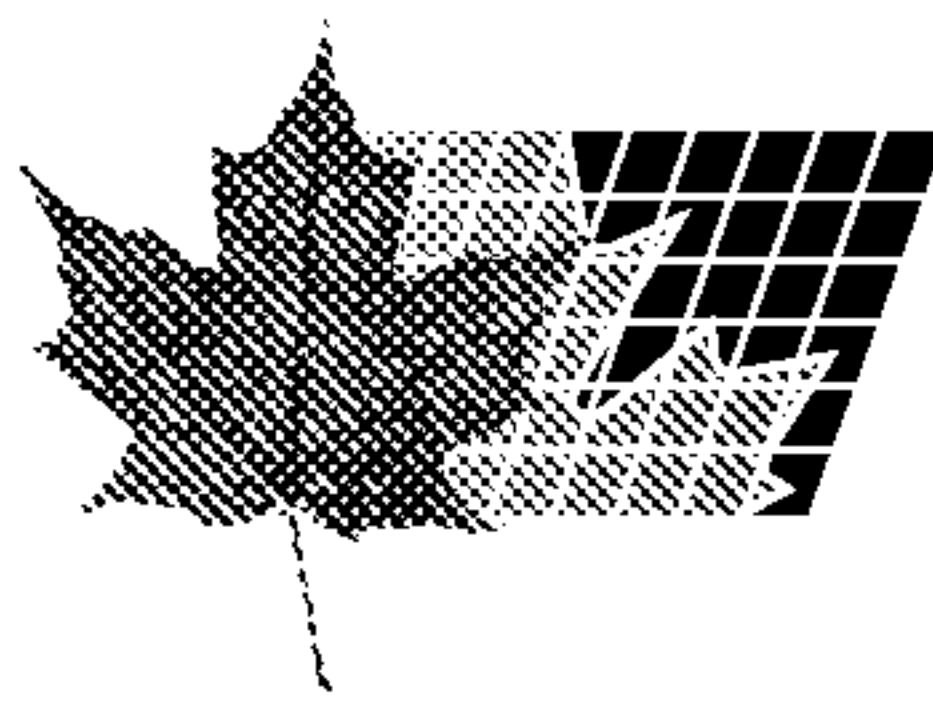




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(54) **UTILISATION D'ANTAGONISTES DU RECEPTEUR NK-1 DANS
LE TRAITEMENT DES TROUBLES BIPOLAIRES**

(54) **USE OF NK-1 RECEPTOR ANTAGONISTS FOR TREATING
BIPOLAR DISORDERS**

(57) La présente invention a pour objet l'utilisation d'un antagoniste du récepteur NK-1, à action prolongée, agissant sur le système nerveux central; et à administration par voie orale, dans la fabrication d'un médicament prévu pour être administré par voie orale permettant de traiter ou de prévenir les troubles bipolaires sans thérapie parallèle par d'autres agents antidépresseurs ou anxiolytiques. L'invention traite également de procédés de traitement à l'aide d'un antagoniste du récepteur NK-1 et de compositions pharmaceutiques comprenant cet antagoniste

(57) The present invention provides the use of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist for the manufacture of a medicament adapted for oral administration for the treatment or prevention of bipolar disorder without concomitant therapy with other antidepressant or anti-anxiety agents, methods of treatment using such an NK-1 receptor antagonist and pharmaceutical compositions comprising the same.

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(21) International Application Number: PCT/EP97/06688 (22) International Filing Date: 25 November 1997 (25.11.97) (30) Priority Data: <table border="0" style="width: 100%;"> <tr> <td style="width: 30%;">9625051.9</td> <td style="width: 40%;">2 December 1996 (02.12.96)</td> <td style="width: 30%;">GB</td> </tr> <tr> <td>9701459.1</td> <td>24 January 1997 (24.01.97)</td> <td>GB</td> </tr> <tr> <td>9713715.2</td> <td>27 June 1997 (27.06.97)</td> <td>GB</td> </tr> <tr> <td>9716467.7</td> <td>4 August 1997 (04.08.97)</td> <td>GB</td> </tr> <tr> <td>9721192.4</td> <td>7 October 1997 (07.10.97)</td> <td>GB</td> </tr> </table> (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BAKER, Raymond [GB/GB]; BBSRC, Polaris House, North Star Avenue, Swindon SN2 1UH (GB). CURTIS, Neil, Roy [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). ELLIOTT, Jason, Matthew [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). HARRISON, Timothy [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). HOLLINGWORTH, Gregory, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). JACKSON, Philip,		9625051.9	2 December 1996 (02.12.96)	GB	9701459.1	24 January 1997 (24.01.97)	GB	9713715.2	27 June 1997 (27.06.97)	GB	9716467.7	4 August 1997 (04.08.97)	GB	9721192.4	7 October 1997 (07.10.97)	GB	Stephen [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). KULAGOWSKI, Janusz, Jozef [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). RUPNIAK, Nadia, Melanie [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SEWARD, Eileen, Mary [IE/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SWAIN, Christopher, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). WILLIAMS, Brian, John [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: HISCOCK, Ian; Merck & Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
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(54) Title: USE OF NK-1 RECEPTOR ANTAGONISTS FOR TREATING BIPOLAR DISORDERS (57) Abstract The present invention provides the use of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist for the manufacture of a medicament adapted for oral administration for the treatment or prevention of bipolar disorder without concomitant therapy with other antidepressant or anti-anxiety agents, methods of treatment using such an NK-1 receptor antagonist and pharmaceutical compositions comprising the same.																	

USE OF NK-1 RECEPTOR ANTAGONISTS FOR TREATING
BIPOLAR DISORDERS

This invention relates to the treatment or prevention of bipolar
5 disorders by the administration of a specific class of NK-1 receptor
antagonists.

Bipolar disorder, otherwise known as manic depressive disorder or
bipolar affective disorder, is characterised by alternating conditions of
mania and depression. The nature of the clinical course of the bipolar
10 disorder may give rise to a diagnosis of bipolar I disorder, bipolar II
disorder or cyclothymic disorder. Bipolar I disorder is generally
considered to be the most severe, being an alternation of major depressive
episodes and manic episodes. Bipolar II disorder refers to an alternation
of major depressive episodes and hypomanic episodes, whilst cyclothymic
15 disorder refers to an alternation of depressive symptoms and hypomanic
symptoms.

Treatment regimens commonly include the use of tricyclic
antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), some
psychotropic drugs, lithium carbonate, and electroconvulsive therapy
20 (ECT) (see R. J. Baldessarini in *Goodman & Gilman's The*
Pharmacological Basis of Therapeutics, 9th Edition, Chapter 19, McGraw-
Hill, 1996 for a review). More recently, new classes of antidepressant
drugs are being developed including selective serotonin reuptake
inhibitors (SSRIs), specific monoamine reuptake inhibitors and 5-HT_{1A}
25 receptor agonists and antagonists.

The most established drug treatment for the management of
depressive episodes are the tricyclic antidepressants. For instance,
depressed patients with prominent sleep disturbance and anxiety may be
treated with a sedating tricyclic antidepressant such as amitriptyline; for
30 other patients, less sedating compounds such as imipramine or
desipramine can be used. As well as inhibiting the uptake of

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noradrenaline and 5-hydroxytryptamine, tricyclic antidepressants also possess antagonist properties at a variety of neurotransmitter receptors, including muscarinic cholinergic receptors, α_1 -adrenoceptors and H_1 -histamine receptors. These receptor antagonist effects account for much of the side-effect profile of the tricyclic antidepressants, and in particular, their anticholinergic side-effects which are particularly troublesome in patients with prostatic enlargement or glaucoma. Other side-effects include dry mouth, tachycardia, difficulty in visual accommodation, constipation, urinary retention, sexual dysfunction, cognitive impairment, postural hypotension, and weight gain.

Monoamine oxidase inhibitors are generally prescribed for patients who have failed to respond to tricyclic antidepressants or electroconvulsive therapy. As with tricyclic antidepressants, there are a number of side-effects associated with the use of MAOIs including dizziness, muscular twitching, insomnia, confusion, mania, tachycardia, postural hypotension, hypertension, dry mouth, blurred vision, impotence, peripheral oedema, hepatocellular damage and leucopenia.

Of the new classes of antidepressant, selective serotonin reuptake inhibitors are increasingly prescribed, particularly in patients where the use of tricyclic antidepressants is contraindicated because of their anticholinergic and cardiotoxic effects. SSRIs such as fluoxetine, fluvoxamine, sertraline and paroxetine are generally non-sedating. Furthermore, SSRIs do not stimulate appetite and may therefore be appropriate in patients in whom weight gain would be undesirable. However, SSRIs are not without their own side-effects, including nausea, diarrhoea, dry mouth, reduced appetite, dyspepsia, vomiting, headache, nervousness, insomnia, anxiety, tremour, dizziness, fatigue, decreased libido, pharyngitis, dyspnoea, skin rash and sexual dysfunction.

Treatment of manic episodes is with drugs and psychological management. Typically, drugs such as haloperidol or chlorpromazine may be used to control symptoms. After more than one episode of mania,

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lithium carbonate is often prescribed. Drugs such as haloperidol and chlorpromazine are typically associated with a number of side-effects, including extrapyramidal symptoms, acute dystonias or dyskinesias, akathisia, tremour, tachycardia, drowsiness, confusion, postural hypotension, blurring of vision, precipitation of glaucoma, dry mouth, constipation, urinary hesitance and impaired sexual function. The therapeutic index of lithium is low and close control of plasma concentrations is required for its safe clinical application. Side-effects of lithium include tremour, nausea, diarrhoea, thirst and polyuria.

10 Whatever drug is used, there is a delay of usually two, three or even four weeks before a therapeutic effect is observed. This period of delay may be particularly difficult for a patient suffering from a bipolar disorder.

15 Neurokinin 1 (NK-1; substance P) receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinins, and in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (see, for instance, International (PCT) patent specification Nos. WO 95/16679, WO 95/18124 and WO 95/23798).

20 More recently, International (PCT) patent specification No. WO 96/24353 (published 15th August 1996) suggests that a more efficacious and safe treatment of psychiatric disorders would be achieved using a combination of a tachykinin antagonist and a serotonin agonist or selective serotonin reuptake inhibitor (SSRI). However, such as regimen would not be free of side-effects due to the serotonin agonist or SSRI.

25 NK-1 receptor antagonists are described in published European Patent Specification Nos. 0 360 390, 0 394 989, 0 429 366, 0 443 132, 0 482 539, 0 512 901, 0 512 902, 0 514 273, 0 514 275, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 30 0 545 478, 0 577 394, 0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006,

0 708 101, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; and in International Patent Specification Nos. 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 5 93/01170, 93/06099, 93/09116, 93/10073, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/01402, 94/02461, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 10 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 96/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 15 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Specification Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689.

20 In view of the short-comings of existing therapy, there is a need for new, safe and effective treatment for bipolar disorders.

The present invention provides the use of a CNS penetrant NK-1 receptor antagonist in an oral, once-a-day medicament for the treatment of bipolar disorder. The compounds of this class advantageously exhibit a rapid onset of action and a reduced side-effect profile when compared 25 against conventional mood-altering agents.

In particular, the present invention provides a means for the identification of NK-1 receptor antagonists which would be effective in an oral once-a-day medicament for the treatment of bipolar disorders. The aforementioned patent specifications which describe NK-1 receptor 30 antagonists provide no reliable method for the identification of such compounds.

The exceptional pharmacology of the class of NK-1 receptor antagonists of use in the present invention enables the treatment of bipolar disorders, without the need for concomitant therapy using tricyclic antidepressants or monoamine oxidase inhibitors or, in particular, without
5 the need for concomitant use of a serotonin agonist or an SSRI.

Furthermore, the exceptional pharmacology of the class of NK-1 receptor antagonists of use in the present invention results in a rapid onset of action.

The present invention accordingly provides the use of an orally
10 active, long acting, CNS-penetrant NK-1 receptor antagonist (as hereinafter defined) for the manufacture of a medicament adapted for oral administration for the treatment or prevention of bipolar disorder without concomitant therapy with other antidepressant or anti-anxiety agents.

The present invention also provides a method for the treatment or
15 prevention of bipolar disorder without concomitant therapy with other antidepressant or anti-anxiety agents, which method comprises the oral administration to a patient in need of such treatment of an effective amount of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist (as hereinafter defined).

20 In a further aspect of the present invention, there is provided an oral pharmaceutical composition for the treatment of bipolar disorder which comprises essentially an orally active, long acting, CNS-penetrant NK-1 receptor antagonist (as hereinafter defined), together with a pharmaceutically acceptable carrier or excipient.

25 There exists a patient population in whom bipolar disorder is inadequately treated with lithium. Furthermore, some patients may be adversely affected by the side-effects of lithium.

The present invention accordingly provides the use of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist for the
30 manufacture of a medicament adapted for oral administration for the treatment or prevention of bipolar disorder, without concomitant therapy

with other antidepressant or anti-anxiety agents, in a patient who is non-responsive to lithium or for whom lithium is contraindicated.

The present invention also provides a method for the treatment or prevention of bipolar disorder, without concomitant therapy with other antidepressant or anti-anxiety agents, in a patient who is non-responsive to lithium or for whom lithium is contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist.

Furthermore, there exists a patient population in whom bipolar disorder is inadequately treated with heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine reuptake inhibitors, dopamine reuptake inhibitors or MAOIs. Furthermore, some patients may be adversely affected by the side-effects of antidepressants.

The present invention accordingly provides the use of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist for the manufacture of a medicament adapted for oral administration for the treatment or prevention of bipolar disorder, without concomitant therapy with other antidepressant or anti-anxiety agents, in a patient who is non-responsive to heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated.

The present invention also provides a method for the treatment or prevention of bipolar disorder, without concomitant therapy with other antidepressant or anti-anxiety agents, in a patient who is non-responsive to heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine reuptake inhibitors, dopamine

reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants (TCAs, tetracyclics, and the like), SSRIs, mixed serotonin and norepinephrine reuptake inhibitors, dopamine reuptake inhibitors or MAOIs are contraindicated, which method comprises oral administration
5 to the patient in need of such treatment of an effective amount of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist.

As used herein, the term "non-responsive" in relation to major depressive disorder means patients who have not had a reasonable clinical response (e.g. a 50% reduction in Hamilton Depression Scale (HAM-D)
10 from a patient's baseline score after treatment with one or more clinical courses of conventional antidepressants).

As used herein, the term "bipolar disorder" includes bipolar I disorder, bipolar II disorder, cyclothymic disorder and bipolar disorder not otherwise specified. Bipolar I disorder is an alternation of major
15 depressive episodes and manic episodes. Bipolar II disorder refers to an alternation of major depressive episodes and hypomanic episodes. Cyclothymic disorder refers to an alternation of depressive symptoms and hypomanic symptoms.

A "major depressive episode" is defined as at least two weeks of
20 depressed mood or loss of interest, which may be accompanied by other symptoms of depression. The symptoms must persist for most of the day (i.e. for at least two thirds of the patients' waking hours), nearly every day (i.e. for at least ten out of fourteen days) for at least two consecutive weeks. A "depressed mood" is often described by the patient as feeling sad,
25 hopeless, helpless or worthless. The patient may also appear sad to an observer, for example, through facial expression, posture, voice and tearfulness. In children and adolescents, the mood may be irritable. A "loss of interest" is often described by the patient as feeling less interested in hobbies or not feeling any enjoyment in activities that were previously
30 considered to be pleasurable.

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A major depressive episode may be accompanied by other symptoms of depression including significant weight loss when not dieting or weight gain (e.g. a change of more than 5% body weight in one month), or decrease or increase in appetite; insomnia or hypersomnia; psychomotor
5 agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive or inappropriate guilt; diminished ability to think or concentrate; or indecisiveness; and recurrent thoughts of death, recurrent suicidal ideation with or without a specific plan, or a suicide attempt.

A "manic episode" is defined by a distinct period during which there
10 is an abnormally and persistently elevated, expansive, or irritable mood. This period of abnormal mood must last at least 1 week (or less if hospitalization is required). The mood disturbance must be accompanied by at least three additional symptoms from a list that includes inflated self-esteem or grandiosity, decreased need for sleep, pressure of speech,
15 flight of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation, and excessive involvement in pleasurable activities with a high potential of painful consequences. If the mood is irritable (rather than elevated or expansive), at least four of the above symptoms must be present. The disturbance must be sufficiently
20 severe to cause marked impairment in social or occupational functioning or to require hospitalization, or it is characterised by the presence of psychotic features.

A "hypomanic episode" is less severe than a manic episode. The symptoms of a hypomanic episode are generally the same as those which
25 define a manic episode, except that delusions and hallucinations are not present and the episode is not severe enough to cause marked impairment of social and occupational functioning or to require hospitalisation of the individual.

As used herein, the term "treatment" refers both to the treatment
30 and to the prevention or prophylactic therapy of the aforementioned conditions.

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Preferred NK-1 receptor antagonists for use in the present invention are selected from the classes of compounds described in European Patent Specification No. 0 577 394, and International Patent Specification Nos. 95/08549, 95/18124, 95/23798 and 96/05181, and
 5 International Patent Application No. PCT/GB97/01630. The preparation of such compounds is fully described in the aforementioned publications.

Particularly preferred NK-1 receptor antagonists of use in the present invention include:

- 10 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine;
- 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine;
- 15 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;
- 20 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 25 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(2-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxyphosphoryl-1H-1,2,4-triazolo)methyl)morpholine;
- 30 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;

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- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-N,N-dimethylaminobut-2-yn-yl)-3-(S)-(4-fluorophenyl)morpholine;
(3S,5R,6S)-3-[2-cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
5 (3R,5R,6S)-3-[2-cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
or a pharmaceutically acceptable salt thereof.

Full descriptions of the preparation of the NK-1 receptor antagonists which may be employed in the present invention may be found
10 in the references cited herein.

Suitable pharmaceutically acceptable salts of the NK-1 receptor antagonists of use in the present invention include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as
15 hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group. Where the compound carries an acidic group, for example a
20 carboxylic acid group, the present invention also contemplates salts thereof, preferably non-toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium and calcium salts thereof.

Preferably the compositions containing an NK-1 receptor antagonist of use according to the present invention are in unit dosage forms such as
25 tablets, pills, capsules, wafers and the like. Additionally, the NK-1 receptor antagonists of use according to the present invention may be presented as granules or powders for extemporaneous formulation as volume defined solutions or suspensions. Alternatively, the NK-1 receptor antagonists of use according to the present invention may be presented in
30 ready-prepared volume defined solutions or suspensions. Preferred forms are tablets and capsules.

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For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil or soybean oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as

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tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Compositions of the present invention may also be administered via the buccal cavity using conventional technology, for example, absorption
5 wafers.

Compositions in the form of tablets, pills, capsules or wafers for oral administration are particularly preferred.

A minimum dosage level for the NK-1 receptor antagonist is about 1mg per day, preferably about 5mg per day and especially about 10mg per
10 day. A maximum dosage level for the NK-1 receptor antagonist is about 1500mg per day, preferably about 1000mg per day and especially about 500mg per day. The compounds are administered once a day.

It will be appreciated that the amount of the NK-1 receptor antagonist required for use in the treatment or prevention of bipolar
15 disorders will vary not only with the particular compounds or compositions selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the patient's physician or pharmacist.

Two compounds of use in the present invention which are described
20 in International Patent Application No. PCT/GB97/01630 may be prepared according to the following methods:

PREPARATION 1

(2S)-1-tert-Butoxycarbonyl-2-phenylpiperidin-3-one

25 Dimethyl sulfoxide (20.80ml, 22.90g, 29.3mmol) in dichloromethane (75ml) was added dropwise to a cooled (-70°C) solution of oxalyl chloride (13.95ml, 20.30g, 160mmol) in dichloromethane (350ml). The mixture was stirred at -70°C for 15 minutes, then (2S,3S)-1-tert-butoxycarbonyl-3-hydroxy-2-phenylpiperidine (prepared by the method described in
30 European Patent Specification number 0 528 495-A; 36.91g, 133mmol) in dichloromethane (150ml) was added dropwise. The mixture was stirred at

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-70 °C for 20 minutes, then allowed to warm to -30°C. The mixture was cooled to -50 °C and triethylamine (55.95ml, 40.45g, 400mmol) was added slowly. The mixture was allowed to warm to 0°C and diluted with ice-cooled dichloromethane (250ml). The mixture was washed with ice cold
5 aqueous citric acid solution (5%, 2x300ml) and water (300ml), dried (MgSO₄), and the solvent was evaporated under reduced pressure to give the title compound as a yellow oil (42.3g), which was used immediately without further purification. ¹H NMR (250MHz, CDCl₃) δ 7.5-7.3 (5H, m), 5.8 (1H, br s), 4.2 (1H, br s), 3.4 (1H, m), 2.6 (2H, m), 2.0 (2H, m), and 1.54
10 (9H, s).

PREPARATION 2

(2S,3R)-1-tert-Butoxycarbonyl-3-hydroxy-3-(2-methylene-3-phenoxypropyl)-2-phenylpiperidine

15 A solution of 3-(chloromagnesio)-2-(phenoxymethyl)-1-propene in THF (0.91M, 3ml) (Louw *et. al.*, *Tetrahedron*, 48, 6087-6104, 1992, prepared from 2.74mmol of 3-chloro-2-(phenoxymethyl)-1-propene) was slowly added to a solution of (2S)-1-tert-butoxycarbonyl-2-phenylpiperidin-3-one (Preparation 1) in THF (3ml). The mixture was stirred at room
20 temperature for 1 hours, then saturated aqueous ammonium chloride (20ml) was added and the mixture was extracted with ethyl acetate (20ml). The organic phase was washed with brine, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate
25 (100:0 increasing to 80:20) to give the title compound. ¹H NMR (360MHz, CDCl₃) δ 7.48 (2H, d, *J*=6.9 Hz), 7.35-7.2 (6H, m), 6.9-6.88 (3H, m), 5.4 (1H, s), 5.15 (2H, d, *J*=13.7 Hz), 4.61 (2H, s), 4.11 (2H, m), 3.17 (1H, m), 2.66 and 2.59 (2H, AB d, *J*=14.0 Hz), 1.95 (2H, m), 1.79 (2H, m), and 1.36 (9H, s). *m/z* (ES⁺) 424 (M+1).

PREPARATION 3**(5*R*,6*S*)-3-Methylene-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane**

To a cooled (-80 °C) solution of (2*S*,3*R*)-1-*tert*-butoxycarbonyl-3-hydroxy-3-(2-methylene-3-phenoxypropyl)-2-phenylpiperidine (Preparation 2, 1.53g, 3.62mmol) in THF (20ml) was added n-butyl lithium (2.5M in hexanes, 1.45ml, 3.62mmol) followed by a solution of zinc chloride (0.5M in THF, 7.24ml, 3.62mmol). The solution was allowed to warm to room temperature and tetrakis(triphenylphosphine)palladium (0) (0.23g, 0.2mmol) was added. The mixture was degassed with bubbling nitrogen and heated under reflux for 16 hours. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and 2M sodium hydroxide. The organic phase was washed with saturated brine, dried (MgSO₄) and purified by chromatography on a column containing silica gel (eluting with hexane containing increasing proportions of ethyl acetate between 0% to 5%). Evaporation of the fractions gave (6*S*,5*R*)-3-methylene-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane. ¹H NMR (360MHz, CDCl₃) δ 7.58 (2H, d, *J*=8.4 Hz), 7.32-7.21 (3H, m), 5.23 (1H, s), 5.06 (1H, m), 4.97 (1H, m), 4.39 (2H, AB d, *J*=13.3 Hz), 3.99 (1H, dd, *J*=13.3, 4.48 Hz), 2.83 (1H, ABd *J*=15.5 Hz), 2.7 (1H, td *J*=12.5, 3.93 Hz), 2.5 (1H, ABd, *J*=15.4 Hz), 2.15 (2H, td, *J*=12., .4 Hz), 1.69 (2H, m), and 1.46 (9H,s). *m/z* (ES⁺) 329 (M+2H-^tBuOCO).

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PREPARATION 4**(5*R*,6*S*)-3-Keto-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane**

Through a cooled (-80 °C) solution of (5*R*,6*S*)-3-methylene-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (Preparation 3; 0.665g) in dichloromethane (5ml) and methanol (5ml) was bubbled a mixture of ozone and oxygen for 45 minutes. After the solution had been purged with nitrogen, dimethyl sulphide (0.5ml) was added and then stirred under

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nitrogen at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic phase was dried (MgSO₄), evaporated and the residue purified by chromatography on a column containing silica gel (eluting with hexane containing increasing proportions of ethyl acetate between 0% to 10%). Evaporation of the fractions gave the title compound. ¹H NMR (250MHz, CDCl₃) δ 7.58 (2H, d, *J*=6.2 Hz), 7.37-7.26 (3H, m), 5.3 (1H, s), 4.15 and 4.09 (2H, AB d, *J*=17.4 Hz), 3.97 (1H, m), 2.80 (1H, td, *J*=12.9, 4.0 Hz), 2.74 and 2.48 (2H, ABd, *J*=18.1 Hz), 2.29 (2H, m), 1.88-1.63 (2H, m), and 1.44 (9H, s). *m/z* (ES⁺) 332 (M+1).

PREPARATION 5

(5*R*,6*S*)-3-Trifluoromethylsulfonyloxy-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]dec-3-ene

To a cooled (-80 °C) solution of 1M sodium hexamethyldisilazide (0.38ml, 0.38mmol) in THF was added a solution of (5*R*,6*S*)-3-keto-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (Preparation 4; 0.105mg, 0.319mmol) in THF (3ml). The solution was stirred for 1 hours at -80°C then a solution of 2-[N,N-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (0.163g, 0.415mmol) in THF (3ml) was added. The solution was stirred at -80°C for 30 minutes then at room temperature for 30 minutes before being quenched by addition of saturated ammonium chloride solution and ethyl acetate. The dried (MgSO₄) organic phase was purified by chromatography on a column containing silica gel (eluting with hexane containing increasing proportions of ethyl acetate between 0% to 5%). Evaporation of the fractions gave the title compound. ¹H NMR (360MHz, CDCl₃) δ 7.4 (2H, d, *J*=7.3 Hz), 7.3-7.22 (3H, m), 6.01 (1H, t, *J*=2.13 Hz), 5.13 (1H, s), 4.56 and 4.26 (2H, ABdd, *J*=12.4, 1.97 Hz), 4.10 (1H, dt, *J*=12.6, 4.22 Hz), 3.00 (1H, m), 2.28-2.04 (2H, m), 1.88-1.76 (2H, m), and 1.37 (9H, s). *m/z* (ES⁺) 464 (M+1).

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PREPARATION 6

(5*R*,6*S*)-3-Trimethylstannyl-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]dec-3-ene

To a degassed solution of (5*R*,6*S*)-3-trifluoromethylsulfonyloxy-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]dec-3-ene (Preparation 5; 0.482g, 1.04mmol), lithium chloride (0.264g, 6.25mmol), lithium carbonate (0.076g) and hexamethyl distannane(0.96g, 2.9mmol) in THF (10ml) was added triphenylphosphine palladium (0) (0.06g). The solution was degassed and then heated at 60°C for 5 hours under nitrogen. Water (20ml) and ethyl acetate (20ml) were added and the dried organic phase was purified by chromatography on a column containing silica gel (eluting with hexane containing increasing proportions of ethyl acetate between 0% to 5%). Evaporation of the fractions gave the title compound as a crystalline solid. ¹H NMR (360MHz, CDCl₃) δ 7.25 (2H, d, *J*=7.3 Hz), 7.1-7.0 (3H, m), 5.83 (1H, t, *J*=2.5 Hz), 4.78 (1H, s), 4.48 and 4.02 (2H, dd, *J*=12.9, 2.3 Hz), 3.96 (1H, dd, *J*=6.16, 13.4 Hz), 2.95 (1H, td, *J*=13.3, 4.5 Hz), 1.84 (1H, m), 1.68 (1H, m), 1.60 (2H, m), 1.19 (9H, s), and 0.0 (6H, s).

PREPARATION 7

(2*S*,3*R*)-1-*tert*-Butoxycarbonyl-3-(3-hydroxypropyn-1-yl)-2-phenylpiperidin-3-ol

O-Trimethylsilylpropargyl alcohol (24.51ml, 20.47g, 160ml) was added slowly to a cooled (-10°C) solution of ethylmagnesium bromide (1M in tetrahydrofuran, 160ml, 160mmol). The mixture was stirred at 0°C for 20 minutes, then at room temperature for 2 hours. The mixture was cooled to -10°C and a solution of (2*S*)-1-*tert*-butoxycarbonyl-2-phenylpiperidin-3-one (Preparation 1; 42.3g) in tetrahydrofuran (200ml) was added dropwise over 30 minutes. (Internal temperature below -5°C). The mixture was stirred at room temperature for 14 hours, poured into water (300ml) and saturated aqueous ammonium chloride (300ml) and extracted with ethyl acetate (2x300ml). The combined organic fractions

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were washed with brine (300ml), dried (MgSO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (500ml) and a solution of tetrabutylammonium fluoride (1M in THF, 160ml, 160mmol) was added dropwise. The mixture was stirred at room temperature for 30 minutes, water (300ml) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2x300ml) and the combined organic fractions were washed with water (300ml) and brine (300ml), dried (MgSO_4) and the solvent was evaporated under reduced pressure to give the crude title compound as an orange oil (45g). The crude material was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (90:10 increasing to 25:75) to give the title compound as an amber oil (32.2g). ^1H NMR (CDCl_3) δ 7.53-7.55 (2H, m), 7.19-7.35 (3H, m), 5.56 (1H, s), 4.27 (2H, s), 3.99-4.03 (1H, m), 3.25 (1H, br s), 2.77-2.81 (1H, m), 2.77 (1H, br s), 2.12-2.20 (1H, m), 1.91-1.99 (2H, m), 1.77-1.83 (1H, m), and 1.39 (9H, s).

PREPARATION 8

2-Bromo-4-(trifluoromethoxy)phenol

To a cooled (0 °C) solution of 4-trifluoromethoxyphenol (35.6g, 0.2mol) in chloroform (280ml) was added dropwise a solution of bromine (32g, 0.2mol) in chloroform (50ml). The solution was stirred at 0°C for 1 hour and at room temperature for 2 hours. Dichloromethane (200ml) and water (400ml) were added and the organic phase was washed further with water (400ml), brine (200ml) and dried (MgSO_4). The solvent was removed and the residue was purified by distillation at reduced pressure to give the title compound. ^1H NMR (250MHz, CDCl_3) δ 7.38 (1H, d, $J=2.1$ Hz), 7.13 (1H, dd, $J=9.1, 2.1$ Hz), 7.03 (1H, d, $J=9.1$ Hz), and 5.53 (1H, s).

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PREPARATION 92-Benzyloxy-5-(trifluoromethoxy)bromobenzene

2-Bromo-4-(trifluoromethoxy)phenol (Preparation 8; 5g, 20mmol) was dissolved in *N,N*-dimethylformamide (60ml), and potassium carbonate (5.4g, 40mmol) was added, followed by benzyl bromide (3.5ml, 30mmol), and the reaction was stirred at ambient temperature for 15 hours. The reaction was diluted with water (150ml) and extracted into ethyl acetate (3x60ml). The combined organic fractions were washed with water (100ml), brine (100ml), dried (MgSO₄) and evaporated *in vacuo*. Purification on silica, eluting with 2% and 5% ethyl acetate in hexane gave the title compound as a clear oil (6.7g, 96%). ¹H NMR (250MHz, CDCl₃) δ 5.47 (2H, s), 7.23 (1H, d, *J*=9 Hz), 7.43 (1H, dd *J*=8.2, 2.9 Hz), and 7.75 (6H, m).

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PREPARATION 10*Z*-(2*S*,3*R*)-1-*tert*-Butoxycarbonyl-3-(3-hydroxyprop-1-en-1-yl)-2-phenylpiperidin-3-ol

Palladium on calcium carbonate, poisoned with lead (Lindlar catalyst, 2g) was added to a solution of (2*S*,3*R*)-1-*tert*-butoxycarbonyl-3-(3-hydroxypropyn-1-yl)-2-phenylpiperidin-3-ol (Preparation 7; 32g, 96.6mmol) in ethyl acetate (300ml) and the mixture was stirred under hydrogen (1 atmosphere) for 4 hours. The mixture was filtered and the solvent was evaporated under reduced pressure to give the title compound as an oil (32g, 100%). ¹H NMR (360MHz, CDCl₃) δ 7.42 (2H, d, *J*=7.6 Hz), 7.35-7.25 (3H, m), 5.83 (1H, d, *J*=12.3 Hz), 5.68 (1H, dt, *J*=12.3, 6.0 Hz), 5.06 (1H, s), 4.27 (1H, m), 4.12 (2H, m), 3.32 (1H, m), 3.13 (1H, s), 2.28 (1H, t, *J*=5.9 Hz), 2.02 (1H, m), 1.92-1.78 (3H, m), and 1.32 (9H, s). *m/z* (ES⁺) 334 (M+1).

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PREPARATION 11(5*R*,6*S*)-6-Phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]dec-3-ene

Diethylazodicarboxylate (18.2ml, 115mmol) in THF (100ml) was added dropwise to a solution of *Z*-(2*S*,3*R*)-1-*tert*-butoxycarbonyl-3-(3-hydroxyprop-1-en-1-yl)-2-phenylpiperidin-3-ol (Preparation 10; 32g, 96mmol) and triphenylphosphine (30.2g, 115mmol) in THF (700ml). The mixture was stirred at 0°C for 30 minutes then at room temperature for 1.5 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate (95:5 increasing to 80:20) to give the title compound as a colorless solid (23.4g, 77%). ¹H NMR (CDCl₃) δ 7.45 (2H, d, *J*=7.4 Hz), 7.27 (2H, t, *J*=7.4 Hz), 7.20 (1H, t, *J*=7.4 Hz), 6.03 (1H, dt, *J*=6.1, 2.0 Hz), 5.68 (1H, dt, *J*=6.1, 2.0 Hz), 5.06 (1H, s), 4.61 (1H, dt, *J*=13.1, 2.0 Hz), 4.32 (1H, dt, *J*=13.1, 2.0 Hz), 4.08 (1H, m), 3.05 (1H, m), 2.05 (1H, m), 1.75 (3H, m), and 1.37 (9H, s). *m/z* (ES⁺) 316 (M+1).

PREPARATION 122-Benzoyloxy-5-(trifluoromethoxy)benzene

Benzyl bromide (66.17ml, 95.35g, 0.56mol) was added to a mixture of 4-(trifluoromethoxy)phenol (90.26g, 0.51mol) and potassium carbonate (140.97g, 1.2mol) in dimethylformamide (160ml) and the mixture was stirred at room temperature for 72 hours. The mixture was poured into water (1.5 l) and extracted with ethyl acetate (3x500ml). The combined organic fractions were washed with aqueous sodium carbonate (saturated, 500ml), dried (MgSO₄) and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (133.5g, 99%). ¹H NMR (360MHz, CDCl₃) δ 7.39 (5H, m), 7.14 (2H, d, *J*=9.0 Hz), 6.95 (2H, d, *J*=9.0 Hz), and 5.05 (2H, s).

PREPARATION 13

2-Benzyloxy-5-(trifluoromethoxy)iodobenzene

Iodine (71.96g, 0.28mol) in chloroform was added dropwise to a mixture of 2-benzyloxy-5-(trifluoromethoxy)benzene (Preparation 12, 73.06g, 0.27mol) and silver trifluoroacetate (71.57g, 0.32mol) in dichloromethane and the mixture was stirred at room temperature for 18 hours. The mixture was filtered through celite, washed with aqueous sodium thiosulfate (5%, 2x2 l), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/ethyl acetate, to give the title compound as a colorless oil (108.03g), containing 11% unreacted 2-benzyloxy-5-(trifluoromethoxy)iodobenzene. ¹H NMR (360MHz, CDCl₃) δ 7.67 (1H, d, *J*=2.8 Hz), 7.40 (5H, m), 7.16 (1H, dd, *J*=8.9, 2.8 Hz), 6.82 (1H, d, *J*=8.9 Hz), and 5.14 (2H, s).

PREPARATION 14

(5*R*,6*S*)-3-(2-Benzyloxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]dec-3-ene

(5*R*,6*S*)-3-Trimethylstannyl-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]dec-3-ene (Preparation 6; 6.43mmol), lithium chloride (0.163g), benzyloxy-5-(trifluoromethoxy)phenol (Preparation 9; 7.7mmol) in toluene (25ml) was degassed before addition of triphenylphosphine palladium (0) (0.37g). The solution was degassed thoroughly before heating to 110°C for 14 hours. The solution was partitioned between water and ethyl acetate and the dried organic phase was purified by chromatography on a column containing silica gel (eluting with hexane containing increasing proportions of ethyl acetate between 0% to 4%) to give the title compound. ¹H NMR (360MHz, CDCl₃) δ 1.33 (9H, s), 1.65 (1H, m), 1.76 (2H, m), 2.08 (1H, m), 3.11 (1H, m), 4.08 (1H, m), 4.60 (1H, dd, *J*=12.2 Hz, *J*=2 Hz), 4.92 (1H, dd, *J*=12.1 Hz, *J*=1.8 Hz), 5.08

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(1H, s), 5.1 (2H, q, $J=11.5$ Hz), 6.65 (1H, s), 6.94 (2H, d, $J=8.9$ Hz), 7.08 (1H, d, $J=9$ Hz), 7.18 (2H, t, $J=8.1$ Hz), 7.25 (3H, m), 7.38 (5H, m).

PREPARATION 15

5 (3*S*,5*R*,6*S*)-3-(2-Hydroxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane

(5*R*,6*S*)-3-(2-Benzyloxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]dec-3-ene (Preparation 14) (3.88g) was dissolved in ethyl acetate (15ml) and methanol (15ml). Palladium
10 hydroxide on carbon (1.00g) was added and the suspension was shaken under a hydrogen atmosphere (50 psi) for 72 hours. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was purified by medium pressure chromatography on silica gel, eluting with hexane/ethyl acetate (75:25) to give (3*R*,5*R*,6*S*)-3-(2-hydroxy-
15 5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (191mg), ^1H NMR (250MHz, CDCl_3) δ 7.70 (2H, d, $J=7.3$ Hz), 7.33 (2H, t, $J=7.3$ Hz), 7.26 (1H, d, $J=7.3$ Hz), 7.05 (1H, br s), 6.96 (2H, m), 6.82 (1H, d, $J=9.4$ Hz), 5.43 (1H, s), 4.27 (1H, m), 4.01 (1H, m), 3.95 (1H, m), 3.73 (1H, m), 2.73 (2H, m), 2.33 (1H, m), 1.87-1.58 (4H, m);
20 and 1.50 (9H, s).and (3*S*,5*R*,6*S*)-3-(2-hydroxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (2.3g), ^1H NMR (360MHz, CDCl_3) δ 1.38 (9H, s), 1.73 (2H, m), 1.81 (1H, m), 2.18 (2H, m), 2.50 (1H, m), 2.81 (1H, m), 3.62 (1H, t, $J=7.2$ Hz), 3.92 (1H, m), 3.98 (1H, d, $J=13.2$ Hz), 4.23 (1H, m), 5.33 (1H, s), 6.75 (1H, d, $J=8.5$ Hz), 6.94 (2H, m), 7.25 (1H, m), 7.31 (2H, m), and 7.55 (2H, d, $J=7.8$ Hz).
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PREPARATION 16

(3*R*,5*R*,6*S*)-3-(2-Benzyloxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane

30 A mixture of 2-benzyloxy-5-(trifluoromethoxy)iodobenzene (Preparation 13, 21.8g, 55.2mmol), (5*R*,6*S*)-6-phenyl-1-oxa-7-(*tert*-

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butoxycarbonyl)aza-spiro[4.5]dec-3-ene (Preparation 11, 7.0g, 22.1mmol), tetra-*n*-butylammonium chloride (6.18g, 22.2mmol), lithium chloride (9.35g, 0.22mol) and potassium formate (5.64g, 67.0mmol) in dimethylformamide (100ml) was degassed with a firestone valve (5 x).

5 Palladium acetate (491mg, 2.2mmol) was added and the mixture was degassed with a firestone valve (5 x). The mixture was stirred at 60°C for 15 hours, then further 2-benzyloxy-5-(trifluoromethoxy)iodobenzene (Preparation 13, 4.32g, 11.0mmol), potassium formate (2.78g, 33.5mmol) and palladium acetate (260mg, 1.1mmol) were added. The mixture was

10 stirred at 60°C for 22 hours, cooled and filtered. The solvent was evaporated under reduced pressure, water (600ml) was added and the mixture was extracted with ethyl acetate (2x300ml). The combined organic fractions were washed with brine (300ml), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified

15 by flash column chromatography on silica gel, eluting with hexane/dichloromethane (75:25 increasing to 0:100) then dichloromethane/ethyl acetate (95:5), to give the title compound (9.42g, 73%). ¹H NMR (360MHz, CDCl₃) δ 7.56 (2H, d, *J*=7.7 Hz), 7.40-7.20 (8H, m), 7.14 (1H, d, *J*=2.0 Hz), 7.00 (1H, dd, *J*=8.9, 2.0 Hz), 6.88 (1H, d, *J*=8.9

20 Hz), 5.30 (1H, s), 5.08 (2H, s), 4.27 (1H, m), 3.97 (1H, m), 3.87 (2H, m), 2.78 (1H, m), 2.56 (1H, m), 2.15 (1H, m), 1.96 (1H, m), 1.67 (3H, m), and 1.42 (9H, s).

PREPARATION 17

25 (3*R*,5*R*,6*S*)-3-(2-Hydroxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane

Palladium on carbon (10%, 0.59g) was added to a solution of (3*R*,5*R*,6*S*)-3-(2-benzyloxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (Preparation 16, 6.10g,

30 10.5mmol) in methanol-water (99:1, 200ml) and the mixture was stirred under hydrogen (50 psi.) for 72 hours. The mixture was filtered, washing

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with ethanol, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with dichloromethane/ethyl acetate (99:1 increasing to 90:10) to give the title compound. ¹H NMR (360MHz, CDCl₃) δ 7.70 (2H, d, *J*=7.3 Hz), 7.33 (2H, t, *J*=7.3 Hz), 7.26 (1H, d, *J*=7.3 Hz), 7.05 (1H, br s), 6.96 (2H, m), 6.82 (1H, d, *J*=9.4 Hz), 5.43 (1H, s), 4.27 (1H, m), 4.01 (1H, m), 3.95 (1H, m), 3.73 (1H, m), 2.73 (2H, m), 2.33 (1H, m), 1.87-1.58 (4H, m), and 1.50 (9H, s).

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PREPARATION 18

(3*S*,5*R*,6*S*)-3-[2-(1-Phenylthiocycloprop-1-yl)oxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane

(3*S*,5*R*,6*S*)-3-(2-Hydroxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (Preparation 15) (290mg, 0.59mmol) was dissolved in toluene (5ml) and silver carbonate (179mg, 0.65mmol) was added in one portion. (1-Iodocycloprop-1-yl)phenylsulfide (Cohen T. and Matz J. R., *J. Am. Chem. Soc.* **1980**, *102*, 6902) (180mg, 0.65mmol) was then added over one minute at room temperature. The mixture was stirred at 55°C for 4 hours, then further portions of silver carbonate (179mg, 0.65mmol) and (1-iodocycloprop-1-yl)phenylsulfide (180mg, 0.65mmol) were added. The mixture was stirred at 55°C for a further 3 hours, cooled, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (90:10 increasing to 80:20) to give the title compound as a colourless oil (120mg, 32%). ¹H NMR (250MHz, CDCl₃) δ 7.55-7.44 (4H, m), 7.36-7.23 (7H, m), 7.13-7.02 (2H, m), 5.16 (1H, br s), 4.09 (1H, t, *J*=6 Hz), 4.03-3.92 (1H, m), 3.67-3.49 (2H, m), 2.94-2.79 (1H, m), 2.26 (1H, dd, *J*=7.9, 12.9 Hz), 2.15-2.01 (2H, m), 1.76-1.59 (3H, m), 1.53-1.45 (4H, m), and 1.36 (9H, s). *m/z* (ES⁺) 642 (M+1).

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PREPARATION 19

(3*R*,5*R*,6*S*)-3-[2-(1-Phenylthiocycloprop-1-yl)oxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane

- 5 Prepared from (3*R*,5*R*,6*S*)-3-(2-hydroxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (Preparation 17) according to the method of Preparation 18. ¹H NMR (360MHz, CDCl₃) δ 7.57 (2H, app. d, *J*=7.6 Hz), 7.45 (2H, app. d, *J*=7.7 Hz), 7.36-7.19 (7H, m), 7.16-7.06 (2H, m), 5.28 (1H, br s), 4.13 (1H, app. t, *J*=7.8 Hz), 3.96 (1H, br. d, *J*=13 Hz), 3.80-3.60 (2H, m), 2.79 (1H, br. t, *J*=13 Hz), 2.50 (1H, dd, *J*=13, 7.9 Hz), 2.17 (1H, dt, *J*=13, 4.6 Hz), 1.80 (1H, dd, *J*=12, 9.8 Hz), 1.75-1.38 (7H, m), and 1.44 (9H, s). *m/z* (ES⁺) 642 (M+1).

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PREPARATION 20

(3*S*,5*R*,6*S*)-3-[2-Cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane

- Naphthalene (120mg, 0.936mmol) was dissolved in THF (1.5ml) under nitrogen and freshly cut lithium metal (7.0mg, 0.94mmol) was added. The mixture was then sonicated at room temperature for 20 minutes to produce a dark green solution of lithium naphthalenide. This solution was cooled to -78 °C, then (3*S*,5*R*,6*S*)-3-[2-(1-phenylthiocycloprop-1-yl)oxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (Preparation 18) (120mg, 0.187mmol) in THF (0.5ml) was added over 1 minute. The reaction mixture was stirred for 30 minutes, then water (5ml) and ether (10ml) were added. The layers were separated and the aqueous layer was extracted with ether (10ml). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (90:10 increasing to 80:20) to give the title compound as a colourless oil

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(58.6mg, 59%). ¹H NMR (250MHz, CDCl₃) δ 7.58-7.52 (2H, m), 7.36-7.17 (4H, m), 7.10-7.01 (2H, m), 5.18 (1H, br s), 4.20 (1H, t, *J*=6.7 Hz), 4.05-3.95 (1H, m), 3.76-3.55 (3H, m), 2.92-2.79 (1H, m), 2.37 (1H, dd, *J*=12.9, 7.8 Hz), 2.18-2.06 (2H, m), 1.80-1.67 (3H, m), 1.38 (9H, s), and 0.86-0.73 (4H, m). *m/z* (ES⁺) 534 (M+1).

PREPARATION 21

(3*R*,5*R*,6*S*)-3-[2-Cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane

10 Naphthalene (120mg, 0.936mmol) was dissolved in THF (1.5ml) under nitrogen and freshly cut lithium metal (7.0mg, 0.94mmol) was added. The mixture was then sonicated at room temperature for 20 minutes to produce a dark green solution of lithium naphthalenide. A solution of (3*R*,5*R*,6*S*)-3-[2-(1-phenylthiocycloprop-1-yl)oxy-5-

15 (trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (Preparation 19, 135mg, 0.21mmol) in THF (2ml) under nitrogen was cooled to -78°C and the solution of lithium naphthalenide in THF was added dropwise until the intense green colour persisted. The reaction was then stirred for one minute, water (5ml) was added and the

20 mixture was warmed to room temperature. Ether (10ml) was added and the layers were separated. The aqueous phase was extracted with a further portion of ether (10ml) and the combined organic phases were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting

25 with hexane/ethyl acetate (50:50) to give the title compound as a colourless oil (87mg, 78%). ¹H NMR (360MHz, CDCl₃) δ 7.59 (2H, app. d, *J*=7.6 Hz), 7.32 (2H, app. t, *J*=7.6 Hz), 7.27-7.18 (2H, m), 7.11-7.03 (2H, m), 5.32 (1H, br s), 4.29-4.21 (1H, m), 3.97 (1H, br. d, *J*=13 Hz), 3.83-3.68 (3H, m), 2.76 (1H, dt, *J*=13, 4.1 Hz), 2.55 (1H, dd, *J*=13, 7.2 Hz), 2.22 (1H, dt, *J*=12, 5.2

30 Hz), 1.85 (1H, dd, *J*=13, 9.9 Hz), 1.80-1.63 (3H, m), 1.46 (9H, s), and 0.82-0.76 (4H, m). *m/z* (ES⁺) 534 (M+1).

COMPOUND A

(3S,5R,6S)-3-[2-Cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane Hydrochloride

5 Trifluoroacetic acid (2.5ml) was added dropwise to a stirred, cooled 0°C) solution of (3S,5R,6S)-3-[2-cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-(*tert*-butoxycarbonyl)aza-spiro[4.5]decane (Preparation 20; 492mg, 0.92mmol) in dichloromethane (25ml) and the mixture was stirred at room temperature for 3 hours. The mixture was poured into
10 water (50ml), the pH was adjusted to 10.0 with aqueous sodium hydroxide (4M) and the mixture was extracted with dichloromethane (3x50ml). The combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with
15 dichloromethane/methanol/ammonia (aq.) (96:4:0.4 increasing to 94:6:0.6). The residue was dissolved in ethanol (20ml), cooled in ice and ethereal hydrogen chloride (1M, 1.8ml, 1.8mmol) was added dropwise. The mixture was stirred at 0°C for 5 minutes, then the solvent was evaporated under reduced pressure. The residue was crystallized from ether (20ml)/ethanol
20 (0.5ml) and the solid was collected and dried *in vacuo* to give the title compound as a colorless solid (354mg, 89%). m.p. 214-216 °C, ¹H NMR (500MHz, CD₃OD) δ 7.59 (2H, m), 7.52 (3H, m), 7.26 (1H, d, *J*=8.9 Hz), 7.03 (1H, dd, *J*=8.9, 2.2 Hz), 6.20 (1H, d, *J*=2.2 Hz), 4.85 (2H, br s), 4.43 (1H, s), 4.19 (1H, t, *J*=8.0 Hz), 3.87 (1H, quin, *J*=8.0 Hz), 3.76 (1H, m),
25 3.44 (1H, m), 3.25 (2H, m) 2.29-1.78 (6H, m), 0.80 (2H, m), and 0.66 (2H, m). m/z (ES⁺) 434 (M+1). Found: C, 61.41; H, 5.51; N, 3.08. C₂₄H₂₆F₃NO₃.HCl requires: C, 61.34; H, 5.79; N, 2.98%.

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COMPOUND B

(3R,5R,6S)-3-[2-Cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane

Prepared from the compound of Preparation 21 according to the method used for Compound A. ¹H NMR (360MHz, CDCl₃) δ 7.50-7.42 (2H, m), 7.36-7.26 (3H, m), 7.03 (1H, d, *J*=8.9 Hz), 6.95 (1H, br. d, *J*=8.9 Hz), 6.81 (1H, br s), 3.92 (1H, t, *J*=7.4 Hz), 3.62-3.53 (2H, m), 3.50 (1H, s), 3.20 (1H, dd, *J*=12, 4.2 Hz), 2.77 (1H, dt, *J*=12, 2.8 Hz), 2.30-1.93 (4H, m), 1.87 (1H, br s), 1.71-1.49 (3H, m), 0.76-0.65 (2H, m), and 0.65-0.54 (2H, m). *m/z* (ES⁺) 434 (M+1).

A further compound and diastereomers thereof of use in the present invention may be prepared according to the following method:

DESCRIPTION 1

2-(1-Phenylthiocycloprop-1-yl)oxy-5-(trifluoromethoxy)benzaldehyde

Silver carbonate (1.2 g, 4.34 mmol) was added to a solution of 2-hydroxy-5-(trifluoromethoxy)benzaldehyde (0.5 g, 2.43 mmol) and (1-iodocycloprop-1-yl)phenylsulfide (Cohen T. and Matz J. R., *J. Am. Chem. Soc.* 1980, 102, 6902) (1.2 g, 4.34 mmol) in toluene (30 mL) and the mixture was stirred at 40 °C overnight. The mixture was cooled, diluted with ethyl acetate and filtered, washing well with ethyl acetate. The mixture was washed with aqueous sodium hydroxide, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/Et₂O (95:5), to give the title compound as a yellow oil (191 mg, 27%). ¹H NMR (360MHz, CDCl₃) δ 1.51-1.56 (2H, m), 1.44-1.48 (2H, m), 7.25-7.35 (7H, m), 7.69 (1H, d, *J* 2.0 Hz), and 10.26 (1H, s).

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DESCRIPTION 2**2-Cyclopropoxy-5-(trifluoromethoxy)benzaldehyde**

Freshly cut lithium metal (97 mg, 13.9 mmol) was added to a solution of naphthalene (1.77 g, 13.9 mmol) in THF (20 mL) and the mixture was sonicated at room temperature for 30 min. to produce a dark green solution of lithium naphthalenide. A solution of 2-(1-phenylthiocycloprop-1-yl)oxy-5-(trifluoromethoxy)benzaldehyde (Description 1, 96 mg, 0.27 mmol) in THF (2 mL) was cooled to -78 °C and the solution of lithium naphthalenide in THF (2 mL) was added dropwise until the intense green colour persisted. The reaction was then stirred for 5 min., water (6 mL) was added and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate, the combined organic fractions were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/Et₂O (80:20), to give to give the title compound as a colourless oil (4 mg, 6%). ¹H NMR (360MHz, CDCl₃) δ 0.86 (4H, m), 3.82-3.9 (1H, m), 7.42 (2H, m), 7.62 (1H, d, *J* 2.5 Hz), and 10.36 (1H, s).

20

DESCRIPTION 3**2-Nitro-4-(trifluoromethoxy)phenol**

Iron(III)nitrate nonahydrate (1.97 g, 4.87 mmol) was added to a solution of 4-(trifluoromethoxy)phenol (2 g, 11.24 mmol) in ethanol (20 mL) and the mixture was heated under reflux overnight. The mixture was allowed to cool to room temperature, acidified to pH 1 with aqueous hydrochloric acid (1M) and extracted with ethyl acetate. The combined organic fractions were dried (MgSO₄), and the solvent was evaporated under reduced pressure. The residue was purified by short column chromatography on silica gel, eluting with hexane/EtOAc (70:30), to give the title compound as a yellow oil (2.25 g, 89%). ¹H NMR (360MHz, CDCl₃)

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δ 10.53 (1H, s), 8.01 (1H, d, J 3.0 Hz), 7.49 (1H, dd, J 9.1, 3.0 Hz), and 7.23 (1H, d, J 9.1 Hz).

DESCRIPTION 45 **2-(1-Phenylthiocycloprop-1-yl)oxy-5-(trifluoromethoxy)nitrobenzene**

Prepared from the compound of Description 3 according to the method of Description 1. ^1H NMR (360MHz, CDCl_3) δ 7.73 (1H, d, J 2.7 Hz), 7.58 (1H, d, J 9.2 Hz), 7.50-7.24 (6H, m), 1.57-1.53 (2H, m), and 1.44-1.40 (2H, m).

10

DESCRIPTION 5**2-Cyclopropoxy-5-(trifluoromethoxy)benzeneamine**

Prepared from the compound of Description 4 according to the method of Description 2. ^1H NMR (360MHz, CDCl_3) δ 7.06 (1H, dd, J 2.8, 6.7 Hz), 6.56 (2H, m), 3.83 (2H, br s), 3.74 (1H, m), and 0.79 (4H, m). m/z (ES $^+$) 234 (M+1).

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DESCRIPTION 6**2-(1-Phenylthiocycloprop-1-yl)oxy-5-(trifluoromethoxy)benzeneamine**

20 Iron powder (13.5 g, 241 mmol) was added to a suspension of 2-(1-phenylthiocycloprop-1-yl)oxy-5-(trifluoromethoxy)nitrobenzene (Description 4, 11.27 g, 30.1 mmol) in water (300 mL) and acetic acid (75 mL) and the mixture was stirred at 80 °C overnight. The mixture was cooled and filtered through celite, washing with ether. The filtrate was
25 extracted with ether, the combined organic fractions were washed with aqueous sodium hydroxide (1M), dried (MgSO_4), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/ Et_2O (90:10 increasing to 80:20), to give the title compound as a yellow solid (8 g, 78%).
30 ^1H NMR (360MHz, CDCl_3) δ 7.48 (2H, m), 7.34-7.23 (3H, m), 7.15 (1H, d, J

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8.74 Hz), 6.60-6.56 (2H, m), 3.78 (2H, br s), 1.49-1.46 (2H, m), and 1.39-1.35 (2H, m).

DESCRIPTION 7

5 2-Cyclopropoxy-5-(trifluoromethoxy)benzeneamine

Prepared from the compound of Description 6 according to the method of Description 2. ¹H NMR (360MHz, CDCl₃) δ 7.06 (1H, dd, *J* 2.8, 6.7 Hz), 6.56 (2H, m), 3.83 (2H, br s), 3.74 (1H, m), and 0.79 (4H, m). *m/z* (ES⁺) 234 (M+1).

10

DESCRIPTION 8

2-Cyclopropoxy-5-(trifluoromethoxy)iodobenzene

An ice-cooled solution of sodium nitrite (3.55 g, 51 mmol) in water (10 mL) was added dropwise to a stirred, cooled (0 °C) solution of

15 2-cyclopropoxy-5-(trifluoromethoxy)benzeneamine (Description 7, 4.8 g, 20.6 mmol) in aqueous hydrochloric acid (5M, 300 mL), maintaining the internal temperature at 0 °C. The mixture was stirred at 0 °C for 30 min., then potassium iodide (8.55 g, 51.5 mmol) in water (10 mL) was added dropwise, maintaining the internal temperature at 0 °C. The mixture was

20 stirred at 0 °C for 30 min., then allowed to warm up to room temperature and stirred until nitrogen evolution ceased. The mixture was extracted with ether, the organic fraction was washed with aqueous sodium thiosulfate (10%), dried (MgSO₄), and the solvent was evaporated under reduced pressure. The residue was purified by flash column

25 chromatography on silica gel, eluting with hexane/Et₂O (98:2 increasing to 95:5), to give the title compound as a colourless oil (6.23 g, 88%). ¹H NMR (360MHz, CDCl₃) δ 7.62 (1H, d, *J* 2.4 Hz), 7.20 (1H, dd, *J* 9.1, 2.4 Hz), 7.15 (1H, d, *J* 9.1 Hz), 3.80 (1H, m), and 0.83 (4H, m).

DESCRIPTION 9**2-Cyclopropoxy-5-(trifluoromethoxy)benzaldehyde**

A solution of 2-cyclopropoxy-5-(trifluoromethoxy)iodobenzene (Description 8, 0.344 g, 1 mmol) in toluene (2.5 mL) was degassed with
5 bubbling nitrogen for 10 min. Tetrakis(triphenylphosphine)palladium (0) (15 mg) was added, the mixture was degassed with bubbling nitrogen for a further 5 min., then carbon monoxide was bubbled through the mixture for 10 min. The mixture was warmed to 50 °C and a solution of tributyl tin hydride (0.3 mL, 1.1 mmol) in toluene (5 mL) was added at a rate of 2
10 mL/h. *via* a syringe pump, maintaining carbon monoxide bubbling throughout. The mixture was cooled, diluted with ether (20 mL) and aqueous potassium fluoride solution (50%) was added. The mixture was stirred at room temperature overnight, filtered and the layers were separated. The organic layer was dried (MgSO₄), and the solvent was
15 evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/Et₂O (80:20), to give the title compound as a colourless oil. ¹H NMR (360MHz, CDCl₃) δ 0.86 (4H, m), 3.82-3.9 (1H, m), 7.42 (2H, m), 7.62 (1H, d, *J* 2.5 Hz), and 10.36 (1H, s).

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DESCRIPTION 10**(±)-(2*RS*)-1-*tert*-Butoxycarbonyl-2-phenylpiperidin-3-one**

Dimethyl sulfoxide (32.0 mL, 35.3 g, 0.45 mol) in dichloromethane (100 mL) was added dropwise to a cooled (-70 °C) solution of oxalyl
25 chloride (18.7 mL, 27.5 g, 0.22 mol) in dichloromethane (1000 mL). The mixture was stirred at -70 °C for 15 min., then (2*S*,3*S*)-1-*tert*-butoxycarbonyl-3-hydroxy-2-phenylpiperidine (prepared by the method described in European Patent Specification number 0 528 495-A; 50 g, 0.18 mol) in dichloromethane (150 mL) was added dropwise.
30 The mixture was stirred at -70 °C for 1 h., then triethylamine (125.8 mL, 91.3 g, 0.9 mol) was added slowly. The mixture was stirred at room

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temperature for 1 h., water (250 mL) and aqueous sodium hydrogen carbonate (saturated, 250 mL) were added and the mixture was stirred at room temperature overnight. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 300 mL). The combined
5 organic fractions were washed with brine, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (90:10), to give the title compound as a yellow oil (45.0 g, 91%). ¹H NMR (250MHz, CDCl₃) δ 7.5-7.3 (5H, m), 5.8 (1H, br s), 4.2 (1H, br s), 3.4 (1H, m), 2.6 (2H,
10 m), 2.0 (2H, m), and 1.54 (9H, s).

DESCRIPTION 11(±)-(2R3R,2S3S)-1-(tert-Butoxycarbonyl)-2-phenylpiperidin-3-amine

A solution of hydroxylamine hydrochloride (17 g, 0.24 mol) and
15 sodium acetate (55.67 g, 0.41 mol) in water (150 mL) was added to a solution of (±)-(2RS)-1-tert-butoxycarbonyl-2-phenylpiperidin-3-one (Description 10, 45 g, 0.16 mol) in ethanol (300 mL) and the mixture was stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure, water was added and the mixture was extracted with
20 ethyl acetate. The organic fraction was washed with brine, dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethanol (400 mL) and Raney nickel (50 g) was added. The mixture was shaken under hydrogen (40 psi) overnight, filtered and the solvent was evaporated under reduced pressure. The residue was purified
25 by flash column chromatography on silica gel, eluting with CH₂Cl₂/MeOH (100:0 increasing to 85:15), to give the title compound as a colorless oil (10.9 g, 24%). ¹H NMR (360MHz, CDCl₃) δ 7.43 (2H, d, *J* 7.0 Hz), 7.30 (3H, m), 5.19 (1H, d, *J* 6.2 Hz), 4.00 (1H, m), 3.17 (2H, m), 1.90-1.64 (4H, m), 1.36 (9H, s), and 1.26 (2H, br s).

33

COMPOUND C

(±)-(2R3R,2S3S)-N-[[2-Cyclopropoxy-5-(trifluoromethoxy)phenyl]methyl]-2-phenylpiperidin-3-amine Dihydrochloride

2-Cyclopropoxy-5-(trifluoromethoxy)benzaldehyde (Description 9, 55
5 mg, 0.21 mmol) was added to (±)-(2R3R,2S3S)-1-(*tert*-butoxycarbonyl)-2-phenylpiperidin-3-amine (Description 11, 58 mg, 0.21 mmol), citric acid (89 mg, 0.42 mmol) and 3Å molecular sieves in dry methanol (5 mL) and the mixture was stirred at room temperature for 1.5 h. Sodium
10 borohydride (30 mg) was added and the mixture was stirred at room temperature for 2 h. Ethyl acetate was added and the mixture was washed with aqueous hydrochloric acid (0.1M, 2 x 25 mL) and brine (25 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (3 mL), cooled to 0 °C and trifluoroacetic acid (2 mL) was added slowly. The mixture was stirred at
15 room temperature for 1 h., the solvent was evaporated under reduced pressure and ethyl acetate was added. The mixture was washed with aqueous sodium hydrogen carbonate (saturated, 2 x 25 mL) and brine (25 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on
20 silica gel, eluting with CH₂Cl₂/MeOH/NH₃(Aq.) (96:4:0.4). The residue was dissolved in ethanol (2 mL), cooled in ice and ethereal hydrogen chloride (1M, 0.24 mL, 0.24 mmol) was added. The solvent was evaporated under reduced pressure and the residue was recrystallised from ethanol to give the title compound as a colorless solid (20 mg, 20%). m.p. 169-171 °C. ¹H
25 NMR (400MHz, CD₃OD) δ 0.64 (1H, m), 0.80 (3H, m), 1.99 (1H, m), 2.24 (1H, m), 2.46 (2H, m), 3.30 (1H, m), 3.64 (1H, m), 3.75 (2H, m), 3.96 (1H, br s), 4.08 (1H, m), 4.95 (1H, s), 7.23 (1H, s), 7.31 (1H, d, *J* 9.0 Hz), 7.37 (1H, d, *J* 9.0 Hz), 7.54 (3H, m), and 7.67 (2H, m). m/z (ES⁺) 407 (M+1).

30 Particularly preferred NK-1 receptor antagonists of use in the present invention are compounds which are potent NK-1 receptor

antagonists, i.e. compounds with an NK-1 receptor affinity (IC_{50}) of less than 10nM, favourably less than 2nM and preferably less than 1nM.

The class of orally active, long acting, CNS-penetrant NK-1 receptor antagonists of use in the present invention is identified using a

5 combination of the following assays:

ASSAY 1: NK-1 Receptor binding

NK-1 receptor binding assays are performed in intact Chinese hamster ovary (CHO) cells expressing the human NK-1 receptor using a
10 modification of the assay conditions described by Cascieri *et al*, *J. Pharmacol. Exp. Ther.*, 1992, 42, 458. Typically, the receptor is expressed at a level of 3×10^5 receptors per cell. Cells are grown in monolayer culture, detached from the plate with enzyme-free dissociation solution (Speciality Media Inc.), and washed prior to use in the assay. ^{125}I -Tyr⁸-
15 substance P (0.1nM, 2000Ci/mmol; New England Nuclear) is incubated in the presence or absence of test compounds (dissolved in 5 μ l dimethylsulphoxide, DMSO) with 5×10^4 CHO cells. Ligand binding is performed in 0.25ml of 50mM Tris-HCl, pH7.5, containing 5mM $MnCl_2$, 150mM NaCl, 0.02% bovine serum albumin (Sigma), 50 μ g/ml chymostatin
20 (Peninsula), 0.1nM phenylmethanesulphonyl fluoride, 2 μ g/ml pepstatin, 2 μ g/ml leupeptin and 2.8 μ g/ml furoyl saccharine. The incubation proceeds at room temperature until equilibrium is achieved (>40 minutes) and the receptor-ligand complex is harvested by filtration over GF/C filters pre-soaked in 0.1% polyethylenimine using a Tomtek 96-well harvester. Non-
25 specific binding is determined using excess substance P (1 μ M) and represents <10% of total binding.

ASSAY 2: Gerbil Foot-Tapping

CNS-penetrant NK-1 receptor antagonists for use in the present
30 invention can be identified by their ability to inhibit foot tapping in gerbils induced by anxiogenic agents (such as pentagastrin) or central infusion of

35

NK-1 receptor agonists such as GR73632, or caused by aversive stimulation such as foot shock or single housing, based on the method of Rupniak & Williams, *Eur. J. Pharmacol.*, 1994, 265, 179.

Male or female Mongolian gerbils (35-70g) are anaesthetised by
5 inhalation of an isoflurane/oxygen mixture to permit exposure of the
jugular vein in order to permit administration of test compounds or vehicle
in an injection volume of 5ml/kg i.v. Alternatively, test compounds may be
administered orally or by subcutaneous or intraperitoneal routes. A skin
incision is then made in the midline of the scalp to expose the skull. An
10 anxiogenic agent (e.g. pentagastrin) or a selective NK-1 receptor agonist
(e.g. GR73632 (d Ala[L-Pro⁹,Me-Leu¹⁰]-substance P-(7-11)) is infused
directly into the cerebral ventricles (e.g. 3pmol in 5µl i.c.v., depending on
test substance) by vertical insertion of a cuffed 27 gauge needle to a depth
of 4.5mm below bregma. The scalp incision is closed and the animal
15 allowed to recover from anaesthesia in a clear perspex observation box
(25cm x 20cm x 20cm). The duration and/or intensity of hind foot tapping
is then recorded continuously for approximately 5 minutes. Alternatively,
the ability of test compounds to inhibit foot tapping evoked by aversive
stimulation, such as foot shock or single housing, may be studied using a
20 similar method of quantification.

ASSAY 3: Ferret Emesis

Individually housed male ferrets (1.0 -2.5 kg) are dosed orally by
gavage with test compound. Ten minutes later they are fed with
25 approximately 100g of tinned cat food. At 60 minutes following oral
dosing, cisplatin (10mg/kg) is given i.v. *via* a jugular vein catheter
inserted under a brief period of halothane anaesthesia. The catheter is
then removed, the jugular vein ligated and the skin incision closed. The
ferrets recover rapidly from the anaesthetic and are mobile within 10-20
30 minutes. The animals are observed continuously during recovery from the
anaesthetic and for 4 hours following the cisplatin injection, after which

time the animals are killed humanely. The numbers of retches and vomits occurring during the 4 hours after cisplatin administration are recorded by trained observers.

5 ASSAY 4: Separation-Induced Vocalisation

Male and female guinea-pigs pups are housed in family groups with their mothers and littermates throughout the study. Experiments are commenced after weaning when the pups are 2 weeks old. Before entering an experiment, the pups are screened to ensure that a vigorous
10 vocalisation response is reproducibly elicited following maternal separation. The pups are placed individually in an observation cage (55cm x 39cm x 19cm) in a room physically isolated from the home cage for 15 minutes and the duration of vocalisation during this baseline period is recorded. Only animals which vocalise for longer than 5 minutes are
15 employed for drug challenge studies (approximately 50% of available pups may fail to reach this criterion). On test days each pup receives an oral dose or an s.c. or i.p. injection of test compound or vehicle and is then immediately returned to the home cage with its mother and siblings for 30 to 60 minutes (or for up to 4 hours following an oral dose, dependent upon
20 the oral pharmacokinetics of the test compound) before social isolation for 15 minutes as described above. The duration of vocalisation on drug treatment days is expressed as a percentage of the pre-treatment baseline value for each animal. The same subjects are retested once weekly for up to 6 weeks. Between 6 and 8 animals receive each test compound at each
25 dose tested.

As used herein, the term "CNS-penetrant" refers to NK-1 receptor antagonists which are able to inhibit NK-1 receptor antagonist-induced foot-tapping in the gerbil as hereinafter defined.

Essentially, hind foot-tapping in the gerbil induced by infusion of
30 the NK-1 receptor agonist, GR73632 (d Ala[L-Pro⁹,Me-Leu¹⁰]-substance P-(7-11)), under anaesthesia, directly into the central ventricles is inhibited

when a CNS-penetrant NK-1 receptor antagonist is administered intravenously immediately prior to GR73632 challenge, wherein hind foot-tapping over a period of five minutes following recovery from the anaesthesia is inhibited with an $ID_{50} \leq 3\text{mg/kg}$, and preferably with an

5 $ID_{50} \leq 1\text{mg/kg}$.

In an alternative method, the NK-1 receptor antagonist is administered orally, 1 hour prior to GR73632 challenge, wherein the foot-tapping over a period of five minutes following recovery from anaesthesia is inhibited with an $ID_{50} \leq 30\text{mg/kg}$, and preferably with an $ID_{50} \leq 10\text{mg/kg}$.

10 CNS-penetrant NK-1 receptor antagonists of use in the present invention are also effective in the attenuation of separation-induced vocalisations by guinea-pig pups as hereinafter defined.

Essentially, a vocalisation response in guinea-pig pups is induced by isolation from their mothers and littermates, which response is attenuated

15 when a CNS-penetrant NK-1 receptor antagonist is administered subcutaneously 30 minutes prior to isolation, wherein vocalisations during the first 15 minutes of isolation are attenuated with an $ID_{50} \leq 20\text{mg/kg}$, preferably with an $ID_{50} \leq 10\text{mg/kg}$, and especially with an $ID_{50} \leq 5\text{mg/kg}$.

In an alternative method, the NK-1 receptor antagonist is

20 administered orally, 4 hours prior to isolation, wherein vocalisations during the first 15 minutes of isolation are attenuated with an $ID_{50} \leq 20\text{mg/kg}$, preferably with an $ID_{50} \leq 10\text{mg/kg}$, and especially with an $ID_{50} \leq 5\text{mg/kg}$.

A suitable selection cascade for NK₁ antagonists of use according to

25 the present invention is as follows:

(i) Determine affinity for human NK₁ receptor in radioligand binding studies (Assay 1); select compounds with $IC_{50} \leq 10\text{nM}$, preferably $IC_{50} \leq 2\text{nM}$, especially $IC_{50} \leq 1\text{nM}$.

(ii) Determine ability of compounds to penetrate CNS by their

30 ability to inhibit foot tapping in gerbils induced by central injection of an NK₁ agonist (Assay 2); select compounds that inhibit foot tapping with

30

$ID_{50} \leq 3\text{mg/kg i.v.}$, and preferably $ID_{50} \leq 1\text{mg/kg i.v.}$ when administered immediately prior to central NK_1 agonist challenge, or $ID_{50} \leq 30\text{mg/kg p.o.}$, and preferably $ID_{50} \leq 10\text{mg/kg p.o.}$ 1 hour prior to challenge.

(iii) Determine central duration of action of compounds in gerbil foot tapping assay following intravenous administration 24 hours prior to central NK_1 agonist challenge; select compounds showing ≤ 25 -fold loss of potency compared with ID_{50} determined in step (ii) above with the proviso that $ID_{50} \leq 10\text{mg/kg i.v.}$, and preferably $\leq 5\text{mg/kg i.v.}$ after 24 hour pre-treatment.

(iv) Determine oral bioavailability of compounds by pharmacokinetic analysis, activity in gerbil foot tapping assay following oral administration and/or by ability to inhibit cisplatin-induced emesis in ferrets (Assay 3); select compounds with $ID_{90} \leq 3\text{mg/kg p.o.}$, and preferably $ID_{90} \leq 1\text{mg/kg p.o.}$

Particularly preferred compounds of use in the present invention are identified using steps (i) to (iv) followed by step (v):

(v) Determine activity of compounds in assays sensitive to conventional antipsychotic drugs (inhibition of distress vocalisations in guinea-pig pups (Assay 4)). Select compounds with $ID_{50} \leq 20\text{mg/kg}$, and preferably $ID_{50} \leq 10\text{mg/kg}$.

Yet further preferred compounds of use in the present invention may be selected from those compounds which satisfy the NK_1 receptor binding criteria of step (i) which, in addition, have ≤ 5 -fold shift in affinity when incubated in the presence of human serum albumin (HSA) to show non-specific protein binding.

One example of a NK_1 receptor antagonist of use in the present invention is the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)-ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-morpholine, the preparation of which is described in International Patent Specification No. WO 95/16679. In the aforementioned assays, this compound has the following activity:

human NK-1 receptor binding:	IC ₅₀ =0.1nM
gerbil foot-tapping (5 mins.):	ID ₅₀ =0.36mg/kg i.v.
gerbil foot-tapping (24 hrs.):	ID ₅₀ =0.33mg/kg i.v.
ferret emesis:	ID ₉₀ <3mg/kg p.o.
guinea-pig vocalisation (4 hr. pre-treatment):	ID ₅₀ =0.73mg/kg p.o.

The following example illustrates pharmaceutical compositions
5 according to the invention.

EXAMPLE 1 Tablets containing 50-300mg of NK-1 antagonist

	<u>Amount mg</u>		
NK-1 antagonist	50.0	100.0	300.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	189.5	139.5	139.5
Magnesium Stearate	0.5	0.5	0.5

The active ingredient, cellulose, lactose and a portion of the corn
10 starch are mixed and granulated with 10% corn starch paste. The
resulting granulation is sieved, dried and blended with the remainder of
the corn starch and the magnesium stearate. The resulting granulation is
then compressed into tablets containing 50mg, 100mg and 300mg of the
NK-1 receptor antagonist per tablet.

40

CLAIMS

1. Use of an orally active, long acting, CNS-penetrant NK-1 receptor
5 antagonist for the manufacture of a medicament adapted for oral
administration for the treatment or prevention of bipolar disorder without
concomitant therapy with other antidepressant or anti-anxiety agents.
2. Use of an orally active, long acting, CNS-penetrant NK-1 receptor
10 antagonist for the manufacture of a medicament adapted for oral
administration for the treatment or prevention of bipolar disorder without
concomitant therapy with other antidepressant or anti-anxiety agents, in a
patient who is non-responsive to lithium or for whom lithium is
contraindicated.
- 15 3. Use of an orally active, long acting, CNS-penetrant NK-1 receptor
antagonist for the manufacture of a medicament adapted for oral
administration for the treatment or prevention of bipolar disorder without
concomitant therapy with other antidepressant or anti-anxiety agents, in a
20 patient who is non-responsive to heterocyclic antidepressants, SSRIs,
mixed serotonin and norepinephrine reuptake inhibitors, dopamine
reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants,
SSRIs, mixed serotonin and norepinephrine reuptake inhibitors, dopamine
reuptake inhibitors or MAOIs are contraindicated.
- 25 4. An oral pharmaceutical composition for the treatment of bipolar
disorder which comprises essentially an orally active, long acting, CNS-
penetrant NK-1 receptor antagonist, together with a pharmaceutically
acceptable carrier or excipient.

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5. A method for the treatment or prevention of bipolar disorder without concomitant therapy with other anti-depressant or anti-anxiety agents, which method comprises the oral administration to a patient in need of such treatment of an effective amount of an orally active, long
5 acting, CNS-penetrant NK-1 receptor antagonist.

6. A method for the treatment or prevention of bipolar disorder without concomitant therapy with other anti-depressant or anti-anxiety agents, in a patient who is non-responsive to lithium or for whom lithium
10 is contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist.

7. A method for the treatment or prevention of bipolar disorder
15 without concomitant therapy with other anti-depressant or anti-anxiety agents, in a patient who is non-responsive to heterocyclic antidepressants, SSRIs, mixed serotonin and norepinephrine reuptake inhibitors, dopamine reuptake inhibitors or MAOIs, or for whom heterocyclic antidepressants, SSRIs, mixed serotonin and norepinephrine reuptake inhibitors, dopamine
20 reuptake inhibitors or MAOIs are contraindicated, which method comprises oral administration to the patient in need of such treatment of an effective amount of an orally active, long acting, CNS-penetrant NK-1 receptor antagonist.

25 8. A use according to claim 1, 2 or 3, or a composition according to claim 4 or a method according to claim 5, 6 or 7 wherein the orally active, long acting, CNS-penetrant NK-1 antagonist is selected from the classes of compounds described in EP-A-0577394, WO-A-9508549, WO-A-9518124, WO-A-9523798, WO-A-9605181 and International Patent Application No.
30 PCT/GB97/01630.

9. A use according to claim 1, 2 or 3, or a composition according to claim 4 or a method according to claim 5, 6 or 7 wherein the orally active, long acting, CNS-penetrant NK-1 antagonist is:

- 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine;
- 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)-3-(S)-phenyl-morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(2-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxyphosphoryl-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-N,N-dimethylaminobut-2-yn-yl)-3-(S)-(4-fluorophenyl)morpholine;
- (3S,5R,6S)-3-[2-cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;

(3R,5R,6S)-3-[2-cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;

(±)-(2*R*3*R*,2*S*3*S*)-N-[[2-cyclopropoxy-5-(trifluoromethoxy)phenyl]methyl]-2-phenylpiperidin-3-amine;

5 or a pharmaceutically acceptable salt thereof.

10. A use according to claim 1, 2 or 3, or a composition according to claim 4 or a method according to claim 5, 6 or 7 wherein the bipolar disorder is bipolar I disorder, bipolar II disorder, cyclothymic disorder or
10 bipolar disorder not otherwise specified.