CNS-PENETRANT NK-1 RECEPTOR ANTAGONISTS AS ANTIDEPRESSANT AND/OR AN ANTI-ANXIETY AGENT

The present invention relates to the treatment or prevention of depression and/or anxiety by the administration of a combination of a specific class of NK-1 receptor antagonists and an antidepressant or anti-anxiety agent. The present invention also provides preclinical screens for anxiolytic and antidepressant activity of NK-1 receptor antagonists.
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CNS–PENETRANT NK–1 RECEPTOR ANTAGONISTS AS ANTIDEPRESSANT AND/OR AN ANTI–ANXIETY AGENT

This invention relates to the treatment or prevention of depression and/or anxiety by the administration of a combination of a specific class of NK-1 receptor antagonists and an antidepressant or anti-anxiety agent. The present invention also provides preclinical screens for anxiolytic and antidepressant activity of NK-1 receptor antagonists.

Major depression is characterised by feelings of intense sadness and despair, mental slowing and loss of concentration, pessimistic worry, agitation, and self-deprecation. Physical changes also occur, especially in severe or "melancholic" depression. These include insomnia or hypersomnia, anorexia and weight loss (or sometimes overeating), decreased energy and libido, and disruption of normal circadian rhythms of activity, body temperature, and many endocrine functions.

Treatment regimens commonly include the use of tricyclic antidepressants, monoamine oxidase inhibitors, some psychotropic drugs, lithium carbonate, and electroconvulsive therapy (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-HT1A receptor agonists, antagonists and partial agonists.

Anxiety is an emotional condition characterised by feelings such as apprehension and fear accompanied by physical symptoms such as tachycardia, increased respiration, sweating and tremor. It is a normal emotion but when it is severe and disabling it becomes pathological.

Anxiety disorders are generally treated using benzodiazepine sedative-antianxiety agents. Potent benzodiazepines are effective in panic disorder as well as in generalised anxiety disorder, however, the risks
associated with drug dependency may limit their long-term use. 5-HT\textsubscript{1A}
receptor partial agonists also have useful anxiolytic and other psychotropic
activity, and less likelihood of sedation and dependance (see R. J.
Baldessarini in Goodman & Gilman's *The Pharmacological Basis of

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 such conditions 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).

It might therefore be desirable to investigate the treatment of
depression and/or anxiety using a combination of a tachykinin antagonist
and an antidepressant and/or an anti-anxiety agent. Indeed, such a
desideratum has already been considered in International (PCT) patent
specification No. WO 96/24353 (published 15th August 1996) which claims
methods for the treatment of psychiatric disorders using a combination of
a tachykinin antagonist and a serotonin agonist or selective serotonin
reuptake inhibitor. However, the disclosure of WO 96/24353 does not
provide any teaching as to whether the claimed combination has any
efficacy and in particular there is no direction towards specific
combinations which might potentiate the antidepressant or anxiolytic
effects of the individual therapeutic agents. There is no clear direction
from WO 96/24353 to which class of tachykinin antagonist (e.g. NK-1,
NK-2 or NK-3 receptor antagonists) would be of use in the claimed
combinations, nor how a person of ordinary skill in the art might identify
suitable compounds for use in combination with a serotonin agonist or a
selective serotonin reuptake inhibitor. Furthermore, there is no teaching
which would enable a person of ordinary skill in the art to identify those
compounds with sustained activity following oral administration for use in
the claimed combinations. At best, WO 96/24353 merely recites in one
document that which was already recognised in the art, namely that
tachykinin antagonists might be of use in the treatment of psychiatric
disorders and that serotonin agonists and selective serotonin reuptake
inhibitors are effective in the treatment of psychiatric disorders.

There therefore remains a need for an effective combination of an
antidepressant and/or an anti-anxiety agent with a NK-1 receptor
antagonist, which combination provides an unexpected and advantageous
antidepressant or anxiolytic effect. Such combinations may for example
provide an enhanced antidepressant or anxiolytic effect. They may also
provide for a rapid onset of action to combat depression and/or anxiety
thereby enabling prescription on an “as-needed” basis.

CNS-penetrant NK-1 receptor antagonists have been found to
provide an unexpected effect relevant to the treatment and prevention of
depression and/or anxiety when used in combination with an
antidepressant or anti-anxiety agent. While not being bound to any
particular theory of operation, an enhanced effect at treating or
preventing a psychological stress response in an animal assay is observed
with the combination of drugs than would be expected from either drug
alone. In particular, combination therapy of a CNS-penetrant NK-1
receptor antagonist selected from the compounds of formulae (I), (II), (III),
(IV) and (V), and a selective serotonin reuptake inhibitor or a 5-HT1A
receptor agonist or antagonist effectively inhibits separation-induced
vocalisations in guinea-pig pups. This is indicative of efficacy in the
treatment of depression and/or anxiety. Such unexpected results would
not have been predicted based on the disclosures in the art.

The present invention accordingly provides the use of a CNS-
penetrant NK-1 receptor antagonist and an antidepressant or anti-anxiety
agent for the manufacture of a medicament for the treatment or
prevention of depression and/or anxiety.
The present invention also provides a method for the treatment or prevention of depression and/or anxiety, which method comprises administration to a patient in need of such treatment an amount of a CNS-penetrant NK-1 receptor antagonist and an amount of an antidepressant or anti-anxiety agent, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a CNS-penetrant NK-1 receptor antagonist and an antidepressant or anti-anxiety agent, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the CNS-penetrant NK-1 receptor antagonist and antidepressant or anti-anxiety agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of depression and/or anxiety. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a CNS-penetrant NK-1 receptor antagonist and an antidepressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of depression and/or anxiety.

It will be appreciated that when using a combination of the present invention, both the CNS-penetrant NK-1 receptor antagonist and the antidepressant or anti-anxiety agent will be administered to a patient, within a reasonable period of time. The compounds may be in the same pharmaceutically acceptable carrier and therefore administered simultaneously. They may be in separate pharmaceutical carriers such as conventional oral dosage forms which are taken simultaneously. The term "combination" also refers to the case where the compounds are provided in separate dosage forms and are administered sequentially. Therefore, by way of example, the antidepressant or anti-anxiety agent may be administered as a tablet and then, within a reasonable period of time, the
CNS-penetrant NK-1 receptor antagonist may be administered either as an oral dosage form such as a tablet or a fast-dissolving oral dosage form. By a “fast dissolving oral formulation” is meant, an oral delivery form which when placed on the tongue of a patient, dissolves within about 10 seconds.

By “reasonable period of time” is meant a time period that is not in excess of about 1 hour. That is, for example, if the antidepressant or anti-anxiety agent is provided as a tablet, then within one hour, the CNS-penetrant NK-1 receptor antagonist should be administered, either in the same type of dosage form, or another dosage form which provides effective delivery of the medicament.

The compositions of the present invention are useful for the treatment of depression. As used herein, the term “depression” includes depressive disorders, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, anxiety and phobias; seasonal affective disorder; or bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder.

Other mood disorders encompassed within the term “depression” include dysthyemic disorder with early or late onset and with or without atypical features; dementia of the Alzheimer’s type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood.

The compositions of the present invention are useful for the treatment of anxiety. As used herein, the term “anxiety” includes anxiety
disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders.

"Generalised anxiety" is typically defined as an extended period (e.g. at least six months) of excessive anxiety or worry with symptoms on most days of that period. The anxiety and worry is difficult to control and may be accompanied by restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disturbed sleep.

"Panic disorder" is defined as the presence of recurrent panic attacks followed by at least one month of persistent concern about having another panic attack. A "panic attack" is a discrete period in which there is a sudden onset of intense apprehension, fearfulness or terror. During a panic attack, the individual may experience a variety of symptoms including palpitations, sweating, trembling, shortness of breath, chest pain, nausea and dizziness. Panic disorder may occur with or without agoraphobia.

"Phobias" includes agoraphobia, specific phobias and social phobias.

"Agoraphobia" is characterised by an anxiety about being in places or situations from which escape might be difficult or embarrassing or in which help may not be available in the event of a panic attack. Agoraphobia may occur without history of a panic attack. A "specific phobia" is characterised by clinically significant anxiety provoked by exposure to a specific feared object or situation. Specific phobias include the following subtypes: animal type, cued by animals or insects; natural environment type, cued by objects in the natural environment, for example storms, heights or water; blood-injection-injury type, cued by the sight of blood or an injury or by seeing or receiving an injection or other invasive medical procedure; situational type, cued by a specific situation such as public transportation, tunnels, bridges, elevators, flying, driving or
enclosed spaces; and other type where fear is cued by other stimuli. Specific phobias may also be referred to as simple phobias. A "social phobia" is characterised by clinically significant anxiety provoked by exposure to certain types of social or performance circumstances. Social phobia may also be referred to as social anxiety disorder.

Other anxiety disorders encompassed within the term "anxiety" include anxiety disorders induced by alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, phencyclidine, sedatives, hypnotics, anxiolytics and other substances, and adjustment disorders with anxiety or with mixed anxiety and depression.

Anxiety may be present with or without other disorders such as depression in mixed anxiety and depressive disorders. The compositions of the present invention are therefore useful in the treatment of anxiety with or without accompanying depression.

The compositions of the present invention are especially useful for the treatment of or prevention of depression and/or anxiety where the use of an antidepressant or anti-anxiety agent is generally prescribed. By the use of a combination of a CNS-penetrant NK-1 receptor antagonist and an antidepressant or anti-anxiety agent in accordance with the present invention, it is now also possible to treat or prevent depression and/or anxiety in patients for whom conventional antidepressant or anti-anxiety therapy might not be wholly successful or where dependance upon the antidepressant or anti-anxiety therapy is prevalent.

Suitable classes of antidepressant agent of use in the present invention include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical antidepressants.
Another class of antidepressant agent of use in the present invention are noradrenergic and specific serotonergic antidepressants (NaSSAs). A suitable example of a NaSSA is mirtazapine.

Suitable norepinephrine reuptake inhibitors of use in the present invention include tertiary amine tricyclics and secondary amine tricyclics. Suitable examples of tertiary amine tricyclics include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine, and pharmaceutically acceptable salts thereof. Suitable examples of secondary amine tricyclics include: amoxapine, desipramine, maprotiline, nortriptyline and protriptyline, and pharmaceutically acceptable salts thereof.

Another norepinephrine reuptake inhibitor of use in the present invention is reboxetine.

Suitable selective serotonin reuptake inhibitors of use in the present invention include: fluoxetine, fluvoxamine, paroxetine and sertraline, and pharmaceutically acceptable salts thereof.

Suitable monoamine oxidase inhibitors of use in the present invention include: isocarboxazid, phenelzine, tranylcypromine and selegiline, and pharmaceutically acceptable salts thereof.

Suitable reversible inhibitors of monoamine oxidase of use in the present invention include: moclobemide, and pharmaceutically acceptable salts thereof.

Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include: venlafaxine, and pharmaceutically acceptable salts thereof.


Suitable atypical antidepressants of use in the present invention include: bupropion, lithium, nefazodone, trazodone and viloxazine, and
pharmacologically acceptable salts thereof. Another suitable atypical antidepressant is sibutramine.

Other antidepressants of use in the present invention include adinazolam, alaprocate, amineptine, amitriptyline/chlordiazepoxide combination, atipamezole, azamianserin, bazinaprine, befuraline, bifemelane, binodaline, bipenamol, brofaromine buproprion, caroxazone, cericlamine, cianopramine, cimoxatone, citalopram, clemeprol, clovoxamine, dazepinil, deanol, demexiptiline, dibenzepin, dothiepin, droxidopa, enefexine, estazolam, etoperidone, femoxetine, fengabine, fezolamine, fluotracen, idazoxan, indalpine, indeloxazine, iprindole, levoprotileine, litoxetine, lofepramine, medifoxamine, metapramine, metralindole, mianserin, milnacipran, minaprine, mirtazapine, montirelin, nebracetam, nefopam, nialamide, nomifensine, norfluoxetine, orotirelin, oxaflozane, pinazepam, pirlindone, pizotyline, ritanserin, rolipram, sercloremine, setiptilene, sibutramine, sulbutiamine, sulpiride, teniloxazine, thozalinone, thymoliberin, tianeptine, tiflucarbine, tofenacin, tofisopam, toloxatone, tomoxetine, veralipride, viqualine, zimelidine and zometapine, and pharmaceutically acceptable salts thereof, and St. John's wort herb, or Hypericum perforatum, or extracts thereof.

Suitable classes of anti-anxiety agent of use in the present invention include benzodiazepines and 5-HT₁A agonists or antagonists, especially 5-HT₁A partial agonists, and corticotropin releasing factor (CRF) antagonists. In addition to benzodiazepines, other suitable classes of anti-anxiety agent are nonbenzodiazepine sedative-hypnotic drugs such as zolpidem; mood-stabilizing drugs such as clobazam, gabapentin, lamotrigine, loreclezole, oxcarbamaepine, stiripentol and vigabatrin; and barbiturates.

Suitable benzodiazepines of use in the present invention include: alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam, and pharmaceutically acceptable salts thereof.
Suitable 5-HT₁A receptor agonists or antagonists of use in the present invention include, in particular, the 5-HT₁A receptor partial agonists buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof. An example of a compound with 5-HT₁A receptor antagonist/partial agonist activity is pindolol.


Another class of anti-anxiety agent of use in the present invention are compounds having muscarinic cholinergic activity. Suitable compounds in this class include m1 muscarinic cholinergic receptor agonists such as those compounds described in European Patent Specification Nos. 0 709 093, 0 709 094 and 0 773 021, and International patent Specification No. WO 96/12711.

Another class of anti-anxiety agent of use in the present invention are compounds acting on ion channels. Suitable compounds in this class include carbamazepine, lamotrigine and valproate, and pharmaceutically acceptable salts thereof.

Particularly preferred CNS-penetrant NK-1 receptor antagonists are those described in European Patent Specification No. 0 577 394, i.e. compounds of formula (I):

![Chemical structure](image)

(I)

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from the group consisting of:
(1) hydrogen;

(2) C_{1-6}alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C_{1-6}alkoxy,
(d) phenyl-C_{1-3}alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -NR^9R^{10}, wherein R^9 and R^{10} are independently selected from:

(i) hydrogen,
(ii) C_{1-6}alkyl,
(iii) hydroxy-C_{1-6}alkyl, and
(iv) phenyl,
(i) -NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,
(j) -NR^9CO_2R^{10}, wherein R^9 and R^{10} are as defined above,
(k) -CONR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(l) -COR^9, wherein R^9 is as defined above,
(m) -CO_2R^9, wherein R^9 is as defined above,
(n) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,
(B) benzofuranyl,
(C) benzthiophenyl,
(D) benzoazolyl,
(E) furanyl,
(F) imidazolyl,
(G) indolyl,
(H) isoxazolyl,
(I) isothiazolyl,
(J) oxadiazolyl,
(K) oxazolyl,
(L) pyrazinyl,
(M) pyrazolyl,
(N) pyridyl,
(O) pyrimidyl,
(P) pyrrolyl,
(Q) quinolyl,
(R) tetrazolyl,
(S) thiadiazolyl,
(T) thiazolyl,
(U) thienyl,
(V) triazolyl,
(W) azetidinyl,
(X) 1,4-dioxanyl,
(Y) hexahydroazepinyl,
(Z) oxanyl,
(AA) piperazinyl,
(AB) piperidinyl,
(AC) pyrrolidinyl,
(AD) tetrahydrofuranyl, and
(AE) tetrahydrothienyl,
and wherein the heterocycle is unsubstituted or substituted with one or
more substituent(s) selected from:

(i) \( C_{1-6} \)alkyl, unsubstituted or substituted with halo, -CF\(_3\),
-OCH\(_3\), or phenyl,
(ii) \( C_{1-6} \)alkoxy,
(iii) oxo,
(iv) hydroxy,
(v) thioxo,
(vi) \(-\text{SR}^9\), wherein \(\text{R}^9\) is as defined above,
(vii) halo,
(viii) cyano,
(ix) phenyl,
(x) trifluoromethyl,
(xi) \(-(\text{CH}_2)_m\text{-NR}^9\text{R}^{10}\), wherein \(m\) is 0, 1 or 2, and \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(xii) \(-\text{NR}^9\text{COR}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(xiii) \(-\text{CONR}^9\text{R}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(xiv) \(-\text{CO}_2\text{R}^9\), wherein \(\text{R}^9\) is as defined above, and
(xv) \(-(\text{CH}_2)_m\text{-OR}^9\), wherein \(m\) and \(\text{R}^9\) are as defined above;
(3) \(\text{C}_2\text{-alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:}\)
(a) hydroxy,
(b) oxo,
(c) \(\text{C}_1\text{-alkoxy,}\)
(d) phenyl-\(\text{C}_1\text{-alkoxy}\),
(e) phenyl,
(f) \(-\text{CN}\),
(g) halo,
(h) \(-\text{CONR}^9\text{R}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(i) \(-\text{COR}^9\), wherein \(\text{R}^9\) is as defined above,
(j) \(-\text{CO}_2\text{R}^9\), wherein \(\text{R}^9\) is as defined above,
(k) heterocycle, wherein the heterocycle is as defined above;
(4) \(\text{C}_2\text{-alkynyl;}\)
(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) \(\text{C}_1\text{-alkoxy,}\)
(c) \(\text{C}_1\text{-alkyl,}\)
(d) \( \text{C}_{2.5}\text{alkenyl} \),
(e) halo,
(f) -CN,
(g) -NO\(_2\),
(h) -CF\(_3\),
(i) -(CH\(_2\))\(_m\)-NR\(^9\)R\(^{10}\), wherein m, R\(^9\) and R\(^{10}\) are as defined above,
(j) -NR\(^9\)COR\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(k) -NR\(^9\)CO\(_2\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(l) -CONR\(^9\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(m) -CO\(_2\)NR\(^9\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(n) -COR\(^9\), wherein R\(^9\) is as defined above,
(o) -CO\(_2\)R\(^9\), wherein R\(^9\) is as defined above;

15 R\(^2\) and R\(^3\) are independently selected from the group consisting of:

(1) hydrogen;

(2) C\(_1\)-\(\text{alkyl} \), unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C\(_1\)-\(\text{alkoxy} \),
(d) phenyl-C\(_1\)-\(\text{alkoxy} \),
(e) phenyl,
(f) -CN,

20

(g) halo,
(h) -NR\(^9\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are independently selected from:

(i) -NR\(^9\)COR\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(j) -NR\(^9\)CO\(_2\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,

30

(k) -CONR\(^9\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(l) -COR\(^9\), wherein R\(^9\) is as defined above, and
(m) -CO₂R⁹, wherein R⁹ is as defined above;

(3) C₂₅alkenyln, unsubstituted or substituted with one or more of the substituent(s) selected from:
   (a) hydroxy,
   (b) oxo,
   (c) C₁₆alkoxy,
   (d) phenyl-C₁₃alkoxy,
   (e) phenyl,
   (f) -CN,
   (g) halo,
   (h) -CONR⁹R¹⁰ wherein R⁹ and R¹⁰ are as defined above,
   (i) -COR⁹, wherein R⁹ is as defined above,
   (j) -CO₂R⁹, wherein R⁹ is as defined above;

(4) C₂₅alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
   (a) hydroxy,
   (b) C₁₆alkoxy,
   (c) C₁₆alkyl,
   (d) C₂₅alkenyln,
   (e) halo,
   (f) -CN,
   (g) -NO₂,
   (h) -CF₃,
   (i) -(CH₂)ₘ-NR⁹R¹⁰ wherein m, R⁹ and R¹⁰ are as defined above,
   (j) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
   (k) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
   (l) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
   (m) -CO₂NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
   (n) -COR⁹, wherein R⁹ is as defined above,
(o) \(-\text{CO}_2\text{R}^9\), wherein \(\text{R}^9\) is as defined above;

and the groups \(\text{R}^1\) and \(\text{R}^2\) may be joined together to form a heterocyclic ring selected from the group consisting of:

5
(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
10
(f) oxazolyl, and
(g) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

15
(i) \(\text{C}_{1-6}\)alkyl,
(ii) oxo,
(iii) \(\text{C}_{1-6}\)alkoxy,
(iv) \(-\text{NR}^9\text{R}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(v) halo, and
(vi) trifluoromethyl;

20
and the groups \(\text{R}^2\) and \(\text{R}^3\) may be joined together to form a carbocyclic ring selected from the group consisting of:

25
(a) cyclopentyl,
(b) cyclohexyl,
(c) phenyl,

and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:

30
(i) \(\text{C}_{1-6}\)alkyl,
(ii) \(\text{C}_{1-6}\)alkoxy,
(iii) \(-\text{NR}^9\text{R}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(iv) halo, and
(v) trifluoromethyl;

and the groups $R^2$ and $R^3$ may be joined together to form a heterocyclic ring selected from the group consisting of:

5 (a) pyrrolidiny1,
   (b) piperidiny1,
   (c) pyrrolyl,
   (d) pyridiny1,
   (e) imidazoly1,
10 (f) furany1,
   (g) oxazoly1,
   (h) thieny1, and
   (i) thiazoly1,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) $C_{1-6}$alkyl,
   (ii) oxo,
   (iii) $C_{1-6}$alkoxy,
   (iv) $-NR^9R^{10}$, wherein $R^9$ and $R^{10}$ are as defined above,
20 (v) halo, and
   (vi) trifluoromethyl;

X is selected from the group consisting of:

(1) -O-,
25 (2) -S-,
   (3) -SO-, and
   (4) -SO$_2$-;

$R^4$ is selected from the group consisting of:

30 (1)
(2) \( Y \)-C\(_{1-8}\)-alkyl, wherein alkyl is unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C\(_{1-6}\)-alkoxy,
(d) phenyl-C\(_{1-3}\)-alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -NR\(^9\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(i) -NR\(^9\)COR\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(j) -NR\(^9\)CO\(_2\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(k) -CONR\(^9\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(l) -COR\(^9\), wherein R\(^9\) is as defined above,
(m) -CO\(_2\)R\(^9\), wherein R\(^9\) is as defined above;

(3) \( Y \)-C\(_{2-6}\)-alkenyl, wherein the alkenyl is unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,
(b) oxo,
(c) C\(_{1-6}\)-alkoxy,
(d) phenyl-C\(_{1-3}\)-alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -CONR\(^9\)R\(^{10}\), wherein R\(^9\) and R\(^{10}\) are as defined above,
(i) -COR\(^9\), wherein R\(^9\) is as defined above,
(j) -CO\(_2\)R\(^9\), wherein R\(^9\) is as defined above,
(4) -O(CO)-phenyl, wherein the phenyl is unsubstituted or substituted with one or more of R^6, R^7 and R^8;

R^5 is selected from the group consisting of:

(1) phenyl, unsubstituted or substituted with one or more of R^{11}, R^{12} and R^{13};

(2) C_{1-6}alkyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6}alkoxy,
(d) phenyl-C_{1-6}alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -NR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(i) -NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,
(j) -NR^9CO_2R^{10}, wherein R^9 and R^{10} are as defined above,
(k) -CONR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(l) -COR^9, wherein R^9 is as defined above,
(m) -CO_2R^9, wherein R^9 is as defined above;

(3) C_{2-6}alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
(a) hydroxy,
(b) oxo,
(c) C_{1-6}alkoxy,
(d) phenyl-C_{1-6}alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -CONR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(i) -COR\textsuperscript{9}, wherein R\textsuperscript{9} is as defined above,
(j) -CO\textsubscript{2}R\textsuperscript{9}, wherein R\textsuperscript{9} is as defined above;

(4) heterocycle, wherein the heterocycle is as defined above;

5 R\textsuperscript{6}, R\textsuperscript{7} and R\textsuperscript{8} are independently selected from the group consisting of:

(1) hydrogen;

(2) C\textsubscript{1-6}alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C\textsubscript{1-6}alkoxy,
(d) phenyl-C\textsubscript{1-3}alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -NR\textsuperscript{9}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,
(i) -NR\textsuperscript{9}COR\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,
(j) -NR\textsuperscript{9}CO\textsubscript{2}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,
(k) -CONR\textsuperscript{9}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,
(l) -COR\textsuperscript{9}, wherein R\textsuperscript{9} is as defined above, and
(m) -CO\textsubscript{2}R\textsuperscript{9}, wherein R\textsuperscript{9} is as defined above;

(3) C\textsubscript{2-6}alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,
(b) oxo,
(c) C\textsubscript{1-6}alkoxy,
(d) phenyl-C\textsubscript{1-3}alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -CONR\textsuperscript{9}R\textsuperscript{10} wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,
(i) -COR\textsuperscript{9} wherein R\textsuperscript{9} is as defined above,

(j) -CO\textsubscript{2}R\textsuperscript{9}, wherein R\textsuperscript{9} is as defined above;

(4) C\textsubscript{2,5}alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the

5 substituent(s) selected from:

(a) hydroxy,

(b) C\textsubscript{1,6}alkoxy,

(c) C\textsubscript{1,6}alkyl,

(d) C\textsubscript{2,5}alkenyl,

10 (e) halo,

(f) -CN,

(g) -NO\textsubscript{2},

(h) -CF\textsubscript{3},

(i) -(CH\textsubscript{2})\textsubscript{m}NR\textsuperscript{9}R\textsuperscript{10}, wherein m, R\textsuperscript{9} and R\textsuperscript{10} are as defined

15 above,

(j) -NR\textsuperscript{9}COR\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,

(k) -NR\textsuperscript{9}CO\textsubscript{2}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,

(l) -CONR\textsuperscript{9}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,

(m) -CO\textsubscript{2}NR\textsuperscript{9}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,

20 (n) -COR\textsuperscript{9}, wherein R\textsuperscript{9} is as defined above;

(o) -CO\textsubscript{2}R\textsuperscript{9}, wherein R\textsuperscript{9} is as defined above;

(6) halo,

(7) -CN,

(8) -CF\textsubscript{3},

25 (9) -NO\textsubscript{2},

(10) -SR\textsuperscript{14}, wherein R\textsuperscript{14} is hydrogen or C\textsubscript{1,5}alkyl,

(11) -SOR\textsuperscript{14}, wherein R\textsuperscript{14} is as defined above,

(12) -SO\textsubscript{2}R\textsuperscript{14}, wherein R\textsuperscript{14} is as defined above,

(13) NR\textsuperscript{9}COR\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,

30 (14) CONR\textsuperscript{9}COR\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,

(15) NR\textsuperscript{9}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,
(16) NR³CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(17) hydroxy,
(18) C₁₋₆alkoxy,
(19) COR⁹, wherein R⁹ is as defined above,
(20) CO₂R⁹, wherein R⁹ is as defined above,

R¹¹, R¹² and R¹³ are independently selected from the definitions of R⁶, R⁷ and R⁸, or -OX;

Y is selected from the group consisting of:

(1) a single bond,
(2) -O-,
(3) -S-,
(4) -CO-,
(5) -CH₂-,
(6) -CHR¹⁵-, and
(7) -CR¹⁵R¹⁶-, wherein R¹⁵ and R¹⁶ are independently selected from the group consisting of:

(a) C₁₋₆alkyl, unsubstituted or substituted with one or more of the substituents selected from:
(i) hydroxy,
(ii) oxo,
(iii) C₁₋₆alkoxy,
(iv) phenyl-C₁₋₆alkoxy,
(v) phenyl,
(vi) -CN,
(vii) halo,
(viii) -NR³R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(ix) -NR³COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(x) -NR³CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(xi) -CONR³R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(xii) \(-\text{COR}^9\), wherein \(R^9\) is as defined above, and
(xiii) \(-\text{CO}_2\text{R}^9\), wherein \(R^9\) is as defined above;
(b) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

- hydroxy,
- \(\text{C}_1-\text{alkoxy}\),
- \(\text{C}_1-\text{alkyl}\),
- \(\text{C}_2-\text{alkenyl}\),
- halo,
- \(-\text{CN}\),
- \(-\text{NO}_2\),
- \(-\text{CF}_3\),
- \(-(\text{CH}_2)_m-\text{NR}^9\text{R}^{10}\), wherein \(m\), \(R^9\) and \(R^{10}\) are as defined above,
- \(-\text{NR}^9\text{COR}^{10}\), wherein \(R^9\) and \(R^{10}\) are as defined above,
- \(-\text{NR}^9\text{CO}_2\text{R}^{10}\), wherein \(R^9\) and \(R^{10}\) are as defined above,
- \(-\text{CONR}^9\text{R}^{10}\), wherein \(R^9\) and \(R^{10}\) are as defined above,
- \(-\text{CO}_2\text{NR}^9\text{R}^{10}\), wherein \(R^9\) and \(R^{10}\) are as defined above,
- \(-\text{COR}^9\), wherein \(R^9\) is as defined above, and
- \(-\text{CO}_2\text{R}^9\), wherein \(R^9\) is as defined above;

\(Z\) is selected from:

- (1) hydrogen,
- (2) \(\text{C}_1-\text{alkyl}\), and
- (3) hydroxy, with the proviso that if \(Y\) is \(-\text{O}-\), \(Z\) is other than hydroxy, or if \(Y\) is \(-\text{CHR}^{15}\), then \(Z\) and \(R^{15}\) may be joined together to form a double bond.

Particularly preferred compounds of formula (1) are those wherein:

\(R^1\) is selected from the group consisting of:

- (1) \(\text{C}_1-\text{alkyl}\), substituted with one or more of the substituents selected from:
(a) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,
(B) imidazolyl,
(C) isoxazolyl,
(D) isothiazolyl,
(E) oxadiazolyl,
(F) pyrazinyl,
(G) pyrazolyl,
(H) pyridyl,
(I) pyrrolyl,
(J) tetrazolyl,
(K) thia Diazoly1,
(L) triazoly1, and
(M) piperidinyl,

and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C_{1-6}alkyl, unsubstituted or substituted with halo, -CF_3, -OCH_3, or phenyl,
(ii) C_{1-6}alkoxy,
(iii) oxo,
(iv) thioxo,
(v) cyano,
(vi) -SCH_3,
(vii) phenyl,
(viii) hydroxy,
(ix) trifluoromethyl,
(x) -(CH_2)_m-NR^9R^{10}, wherein m is 0, 1 or 2, and R^9 and R^{10}

are independently selected from:

(I) hydrogen,
(II) C_{1-6}alkyl,
(III) hydroxyC<sub>1-6</sub>alkyl, and
(IV) phenyl,
(xii) -NR<sup>9</sup>COR<sup>10</sup>, wherein R<sup>9</sup> and R<sup>10</sup> are as defined above, and
(xii) -CONR<sup>9</sup>R<sup>10</sup>, wherein R<sup>9</sup> and R<sup>10</sup> are as defined above,
R<sup>2</sup> and R<sup>3</sup> are independently selected from the group consisting of:
(1) hydrogen;
(2) C<sub>1-6</sub>alkyl
(3) C<sub>2-6</sub>alkenyl, and
(5) phenyl;
X is -O-;
R<sup>4</sup> is

![Diagram]

R<sup>5</sup> is phenyl, unsubstituted or substituted with halo;
R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of:
(1) hydrogen,
(2) C<sub>1-6</sub>alkyl,
(3) halo, and
(4) -CF<sub>3</sub>;
Y is -O-; and
Z is hydrogen or C<sub>1-4</sub>alkyl;
and pharmaceutically acceptable salts thereof.

A particularly preferred compound of formula (I) is 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; or a pharmaceutically acceptable salt thereof.
Further preferred CNS-penetrant NK-1 receptor antagonists are those described in International (PCT) Patent Specification No. WO 95/18124, i.e. compounds of formula (II):

or a pharmaceutically acceptable salt or prodrug thereof, wherein

- $R^1$ is hydrogen, halogen, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, CF$_3$, NO$_2$, CN, SR$_a$, SOR$_a$, SO$_2$R$_a$, CO$_2$R$_a$, CONR$_a$R$_b$, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl or C$_{1-4}$alkyl substituted by C$_{1-4}$alkoxy, where $R^a$ and $R^b$ each independently represent hydrogen or C$_{1-4}$alkyl;

- $R^2$ is hydrogen, halogen, C$_{1-6}$alkyl, C$_{1-6}$alkoxy substituted by C$_{1-4}$alkoxy or CF$_3$;

- $R^3$ is hydrogen, halogen or CF$_3$;

- $R^4$ is hydrogen, halogen, C$_{1-6}$alkyl, C$_{1-6}$alkoxy, CF$_3$, NO$_2$, CN, SR$_a$, SOR$_a$, SO$_2$R$_a$, CO$_2$R$_a$, CONR$_a$R$_b$, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl or C$_{1-4}$alkyl substituted by C$_{1-4}$alkoxy, where $R^a$ and $R^b$ each independently represent hydrogen or C$_{1-4}$alkyl;

- $R^5$ is hydrogen, halogen, C$_{1-4}$alkyl, C$_{1-6}$alkoxy substituted by C$_{1-4}$alkoxy or CF$_3$;

- $R^6$ is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C$_{1-4}$alkyl group, and optionally substituted by a group of the formula ZNR$_7$R$_8$ where $Z$ is C$_{1-6}$alkylene or C$_{3-6}$cycloalkylene;

- $R^7$ is hydrogen, C$_{1-4}$alkyl, C$_{3-7}$cycloalkyl or C$_{3-7}$cycloalkylC$_{1-4}$alkyl, or C$_{2-4}$alkyl substituted by C$_{1-4}$alkoxy or hydroxyl.
R^8 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by a hydroxy group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)_2 or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or R^7, R^8 and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R^{9a} and R^{9b} are each independently hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring;

X is an alkylene chain of 1 to 4 carbon atoms optionally substituted by oxo; and

Y is a C_{1-4}alkyl group optionally substituted by a hydroxyl group;

with the proviso that if Y is C_{1-4}alkyl, R^6 is substituted at least by a group of formula ZNR^7R^8 as defined above.

Particularly preferred compounds of formula (II) are those of formula (IIa) and pharmaceutically acceptable salts thereof:
wherein:

A\(^1\) is fluorine or CF\(_3\);
A\(^2\) is fluorine or CF\(_3\);

A\(^3\) is fluorine or hydrogen;

and X, Y and R\(^8\) are as defined in relation to formula (II).

Particularly preferred compounds of formula (II) include:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;

and pharmaceutically acceptable salts thereof.

Further preferred CNS-penetrant NK-1 receptor antagonists are those described in European Patent Specification No. WO 95/23798, i.e.

compounds of formula (III):

or a pharmaceutically acceptable salt thereof, wherein:
R² and R³ are independently selected from the group consisting of:

(1) hydrogen,

(2) C₁₋₆alkyl, unsubstituted or substituted with one or more of the substituents selected from:

5
(a) hydroxy,
(b) oxo,
(c) C₁₋₆alkoxy,
(d) phenyl-C₁₋₃alkoxy,
(e) phenyl,

10
(f) -CN,
(g) halo,
(h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently selected from:
   (I) hydrogen,
   (ii) C₁₋₆alkyl,
   (iii) hydroxy-C₁₋₆alkyl, and
   (iv) phenyl,
   (i) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
   (j) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
   (k) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
   (l) -COR⁹, wherein R⁹ is as defined above, and
   (m) -CO₂R³, wherein R³ is as defined above;

(3) C₂₋₆alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

25
(a) hydroxy,
(b) oxo,
(c) C₁₋₆alkoxy,
(d) phenyl-C₁₋₃alkoxy,
(e) phenyl,

30
(f) -CN,
(g) halo,
(h) \(-\text{CONR}^9\text{R}^{10}\) wherein \text{R}^9 and \text{R}^{10} are as defined above,

(i) \(-\text{COR}^9\) wherein \text{R}^9 is as defined above,

(j) \(-\text{CO}_2\text{R}^9\), wherein \text{R}^9 is as defined above;

(4) \text{C}_2.6\text{alkynyl};

(5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,

(b) \text{C}_1.6\text{alkoxy},

(c) \text{C}_1.6\text{alkyl},

(d) \text{C}_2.5\text{alkenyl},

(e) halo,

(f) \text{-CN},

(g) \text{-NO}_2,

(h) \text{-CF}_3,

(i) \(-(\text{CH}_2)_m\cdot\text{NR}^9\text{R}^{10}\), wherein \text{m}, \text{R}^9 and \text{R}^{10} are as defined above,

(j) \text{-NR}^9\text{COR}^{10}, wherein \text{R}^9 and \text{R}^{10} are as defined above,

(k) \text{-NR}^9\text{CO}_2\text{R}^{10}, wherein \text{R}^9 and \text{R}^{10} are as defined above,

(l) \text{-CONR}^9\text{R}^{10}, wherein \text{R}^9 and \text{R}^{10} are as defined above,

(m) \text{-CO}_2\text{NR}^9\text{R}^{10}, wherein \text{R}^9 and \text{R}^{10} are as defined above,

(n) \text{-COR}^9, wherein \text{R}^9 is as defined above,

(o) \text{-CO}_2\text{R}^9, wherein \text{R}^9 is as defined above;

and the groups \text{R}^2 and \text{R}^3 may be joined together to form a carbocyclic ring selected from the group consisting of:

(a) cyclopentyl,

(b) cyclohexyl,

(c) phenyl,

and wherein the carbocyclic ring is unsubstituted or substituted with one or more substituents selected from:

(i) \text{C}_1.6\text{alkyl},
(ii) C<sub>1</sub>-alkoxy,
(iii) -NR<sub>9</sub>R<sub>10</sub>, wherein R<sub>9</sub> and R<sub>10</sub> are as defined above,
(iv) halo, and
(v) trifluoromethyl;

and the groups R<sup>2</sup> and R<sup>3</sup> may be joined together to form a heterocyclic ring selected from the group consisting of:

(a) pyrrolidinyl,
(b) piperidinyl,
(c) pyrrolyl,
(d) pyridinyl,
(e) imidazolyl,
(f) furanyl,
(g) oxazolyl,
(h) thienyl, and
(i) thiazolyl,

and wherein the heterocyclic ring is unsubstituted or substituted with one or more substituent(s) selected from:

(i) C<sub>1</sub>-alkyl,
(ii) oxo,
(iii) C<sub>1</sub>-alkoxy,
(iv) -NR<sub>9</sub>R<sub>10</sub>, wherein R<sub>9</sub> and R<sub>10</sub> are as defined above,
(v) halo, and
(vi) trifluoromethyl;

R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are independently selected from the group consisting of:

(1) hydrogen;

(2) C<sub>1</sub>-alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C₆alkoxy,
(d) phenyl-C₆alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(i) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(j) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(k) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(l) -COR⁹, wherein R⁹ is as defined above, and
(m) -CO₂R⁹, wherein R⁹ is as defined above;

(3) C₆alkenyl, unsubstituted or substituted with one or more of the
substituent(s) selected from:
   (a) hydroxy,
   (b) oxo,
   (c) C₆alkoxy,
   (d) phenyl-C₆alkoxy,
   (e) phenyl,
   (f) -CN,
   (g) halo,
   (h) -CONR⁹R¹⁰ wherein R⁹ and R¹⁰ are as defined above,
   (i) -COR⁹ wherein R⁹ is as defined above,
   (j) -CO₂R⁹, wherein R⁹ is as defined above;

(4) C₆alkynyl;

(5) phenyl, unsubstituted or substituted with one or more of the
substituent(s) selected from:
   (a) hydroxy,
   (b) C₆alkoxy,
   (c) C₆alkyl,
   (d) C₆alkenyl,
   (e) halo,
(f) -CN,
(g) -NO₂,
(h) -CF₃,
(i) -(CH₂)ₘ-NR⁹R¹⁰, wherein m, R⁹ and R¹⁰ are as defined above,
(j) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(k) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(l) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(m) -CO₂NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(n) -COR⁹, wherein R⁹ is as defined above,
(o) -CO₂R⁹, wherein R⁹ is as defined above;
(6) halo,
(7) -CN,
(8) -CF₃,
(9) -NO₂,
(10) -SR₁⁴, wherein R₁⁴ is hydrogen or C₁-₅alkyl,
(11) -SOR₁⁴, wherein R₁⁴ is as defined above,
(12) -SO₂R₁⁴, wherein R₁⁴ is as defined above,
(13) NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(14) CONR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(15) NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(16) NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(17) hydroxy,
(18) C₁-₅alkoxy,
(19) COR⁹, wherein R⁹ is as defined above,
(20) CO₂R⁹, wherein R⁹ is as defined above,
(21) 2-pyridyl,
(22) 3-pyridyl,
(23) 4-pyridyl,
(24) 5-tetrazolyl,
(25) 2-oxazolyl, and
(26) 2-thiazoyl;

R^{11}, R^{12} and R^{13} are independently selected from the definitions of R^6, R^7 and R^8, or -OX;

A is selected from the group consisting of:

(1) C_{1-6}alkyl, unsubstituted or substituted with one or more of the substituents selected from:

(a) hydroxy,
(b) oxo,
(c) C_{1-6}alkoxy,
(d) phenyl-C_{1-3}alkoxy,
(e) phenyl,
(f) -CN,
(g) halo, wherein halo is fluoro, chloro, bromo or iodo,
(h) -NR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(i) -NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,
(j) -NR^9CO_2R^{10}, wherein R^9 and R^{10} are as defined above,
(k) -CONR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(l) -COR^9, wherein R^9 is as defined above, and
(m) -CO_2R^9, wherein R^9 is as defined above;

(2) C_{2-6}alkenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(a) hydroxy,
(b) oxo,
(c) C_{1-6}alkoxy,
(d) phenyl-C_{1-3}alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
(h) -CONR^9R^{10} wherein R^9 and R^{10} are as defined above,

(i) -COR^9 wherein R^9 is as defined above, and

(j) -CO_2R^9, wherein R^9 is as defined above; and

(3) C_2,6-alkynyl;

B is a heterocycle, wherein the heterocycle is selected from the group consisting of:

\[
\begin{align*}
\text{N-N} & \quad \text{N-N} & \quad \text{N-N} \\
\text{H} & \quad \text{X} & \quad \text{X} \\
\text{N} & \quad \text{O} & \quad \text{O} \\
\text{X} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{S} & \quad \text{S} \\
\text{X} & \quad \text{N} & \quad \text{N} \\
\text{X} & \quad \text{S} & \quad \text{S} \\
\text{X} & \quad \text{N} & \quad \text{N} \\
\text{X} & \quad \text{N} & \quad \text{N} \\
\text{X} & \quad \text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{X} & \quad \text{N} & \quad \text{N} \\
\text{X} & \quad \text{N} & \quad \text{N} \\
\text{X} & \quad \text{N} & \quad \text{N} \\
\end{align*}
\]
and wherein the heterocycle may be substituted in addition to -X with one or more substituent(s) selected from:

(i) $\text{C}_1-\text{alkyl}$, unsubstituted or substituted with halo, $-\text{CF}_3$,

5 $-\text{OCH}_3$, or phenyl,

(ii) $\text{C}_1-\text{alkoxy}$,

(iii) oxo,

(iv) hydroxy,

(v) thioxo,

10 (vi) $-\text{SR}^9$, wherein $R^9$ is as defined above,

(vii) halo,

(viii) cyano,

(ix) phenyl,

(x) trifluoromethyl,

15 (xi) $-(\text{CH}_2)_m-\text{NR}^9\text{R}^{10}$, wherein $m$ is 0, 1 or 2, and $R^9$ and $R^{10}$ are as defined above,
(xii) -NR^9COR^{10}, wherein R^9 and R^{10} are as defined above,
(xiii) -CONR^9R^{10}, wherein R^9 and R^{10} are as defined above,
(xiv) -CO_2R^9, wherein R^9 is as defined above, and
(xv) -(CH_2)_m-OR^9, wherein m and R^9 are as defined above;

p is 0 or 1;

X is selected from:

(a) -PO(OH)O^- \cdot M^+, wherein M^+ is a pharmaceutically
acceptable monovalent counterion,
(b) -PO(O^-)_2 \cdot 2M^+,
(c) -PO(O^-)_2 \cdot D^{2+}, wherein D^{2+} is a pharmaceutically acceptable
divalent counterion,
(d) -CH(R^4)-PO(OH)O^- \cdot M^+, wherein R^4 is hydrogen or C_1-3alkyl,
(e) -CH(R^4)-PO(O^-)_2 \cdot 2M^+,
(f) -CH(R^4)-PO(O^-)_2 \cdot D^{2+},
(g) -SO_3^- \cdot M^+,
(h) -CH(R^4)-SO_3^- \cdot M^+,
(i) -CO-CH_2CH_2-CO_2^- \cdot M^+,
(j) -CH(CH_3)-O-CO-R^5, wherein R^5 is selected from the group
consisting of:
(i) \[ \text{O} - \text{NH}_3^+ \text{M}^+ \],

(ii) \[ \text{O} - \text{N}_2^+ \text{M}^+ \],

(iii) \[ \text{O} - \text{CO}_2^- \text{M}^+ \],

(iv) \[ \text{O} - \text{CO}_2^- \text{M}^+ \],

(v) \[ \text{O} - \text{NH}_3^+ \text{CO}_2^- \],

(vi) \[ \text{O} - \text{CO}_2^+ \text{M}^+ \text{CO}_2^- \],

(vii) \[ \text{O} - \text{CO}_2^- \text{M}^+ \]; and

(k) hydrogen, with the proviso that if p is 0 and none of \( R_{11} \), \( R_{12} \) or \( R_{13} \) are -OX, then X is other than hydrogen;

5 Y is selected from the group consisting of:
   (1) a single bond,
   (2) -O-,
   (3) -S-,
   (4) -CO-,
(5) \(-\text{CH}_2\),

(6) \(-\text{CHR}^{15}\), and

(7) \(-\text{CR}^{15}\text{R}^{16}\), wherein \(\text{R}^{15}\) and \(\text{R}^{16}\) are independently selected from the group consisting of:

5  
(a) \(\text{C}_{1-6}\text{alkyl}\), unsubstituted or substituted with one or more of the substituents selected from:

(i) hydroxy,

(ii) oxo,

(iii) \(\text{C}_{1-6}\text{alkoxy}\),

(iv) phenyl-\(\text{C}_{1-3}\text{alkoxy}\),

(v) phenyl,

(vi) \(-\text{CN}\),

(vii) halo,

(viii) \(-\text{NR}^{9}\text{R}^{10}\), wherein \(\text{R}^{9}\) and \(\text{R}^{10}\) are as defined above,

(ix) \(-\text{NR}^{9}\text{COR}^{10}\), wherein \(\text{R}^{9}\) and \(\text{R}^{10}\) are as defined above,

(x) \(-\text{NR}^{9}\text{CO}_2\text{R}^{10}\), wherein \(\text{R}^{9}\) and \(\text{R}^{10}\) are as defined above,

(xi) \(-\text{CONR}^{9}\text{R}^{10}\), wherein \(\text{R}^{9}\) and \(\text{R}^{10}\) are as defined above,

(xii) \(-\text{COR}^{9}\), wherein \(\text{R}^{9}\) is as defined above, and

(xiii) \(-\text{CO}_2\text{R}^{9}\), wherein \(\text{R}^{9}\) is as defined above;

(b) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

(i) hydroxy,

(ii) \(\text{C}_{1-6}\text{alkoxy}\),

(iii) \(\text{C}_{1-6}\text{alkyl}\),

(iv) \(\text{C}_{2-5}\text{alkenyl}\),

(v) halo,

(vi) \(-\text{CN}\),

(vii) \(-\text{NO}_2\),

(viii) \(-\text{CF}_3\),

(ix) \(-\left(\text{CH}_2\right)_m\cdot\text{NR}^{9}\text{R}^{10}\), wherein \(m\), \(\text{R}^{9}\) and \(\text{R}^{10}\) are as defined above,
(x) \(-\text{NR}^9 \text{COR}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(xii) \(-\text{NR}^9 \text{CO}_2\text{R}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(xii) \(-\text{CONR}^9\text{R}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(xiii) \(-\text{CO}_2\text{NR}^9\text{R}^{10}\), wherein \(\text{R}^9\) and \(\text{R}^{10}\) are as defined above,
(xiv) \(-\text{COR}^9\), wherein \(\text{R}^9\) is as defined above, and
(xv) \(-\text{CO}_2\text{R}^9\), wherein \(\text{R}^9\) is as defined above;

\(Z\) is selected from:

(1) hydrogen,
(2) \(\text{C}_{1-6}\text{alkyl}\), and
(3) hydroxy, with the proviso that if \(Y\) is \(-\text{O}-\), \(Z\) is other than hydroxy, or if \(Y\) is \(-\text{CHR}^{15}\), then \(Z\) and \(\text{R}^{15}\) may be joined together to form a double bond.

Particularly preferred compounds of formula (III) are those wherein:

\(\text{R}^2\) and \(\text{R}^3\) are independently selected from the group consisting of:

(1) hydrogen,
(2) \(\text{C}_{1-6}\text{alkyl}\),
(3) \(\text{C}_{2-6}\text{alkenyl}\), and
(4) phenyl;

\(\text{R}^6\), \(\text{R}^7\) and \(\text{R}^8\) are independently selected from the group consisting of:

(1) hydrogen,
(2) \(\text{C}_{1-6}\text{alkyl}\),
(3) fluoro,
(4) chloro,
(5) bromo,
(6) iodo, and
(7) \(-\text{CF}_3\);
(4) iodo;

A is unsubstituted 1-alkyl;

B is selected from the group consisting of:

\[
\begin{align*}
\text{N-H} & \quad \text{N-H} & \quad \text{N-H} & \quad \text{N-H} \\
\text{N-O} & \quad \text{N-O} & \quad \text{N-O} & \quad \text{N-O} \\
\text{N-S} & \quad \text{N-S} & \quad \text{N-S} & \quad \text{N-S} \\
\text{N-N} & \quad \text{N-N} & \quad \text{N-N} & \quad \text{N-N} \\
\end{align*}
\]

\[
\begin{align*}
\text{N-O} & \quad \text{N-O} & \quad \text{N-O} & \quad \text{N-O} \\
\text{N-S} & \quad \text{N-S} & \quad \text{N-S} & \quad \text{N-S} \\
\text{N-N} & \quad \text{N-N} & \quad \text{N-N} & \quad \text{N-N} \\
\end{align*}
\]

p is 0 or 1;

X is selected from:

(a) \(-\text{PO(OH)}\text{O}^- \cdot \text{M}^+\), wherein \text{M}^+ is a pharmaceutically acceptable monovalent counterion,

(b) \(-\text{PO(O)}_2 \cdot 2\text{M}^+\),

(c) \(-\text{PO(O)}_2 \cdot \text{D}^{2+}\), wherein \text{D}^{2+} is a pharmaceutically acceptable divalent counterion,

(d) \(-\text{CH(R)}^+\text{PO(OH)}\text{O}^- \cdot \text{M}^+\), wherein \text{R}^+ is hydrogen or \text{C}_{1-3}\text{alkyl},
(e) \(-\text{CH}(R^\dagger)\cdot\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+\),

(f) \(-\text{CH}(R^\dagger)\cdot\text{PO}(\text{O}^-)_2 \cdot \text{D}^2+\),

(i) \(-\text{CO-CH}_2\text{CH}_2\text{-CO}_2^- \cdot \text{M}^+\),

(j) \(-\text{CH}(\text{CH}_3)_\cdot\text{O-\text{CO-R}}^\circ\), wherein \(R^\circ\) is selected from the group consisting of:

(i) \(\text{O} \quad \text{NH}_3^+ \quad \text{M}^-\)

(ii) \(\text{O} \quad \text{H}_2^+ \quad \text{M}^- \quad \text{OH}^-\)

(iii) \(\text{O} \quad \text{CO}_2^- \quad \text{M}^+\)

(iv) \(\text{O} \quad \text{CO}_2^- \quad \text{M}^+\)

(v) \(\text{O} \quad \text{CO}_2^- \quad \text{NH}_3^+\)

(vi) \(\text{O} \quad \text{CO}_2^- \quad \text{M}^+\)

(vii) \(\text{O} \quad \text{CO}_2^- \quad \text{M}^+\)

; and

\(Y\) is \(-\text{O}_\cdot\);  
\(Z\) is hydrogen or \(\text{C}_{1,6}\text{alkyl}\);  
and pharmaceutically acceptable salts thereof.
Particularly preferred compounds of formula (III) include:

(1) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine N-oxide;

(2) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(4-ethoxycarbonyloxy-1-ethyl)-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;

(3) 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;

(4) 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;

(5) 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;

(6) 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;

(7) 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;

and pharmaceutically acceptable salts thereof.

Further preferred CNS-penetrant NK-1 receptor antagonists are those described in European Patent Specification No. WO 96/05181, i.e. compounds of formula (IV):
wherein

X is a group of the formula NR^6R^7 or a C- or N-linked imidazolyl
5 ring;

Y is hydrogen or C_{1-4}alkyl optionally substituted by a hydroxy
group;

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a,
10 SOR^a, SO_2R^a, CO_2R^a, CONR^aR^b, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl
substituted by C_{1-4}alkoxy, wherein R^a and R^b each independently represent
hydrogen or C_{1-4}alkyl;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by
C_{1-4}alkoxy or CF_3;

R^3 is hydrogen, halogen or CF_3;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CF_3, NO_2,
15 CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, CONR^aR^b, C_{2-6}alkenyl, C_{2-6}alkynyl or
C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b are as previously
defined;

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by
20 C_{1-4}alkoxy or CF_3;

R^6 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl,
phenyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxy;

R^7 is hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl,
phenyl, or C_{2-4}alkyl substituted by one or two substituents selected from
C₁₄alkoxy, hydroxy or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a saturated or partially saturated heterocyclic ring of 4 to 7 ring atoms, which ring may optionally contain in the ring one oxygen or sulphur atom or a group selected from NR₈, S(O) or S(O)₂ and which ring may be optionally substituted by one or two groups selected from hydroxyC₁₄alkyl, C₁₄alkoxyC₁₄alkyl, oxo, COR³ or CO₂R³ where R³ is as previously defined;

or R⁶ and R⁷ together with the nitrogen atom to which they are attached, form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

R⁹ is hydrogen, C₁₄alkyl, hydroxyC₁₄alkyl or C₁₄alkoxyC₁₄alkyl;

and

R⁹ᵃ and R⁹ᵇ are each independently hydrogen or C₁₄alkyl, or R⁹ᵃ and R⁹ᵇ are joined so, together with the carbon atoms to which they are attached, there is formed a C₅₋₇ ring;

and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of formula (IV) are those of formula (IVA) and pharmaceutically acceptable salts thereof:

wherein

A¹ is fluorine or CF₃;
A² is fluorine or CF₃;
A³ is fluorine or hydrogen;
and X and Y are as defined in relation to formula (I).

Specific compounds of formula (IV) of use in the present invention include:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-morpholinobut-2-yn-yl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-N,N-dimethylaminobut-2-yn-yl)-3-(S)-(4-fluorophenyl)morpholine;
10 4-(4-azetidinylbut-2-yn-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;
4-(4-azetidinylbut-2-yn-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-imidazolylbut-2-yn-yl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-(N-methylpiperazinyl)but-2-yn-yl)morpholine;
15 4-(4-(2-methoxyethyl)aminobut-2-yn-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-pyrrolidinobut-2-yn-yl)morpholine;
20 3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)-4-(4-morpholinobut-2-yn-yl)morpholine;
3-(S)-(4-fluorophenyl)-4-(4-morpholinobut-2-yn-yl)-2-(R)-(1-(R)-(3-(trifluoromethyl)phenyl)ethoxy)morpholine;
4-(4-azetidinylbut-2-yn-yl)-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-(trifluoromethyl)phenyl)ethoxy)morpholine;
25 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-(N-(2-methoxyethyl)-N-methyl)aminobut-2-yn-yl)-3-(S)-phenylmorpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-(N-cyclopropyl-N-(2-methoxyethyl)amo)but-2-yn-yl)-3-(S)-phenylmorpholine;
30 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-(N-isopropyl-N-(2-methoxyethyl)amo)but-2-yn-yl)-3-(S)-phenylmorpholine;
4-((N,N-dimethylamino)but-2-yn-yl)-3-(S)-(4-fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;  
4-((4-azetidinyl)but-2-yn-yl)-3-(S)-(4-fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;  
2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-((N,N-dimethylamino)but-2-yn-yl)-3-(S)-(4-fluorophenyl)morpholine;  
4-((4-azetidinyl)but-2-yn-yl)-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)morpholine;  
4-((4-N-bis(2-methoxyethyl)-N-methylamino)but-2-yn-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;  
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;  
4-((4-(2-(S)-(methoxymethyl)pyrrolidino)but-2-yn-yl)morpholine;  
4-((4-(7-azabicyclo[2.2.1]heptano)but-2-yn-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;  
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-diisopropylaminobut-2-yn-yl)-3-(S)-(4-fluorophenyl)morpholine;  
2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)-4-(4-(2-(S)-(methoxymethyl)pyrrolidino)but-2-yn-yl)-3-(S)-phenylmorpholine;  
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-(2-(S)-(hydroxymethyl)pyrrolidino)but-2-yn-yl)morpholine;  
and pharmaceutically acceptable salts thereof.

Further preferred CNS-penetrant NK-1 receptor antagonists are those described in European Patent Specification No. WO 96/07649, i.e. compounds of formula (V):
wherein

\[ R^1 \text{ is hydrogen, halogen, } C_{1-6} \text{alkyl, } C_{1-6} \text{alkoxy, } CF_3, NO_2, \text{CN, } CO_2R^a, \]

\[ \text{CONR}^aR^b, C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl or } C_{1-4} \text{alkyl substituted by } C_{1-4} \text{alkoxy,} \]

and wherein \( R^a \) and \( R^b \) are each independently hydrogen or \( C_{1-4} \text{alkyl}; \)

\[ R^2 \text{ is hydrogen, halogen, } C_{1-6} \text{alkyl, } C_{1-6} \text{alkoxy substituted by } C_{1-4} \text{alkoxy or } CF_3; \]

\[ R^3 \text{ is hydrogen, halogen or } CF_3; \]

\[ R^4 \text{ is hydrogen, halogen, } C_{1-6} \text{alkyl, } C_{1-6} \text{alkoxy, hydroxy, } CF_3, NO_2, \]

\[ \text{CN, } CO_2R^a, \text{CONR}^aR^b, C_{2-6} \text{alkenyl, } C_{2-6} \text{alkynyl or } C_{1-4} \text{alkyl substituted by } C_{1-4} \text{alkoxy, wherein } R^a \text{ and } R^b \text{ are as previously defined; } \]

\[ R^5 \text{ is hydrogen, halogen, } C_{1-6} \text{alkyl, } C_{1-6} \text{alkoxy substituted by } C_{1-4} \text{alkoxy or } CF_3; \]

\[ R^6 \text{ is hydrogen, } C_{1-6} \text{alkyl, } C_{3-7} \text{cycloalkyl, } C_{3-7} \text{cycloalkylC}_{1-4} \text{alkyl, } \]

\[ \text{phenyl, or } C_{2-4} \text{alkyl substituted by } C_{1-4} \text{alkoxy or hydroxy; } \]

\[ R^7 \text{ is hydrogen, } C_{1-6} \text{alkyl, } C_{3-7} \text{cycloalkyl, } C_{3-7} \text{cycloalkylC}_{1-4} \text{alkyl, } \]

\[ \text{phenyl, } C_{2-4} \text{alkyl substituted by } C_{1-4} \text{alkoxy or hydroxy, or the group } \]

\[ C(=NR^c)NR^aR^b, \text{ where } R^a \text{ and } R^b \text{ are as previously defined and } R^c \text{ is } \]

\[ \text{hydrogen, } C_{1-6} \text{alkyl, CN or } COR^a; \]

or \( R^6 \) and \( R^7 \), together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring of 4 to 7 ring atoms which may optionally contain in the ring one oxygen or sulphur atom or a group selected from \( NR^8, S(O) \) or \( S(O)_2 \) and which ring may be optionally

\[ \text{substituted by one or two groups selected from phenyl, benzyl,} \]
hydroxyC₁₄alkyl, C₁₄alkoxyC₁₄alkyl, hydroxy, oxo, CORⁿ or CO₂Rⁿ where Rⁿ is as previously defined;

or R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a piperidino ring substituted by a spiro-fused indene or indoline group, each of which may be unsubstituted or substituted on any available carbon atom by a group selected from C₁₆alkyl, C₁₆alkoxy, hydroxy, halogen, cyano, trifluoromethyl, SO₂C₁₆alkyl, NRⁿRᵇ, NRⁿCORᵇ or CONRⁿRᵇ; or, in the case of an indoline group, on the nitrogen atom by a group selected from C₁₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₄alkyl, phenylC₁₄alkyl, CO₂Rⁿ, CONRⁿRᵇ, SORⁿ or SO₂Rⁿ, where Rⁿ and Rᵇ are as previously defined;

R⁸ is hydrogen, C₁₄alkyl, hydroxyC₁₄alkyl or C₁₄alkoxyC₁₄alkyl;
R⁹ᵃ and R⁹ᵇ are each independently hydrogen or C₁₄alkyl, or R⁹ᵃ and R⁹ᵇ are joined so, together with the carbon atoms to which they are attached, there is formed a C₅₋₇ ring;

X is selected from -CH₂CH₂-, -COCH₂- or -CH₂CO⁻; and

Y is hydrogen, or C₁₄alkyl optionally substituted by a hydroxyl group;

or a pharmaceutically acceptable salt thereof.

Particularly preferred compounds of formula (V) are those of formula (Va) and pharmaceutically acceptable salts thereof:

wherein
A¹ is hydrogen, fluorine or CF₃;
A² is fluorine or CF₃;
A³ is fluorine or hydrogen;
and X, Y, R⁶ and R⁷ are as defined in relation to formula (V).

Specific compounds of formula (V) of use in the present invention include:

4-(2-aminoethyl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-
4-(2-pyrrolidinoethyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-
4-(2-morpholinoethyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2-(2'--(S)-
carboxypyrrolidino)ethyl)-3-(S)-(4-fluorophenyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-
4-(2-(2'-hydroxymethylpyrrolidino)ethyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2-(4'-carbomethoxy-
2'-oxopyrrolidino)ethyl)-3-(S)-(4-fluorophenyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2-(N'-carboethoxy-
guanidino)ethyl)-3-(S)-(4-fluorophenyl)morpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(2-(4-
phenylpiperidino)ethyl)morpholine;
3-(S)-phenyl-4-(2-(4-phenylpiperidino)ethyl)-2-(R)-(1-(R)-(3-
(trifluoromethyl)phenyl)ethoxy)morpholine;
2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(2-
(spiro(indene-3',4-piperidino))ethyl)morpholine;
2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(2-
(4-phenylpiperidino)ethyl)morpholine;
2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)-4-(2-(1'-
methylsulfonyl-spiro(indoline-3',4-piperidino))ethyl)-3-(S)-
phenylmorpholine;
2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(2-(4-piperidino)ethyl)morpholine;  
2-(S)-(3,5-bis(trifluoromethyl)phenyl)methoxy)-3-(S)-phenyl-4-(2-(4-phenylpiperidino)ethyl)morpholine;  
4-(2-(4-benzylpiperidino)ethyl)-2-(S)-(3,5-bis(trifluoromethyl)phenyl)methoxy)-3-(S)-phenylmorpholine;  
and pharmaceutically acceptable salts thereof.

The preferred compounds of formulae (I), (II), (III), (IV) and (V) will have the 2- and 3-substituents on the morpholine ring in the cis arrangement, the preferred stereochemistry being as shown in the following general formula:

![Chemical structure](image)

Where the benzyloxy moiety is α-substituted, the preferred stereochemistry of the α-carbon is either (R) when the substituent is an alkyl (e.g. methyl) group or (S) when the substituent is a hydroxyalkyl (e.g. hydroxymethyl) group.

Unless otherwise defined herein, suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl and tert-butyl.

Unless otherwise defined herein, suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.
Unless otherwise defined herein, suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Unless otherwise defined herein, suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Unless otherwise defined herein, suitable aryl groups include phenyl and naphthyl groups.

A particular aryl-C_1₆ alkyl, e.g. phenyl-C_1₆ alkyl, group is benzyl.

Unless otherwise defined herein, suitable heteroaryl groups include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, thiényl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine.

The compounds of use in this invention may have one or more asymmetric centres and can therefore exist as enantiomers and possibly as diastereoisomers. It is to be understood that the present invention relates to the use of all such isomers and mixtures thereof.

Suitable pharmaceutically acceptable salts of the CNS-penetrant 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 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 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.

Suitable pharmaceutically acceptable salts of the antidepressant or anti-anxiety agent of use in the present invention include those salts described above in relation to the salts of CNS-penetrant NK-1 receptor antagonists.

The present invention accordingly provides the use of a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an antidepressant or anti-anxiety agent for the manufacture of a medicament for the treatment or prevention of depression and/or anxiety.

The present invention also provides a method for the treatment or prevention of depression and/or anxiety, which method comprises administration to a patient in need of such treatment an amount of a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an amount of an antidepressant or anti-anxiety agent such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an antidepressant or anti-anxiety agent together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an antidepressant or anti-anxiety agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of depression and/or anxiety. Such combined preparations may be, for example, in the form of a twin pack.

In a further or alternative aspect of the present invention, there is therefore provided a product comprising a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and
(V) and an antidepressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of depression and/or anxiety.

In a preferred aspect, the present invention accordingly provides the use of a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an antidepressant agent selected from the group consisting of: norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, reversible monoamine oxidase inhibitors, serotonin and noradrenaline reuptake inhibitors, corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical antidepressants, for the manufacture of a medicament for the treatment or prevention of depression and/or anxiety.

The present invention also provides a method for the treatment or prevention of depression and/or anxiety, which method comprises administration to a patient in need of such treatment an amount of a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an antidepressant agent selected from the group consisting of: norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, reversible monoamine oxidase inhibitors, serotonin and noradrenaline reuptake inhibitors, corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical antidepressants, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an antidepressant agent selected from the group consisting of: norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, reversible monoamine oxidase inhibitors, serotonin and noradrenaline reuptake inhibitors, corticotropin
releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical antidepressants, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an antidepressant agent selected from the group consisting of: norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, reversible monoamine oxidase inhibitors, serotonin and noradrenaline reuptake inhibitors, corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical antidepressants, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of depression and/or anxiety.

A particularly preferred class of antidepressant agent is the selective serotonin reuptake inhibitors, thus in a further preferred aspect, the present invention accordingly provides the use of a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and a selective serotonin reuptake inhibitor for the manufacture of a medicament for the treatment or prevention of depression and/or anxiety.

The present invention also provides a method for the treatment or prevention of depression and/or anxiety, which method comprises administration to a patient in need of such treatment an amount of a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an amount of a selective serotonin reuptake inhibitor, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and a selective serotonin reuptake inhibitor, together with at least one pharmaceutically acceptable carrier or excipient.
In a further or alternative aspect of the present invention, there is provided a product comprising a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and a selective serotonin reuptake inhibitor as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of depression and/or anxiety.

A particularly preferred class of anti-anxiety agent is the 5-HT\textsubscript{1A} agonists or antagonists, especially the 5-HT\textsubscript{1A} partial agonists, thus in a further preferred aspect, the present invention accordingly provides the use of a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and a 5-HT\textsubscript{1A} receptor agonist or antagonist for the manufacture of a medicament for the treatment or prevention of depression and/or anxiety.

The present invention also provides a method for the treatment or prevention of depression and/or anxiety, which method comprises administration to a patient in need of such treatment an amount of a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and an amount of a 5-HT\textsubscript{1A} receptor agonist or antagonist, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and a 5-HT\textsubscript{1A} receptor agonist or antagonist, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a CNS-penetrant NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV) and (V) and a 5-HT\textsubscript{1A} receptor agonist or antagonist as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of depression and/or anxiety.
As stated above, the CNS-penetrant NK-1 receptor antagonist and the antidepressant or anti-anxiety agent may be formulated in a single pharmaceutical composition or alternatively in individual pharmaceutical compositions for simultaneous, separate or sequential use in accordance with the present invention.

It will be appreciated that it may be desirable to combine the CNS-penetrant NK-1 receptor antagonist with more than one antidepressant and/or anti-antiety agent. Thus "triple combination" or "multiple combination" therapy is envisaged within the scope of the present invention, for example, use of a CNS-penetrant NK-1 receptor antagonist of formulae (I), (II), (III), (IV) or (V) in combination with a selective serotonin reuptake inhibitor, such as fluoxetine, and a compound with 5-HT_{1A} antagonist activity, such as pindolol.

Preferably the compositions according to the present invention are in unit dosage forms such as tablets, pills, capsules, wafers and the like. Additionally, the active ingredients may be presented as granules or powders for extemporaneous formulation as volume defined solutions or suspensions. Alternatively, the active ingredients may be presented in ready-prepared volume defined solutions or suspensions. Preferred forms are tablets and capsules.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tablinging 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 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 wafers.

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

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a CNS-penetrant NK-1 receptor antagonist and an antidepressant or anti-anxiety agent, which process comprises bringing a CNS-penetrant NK-1 receptor antagonist
and an antidepressant or anti-anxiety agent, into association with a pharmaceutically acceptable carrier or excipient.

When administered in combination, either as a single or as separate pharmaceutical composition(s), the CNS-penetrant NK-1 receptor antagonist and an antidepressant or anti-anxiety agent, are presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of the CNS-penetrant NK-1 receptor antagonist and the antidepressant or anti-anxiety agent will suitably be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

A suitable dosage level for the CNS-penetrant NK-1 receptor antagonist about 0.05 to 1500mg per day, preferably about 0.25 to 1500mg per day, and especially about 0.25 to 500mg per day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily.

A suitable dosage level for the antidepressant agent is about 0.5 to 1500mg per day, preferably about 2.5 to 1000mg per day, and especially about 2.5 to 500mg per day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily.

A suitable dosage level for the anti-anxiety agent is about 0.5 to 1500mg per day, preferably about 2.5 to 1000mg per day, and especially about 2.5 to 500mg per day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily.

It will be appreciated that the amount of the CNS-penetrant NK-1 receptor antagonist and the antidepressant or anti-anxiety agent required for use in the treatment or prevention of depression and/or anxiety 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.

As used herein the term "patient" includes animals of economic
importance such as bovine, ovine, and porcine animals, especially those
that produce meat, as well as domestic animals (e.g. cats and dogs), sports
animals (e.g. horses), zoo animals, and humans, the latter being preferred.

The compounds of formulae (I), (II), (III), (IV) and (V) may be
prepared by the methods described in EP-A-0 577 394 (or WO 95/16679),
WO 95/18124, WO 95/23798, WO 96/05181 and WO 96/07649,
respectively.

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
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 ID₅₀≤3mg/kg, and preferably with an
ID₅₀≤1mg/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 ID₅₀≤30mg/kg, and preferably with an ID₅₀≤10mg/kg.

CNS-penetrant NK-1 receptor antagonists of use in the present
invention are also effective in the attenuation of separation-induced
cocalisations 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 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$_{50}$≤20mg/kg, preferably with an ID$_{50}$≤10mg/kg, and especially with an ID$_{50}$≤5mg/kg.

In an alternative method, the NK-1 receptor antagonist is administered orally, 4 hours prior to isolation, wherein vocalisations during the first 15 minutes of isolation are attenuated with an ID$_{50}$≤20mg/kg, preferably with an ID$_{50}$≤10mg/kg, and especially with an ID$_{50}$≤5mg/kg.

Whilst it is recognised in many of the aforementioned patent specifications that NK-1 receptor antagonists may be used to treat depression and/or anxiety, there remains a need for simple and reliable methods for the identification of compounds with NK-1 receptor antagonist activity which would be effective in the treatment of depression and/or anxiety.

The present invention accordingly provides a preclinical screen for antidepressant and/or anxiolytic activity of CNS-penetrant NK-1 receptor antagonists, which comprises:

a) to a guinea-pig pup, administration of a NK-1 receptor antagonist or vehicle by intravenous, subcutaneous, intraperitoneal or oral routes;

b1) 30-60 minutes after intravenous, subcutaneous or intraperitoneal administration, socially isolating the treated guinea-pig pups by removal from their mother and littermates; or

b2) up to 4 hours after oral administration, socially isolating the treated guinea-pig pups by removal from their mother and littermates;

c) recording the number or duration of vocalisations (isolation calls) during a specified period and comparing the effects on guinea-pig pups treated with NK-1 receptor antagonists against their own baseline or against guinea-pig pups that receive no test compound or vehicle.
Preferably the NK-1 receptor antagonist is administered by subcutaneous injection or orally by gavage.

An advantage of the present invention is that the guinea-pig is a mammal with human-like NK-1 receptor pharmacology.

The guinea-pig preclinical screen described herein has been shown to be sensitive not only to the anxiolytic and antidepressant effects of NK-1 receptor antagonists, but also to the effects of established anxiolytic and antidepressant drugs. Thus, for example, buspirone, diazepam, fluoxetine, and imipramine were all active in this assay (ID$_{50}$=0.5mg/kg s.c., 0.7mg/kg s.c., 2.7mg/kg i.p. and 5.4mg/kg s.c., respectively).

According to a further aspect of the present invention, there is provided a preclinical screen for antidepressant and/or anxiolytic activity of CNS-penetrant NK-1 receptor antagonists, which comprises:

a) to a gerbil, administration of a NK-1 receptor antagonist or vehicle by intravenous, subcutaneous, intraperitoneal or oral routes;

b) administration by injection under anaesthetic of NK-1 receptor agonists or anxiogenic agents, administered centrally or systemically; or subjecting the gerbil to stressors such as single housing or foot shock;

c) recording the duration of repetitive hindfoot tapping and comparing the effects on gerbils treated with NK-1 receptor antagonists against gerbils that receive no test compound or vehicle.

Preferably the NK-1 receptor antagonist is administered by intravenous injection or orally by gavage.

Suitable NK-1 receptor agonists which elicit repetitive hindfoot tapping include GR73632 (d-Ala[L-Pro$^0$, Me-Leu$^{10}$]substance P-(7-11)), [Sar$^9$, Met(O$_2$)$_{11}$]substance P and substance P. Suitable anxiogenic agents include pentagastrin and adrenaline.

The NK-1 receptor antagonist may be administered intravenously about 5 minutes before challenge with the NK-1 receptor agonist or anxiogenic agent or before the aversive stimulation, in order to measure
the acute effect of the NK-1 receptor antagonist. If oral administration is chosen, it may be preferable to administer the NK-1 receptor antagonist at least one hour prior to central injection of the NK-1 receptor agonist or anxiogenic agent, or the aversive stimulus. In order to measure the central duration of action of a NK-1 receptor antagonist, the test compound is conveniently administered approximately 24 hours prior to central injection of the NK-1 receptor agonist or anxiogenic agent, or the aversive stimulus.

Whilst there are many different genera of gerbil, the preferred genus is the Mongolian gerbil (Meriones unguiculatus). An advantage of the present invention is that the gerbil is a mammal with human-like NK-1 receptor pharmacology.

The preclinical screens described herein have been shown to be sensitive not only to the anxiolytic and antidepressant effects of NK-1 receptor antagonists, but also to the effects of an established antidepressant drug, imipramine (ID_{50}=3.8mg/kg s.c. following foot-tapping induced by substance P) and the anxiolytic drug, buspirone (ID_{50}=3.4mg/kg s.c.).

The identification of CNS-penetrant NK_{1} receptor antagonists of use as anxiolytic or antidepressant agents is carried out as follows:

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

(ii) Determine activity of compounds for their ability to inhibit distress vocalisations in guinea-pig pups (Assay 2)). Select compounds with ID_{50} ≤ 20mg/kg, and preferably ID_{50} ≤ 10mg/kg, and especially ID_{50} ≤ 5mg/kg.

According to an alternative aspect of the present invention, the identification of NK_{1} receptor antagonists of use as anxiolytic or antidepressant agents is carried out as follows:
(i) Determine affinity for human NK₁ receptor in radioligand binding studies (Assay 1); select compounds with IC₅₀ ≤ 10nM, preferably IC₅₀ ≤ 2nM, especially IC₅₀ ≤ 1nM.

(ii) Determine ability of compounds to penetrate CNS by their ability to inhibit foot tapping in gerbils induced by central injection of an NK₁ agonist (Assay 3); select compounds that inhibit foot tapping with ID₅₀ ≤ 3mg/kg i.v., and preferably ID₅₀ ≤ 1mg/kg i.v. when administered immediately prior to central NK₁ agonist challenge, or ID₅₀ ≤ 30mg/kg p.o., and preferably ID₅₀ ≤ 10mg/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 NK₁ agonist challenge; select compounds showing ≤ 25-fold loss of potency compared with ID₅₀ determined in step (ii) above with the proviso that ID₅₀ ≤ 10mg/kg i.v., and preferably ≤ 5mg/kg i.v. after 24 hour pre-treatment.

Yet further preferred compounds of use as anxiolytic or antidepressant agents may be selected, according to either of the “selection cascades” described above, 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.

It will be appreciated that, if desired, the above “selection cascades” may be combined. Thus, a further method for the identification of NK-1 receptor antagonists of use as anxiolytic or antidepressant agents involves the use of Assay 1, Assay 2 and Assay 3, incorporating the selection criteria defined herein.

Particularly active CNS-penetrant NK-1 receptor antagonists include:

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-(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;

According to a further aspect of the present invention, there is provided the use of a CNS-penetrant NK-1 receptor antagonist identified according to either of the preclinical screens defined herein for the manufacture of a medicament for the treatment or prevention of depression and/or anxiety as previously defined.

Similarly, there is also provided a method for the treatment or prevention of depression and/or anxiety as previously defined, which method comprises administration to a patient in need of such treatment an effective amount of a CNS-penetrant NK-1 receptor antagonist identified according to either of the preclinical screens defined herein.

Particularly preferred CNS-penetrant NK-1 receptor antagonists of the formulae (I), (II), (III), (IV) and (V) for use in the present invention are compounds which are potent NK-1 receptor antagonists, i.e. compounds with an NK-1 receptor affinity (IC₅₀) of less than 100nM. Preferably, the
NK-1 receptor antagonist has IC$_{50}$ ≤ 10nM, in particular IC$_{50}$ ≤ 2nM, and most especially IC$_{50}$ ≤ 1nM.

NK-1 receptor binding assays are well known in the art. The following assay is one such protocol based upon the displacement of $^{125}$I-Tyr$^8$-substance P binding to cloned human NK-1 receptors in vitro:

**ASSAY 1: NK-1 Receptor binding Assay**

NK-1 receptor binding assays are performed in intact Chinese hamster ovary (CHO) cells expressing the human NK-1 receptor using a 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 3x10$^5$ 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-Tyr$^8$-substance P (0.1nM, 2000Ci/mmole; New England Nuclear) is incubated in the presence or absence of test compounds (dissolved in 5µl dimethylsulphoxide, DMSO) with 5x10$^4$ 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), 50µg/ml chymostatin (Peninsula), 0.1nM phenylmethylsulphonyl fluoride, 2µg/ml pepstatin, 2µg/ml leupeptin and 2.8µg/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-specific binding is determined using excess substance P (1µM) and represents <10% of total binding.

Pharmacological assays for the study of antidepressant or anti-anxiety activity are well known in the art. Many are based upon the ability of antidepressants to support animal behaviour in stressful situations that ordinarily lead to diminished behavioural responsiveness.
(“learned helplessness”), such as repeated noxious shocks, forced swimming, or separation from other animals. For example, the following assay, which involves the inhibition of separation-induced vocalisations in guinea-pig pups, may be used to evaluate the methods of the present invention in the treatment or prevention of depression and/or anxiety.

ASSAY 2: 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 at least 2 weeks old. Before entering an experiment, the pups may be screened to ensure that a vigorous vocalisation response is reproducibly elicited following maternal separation. The pups are placed individually in an observation cage (approximately 55cm x 39cm x 19cm) in a room physically isolated from the home cage for approximately 15 minutes and the duration and/or number of vocalisation during this baseline period is recorded. Those animals which vocalise for longer than 5 minutes may be 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, typically for at least 30 to 60 minutes (or for up to 4 hours following an oral dose, dependent upon the oral pharmacokinetics of the test compound) before social isolation for 15 minutes as described above. The duration and/or number of vocalisation on drug treatment days may be expressed as a percentage of the pre-treatment baseline value for each animal or compared with values obtained in vehicle-treated animals. The same subjects may be retested once weekly for up to 6 weeks. Between 6 and 8 animals typically receive each test compound at each dose tested.
ASSAY 3: Gerbil Foot-Tapping (CNS Penetration) Assay

CNS-penetrant NK-1 receptor antagonists for use in the present invention can be identified by their ability to inhibit foot tapping in gerbils induced by anxiogenic agents (such as pentagastrin) or central infusion of 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 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 approximately 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 anxiogenic agent (e.g. pentagastrin) or a selective NK-1 receptor agonist (e.g. GR73632 (d-Ala[6-Pro,Me-Leu]-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 allowed to recover from anaesthesia in a clear perspex observation box (approximately 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 similar method of quantification.

It will be appreciated that CNS-penetration as defined by this assay and as used herein is a property of the NK-1 receptor antagonist and is not conferred by co-administration or co-formulation of the NK-1 receptor antagonist with a carrier or excipient designed to transiently open the blood-brain barrier.
One example of a NK-1 receptor antagonist active in the preclinical screens of 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: $IC_{50}=0.1nM$

guinea-pig vocalisation $ID_{50}=0.73mg/kg$ p.o.

(4 hrs. pretreatment)

gerbil foot-tapping (5 mins.): $ID_{50}=0.36mg/kg$ i.v.

gerbil foot-tapping (24 hrs.): $ID_{50}=0.33mg/kg$ i.v.

Another example of a NK-1 receptor antagonist active in the preclinical screens of the present invention is the compound 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, the preparation of which is described in International Patent Specification No. WO 95/18124. In the aforementioned assays, this compound has the following activity:

human NK-1 receptor binding: $IC_{50}=0.25nM$

guinea-pig vocalisation: $ID_{50}=0.5mg/kg$ s.c.

gerbil foot-tapping (5 mins.): $ID_{50}=0.12mg/kg$ i.v.

gerbil foot-tapping (24 hrs.): $ID_{50}=0.17mg/kg$ i.v.

Combinations of a CNS-penetrant NK-1 receptor antagonist with the anti-anxiety and antidepressant agents, buspirone and fluoxetine, have been tested in the guinea-pig vocalisation assay (Assay 3):
Test Compound A is 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine.

Test Compound B is the less active enantiomer of Test Compound A - i.e. 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(R)-phenylmorpholine.

Test Compounds A and B and buspirone were dissolved in 0.9% saline and administered s.c. in the flank. Due to limitations of solubility, fluoxetine was suspended in 0.5% methocel and given i.p. The injection volume was 1 ml/kg.

**Results**

Guinea-pig pups isolated from their mothers and littermates emitted a vigorous vocalisation response during the first 15 minutes of separation (total duration approximately 8 minutes during this period). Administration of the highly CNS penetrant NK-1 receptor antagonist Test Compound A (0.25mg/kg s.c.), buspirone (0.25mg/kg s.c.), or fluoxetine (2mg/kg i.p.) alone 30 minutes previously attenuated separation-induced vocalisations by approximately 25% compared with the baseline vocalisation response determined using the same animals on the previous day. Combined administration of Test Compound A (0.25mg/kg s.c.) with either buspirone (0.25mg/kg s.c.) or fluoxetine (2mg/kg i.p.) virtually abolished separation-induced vocalisations (Figures 1 & 2). The NK-1 receptor specificity of this effect was confirmed by the failure of the less active enantiomer, Test Compound B (0.25mg/kg s.c.) to attenuate separation-induced vocalisations when administered alone, or to potentiate the inhibitory effect of buspirone (0.25mg/kg s.c.; Figure 1).

The above results provide evidence for a synergistic interaction between a centrally acting NK-1 receptor antagonist (Test Compound A) with the anti-anxiety and antidepressant drugs buspirone and fluoxetine in a distress vocalisation assay using guinea-pigs. This appears to reflect
a specific NK-1 receptor mediated interaction, since co-administration of
the less active enantiomer, Test Compound B, at the same dose failed to
potentiate the ability of buspirone to inhibit vocalisations. The findings
provide the first experimental evidence that centrally acting NK-1
receptor antagonists may augment the therapeutic response to clinically
used anti-anxiety and antidepressant drugs, including agents acting as
agonists or antagonists at the 5-HT$_{1A}$ receptor (such as buspirone), and
selective serotonin reuptake inhibitors (such as fluoxetine).

It will be appreciated from the foregoing description that an
advantage of the combinations of the present invention is the oral
bioavailability of the NK-1 receptor antagonists of use in such
combinations. Pharmacokinetic analysis to determine the oral
bioavailability of the NK-1 receptor antagonists may be effected simply by
measuring the ability of the NK-1 receptor antagonist to inhibit NK-1
receptor agonist-induced foot-tapping in the gerbil following oral
administration of the NK-1 receptor antagonist. Compounds with an
ID$_{50}$≤30mg/kg p.o., and preferably ID$_{50}$≤10mg/kg p.o., following
administration 1 hour prior to central NK-1 receptor agonist challenge are
considered to be orally active according to the present invention.

An alternative pharmacokinetic analysis takes advantage of the
ability of CNS-penetrant NK-1 receptor antagonists to attenuate cisplatin-
induced emesis. Orally active, CNS-penetrant NK-1 receptor antagonists
demonstrate this activity in the following assay:

**ASSAY 4: 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
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 minutes. The animals are observed continuously during recovery from the anaesthetic and for 4 hours following the cisplatin injection. The numbers of retches and vomits occurring during the 4 hours after cisplatin administration are recorded by trained observers.

Oral bioavailability of the NK-1 receptor antagonist is determined by its ability to inhibit cisplatin-induced emesis in ferrets following oral administration (Assay 4). Compounds with an ID<sub>50</sub>≤3mg/kg p.o., and preferably ID<sub>90</sub>≤1mg/kg p.o., are considered to be orally active according to the present invention. Thus, for example, the NK-1 receptor antagonist 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, mentioned above, has an ID<sub>90</sub> in the ferret emesis assay (Assay 4) of <3mg/kg p.o.

The following examples illustrate pharmaceutical compositions according to the invention.

These formulations may be prepared with separate active ingredients or with a combination of active ingredients in one composition. In such combined preparations, the ratio of the CNS-penetrant NK-1 receptor antagonist and the antidepressant or anti-anxiety agent will depend upon the choice of active ingredients.
EXAMPLE 1  Tablets containing 50-300mg of NK-1 antagonist and 5-10mg of buspirone

<table>
<thead>
<tr>
<th></th>
<th>Amount mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK-1 antagonist</td>
<td>50.0</td>
</tr>
<tr>
<td>buspirone</td>
<td>5.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>80.0</td>
</tr>
<tr>
<td>Modified food corn starch</td>
<td>80.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>184.5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.5</td>
</tr>
</tbody>
</table>

EXAMPLE 2  Tablets containing 50-300mg of NK-1 antagonist and 20mg of fluoxetine

<table>
<thead>
<tr>
<th></th>
<th>Amount mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK-1 antagonist</td>
<td>50.0</td>
</tr>
<tr>
<td>fluoxetine</td>
<td>20.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>80.0</td>
</tr>
<tr>
<td>Modified food corn starch</td>
<td>80.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>169.5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The active ingredients cellulose, lactose and a portion of the corn 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 CNS-penetrant NK-1 receptor antagonist per tablet.
CLAIMS:

1. Use of a NK-1 receptor antagonist and an antidepressant or anti-anxiety agent for the manufacture of a medicament for the treatment or prevention of depression and/or anxiety, characterised in that said NK-1 receptor antagonist is CNS-penetrant as determined by its ability to inhibit NK-1 receptor agonist-induced foot-tapping in the gerbil, and is effective in the attenuation of separation-induced vocalisations by guinea-pig pups, and wherein said medicament is adapted for oral administration.

2. Use as claimed in claim 1 wherein the NK-1 receptor antagonist inhibits NK-1 receptor agonist-induced foot-tapping in the gerbil with an ID$_{50}$≤3mg/kg i.v. when administered immediately prior to central NK-1 receptor agonist challenge; or an ID$_{50}$≤30mg/kg p.o. when administered 1 hour prior to central NK-1 receptor agonist challenge.

3. Use as claimed in claim 2 wherein the NK-1 receptor antagonist additionally shows ≤25-fold loss of potency in its inhibition of NK-1 receptor agonist-induced foot-tapping in the gerbil following intravenous administration 24 hours prior to central NK-1 receptor agonist challenge, with the proviso that the ID$_{50}$≤10mg/kg i.v. after 24 hour pre-treatment.

4. Use as claimed in any one of claims 1 to 3 wherein the NK-1 receptor antagonist attenuates separation-induced vocalisations by guinea-pig pups with an ID$_{50}$≤20mg/kg.

5. Use as claimed in any one of claims 1 to 4 wherein the NK-1 receptor antagonist has an affinity for the human NK-1 receptor of IC$_{50}$≤10nM.
6. Use as claimed in any one of claims 1 to 5 wherein the NK-1 receptor antagonist is a compound of formula (I):

\[
\begin{array}{c}
\text{R}^3 \quad X \quad \text{R}^4 \\
\text{R}^2 \quad \text{N} \quad \text{R}^5 \\
\text{R}^1
\end{array}
\]  

(I)

or a pharmaceutically acceptable salt thereof, wherein:

\( \text{R}^1 \) is selected from the group consisting of:

(1) \( \text{C}_{1-6} \text{alkyl} \), substituted with one or more of the substituents selected from:

10 (a) heterocycle, wherein the heterocycle is selected from the group consisting of:

(A) benzimidazolyl,
(B) imidazolyl,
(C) isoxazolyl,
(D) isothiazolyl,
(E) oxadiazolyl,
(F) pyrazinyl,
(G) pyrazolyl,
(H) pyridyl,
(I) pyrrolyl,
(J) tetrazolyl,
(K) thiaadiazolyl,
(L) triazolyl, and
(M) piperidinyl,

20 and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:

(i) \( \text{C}_{1-6} \text{alkyl} \), unsubstituted or substituted with halo, -CF\(_3\), -OCH\(_3\), or phenyl,
(ii) C\textsubscript{1-6}alkoxy,
(iii) oxo,
(iv) thioxo,
(v) cyano,
(vi) -SCH\textsubscript{3},
(vii) phenyl,
(viii) hydroxy,
(ix) trifluoromethyl,
(x) -(CH\textsubscript{2})\textsubscript{m}-NR\textsuperscript{9}R\textsuperscript{10}, wherein m is 0, 1 or 2, and R\textsuperscript{9} and R\textsuperscript{10}

are independently selected from:

(I) hydrogen,
(II) C\textsubscript{1-6}alkyl,
(III) hydroxyC\textsubscript{1-6}alkyl, and
(IV) phenyl,

(xii) -NR\textsuperscript{9}COR\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above, and

(xii) -CONR\textsuperscript{9}R\textsuperscript{10}, wherein R\textsuperscript{9} and R\textsuperscript{10} are as defined above,

R\textsuperscript{2} and R\textsuperscript{3} are independently selected from the group consisting of:

(1) hydrogen;
(2) C\textsubscript{1-6}alkyl
(3) C\textsubscript{2-6}alkenyl, and
(5) phenyl;

X is -O-;
R\textsuperscript{4} is

\[
\begin{array}{c}
\text{Y} \\
\text{Z} \\
\text{R}^6 \\
\text{R}^7 \\
\text{R}^8
\end{array}
\]

R\textsuperscript{5} is phenyl, unsubstituted or substituted with halo;

R\textsuperscript{6}, R\textsuperscript{7} and R\textsuperscript{8} are independently selected from the group consisting of:

(1) hydrogen,
(2) C₁₆alkyl,
(3) halo, and
(4) -CF₃;
Y is -O--; and
5 Z is hydrogen or C₁₄alkyl.

7. Use as claimed in any one of claims 1 to 5 wherein the NK-1 receptor antagonist is a compound of formula (IIa):

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein:
A¹ is fluorine or CF₃;
A² is fluorine or CF₃;
A³ is fluorine or hydrogen;
15 R⁶ is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C₁₄alkyl group, and optionally substituted by a group of the formula ZNR⁷R⁸ where
Z is C₁₆alkylene or C₃₆cycloalkylene;
R⁷ is hydrogen, C₁₄alkyl, C₃₇cycloalkyl or C₃₇cycloalkylC₁₄alkyl, or
C₂₄alkyl substituted by C₁₄alkoxy or hydroxyl;
20 R⁸ is hydrogen, C₁₄alkyl, C₃₇cycloalkyl or C₃₇cycloalkylC₁₄alkyl, or C₂₄alkyl substituted by one or two substituents selected from C₁₄alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;
or R⁷, R⁸ and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by a hydroxy group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)₂ or a second nitrogen atom which will be part of a NH or NR⁶ moiety where R⁶ is C₁₋₄ alkyl optionally substituted by hydroxy or C₁₋₄ alkoxy;

or R⁷, R⁸ and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R⁷ and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

X is an alkylene chain of 1 to 4 carbon atoms optionally substituted by oxo; and

Y is a C₁₋₄ alkyl group optionally substituted by a hydroxyl group;

with the proviso that if Y is C₁₋₄ alkyl, R⁶ is substituted at least by a group of formula ZNR⁷R⁸ as defined above.

8. Use as claimed in any one of claims 1 to 5 wherein the NK-1 receptor antagonist is a compound of formula (III):

or a pharmaceutically acceptable salt thereof, wherein:

R² and R³ are independently selected from the group consisting of:

1. hydrogen,

2. C₁₋₄ alkyl,
(3) C₆-alkenyl, and
(4) phenyl;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of:
(1) hydrogen,
(2) C₆-alkyl,
(3) fluoro,
(4) chloro,
(5) bromo,
(6) iodo, and
(7) -CF₃;

R¹¹, R¹² and R¹³ are independently selected from the group consisting of:
(1) fluoro,
(2) chloro,
(3) bromo, and
(4) iodo;

A is unsubstituted C₆-alkyl;

B is selected from the group consisting of:
p is 0 or 1;
X is selected from:

(a) $\text{-PO(OH)O}^- \cdot M^+$, wherein $M^+$ is a pharmaceutically acceptable monovalent counterion,

(b) $\text{-PO(O^-)₂} \cdot 2M^+$,

(c) $\text{-PO(O^-)₂} \cdot D^{2+}$, wherein $D^{2+}$ is a pharmaceutically acceptable divalent counterion,

(d) $\text{-CH(R^4)-PO(OH)O}^- \cdot M^+$, wherein $R^4$ is hydrogen or $C_{1-3}$alkyl,

(e) $\text{-CH(R^4)-PO(O^-)₂} \cdot 2M^+$,

(f) $\text{-CH(R^4)-PO(O^-)₂} \cdot D^{2+}$,

(i) $\text{-CO-CH₂CH₃-CO₂}^- \cdot M^+$,

(j) $\text{-CH(CH₃)-O-CO-R^5}$, wherein $R^5$ is selected from the group consisting of:
Y is -O-; and
Z is hydrogen or C_{1,6}alkyl.

9. Use as claimed in any one of claims 1 to 5 wherein the NK-1 receptor antagonist is a compound of formula (IVa):
or a pharmaceutically acceptable salt thereof, wherein:

A¹ is fluorine or CF₃;

A² is fluorine or CF₃;

A³ is fluorine or hydrogen;

X is a group of the formula NR⁶R⁷ or a C- or N-linked imidazolyl ring;

Y is hydrogen or C₁₋₄ alkyl optionally substituted by a hydroxy group;

R⁶ is hydrogen, C₁₋₄ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄ alkyl, phenyl, or C₂₋₄ alkyl substituted by C₁₋₄ alkoxy or hydroxy;

R⁷ is hydrogen, C₁₋₄ alkyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkylC₁₋₄ alkyl, phenyl, or C₂₋₄ alkyl substituted by one or two substituents selected from C₁₋₄ alkoxy, hydroxy or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a saturated or partially saturated heterocyclic ring of 4 to 7 ring atoms, which ring may optionally contain in the ring one oxygen or sulphur atom or a group selected from NR⁶, S(O) or S(O)₂ and which ring may be optionally substituted by one or two groups selected from hydroxyC₁₋₄ alkyl, C₁₋₄ alkoxyC₁₋₄ alkyl, oxo, COR³ or CO₂R³ where R³ is hydrogen or C₁₋₄ alkyl;
or $R^6$ and $R^7$ together with the nitrogen atom to which they are attached, form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms; and

$R^8$ is hydrogen, $C_{1-4}$-alkyl, hydroxy$C_{1-4}$-alkyl or $C_{1-4}$-alkoxy$C_{1-4}$-alkyl.

10. Use as claimed in any one of claims 1 to 5 wherein the NK-1 receptor antagonist is a compound of formula (Va):

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

- $A^1$ is hydrogen, fluorine or $CF_3$;
- $A^2$ is fluorine or $CF_3$;
- $A^3$ is fluorine or hydrogen;

$R^8$ is hydrogen, $C_{1-4}$-alkyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl$C_{1-4}$-alkyl, phenyl, or $C_{2-4}$-alkyl substituted by $C_{1-4}$-alkoxy or hydroxy;

$R^7$ is hydrogen, $C_{1-4}$-alkyl, $C_{3-7}$-cycloalkyl, $C_{3-7}$-cycloalkyl$C_{1-4}$-alkyl, phenyl, $C_{2-4}$-alkyl substituted by $C_{1-4}$-alkoxy or hydroxy, or the group $C(=NR^c)NR^aR^b$, where $R^a$ and $R^b$ are each independently hydrogen or $C_{1-4}$-alkyl and $R^c$ is hydrogen, $C_{1-6}$-alkyl, CN or COR$^a$;

or $R^6$ and $R^7$, together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring of 4 to 7 ring atoms which may optionally contain in the ring one oxygen or sulphur atom or a group selected from NR$^8$, S(O) or S(O)$_2$ and which ring may be optionally
substituted by one or two groups selected from phenyl, benzyl, hydroxyC$_{1-4}$alkyl, C$_{1-4}$alkoxyC$_{1-4}$alkyl, hydroxy, oxo, COR$^a$ or CO$_2$R$^a$ where R$^a$ is as previously defined;

or R$^6$ and R$^7$, together with the nitrogen atom to which they are attached, form a piperidino ring substituted by a spiro-fused indene or indoline group, each of which may be unsubstituted or substituted on any available carbon atom by a group selected from C$_1$-alkyl, C$_1$-alkoxy, hydroxy, halogen, cyano, trifluoromethyl, SO$_2$C$_{1-6}$alkyl, NR$^a$R$^b$, NR$^a$COR$^b$ or CONR$^a$R$^b$; or, in the case of an indoline group, on the nitrogen atom by a group selected from C$_1$-alkyl, C$_3$-cycloalkyl, C$_3$-cycloalkylC$_{1-4}$alkyl, pherylC$_{1-4}$alkyl, CO$_2$R$^a$, CONR$^a$R$^b$, SOR$^a$ or SO$_2$R$^a$, where R$^a$ and R$^b$ are as previously defined;

R$^5$ is hydrogen, C$_{1-4}$alkyl, hydroxyC$_{1-4}$alkyl or C$_{1-4}$alkoxyC$_{1-4}$alkyl;

X is selected from -CH$_2$CH$_2$-, -COCH$_2$- or -CH$_2$CO-; and

Y is hydrogen, or C$_{1-4}$alkyl optionally substituted by a hydroxyl group.

11. Use as claimed in any one or claims 1 to 10 wherein the antidepressant agent is selected from norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, atypical antidepressants, and noradrenergic and specific serotonergic antidepressants (NaSSAs).

12. Use as claimed in any one of claims 1 to 10 wherein the anti-anxiety agent is selected from benzodiazepines, 5-HT$_{1A}$ agonists, antagonists or partial agonists, corticotropin releasing factor (CRF) antagonists and m1 muscarinic cholinergic receptor agonists.
13. An oral pharmaceutical composition comprising a NK-1 receptor antagonist and an antidepressant or anti-anxiety agent, together with at least one pharmaceutically acceptable carrier or excipient, characterised in that said NK-1 receptor antagonist is CNS-penetrant as determined by its ability to inhibit NK-1 receptor agonist-induced foot-tapping in the gerbil, and is effective in the attenuation of separation-induced vocalisations by guinea-pig pups.

14. A product comprising a NK-1 receptor antagonist and an antidepressant or anti-anxiety agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of depression and/or anxiety, characterised in that said NK-1 receptor antagonist is CNS-penetrant as determined by its ability to inhibit NK-1 receptor agonist-induced foot-tapping in the gerbil, and is effective in the attenuation of separation-induced vocalisations by guinea-pig pups.

15. A method for the treatment or prevention of depression and/or anxiety, which method comprises oral administration to a patient in need of such treatment an amount of a NK-1 receptor antagonist and an amount of an antidepressant or anti-anxiety agent, such that together they give effective relief, wherein said NK-1 receptor antagonist is CNS-penetrant as determined by its ability to inhibit NK-1 receptor agonist-induced foot-tapping in the gerbil, and is effective in the attenuation of separation-induced vocalisations by guinea-pig pups.

16. A method as claimed in claim 15 wherein the NK-1 receptor antagonist is selected from the compounds of any one of formulae (I), (IIa), (III), (IVa) and (Va) as defined in claims 6 to 10.

17. A method as claimed in claim 15 wherein the antidepressant agent is selected from the group consisting of: norepinephrine reuptake
inhibitors, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, reversible monoamine oxidase inhibitors, serotonin and noradrenaline reuptake inhibitors, corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists and atypical antidepressants.

18. A method as claimed in claim 15 wherein the anti-anxiety agent is selected from the group consisting of benzodiazepines, 5-HT_1A agonists, antagonists or partial agonists, corticotropin releasing factor antagonists and m1 muscarinic cholinergic receptor agonists.

19. A method for the identification of antidepressant and/or anxiolytic activity of CNS-penetrant NK-1 receptor antagonists, which comprises:
   a) to a guinea-pig pup, administration of a NK-1 receptor antagonist or vehicle by intravenous, subcutaneous, intraperitoneal or oral routes;
   b1) 30-60 minutes after intravenous, subcutaneous or intraperitoneal administration, socially isolating the treated guinea-pig pups by removal from their mother and littermates; or
   b2) up to 4 hours after oral administration, socially isolating the treated guinea-pig pups by removal from their mother and littermates; and
   c) recording the number or duration of vocalisations (isolation calls) during a specified period and comparing the effects on guinea-pig pups treated with NK-1 receptor antagonists against their own baseline or against guinea-pig pups that receive no test compound or vehicle.

20. A method for the identification of antidepressant and/or anxiolytic activity of CNS-penetrant NK-1 receptor antagonists, which comprises:
a) to a gerbil, administration of a NK-1 receptor antagonist or vehicle by intravenous, subcutaneous, intraperitoneal or oral routes; 

b) administration by injection under anaesthetic of NK-1 receptor agonists or anxiogenic agents, administered centrally or systemically; or subjecting the gerbil to stressors such as single housing or foot shock; and 

c) recording the duration of repetitive hindfoot tapping and comparing the effects on gerbils treated with NK-1 receptor antagonists against gerbils that receive no test compound or vehicle.

21. A method as claimed in claim 19 or claim 20 wherein the NK-1 receptor antagonist is administered by intravenous injection or orally by gavage.

22. A method for the identification of CNS-penetrant NK-1 receptor antagonists of use as anxiolytic or antidepressant agents which comprises:

(i) Determine affinity for human NK-1 receptor in radioligand binding studies and select compounds with IC$_{50} \leq$ 10nM; and

(ii) Determine activity of compounds for their ability to inhibit distress vocalisations in guinea-pig pups and select compounds with ID$_{50} \leq$ 20mg/kg.

23. A method for the identification of NK-1 receptor antagonists of use as anxiolytic or antidepressant agents which comprises:

(i) Determine affinity for human NK-1 receptor in radioligand binding studies and select compounds with IC$_{50} \leq$ 10nM;

(ii) Determine ability of compounds to penetrate CNS by their ability to inhibit foot tapping in gerbils induced by central injection of an NK-1 agonist and; select compounds that inhibit foot tapping with ID$_{50} \leq$ 3mg/kg i.v., when administered immediately prior to central NK-1
agonist challenge, or ID\textsubscript{50} \leq 30mg/kg p.o. when administered 1 hour prior to central NK-1 agonist challenge; and

(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 and select compounds showing \leq 25-fold loss of potency compared with ID\textsubscript{50} determined in step (ii) above with the proviso that ID\textsubscript{50} \leq 10mg/kg i.v. after 24 hour pre-treatment.

24. A method as claimed in claim 22 or claim 23 which comprises the identification of compounds which satisfy the NK-1 receptor binding criteria of step (i) and which, in addition, have \leq 5-fold shift in affinity when incubated in the presence of human serum albumin (HSA).

25. Use of a CNS-penetrant NK-1 receptor antagonist identified according to a method as claimed in any one of claims 19 to 24 for the manufacture of a medicament for the treatment or prevention of depression and/or anxiety.

26. A method for the treatment or prevention of depression and/or anxiety, which method comprises administration to a patient in need of such treatment an effective amount of a CNS-penetrant NK-1 receptor antagonist identified according to the method of claim 20 or claim 21.
FIG. 1.
FIG. 2.

% Inhibition

Compound B

Compound A

100% 80% 60% 40% 20% 0%

Compound B + fluoxetine

Fluoxetine 2 (i.p.)

Compound B 0.25 (s.c.)

Compound A + fluoxetine

Fluoxetine 2 (i.p.)

Compound A 0.25 (s.c.)

Treatment and dose (mg/kg)

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