) 7.45 (d, 1 H) 7.39 (dd, 1 H) 4.39 (t, 2 H) 3.89 (d, 1 H) 3.50 (m, 3 H) 3.2 (m, 1 H) 3.10 (s, 3 H) 3.03 (m, 1 H) 2.85 (m, 1 H) 2.34 (m, 1 H) 2.16 (m, 1 H) 1.28 (d, 1 H) 1.18 (d, 3 H); MS (m/s) = 394 [MH^+].

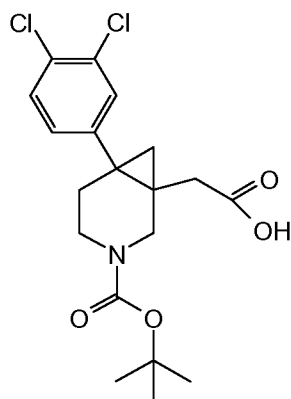
Intermediate 23: 1,1-Dimethylethyl (1R,6S/1S,6R)-1-(diazoacetyl)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (Racemate)



- 25 To a suspension of (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-[(1,1-dimethylethyl)oxy]carbonyl-3-azabicyclo[4.1.0]heptane-1-carboxylic acid (2.24 g, 5.80 mmol) (Intermediate 31) in dry DCM (60 ml) at 0 °C under a nitrogen atmosphere were added triethylamine (1.212 ml, 8.70 mmol), oxalyl chloride (0.761

ml, 8.70 mmol) and DMF (0.180 ml, 2.320 mmol) and the mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. Reaction mixture was evaporated under reduced pressure and the residue was dissolved in a mixture of anhydrous THF (30 ml) and anhydrous acetonitrile (30 ml) and to this mixture was added TMS-diazomethane (2M in diethyl ether, 8.70 ml, 17.40 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 0 °C for 1 h and then for an additional 2 h at room temperature. The solvent was evaporated and the residue purified using a Biotage SP-1 system using 100 g Si SNAP column, eluting with cyclohexane/ethyl-acetate gradient (0-30 % of ethyl-acetate / 15 CV) to give the title compound (1.14 g, 2.77 mmol, 47.8 % yield) as a yellow foam; MS (m/z): 410 [MH]⁺.

Intermediate 24: (1R,6S/1S,6R)-6-(3,4-Dichlorophenyl)-3-[(1,1-dimethylethyl)oxy]carbonyl]-3-azabicyclo[4.1.0]hept-1-yl)acetic acid (Racemate)

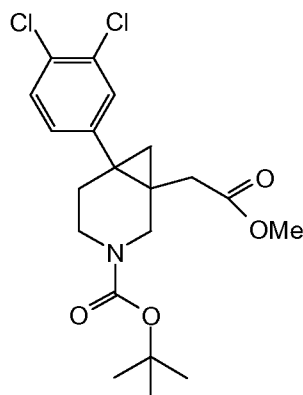


15

To a solution of 1,1-dimethylethyl (1R,6S/1S,6R)-1-(diazocetyl)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 23) (1.14 g, 2.77 mmol) in THF\water (3:1) (20 mL) was added silver benzoate (190 mg, 0.832 mmol). The mixture became muddy brown and on sonication using an ultrasound bath, gas evolution increased. The progress of the reaction was monitored by UPLC. The reaction ceased before complete consumption of starting material, so further silver benzoate (127 mg, 0.554 mmol) was added. After 1.5 h of sonication, UPLC showed complete conversion of starting material. The mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate and filtered through celite. The solvent was evaporated, and the residue was partitioned between diethyl ether and a saturated solution of NaHCO₃. The organic phase was

separated, washed with brine, dried and concentrated under vacuum to give the title product (720 mg) as white solid; MS (m/z): 400 [MH]⁺.

5 Intermediate 25: 1,1-Dimethylethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-1-[2-(methoxy)-2-oxoethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Racemate)

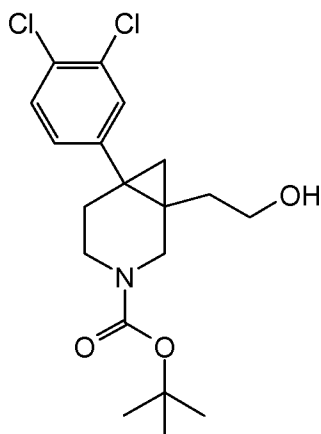


To a solution of (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-[[1,1-dimethylethyl]oxy]carbonyl]-3-azabicyclo[4.1.0]hept-1-yl)acetic acid (Intermediate 24) (310 mg, 0.774 mmol) in methanol (2.5 mL) and DCM (1.25 mL) was added dropwise TMS-diazomethane (2 M in hexane, 0.774 mL, 1.549 mmol) under an atmosphere of nitrogen at room temperature and the mixture was stirred for 2 h at room temperature. The mixture was evaporated under reduced pressure and the residue was purified on a Biotage SP-1 system using 25 g Si SNAP column, eluting with a cyclohexane/ethyl-acetate gradient (0-30 % of ethyl-acetate/15 column volumes) to give the title product as a yellow oil: ¹H NMR (CDCl₃, 400 MHz) δ ppm 1.04 (d, 1 H) 1.08 (d, 1 H) 1.50 (s, 9 H) 1.90 - 2.06 (m, 2 H) 2.07 - 2.16 (m, 2 H) 3.25 - 3.36 (m, 1 H) 3.40 - 3.53 (m, 1 H) 3.57 (d, 1 H) 3.63 (s, 3 H) 3.92 - 4.03 (m, 1 H) 7.11 (dd, 1 H) 7.35 (d, 1 H) 7.38 (d, 1 H); MS (m/z): 414 [MH]⁺.

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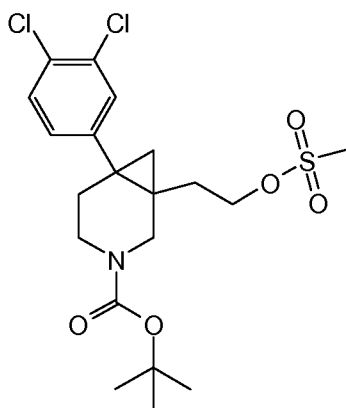
Intermediate 26: 1,1-dimethylethyl (1R,6S)(1S,6R)-6-(3,4-dichlorophenyl)-1-(2-hydroxyethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (Racemate)

44



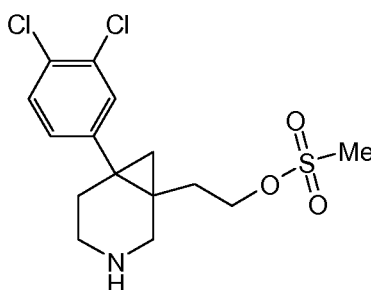
To a solution of 1,1-dimethylethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-1-[2-(methoxy)-2-oxoethyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 25) (1.04 g, 2.51 mmol) in dry toluene (35 ml) at -20 °C was added LiAlH₄ (2M solution in THF, 1.255 ml, 2.51 mmol) dropwise and the reaction mixture was stirred at -20 °C for 1 h. The reaction was quenched with NH₄Cl sat. solution and then ethyl acetate was added. The organic phase was separated, washed with water, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified on Biotage SP-1 system using 100 g Si SNAP column, eluting with cyclohexane / ethyl-acetate gradient (0-30 % of ethyl-acetate / 20 CV; 30 % of ethyl-acetate / 10 column volumes) to give the title compound; ¹H NMR (CDCl₃, 500 MHz) δ ppm 0.83 - 0.92 (m, 1 H) 0.93 - 1.01 (m, 2 H) 1.47 (s, 9 H) 1.59 - 1.67 (m, 1 H) 1.90 - 2.04 (m, 1 H) 2.05 - 2.11 (m, 1 H) 3.22 - 3.32 (m, 1 H) 3.33 - 3.46 (m, 2 H) 3.61 - 3.76 (m, 2 H) 3.83 - 4.03 (m, 1 H) 7.06 (dd, 1 H) 7.30 (d, 1 H) 7.37 (d, 1 H).

Intermediate 27: 1,1-dimethylethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-1-{2-[(methylsulfonyl)oxy]ethyl}-3-azabicyclo[4.1.0]heptane-3-carboxylate (Racemate)



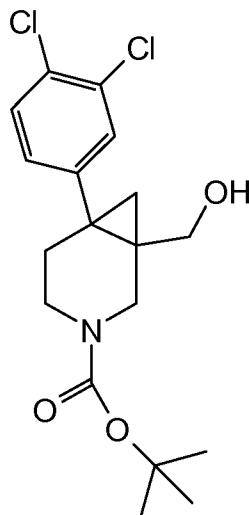
To a solution of 1,1-dimethylethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-1-(2-hydroxyethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (800 mg, 2.071 mmol) in dry dichloromethane (DCM) (40 mL) at 0 °C were added mesyl chloride (0.484 mL, 6.21 mmol) and DIPEA (1.085 mL, 6.21 mmol) and the reaction mixture was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure and the residue was portioned between ethyl acetate and water. The organic phase was separated, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified on a Biotage SP-1 system using 50 g Si SNAP column, eluting with cyclohexane / ethyl-acetate gradient (0-40 % of ethyl-acetate / 15 column volumes; 40 % of ethyl-acetate / 10 CV) to give the title compound (880 mg); ¹H NMR (CDCl₃, 500 MHz) δ ppm 0.99 - 1.07 (m, 3 H) 1.48 (s, 9 H) 1.78 - 1.89 (m, 1 H) 1.92 - 2.05 (m, 1 H) 2.05 - 2.12 (m, 1 H) 2.97 (s, 3 H) 3.24 - 3.32 (m, 1 H) 3.32 - 3.42 (m, 1 H) 3.42 (d, 1 H) 3.87 - 4.02 (m, 1 H) 4.19 - 4.27 (m, 2 H) 7.05 (dd, 1 H) 7.30 (d, 1 H) 7.39 (d, 1 H); MS (m/z): 408 [MH-56]⁺.

Intermediate 28: 2-[(1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-1-yl]ethyl methanesulfonate (Racemate)



To a solution of 1,1-dimethylethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-1-{2-[(methanesulfonyl)oxy]ethyl}-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 27) (880 mg, 1.895 mmol) in dry DCM (100 mL) at 0 °C was added TFA (3.65 mL, 47.4 mmol) and the reaction mixture was stirred at room temperature for 5 h. NaHCO₃ sat. solution was added and the organic phase was separated. The organic phase was washed with water, dried and concentrated under vacuum to give the title compound (670 mg); ¹H NMR (CDCl₃, 500 MHz) δ ppm 0.93 - 1.00 (m, 1 H) 1.02 (d, 1 H) 1.08 (d, 1 H) 1.79 - 1.86 (m, 1 H) 1.89 - 1.96 (m, 1 H) 1.97 - 2.04 (m, 1 H) 2.68 - 2.80 (m, 2 H) 2.96 (s, 3 H) 3.06 (d, 1 H) 3.19 (d, 1 H) 4.17 - 4.23 (m, 2 H) 7.09 (dd, 1 H) 7.33 (d, 1 H) 7.38 (d, 1 H); MS (m/z): 364 [MH]⁺.

Intermediate 29 and Intermediate 30: 1,1-dimethylethyl (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (single diastereoisomers, single enantiomers)



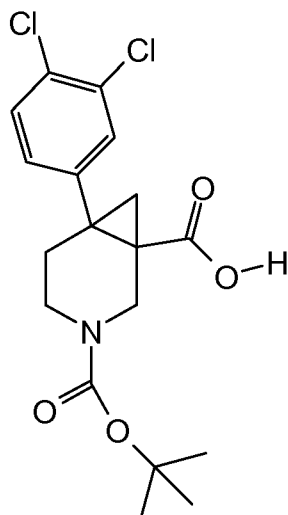
- 5 Racemate 1,1-dimethylethyl (1S,6R/ 1R,6S)-6-(3,4-dichlorophenyl)-1-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (3.2 g) (for preparation see international patent publication WO2008/031772, Preparation 5) were separated by Chiral preparative liquid chromatography. Chromatography conditions: Column: Chiralpak AD-H (25 x 2 cm); Mobil phase: n-Hexane/Isopropanol 90/10% v/v; UV
10 detection: 215 nm; Flow Rate (mL/min): 17; Injection: 100 mg.

Intermediate 29 was obtained as the first eluting compound as white foam (1.51 g);
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.43 (br. s, 1 H) 7.39 (d, 1 H) 7.17 (d, 1 H) 3.75 – 3.90 (q, 2 H) 3.30 - 3.45 (m, 3 H) 3.05 – 3.25 (m, 1 H) 2.10(m, 1 H) 2.00 (br. s, 1 H)
 15 1.50 (s, 9 H) 1.05 (d, 1 H) 0.97 (br. s, 1 H); MS (m/z) = 372 [MH];

Intermediate 30 was obtained as the second eluting compound as white foam (1.65 g);
¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.43 (br. s, 1 H) 7.39 (d, 1 H) 7.16 (d, 1 H) 3.75 – 3.90 (q, 2 H) 3.30 - 3.45 (m, 3 H) 3.05 – 3.25 (m, 1 H) 2.07 (m, 1 H) 2.00 (br.
 20 s, 1 H) 1.53 (s, 9 H) 1.05 (d, 1 H) 0.97 (br. s, 1 H); MS (m/z) = 372 [MH].

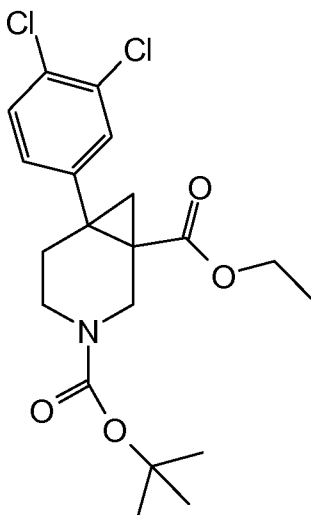
Intermediate 31: (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-[(1,1-dimethylethyl)oxy]carbonyl]-3-azabicyclo[4.1.0]heptane-1-carboxylic acid (Racemate)

47



3-(1,1-Dimethylethyl) 1-ethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (Intermediate 32) (0.170 g, 0.410 mmol) was dissolved in ethanol (3 ml). Potassium tert-butoxide (0.368 g, 3.28 mmol) was added followed by water (0.148 ml, 8.21 mmol). The reaction mixture was stirred at room temperature for 18h and then heated to 50°C for 6 h. The reaction mixture was cooled to RT and the solvent evaporated. The residue was partitioned between saturated ammonium chloride solution (10 ml) and DCM (10 ml). The organic phase was dried and concentrated to give a white foam (150 mg).

Intermediate 32: 3-(1,1-dimethylethyl) 1-ethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]heptane-1,3-dicarboxylate (Racemate)

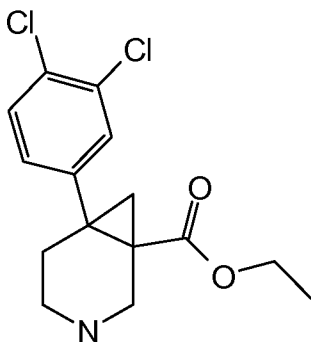


Ethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]heptane-1-carboxylate (Intermediate 33) (1.795 g, 5.71 mmol) was dissolved in dry DCM. The solution was

treated with Boc_2O (1.459 mL, 6.28 mmol), followed by TEA (1.593 mL, 11.43 mmol) and the solution was stirred at RT overnight. The organic phase was washed with NaCl saturated solution (2X), dried and concentrated *in vacuo* to obtain the title compound.

5

Intermediate 33: Ethyl (1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]heptane-1-carboxylate (Racemate)

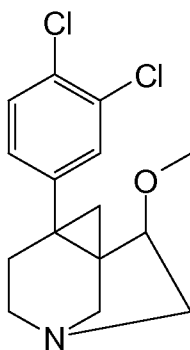


3-(1,1-Dimethylethyl) (1S,6R/1R,6S)-1-ethyl 6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-4-ene-1,3-dicarboxylate (for preparation see International Patent publication WO2008/031772, Preparation 57) (3.3 g, 8.00 mmol) was dissolved in dry toluene and the solution was treated with triethylsilane (1.534 mL, 9.60 mmol), followed by TFA (4.62 mL, 60.0 mmol). The reaction was stirred for 2h at RT, then quenched with 1N NaOH (44 mL) and stirred for 10 mins. The phases were separated and the organic layer was dried and concentrated under vacuum. The residue was purified by SCX cartridge and the methanol/ammonia fractions were concentrated *in vacuo* to give the title compound (2.04 g); ^1H NMR (400 MHz, CHCl_3 - d): δ ppm 7.30-7.36 (m, 2 H) 7.11 (m, 1 H) 4.8 (s, 2H) 3.70 – 3.40 (m, 2 H) 3.5 (m, 1 H) 2.6 -3.1 (m, 3 H) 2.10-1.90 (m., 2H) 1.28 (m, 1 H) 0.90 (m, 3 H).

20

Compound 1: (1S,3R,8S or 1R,3S,8R)-3-(3,4-dichlorophenyl)-8-(methoxy)-6-azatricyclo[4.2.1.0^{1,3}]nonane (single enantiomer)

49

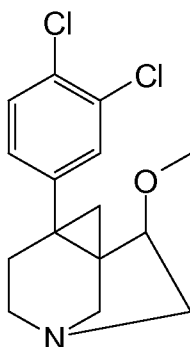


In a round bottom flask (1S,6R or 1R,6S)-6-(3,4-dichlorophenyl)-1-{1-(methoxy)-2-[(methanesulfonyl)oxy]ethyl}-3-azoniabicyclo[4.1.0]heptane trifluoroacetate

- 5 (Intermediate 8) (95 mg) was dissolved in dry DCM and treated with a saturated solution of NaHCO_3 and stirred for 10 minutes. The organic phase was separated, dried over Na_2SO_4 and concentrated to dryness to give the free base as yellow oil. This oil was dissolved in dry DMF (1.5 ml) and sodium iodide (33.2 mg, 0.222 mmol) was added. The mixture was exposed to microwave irradiation (x 9) heating to 120°
- 10 C for 15 minutes; then at 120 °C for 2 hours and then at 130 °C. The volatiles were evaporated under reduced pressure and the residue was purified by SCX cartridge chromatography eluting firstly with MeOH and then with ammonia/MeOH 0.5 M. The ammonia fractions were collected and concentrated under reduced pressure. The residue was purified by preparative HPLC purification (column: Phenomenex Gemini
- 15 AXIA C18, 50 x 21 mm, 5 μm , mobile phase A: 10 mM NH_4HCO_3 sol. + NH_3 pH 10; B: CH_3CN , gradient: from 30%(B) to 35%(B) in 1 min, from 35%(B) to 75%(B) in 10.5 min, from 75%(B) to 100%(B) in 1 min, 100%(B) for 2 min, flow rate 17ml/min, UV range 210-350 nm, ionization ES+) to give the title compound (3.5 mg) (R_t = 5.78 min); ^1H NMR (500 MHz, $\text{CHLOROFORM-}d$) δ ppm 7.46 (1 H, d), 7.25 - 7.31 (2 H, m), 4.09 - 4.19 (1 H, m), 3.66 - 3.90 (2 H, m), 3.19 - 3.31 (1 H, m), 2.86 (3 H, s), 2.76 - 2.83 (1 H, m), 2.58 - 2.67 (1 H, m), 2.21 - 2.29 (1 H, m), 2.11 (1 H, d), 1.89 - 1.99 (1 H, m), 1.70 - 1.77 (1 H, m), 1.38 (1 H, d); MS (m/z): 298.

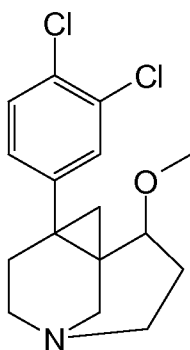
- 25 Compound 2: (1S,3R or 1R,3S)-3-(3,4-dichlorophenyl)-8-(methoxy)-6-azatricyclo[4.2.1.0^{1,3}]nonane (single diastereoisomer 2, single enantiomer)

50



2-[(1S,6R or 1R,6S)-6-(3,4-Dichlorophenyl)-3-azabicyclo[4.1.0]hept-1-yl]-2-(methoxy)ethyl methanesulfonate trifluoroacetate (Intermediate 12) (11.7 mg, 0.023 mmol) was dissolved in dry DCM (40 ml) and washed with a NaHCO₃ saturated solution (2 x 20 ml). The organic layer was separated, dried over Na₂SO₄ and filtered. The solvent was removed under reduced pressure to give a yellow oil (11.7 mg). This oil was dissolved in dry DMF (1.5 ml), sodium iodide (18 mg) was added, and the mixture was exposed to microwave radiation (15 minutes at 120 °C). The cooled mixture was absorbed on to a SCX cartridge and eluted first with MeOH and then with NH₃/MeOH 0.5 M. The ammonia fractions were collected and concentrated to dryness to obtain title compound (6.7 mg) as yellow oil; ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.4 (d, 1 H) 7.32 (d, 1 H) 7.08 (dd, 1 H) 3.60 (dd, 1 H) 3.23 (s + t, 4 H) 3.13 (dd, 1 H) 3.05 (d, 1 H) 2.88 (m, 1 H) 2.79 (m, 1 H) 2.28 (d, 1 H) 2.19 (d, 1 H) 2.07 (dd, 1 H) 1.65 (m, 1 H) 1.62 (d, 1 H); MS (m/z) = 298 [MH⁺].

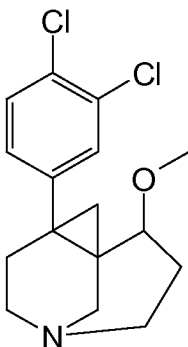
Compound 3: (1S,3R,9S or 1R,3S,9R)-3-(3,4-dichlorophenyl)-9-(methoxy)-6-azatricyclo[4.3.1.0^{1,3}]decane (single enantiomer)



To a solution of 1,1-dimethylethyl (1S,6R or 1R, 6S)-6-(3,4-dichlorophenyl)-1-[3-hydroxy-1-(methoxy)propyl]-3-azabicyclo[4.1.0]heptane-3-carboxylate (Intermediate 16) (128 mg, 0.297 mmol) in dry DCM, at 0 °C were added methanesulfonyl chloride

(0.035 mL, 0.446 mmol) and TEA (0.058 mL, 0.416 mmol) and the reaction mixture was stirred at RT for 3h. The reaction was quenched with NH_4Cl sat. solution and diluted with DCM. The organic layer was then dried and concentrated under reduced pressure. To the residue was added DCM (1 mL) and TFA (0.229 mL, 2.97 mmol) and then the mixture was stirred at RT for 1h. The reaction mixture was then concentrated under reduced pressure to give the trifluoroacetic acid salt of 3-[6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-1-yl]-3-(methyloxy)propyl methanesulfonate, (170 mg). To a solution of 3-[6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-1-yl]-3-(methyloxy)propyl trifluoromethanesulfonate (120 mg, 0.230 mmol) in dry DMF were added TEA (0.048 mL, 0.345 mmol) and sodium iodide (37.9 mg, 0.253 mmol) and the reaction mixture was heated at 100°C in a microwave reactor for 15 min (2X). The solution was concentrated under reduced pressure and the residue was purified by SCX cartridge chromatography and then by liquid chromatography to give the title compound (10 mg); Chromatography conditions: (Phenomenex Gemini AXIA C18 (50x21.2mm, 5.0um) column temperature ambient. (LC/MS - ES (+): mobile phase: A-10mM Ammonium Bicarbonate + Ammonia (pH 10) / B - CH_3CN HCOOH , Flow rate: 17 mL/min, Gradient: t = 0 min 30% B, t = 1 min 35% B, t = 8 min 65% B, t = 9 min 100% B, t = 11 min 100%); ^1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.47 (d, 1 H) 7.27 (dd, 1 H) 7.24 (dd, 1 H) 3.68 (dd, 1 H) 3.60 (dd, 1 H) 3.14 (s, 3 H) 3.04 - 3.11 (m, 1 H) 2.90 - 2.98 (m, 1 H) 2.69 (d, 1 H) 2.56 (dd, 1 H) 2.14 (dd, 1 H) 1.99 (d, 1 H) 1.61 - 1.74 (m, 3 H) 1.44 - 1.57 (m, 1 H) 0.84 (d, 1 H); MS (m/z) = 312 [MH^+].

Compound 4: (1S,3R,9S or 1R,3S,9R)-3-(3,4-dichlorophenyl)-9-(methyloxy)-6-azatricyclo[4.3.1.0^{1,3}]decane (single enantiomer)

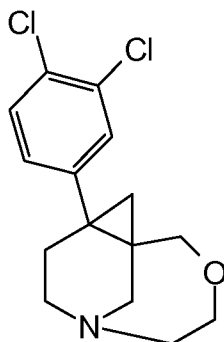


To a solution of 3-[6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-1-yl]-3-(methyloxy)propyl methanesulfonate (Intermediate 19) (47 mg, 0.090 mmol) in dry DMF were added TEA (0.019 mL, 0.135 mmol) and sodium iodide (14.84 mg, 0.099

mmol) and the reaction mixture was heated at 90 °C in a microwave reactor for 15 min. The solution was concentrated under reduced pressure and the residue was purified by SCX cartridge chromatography to give title compound (12 mg) as colourless oil; ¹H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 7.35 - 7.42 (m, 2 H)

- 5 7.16 (dd, 1 H) 3.59 - 3.68 (m, 1 H) 3.55 (d, 1 H) 3.33 - 3.40 (m, 1 H) 3.32 (s, 3 H) 3.00 - 3.09 (m, 1 H) 2.94 - 2.99 (m, 1 H) 2.65 - 2.73 (m, 1 H) 2.19 - 2.34 (m, 2 H) 1.88 (d, 1 H) 1.71 - 1.81 (m, 1 H) 1.45 - 1.56 (m, 1 H) 1.22 - 1.37 (m, 1 H) 1.03 (d, 0 H); MS (m/z) = 312 [MH⁺].

- 10 Compound 5: (1S,3R or 1R,6S)-3-(3,4-dichlorophenyl)-9-oxa-6-azatricyclo[4.4.1.0^{1,3}]-undecane (single enantiomer)

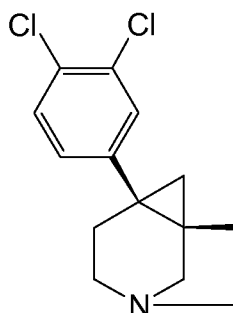


To a solution of 2-({[(1R,6S)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-1-yl]methyl}oxy)ethyl methanesulfonate (Intermediate 22) (86 mg, 0.169 mmol) in dry

- 15 DMF were added TEA (0.035 mL, 0.254 mmol) and sodium iodide (27.9 mg, 0.186 mmol) and the reaction mixture was irradiated three times at 100 °C for 15 min. The solution was concentrated under reduced pressure and the residue was purified by SCX then by chromatography to give title compound (2.5 mg); ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 7.43 (d, 1 H) 7.32 (d, 1 H) 7.11 (dd, 1 H) 3.81 (d, 1 H) 3.58 (m, 1 H) 3.52 (d, 1 H) 3.46 (m, 1 H) 3.13 (m, 1 H) 3.06 (m, 1 H) 2.84 (dt, 1 H) 2.64 (d, 20 2 H) 2.42 (dd, 1 H) 1.72 (m, 1 H) 1.27 (m, 2 H) 0.79 (d, 1 H); MS (m/s) = 298 [MH⁺].

Compound 6: (1R,3S/1S,3R)-3-(3,4-dichlorophenyl)-6-azatricyclo[4.2.1.0^{1,3}]-nonane (Racemate)

53



To a solution of 2-[(1R,6S/1S,6R)-6-(3,4-dichlorophenyl)-3-azabicyclo[4.1.0]hept-1-yl]ethyl methanesulfonate (670 mg, 1.839 mmol, Intermediate 28) in dry N,N-

5 dimethylformamide (DMF) (120 mL) was added sodium iodide (414 mg, 2.76 mmol) and the reaction mixture was stirred at 80 °C for 2 h and then at room temperature overnight. The progress of the reaction was monitored by HPLC. In the morning HPLC analysis showed uncompleted conversion of the starting material into the

10 reaction was completed. The mixture was then purified by chromatography using a SCX cartridge (50 g). The cartridge was first equilibrated with MeOH. The reaction mixture was concentrated *in vacuo* to (ca 20 mL) and loaded on to the SCX cartridge. The cartridge was first washed with methanol and then with a 2 M solution of ammonia in MeOH. The methanol/ammonia fractions were concentrated *in vacuo*
 15 to give the title compound as a (410 mg) as a yellow oil; ¹H NMR (CDCl₃, 600 MHz) δ ppm 1.08 - 1.14 (m, 1 H) 1.49 (d, 1 H) 1.51 - 1.57 (m, 1 H) 1.65 - 1.71 (m, 1 H) 1.95 (d, 1 H) 2.10 (dd, 1 H) 2.30 - 2.36 (m, 2 H) 2.63 (d, 1 H) 2.84 - 2.91 (m, 1 H) 3.35 - 3.41 (m, 1 H) 3.66 (dd, 1 H) 7.03 (dd, 1 H) 7.27 (overlapped with CDCl₃, 1 H) 7.33 (d, 1 H); MS (m/z): 268 [MH]⁺.

20 The affinity of compounds of the invention for SERT, NET and DAT may be tested in one or other of the following affinity assays.

a) Filtration Binding Assay using membranes from hSERT, hNET, and hDAT Lewis

25 Lung Carcinoma Porcine tubule Kidney (LLCPK) cell lines

- Membrane preparation

hSERT-LLCPK, hDAT-LLCPK or hNET-LLCPK cell lines are used for the membrane preparations for radioligand binding assays. Stable cell lines may be generated as follows: i) hSERT - generated by transfecting LLC-PK1 or LLCPK cells with hSERT

cloned into the mammalian expression vector pCDNA3.1 Hygro(+); ii) hNET - generated by transfecting LLC PK cells with hNET cloned into the mammalian expression vector pRC/CMV; iii) hDAT- generated by transfecting LLC PK cells with hDAT cloned into the mammalian expression vector pDESTCDNA3.1 (an example of
5 a procedure for transfecting LLC PK cells with hDAT, hSERT and hNET may be found in H. Gu, S.C. Wall and G. Rudnick, J. Biol. Chem. (1994) 269 : 7124-7130.)

Each cell line is cultured independently in Dulbecco's modified Eagle's medium (DMEM) containing 10% of Foetal Bovine Serum (FBS) supplemented with 400
10 µg/ml hygromycin (hSERT) or geneticin at 500 µg/ml (hNET) or at 1000 µg/ml (hDAT). Cells are maintained at 37°C in a humidified environment containing 5% CO₂ in air.

When cells are at 70-80% of confluence, the culture medium is removed and the
15 cells harvested with phosphate buffered saline (PBS) containing 5 mM EDTA. The cell suspension is centrifuged at 900g for 5 minutes at 4°C. The resultant pellets are re-suspended in 30-50 volumes of Assay Buffer (50mM Tris pH 7.7 containing 120mM NaCl, 5mM KCl, 10µM pargyline and 0.1% ascorbic acid) and homogenized using a glass-teflon Potter homogeniser and centrifuged at 48000g for 20 minutes at
20 4°C. The resultant membrane pellets are re-suspended in the same volume of Assay Buffer, incubated for 20 minutes at 37°C and centrifuged as before at 48000g. The final protein concentration for each preparation is adjusted to give approximately 480µg protein/ml for hSERT-LLC PK, hDAT-LLC PK and hNET-LLC PK, as determined by the Bio-Rad Protein Assay kit. Membranes are stored at -80°C as 1ml
25 aliquots until required.

- Assay Protocol (For general references to monoamine transporters filtration binding assays see: Michael J. Owens, et al, Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites, JPET, 283:1305-1322, 1997;
30 Per Allard, Jan O. Marcusson, Svate B. Ross, [³H]WIN-35,428 binding in the human brain, Brain Res., 706: 347-350, 1996.)

The affinity of the compounds of the invention to bind the re-uptake site of SERT may be assessed using [³H]citalopram filtration binding assay performed on hSERT-
35 LLC PK cell membranes. The competition binding assay is conducted in deep-well 96

well plates (1ml, NUNC, cod.260252) in a total volume of 400µl, with each concentration in duplicate. 4µl of test compound (100X solution in neat DMSO as 7 point curve ranging from 10^{-6} to 10^{-12} M, final concentration) or DMSO (to define total binding) or a final concentration of 10µM fluoxetine in DMSO (to define non-specific binding, NSB) are added to wells; after this, 200µl of [N-Methyl- ^{3} H]citalopram (Amersham Biosciences, 80 Ci/mmol) at the final concentration of 0.25nM in Assay Buffer, is added to all wells and finally the reaction is started by adding 200µl/well of membranes diluted 1:80 in Assay Buffer at concentration of about 2.5µg/well of protein. The reaction is carried out at room temperature for 2 hours and then stopped by rapid filtration through GF/B Unifilter 96-filterplate (Perkin-Elmer) pre-soaked in 0.5% polyethylenimine (PEI) using a Perkin-Elmer FilterMat-196 harvester. Filterplate is washed 3 times with 1ml/well ice-cold 0.9% NaCl solution. The plate is dried in an oven for 60 min at 50°C then opaque bottom-seal is placed on the underside of the plate and 50µl of Microscint 20 (Perkin-Elmer) added to each well. Plate is sealed with a TopSeal and the radioactivity in the samples is counted for 4 min using TopCount liquid scintillation counter (Packard-Perkin-Elmer) and recorded as counts per minute (CPM).

Competition binding assay for hNET may be conducted essentially as previously reported for hSERT in 96 well format and in a final assay volume of 400µl, except for the use of hNET-LLCPK cell membranes (1:40 dilution i.e. 4.8µg of protein/well) and [^{3} H]nisoxetine as radioligand (1.5nM [N-methyl- ^{3} H]nisoxetine, Amersham Biosciences, 84 Ci/mmol). 10µM desipramine is used for NSB.

Competition binding assay for hDAT may also be conducted essentially as previously reported for hSERT and hNET in 96 well format and in a final assay volume of 400µl, except for the use of hDAT-LLCPK cell membranes (1:20 i.e. 9.6µg of protein/well) and [^{3} H]WIN-35,428 as radioligand (10nM [N-Methyl- ^{3} H]WIN-35,428, Perkin Elmer, 85.6 Ci/mmol). Furthermore, 10µM GBR-12909 is used for NSB and the incubation time of the binding reaction is 1 hour at room temperature.

b) Scintillation Proximity Assay (SPA) for human DAT, NET and SERT binding
- Generation of BacMam viruses for the expression of hSERT, hNET, and hDAT in mammalian cells

Membranes for the SPA-binding assays are produced by HEK-293F cell infection with BacMam viruses generated for each single human SERT, NET, and DAT transporter. hSERT and hDAT are cloned into pFBMRfA vector whereas hNET is cloned into pFASTBacMam1 vector. The generation and use of BacMam viruses is described in Condreay JP et al, Proc. Natl. Acad. Sci. USA, 1999, 96:127-132 and Hassan NJ et al, Protein Expression and Purification, 47(2): 591-598, 2006.

- Transduction of HEK-293F cells with hSERT/hDAT/hNET BacMam viruses

The HEK-293F suspension cell line (Invitrogen) is routinely grown in 293_Freestyle Expression media (Invitrogen) in shake flask suspension culture. The culture is transduced with the appropriate transporter BacMam at a MOI (multiplicity of infection) of 100 virus particles per cell and incubated for 48hrs at 37°C, 5% CO₂ in air, shaken at 90rpm in a humidified shaker incubator. The culture is then harvested by centrifugation at 1000g, 4°C, for 10 minutes and the cell pellet stored at -80°C until required.

- Preparation of BacMam hSERT/hDAT/hNET-HEL293F cell membranes

Transduced cell pellets are re-suspended to 10x volume with buffer-A (50mM HEPES, 1mM EDTA, 1mM leupeptin, 25ug/mL bacitracin, 1mM phenylmethylsulfonylfluoride, PMSF, 2μM pepstatin A, pH 7.7) and homogenised with 2x 15 second bursts in a glass Waring blender. The homogenate is then centrifuged for 20 minutes at 500g. Following this, the supernatant is pooled and centrifuged at 13,000g for 30 minutes. Pellets are then re-suspended to 4x original pellet volume with buffer-B (50mM TRIS pH 7.4, 130mM NaCl) and forced through a 0.8mm needle to give a homogeneous suspension. Membrane aliquots are stored at -80°C until required. The protein concentration is quantified by Bradford assay.

- Assay Protocol

The affinity of the compounds of the invention for hSERT, hNET or hDAT may also be assessed by using the [³H]citalopram, [³H]nisoxetine or [³H]WIN-35,428 binding assays with the SPA technology on BacMam-recombinant human SERT, NET and DAT membranes produced as described before. With the SPA technology (GE Healthcare, Amersham) only transporter-bound radioactivity can elicit bead excitation thus no separation of the bound/ unbound radioligand is required.

The protocol for hSERT binding SPA is based on Trilux beta-counter (Wallac, Perkin-Elmer). Briefly, 0.5µL of test compound in neat DMSO (or 1µM fluoxetine as positive control) is added by 50µL of the SPA mixture, containing 2mg/mL SPA beads (Amersham RPNQ0001), 4µg/mL hSERT Bacmam membranes, 0.01% pluronic F-127, 2.5nM [³H]citalopram in the assay buffer (20mM HEPES, 145mM NaCl, 5mM KCl, pH 7.3). Incubation are performed at room temperature for at least 2 hours. Counts are stable and could be read up to 3 days.

Alternatively, hDAT hNET and hSERT SPA-binding assays are performed by using a Viewlux beta-counter (Wallac, Perkin-Elmer) with imaging PS-WGA beads (Amersham RPNQ0260) in a final assay volume of 30µL and in a 384-well plate format (Greiner 781075). Briefly, 0.3µL of test compound in neat DMSO and 0% and 100% effect controls (DMSO for total binding and 10 or 1µM indatraline as positive control) are added to the wells by using a Hummingbird (Genomic Solutions), followed by the addition of 30µL of the SPA mixture, containing 1mg/mL SPA beads (hSERT) or 2mg/ml SPA beads (hDAT and hNET), 40µg/ml or 20µg/ml or 6 µg/ml of hDAT or hNET or hSERT BacMam membranes, 0.02% pluronic F-127, 10nM [³H]WIN-35,428 or 10nM [³H]nisoxetine or 3nM [³H]citalopram for hDAT or hNET or hSERT binding SPA in the assay buffer (20mM HEPES, 145mM NaCl, 5mM KCl, pH 7.3-7.4). Incubation is performed at room temperature for at least 2 hours, best overnight in the dark. Bound radioactivity is recorded by using a 600s 6x binning and 613nm emission filter with the Viewlux instrument.

Calculation

The affinity of the compounds of the invention for a particular transporter may be calculated from the IC₅₀ obtained in competition experiments as the concentration of a compound necessary to displace 50% of the radiolabeled ligand from the transporter, and is reported as a "K_i" value calculated by the following equation:

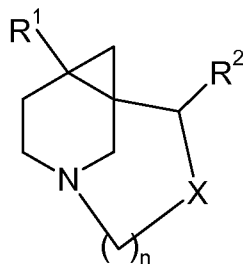
$$K_i = \frac{IC_{50}}{1 + L / K_D}$$

where L = radioligand and K_D = affinity of radioligand for transporter (Cheng and Prusoff, *Biochem. Pharmacol.* 22:3099, 1973). Results are presented below as the pK_i (i.e. the antilogarithm of K_i).

Compounds 1 to 6 were tested in assay b) using hSERT, hNET and hDAT. Each test was performed at least twice for each compound against each receptor. Using this assay, all the compounds gave an average pKi equal to or greater than 6.9 for hSERT, equal to or greater than 5.5 against hNET and equal to or greater than 5.7 against hDAT.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof



(I)

wherein

- 5 R^1 is 3,4-dichlorophenyl or naphthyl;

R^2 is H or C_{1-4} alkoxy;

n is 0, 1 or 2; and

X is CH_2 or O;

wherein when n is 0 or 1, X is CH_2 .

10

2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R^1 is 3,4-dichlorophenyl.

15

3. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X is CH_2 and R^2 is C_{1-4} alkoxy.

4. A compound according to claim 1 selected from the list:

(1S,3R,8S or 1R,3S,8R)-3-(3,4-dichlorophenyl)-8-(methyloxy)-6-azatricyclo[4.2.1.0^{1,3}]nonane (single enantiomer) (Compound 1);

20

(1S,3R or 1R,3S)-3-(3,4-dichlorophenyl)-8-(methyloxy)-6-azatricyclo[4.2.1.0^{1,3}]nonane (single diastereoisomer 2, single enantiomer) (Compound 2);

(1S,3R,9S or 1R,3S,9R)-3-(3,4-dichlorophenyl)-9-(methyloxy)-6-azatricyclo[4.3.1.0^{1,3}]decane (single enantiomer) (Compound 3);

25

(1S,3R,9S or 1R,3S,9R)-3-(3,4-dichlorophenyl)-9-(methyloxy)-6-azatricyclo[4.3.1.0^{1,3}]decane (single enantiomer) (Compound 4);

(1S,3R or 1R,6S)-3-(3,4-dichlorophenyl)-9-oxa-6-azatricyclo[4.4.1.0^{1,3}]undecane (single enantiomer) (Compound 5); and

(1R,3S/1S,3R)-3-(3,4-dichlorophenyl)-6-azatricyclo[4.2.1.0^{1,3}]-nonane (Racemate)
(Compound 6);

or a pharmaceutically acceptable salt thereof.

- 5 5. A pharmaceutical composition comprising a) a compound defined in any preceding claim or a pharmaceutically acceptable salt thereof and b) one or more pharmaceutically-acceptable excipients.

- 10 6. A compound defined in any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof for use in treating a disease or condition.

- 15 7. A compound defined in any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof for use in treating a disease or condition for which inhibition of monoamine neurotransmitter re-uptake is beneficial.

8. A method of treating a disease or condition for which inhibition of monoamine neurotransmitter re-uptake is beneficial in a human comprising administering an effective amount of a compound defined in any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof.

9. A compound according to claim 7 or a pharmaceutically acceptable salt thereof for use in treating depression or an anxiety disorder.

- 20 10. A compound according to claim 7 or a pharmaceutically acceptable salt thereof for use in treating an eating disorder.

11. A method according to claim 8 for treating depression or an anxiety disorder.

12. A method according to claim 8 for treating an eating disorder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/058331

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/10 C07D498/10 A61K31/553 A61K31/439 A61P25/30
A61P25/24 A61P25/16 A61P25/22 A61P25/28

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/031772 A1 (GLAXO GROUP LTD [GB]; BERTANI BARBARA [IT]; DI FABIO ROMANO [IT]; MICH) 20 March 2008 (2008-03-20) cited in the application claims 1-22 -----	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

13 July 2010

Date of mailing of the international search report

03/08/2010

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/058331

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008031772 A1	20-03-2008	AR 062737 A1	26-11-2008
		AU 2007296301 A1	20-03-2008
		CA 2662538 A1	20-03-2008
		CL 26192007 A1	18-04-2008
		EA 200970266 A1	28-08-2009
		EP 2064186 A1	03-06-2009
		JP 4448198 B2	07-04-2010
		JP 2010502761 T	28-01-2010
		KR 20090064447 A	18-06-2009
		US 2010035914 A1	11-02-2010
		US 2008114049 A1	15-05-2008
