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(54) Title: USE OF NK-1 RECEPTOR ANTAGONISTS FOR TREATING EATING DISORDERS																					
(57) Abstract The present invention provides the use of an NK-1 receptor antagonist, optionally with an anorectic agent, for the manufacture of a medicament for the treatment or prevention of eating disorders, methods of treatment using the NK-1 receptor antagonist and pharmaceutical compositions and products containing it.																					
Effect of dexfenfluramine and GR205171 on food intake in diet-induced obese C57BL6/J mice. <table border="1"> <caption>Data for Figure: % inhibition (relative to saline)</caption> <thead> <tr> <th>Group</th> <th>Treatment</th> <th>% inhibition (relative to saline)</th> </tr> </thead> <tbody> <tr> <td>a</td> <td>dexfenfluramine, 3mg/kg</td> <td>-20</td> </tr> <tr> <td>b</td> <td>GR205171, 20mg/kg</td> <td>-20</td> </tr> <tr> <td>c</td> <td>dexfenfluramine, 3mg/kg + GR205171, 5mg/kg</td> <td>-28</td> </tr> <tr> <td>d</td> <td>dexfenfluramine, 3mg/kg + GR205171, 10mg/kg</td> <td>-52*</td> </tr> <tr> <td>e</td> <td>dexfenfluramine, 3mg/kg + GR205171, 20mg/kg</td> <td>-38</td> </tr> </tbody> </table> a dexfenfluramine, 3mg/kg b GR205171, 20mg/kg c dexfenfluramine, 3mg/kg + GR205171, 5mg/kg d dexfenfluramine, 3mg/kg + GR205171, 10mg/kg e dexfenfluramine, 3mg/kg + GR205171, 20mg/kg * p<0.01 vs. dexfenfluramine, 3mg/kg p<0.01 vs. GR205171, 20mg/kg				Group	Treatment	% inhibition (relative to saline)	a	dexfenfluramine, 3mg/kg	-20	b	GR205171, 20mg/kg	-20	c	dexfenfluramine, 3mg/kg + GR205171, 5mg/kg	-28	d	dexfenfluramine, 3mg/kg + GR205171, 10mg/kg	-52*	e	dexfenfluramine, 3mg/kg + GR205171, 20mg/kg	-38
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USE OF NK-1 RECEPTOR ANTAGONISTS FOR
TREATING EATING DISORDERS

This invention relates to the treatment or prevention of eating
5 disorders by the administration of a NK-1 receptor antagonist, optionally
in combination with an anorectic agent.

Eating disorders commonly arise through an imbalance in a
subject's appetite, or desire to eat. It is recognised that appetite is
influenced by the interaction of central and peripheral systems, most
10 likely acting through the effects of neuropeptides on the so-called feeding
and satiety centres in the hypothalamus region of the brain. For instance,
neuropeptides released by the gut in response to a meal may serve to
modulate the intake of further food.

Alterations of appetite may lead to eating disorders including
15 obesity, bulimia nervosa, and compulsive eating disorders.

Obesity is a chronic disease that is highly prevalent in modern
society and is associated not only with a social stigma, but also with
decreased life span and numerous medical problems, including adverse
psychological development, reproductive disorders such as polycystic
20 ovarian disease, dermatological disorders such as infections, varicose
veins, *Acanthosis nigricans*, and eczema, exercise intolerance, diabetes
mellitus, insulin resistance, hypertension, hypercholesterolemia,
cholelithiasis, osteoarthritis, orthopedic injury, thromboembolic disease,
cancer, and coronary heart disease. Rissanen *et al*, *British Medical*
25 *Journal*, 301:835-837 (1990).

Bulimia nervosa is characterised by recurrent episodes of
overeating, or binges, followed by severe dieting often associated with self-
induced vomiting, abuse of laxatives or diuretics, or excessive exercise to
avoid weight gain. Frequent vomiting or purging may result in electrolyte
30 disturbances and erosion of dental enamel.

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Compulsive eating disorders may or may not be associated with other neurological disorders. One well characterised compulsive eating disorder is Prader-Willi syndrome, a congenital disorder characterised by infantile hypotonia, hypogonadism and facial dysmorphism, with
5 subsequent development of hyperplasia and abnormalities of behaviour and intellect.

Treatment regimens for eating disorders typically include the use of anorectic agents, such as amphetamine derivatives.

p-Chloroamphetamine and other halogenated amphetamines promote
10 serotonin (5-hydroxytryptamine; 5-HT) release from platelets and neurons. A rapid release of serotonin is followed by a prolonged and selective depletion of serotonin in the brain. The most widely used example of this class of compound is fenfluramine and its (*S*)-isomer, dexfenfluramine. The precise mechanism of action of these compounds is uncertain,
15 however, fenfluramine and dexfenfluramine are both useful in the treatment of bulimia nervosa and obesity, and fenfluramine has also produced promising results in the management of Prader-Willi syndrome.

Neurokinin 1 (NK-1; substance P) receptor antagonists are being developed for the treatment of a number of physiological disorders
20 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).

25 We have now found that NK-1 receptor antagonists are effective in the treatment of eating disorders, as evidenced by their activity *in vivo* in a model of diet-induced obesity.

Furthermore, a combination of an anorectic agent with a NK-1 receptor antagonist may provide an enhanced anorectic effect. They may
30 also provide for a rapid onset of action to combat eating disorders thereby enabling prescription on an "as-needed" basis.

A particularly preferred class of NK-1 receptor antagonists of use in the present invention are those which are able to cross the blood-brain barrier, otherwise known as CNS- or brain-penetrant compounds.

The present invention accordingly provides the use of a NK-1
5 receptor antagonist for the manufacture of a medicament for the treatment or prevention of eating disorders.

The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an effective amount of a NK-1 receptor
10 antagonist.

In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of eating disorders comprising a NK-1 receptor antagonist, together with at least one pharmaceutically acceptable carrier or excipient.

15 In a further embodiment of the present invention there is provided the use of a NK-1 receptor antagonist for the manufacture of a medicament for the treatment or prevention of obesity.

The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient
20 in need of such treatment an effective amount of a NK-1 receptor antagonist.

In an alternative embodiment of the present invention there is provided the use of a NK-1 receptor antagonist for the manufacture of a medicament for the treatment or prevention of bulimia nervosa.

25 The present invention also provides a method for the treatment or prevention of bulimia nervosa, which method comprises administration to a patient in need of such treatment an effective amount of a NK-1 receptor antagonist.

In a further embodiment of the present invention there is provided
30 the use of a NK-1 receptor antagonist for the manufacture of a

medicament for the treatment or prevention of compulsive eating disorders.

The present invention also provides a method for the treatment or prevention of compulsive eating disorders, which method comprises
5 administration to a patient in need of such treatment an effective amount of a NK-1 receptor antagonist.

In an alternative embodiment of the present invention there is provided the use of a NK-1 receptor antagonist for the manufacture of a medicament for reducing the total body fat mass in an obese mammal,
10 especially a human.

The present invention also provides a method for reducing the total body fat mass in an obese mammal, especially a human, which method comprises administration to a patient in need of such treatment an effective amount of a NK-1 receptor antagonist.

15 The present invention further provides the use of a NK-1 receptor antagonist and an anorectic agent for the manufacture of a medicament for the treatment or prevention of eating disorders.

The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to
20 a patient in need of such treatment an amount of a NK-1 receptor antagonist and an amount of an anorectic agent, such that together they give effective relief.

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

It will be appreciated that the NK-1 receptor antagonist and anorectic agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention
30 of eating disorders. 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 NK-1 receptor antagonist and an anorectic agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of eating disorders.

5 In a further embodiment of the present invention there is provided the use of a NK-1 receptor antagonist and an anorectic agent for the manufacture of a medicament for the treatment or prevention of obesity.

 The present invention also provides a method for the treatment or prevention of obesity, which method comprises administration to a patient
10 in need of such treatment an amount of a NK-1 receptor antagonist and an amount of an anorectic agent, such that together they give effective relief.

 It will be appreciated that the NK-1 receptor antagonist and anorectic agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention
15 of obesity. 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 NK-1 receptor antagonist and an anorectic agent as a combined preparation for simultaneous, separate
20 or sequential use in the treatment or prevention of obesity.

 In an alternative embodiment of the present invention there is provided the use of a NK-1 receptor antagonist and an anorectic agent for the manufacture of a medicament for the treatment or prevention of bulimia nervosa.

25 The present invention also provides a method for the treatment or prevention of bulimia nervosa, which method comprises administration to a patient in need of such treatment an amount of a NK-1 receptor antagonist and an amount of an anorectic agent, such that together they give effective relief.

30 It will be appreciated that the NK-1 receptor antagonist and anorectic agent may be present as a combined preparation for

simultaneous, separate or sequential use for the treatment or prevention of bulimia nervosa. Such combined preparations may be, for example, in the form of a twin pack.

5 In a further or alternative aspect of the present invention, there is therefore provided a product comprising a NK-1 receptor antagonist and an anorectic agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of bulimia nervosa.

10 In a further embodiment of the present invention there is provided the use of a NK-1 receptor antagonist and an anorectic agent for the manufacture of a medicament for the treatment or prevention of compulsive eating disorders.

15 The present invention also provides a method for the treatment or prevention of compulsive eating disorders, which method comprises administration to a patient in need of such treatment an amount of a NK-1 receptor antagonist and an amount of an anorectic agent, such that together they give effective relief.

20 It will be appreciated that the NK-1 receptor antagonist and anorectic agent may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of compulsive eating disorders. Such combined preparations may be, for example, in the form of a twin pack.

25 In a further or alternative aspect of the present invention, there is therefore provided a product comprising a NK-1 receptor antagonist and an anorectic agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of compulsive eating disorders.

30 In an alternative embodiment of the present invention there is provided the use of a NK-1 receptor antagonist and an anorectic agent for the manufacture of a medicament for reducing the total body fat mass in an obese mammal, especially a human.

The present invention also provides a method for reducing the total body fat mass in an obese mammal, especially a human, which method comprises administration to a patient in need of such treatment an amount of a NK-1 receptor antagonist and an amount of an anorectic agent, such that together they give effective relief.

It will be appreciated that the NK-1 receptor antagonist and anorectic agent may be present as a combined preparation for simultaneous, separate or sequential use for reducing the total body fat mass in an obese mammal, especially a human. 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 NK-1 receptor antagonist and an anorectic agent as a combined preparation for simultaneous, separate or sequential use in reducing the total body fat mass in an obese mammal, especially a human.

It will be appreciated that when using a combination of the present invention, both the NK-1 receptor antagonist and the anorectic 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 anorectic agent may be administered as a tablet and then, within a reasonable period of time, the 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 anorectic agent is provided as a tablet, then within one hour, the 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 prevention or treatment of eating disorders. As used herein, the term "eating disorders" includes obesity, bulimia nervosa and compulsive eating disorders.

As used herein "obesity" refers to a condition whereby a mammal has a Body Mass Index (BMI), which is calculated as weight per height squared (kg/m^2), of at least 25.9. Conventionally, those persons with normal weight, have a BMI of 19.9 to less than 25.9.

The obesity herein may be due to any cause, whether genetic or environmental. Examples of disorders that may result in obesity or be the cause of obesity include overeating and bulimia, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, Type II diabetes, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g, children with acute lymphoblastic leukemia.

"Treatment" refers to reducing the BMI of the mammal to less than about 25.9, and maintaining that weight for at least 6 months. The treatment suitably results in a reduction in food or calorie intake by the mammal.

"Prevention" refers to preventing obesity from occurring if the treatment is administered prior to the onset of the obese condition. Moreover, if treatment is commenced in already obese subjects, such treatment is expected to prevent, or to prevent the progression of, the medical sequelae of obesity, such as, e.g., arteriosclerosis, Type II diabetes,

polycystic ovarian disease, cardiovascular diseases, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, and cholelithiasis.

Thus, in one aspect, this invention relates to the inhibition and/or
5 complete suppression of lipogenesis in obese mammals, i.e., the excessive accumulation of lipids in fat cells, which is one of the major features of human and animal obesity, as well as loss of total body weight. In another aspect, the invention ameliorates the conditions that are a consequence of the disease, such as preventing or arresting the progression of polycystic
10 ovarian disease so that the patient is no longer infertile, and increasing the insulin sensitivity and/or decreasing or eliminating the need or usage of insulin in a diabetic patient, e.g., one with adult-onset diabetes or Type II diabetes.

"Mammals" include animals of economic importance such as bovine,
15 ovine, and porcine animals, especially those that produce meat, as well as domestic animals, sports animals, zoo animals, and humans, the latter being preferred.

The compositions of the present invention are especially useful for the treatment of or prevention of eating disorders where the use of an
20 anorectic agent is generally prescribed. By the use of a combination of a NK-1 receptor antagonist and an anorectic agent in accordance with the present invention, it is now also possible to treat or prevent eating disorders in patients for whom conventional anorectic therapy might not be wholly successful or where dependence upon the anorectic therapy is
25 prevalent.

Suitable anorectic agents of use in the combinations of the present invention include, but are not limited to, aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine,
30 dextroamphetamine, diethylpropion, diphemethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex,

fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine,
levophacetoperane, mazindol, mefenorex, metamfepramone,
methamphetamine, norpseudoephedrine, pentorex, phendimetrazine,
phenmetrazine, phentermine, phenylpropanolamine, picilorex and
5 sibutramine; and pharmaceutically acceptable salts thereof.

Particularly preferred anorectic agents include amphetamine and
derivatives thereof such as amphetamine, benzphetamine,
chlorphentermine, clobenzorex, cloforex, clortermine, dexfenfluramine,
dextroamphetamine, diethylpropion, *N*-ethylamphetamine, fenfluramine,
10 fenproporex, furfurylmethylamphetamine, levamfetamine, mefenorex,
metamfepramone, methamphetamine, norpseudoephedrine, pentorex,
phenmetrazine, phentermine, phenylpropanolamine,
picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

A particularly suitable class of anorectic agent are the halogenated
15 amphetamine derivatives, including chlorphentermine, cloforex,
clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine;
and pharmaceutically acceptable salts thereof;

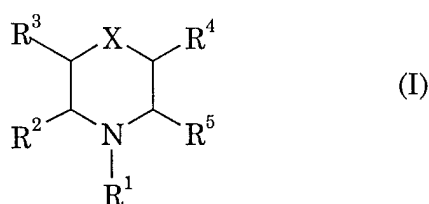
Particularly preferred halogenated amphetamine derivatives of use
in the present invention include: fenfluramine and dexfenfluramine, and
20 pharmaceutically acceptable salts thereof.

Another particularly preferred anorectic agent is phentermine.

NK-1 receptor antagonists of use in the present invention are
described in published European Patent Specification Nos. 0 360 390,
0 394 989, 0 429 366, 0 443 132, 0 482 539, 0 512 901, 0 512 902,
25 0 514 273, 0 514 275, 0 517 589, 0 520 555, 0 522 808, 0 528 495,
0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 577 394, 0 590 152,
0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535,
0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 714 891, 0 723 959, 0 733 632
and 0 776 893; and in International Patent Specification Nos. 90/05525,
30 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585,
92/17449, 92/20661, 92/20676, 92/21677, 93/00330, 93/00331, 93/01159,

93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14113,
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 5 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740,
 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908,
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 10 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317,
 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554,
 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942
 and 97/21702; and in British Patent Specification Nos. 2 266 529, 2 268
 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and
 15 2 302 689.

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



20

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from the group consisting of:

(1) hydrogen;

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

25 substituents selected from:

(a) hydroxy,

(b) oxo,

(c) C₁₋₆alkoxy,

- (d) phenyl-C₁₋₃alkoxy,
(e) phenyl,
(f) -CN,
(g) halo,
5 (h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are independently ...
selected from:
(i) hydrogen,
(ii) C₁₋₆alkyl,
(iii) hydroxy-C₁₋₆alkyl, and
10 (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,
15 (m) -CO₂R⁹, wherein R⁹ is as defined above,
(n) heterocycle, wherein the heterocycle is selected from
the group consisting of:
(A) benzimidazolyl,
(B) benzofuranyl,
20 (C) benzthiophenyl,
(D) benzoxazolyl,
(E) furanyl,
(F) imidazolyl,
(G) indolyl,
25 (H) isoxazolyl,
(I) isothiazolyl,
(J) oxadiazolyl,
(K) oxazolyl,
(L) pyrazinyl,
30 (M) pyrazolyl,
(N) pyridyl,

- 5 (O) pyrimidyl,
(P) pyrrolyl,
(Q) quinolyl,
(R) tetrazolyl,
(S) thiadiazolyl,
(T) thiazolyl,
(U) thienyl,
(V) triazolyl,
(W) azetidinyll,
10 (X) 1,4-dioxanyl,
(Y) hexahydroazepinyl,
(Z) oxanyl,
(AA) piperazinyl,
(AB) piperidinyl,
15 (AC) pyrrolidinyl,
(AD) tetrahydrofuranyl, and
(AE) tetrahydrothienyl,

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

- 20 (i) C₁₋₆alkyl, unsubstituted or substituted with halo, -CF₃,
-OCH₃, or phenyl,
(ii) C₁₋₆alkoxy,
(iii) oxo,
(iv) hydroxy,
25 (v) thioxo,
(vi) -SR⁹, wherein R⁹ is as defined above,
(vii) halo,
(viii) cyano,
(ix) phenyl,
30 (x) trifluoromethyl,

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

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

5 (xiv) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above, and

(xv) $-(\text{CH}_2)_m\text{-OR}^9$, wherein m and R^9 are as defined above;

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

- 10 (a) hydroxy,
(b) oxo,
(c) C_{1-6} alkoxy,
(d) phenyl- C_{1-3} alkoxy,
(e) phenyl,
(f) $-\text{CN}$,
15 (g) halo,
(h) $-\text{CONR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
(i) $-\text{COR}^9$, wherein R^9 is as defined above,
(j) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above,
(k) heterocycle, wherein the heterocycle is as defined
20 above;

(4) C_{2-6} alkynyl;

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

- 25 (a) hydroxy,
(b) C_{1-6} alkoxy,
(c) C_{1-6} alkyl,
(d) C_{2-5} alkenyl,
(e) halo,
(f) $-\text{CN}$,
30 (g) $-\text{NO}_2$,
(h) $-\text{CF}_3$,

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

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

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

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

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

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

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

10 R^2 and R^3 are independently 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,

15 (b) oxo,

(c) C_{1-6} alkoxy,

(d) phenyl- C_{1-3} alkoxy,

(e) phenyl,

(f) $-\text{CN}$,

20 (g) halo,

(h) $-\text{NR}^9\text{R}^{10}$, wherein R^9 and R^{10} are independently

selected from:

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

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

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

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

(m) $-\text{CO}_2\text{R}^9$, 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:

30 (a) hydroxy,

(b) oxo,

- (c) C₁₋₆alkoxy,
(d) phenyl-C₁₋₃alkoxy,
(e) phenyl,
(f) -CN,
5 (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) C₂₋₆alkynyl;
- 10 (5) phenyl, unsubstituted or substituted with one or more of the
substituent(s) selected from:
- (a) hydroxy,
(b) C₁₋₆alkoxy,
(c) C₁₋₆alkyl,
15 (d) C₂₋₅alkenyl,
(e) halo,
(f) -CN,
(g) -NO₂,
(h) -CF₃,
20 (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,
25 (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;

and the groups R¹ and R² may be joined together to form a heterocyclic
30 ring selected from the group consisting of:

- (a) pyrrolidinyl,

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

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

- (i) C₁₋₆alkyl,
10 (ii) oxo,
(iii) C₁₋₆alkoxy,
(iv) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(v) halo, and
(vi) trifluoromethyl;

15

and the groups R² and R³ may be joined together to form a carbocyclic ring selected from the group consisting of:

- (a) cyclopentyl,
(b) cyclohexyl,
20 (c) phenyl,

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

- (i) C₁₋₆alkyl,
(ii) C₁₋₆alkoxy,
25 (iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(iv) halo, and
(v) trifluoromethyl;

and the groups R² and R³ may be joined together to form a heterocyclic ring selected from the group consisting of:

- 30 (a) pyrrolidinyl,

- 5 (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
 10 or more substituent(s) selected from:

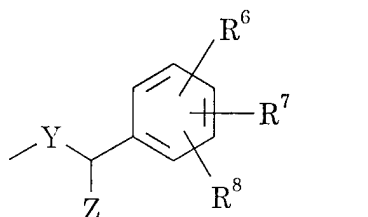
- (i) C₁₋₆alkyl,
 (ii) oxo,
 (iii) C₁₋₆alkoxy,
 (iv) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 15 (v) halo, and
 (vi) trifluoromethyl;

X is selected from the group consisting of:

- (1) -O-,
 20 (2) -S-,
 (3) -SO-, and
 (4) -SO₂;

R⁴ is selected from the group consisting of:

- 25 (1)



- (2) -Y-C₁₋₈alkyl, wherein alkyl is 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,
 (f) -CN,
 (g) halo,
 (h) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 (i) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 10 (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,
 (m) -CO₂R⁹, wherein R⁹ is as defined above;

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

- (a) hydroxy,
 (b) oxo,
 (c) C₁₋₆alkoxy,
 (d) phenyl-C₁₋₃alkoxy,
 20 (e) phenyl,
 (f) -CN,
 (g) halo,
 (h) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 (i) -COR⁹, wherein R⁹ is as defined above,
 25 (j) -CO₂R⁹, wherein R⁹ is as defined above,

(4) -O(CO)-phenyl, wherein the phenyl is unsubstituted or
 substituted with one or more of R⁶, R⁷ and R⁸;

R⁵ is selected from the group consisting of:

- 30 (1) phenyl, unsubstituted or substituted with one or more of R¹¹, R¹²
 and R¹³;

(2) C₁₋₈alkyl, unsubstituted or substituted with one or more of the substituent(s) selected from:

- (a) hydroxy,
- (b) oxo,
- 5 (c) C₁₋₆alkoxy,
- (d) phenyl-C₁₋₃alkoxy,
- (e) phenyl,
- (f) -CN,
- (g) halo,
- 10 (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,
- 15 (m) -CO₂R⁹, wherein R⁹ is as defined above;

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

- (a) hydroxy,
- (b) oxo,
- 20 (c) C₁₋₆alkoxy,
- (d) phenyl-C₁₋₃alkoxy,
- (e) phenyl,
- (f) -CN,
- (g) halo,
- 25 (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) heterocycle, wherein the heterocycle is as defined above;

30 R⁶, R⁷ and R⁸ 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:

- (a) hydroxy,
- (b) oxo,
- 5 (c) C₁₋₆alkoxy,
- (d) phenyl-C₁₋₃alkoxy,
- (e) phenyl,
- (f) -CN,
- (g) halo,
- 10 (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
- 15 (m) -CO₂R⁹, wherein R⁹ is as defined above;

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

- (a) hydroxy,
- (b) oxo,
- 20 (c) C₁₋₆alkoxy,
- (d) phenyl-C₁₋₃alkoxy,
- (e) phenyl,
- (f) -CN,
- (g) halo,
- 25 (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) C₂₋₆alkynyl;

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

- (a) hydroxy,

- (b) C₁₋₆alkoxy,
 (c) C₁₋₆alkyl,
 (d) C₂₋₅alkenyl,
 (e) halo,
 5 (f) -CN,
 (g) -NO₂,
 (h) -CF₃,
 (i) -(CH₂)_m-NR⁹R¹⁰, wherein m, R⁹ and R¹⁰ are as defined
 above,
 10 (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;
 15 (o) -CO₂R⁹, wherein R⁹ is as defined above;
 (6) halo,
 (7) -CN,
 (8) -CF₃,
 (9) -NO₂,
 20 (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,
 25 (15) NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 (16) NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
 (17) hydroxy,
 (18) C₁₋₆alkoxy,
 (19) COR⁹, wherein R⁹ is as defined above,
 30 (20) CO₂R⁹, wherein R⁹ is as defined above,

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

Y is selected from the group consisting of:

- 5 (1) a single bond,
 (2) -O-,
 (3) -S-,
 (4) -CO-,
 (5) -CH₂-,
10 (6) -CHR¹⁵-, and
 (7) -CR¹⁵R¹⁶-, wherein R^{15} and R^{16} are independently selected from
the group consisting of:
- (a) C₁₋₆alkyl, unsubstituted or substituted with one or
more of the substituents selected from:
- 15 (i) hydroxy,
 (ii) oxo,
 (iii) C₁₋₆alkoxy,
 (iv) phenyl-C₁₋₃alkoxy,
 (v) phenyl,
20 (vi) -CN,
 (vii) halo,
 (viii) -NR⁹R¹⁰, wherein R^9 and R^{10} are as defined above,
 (ix) -NR⁹COR¹⁰, wherein R^9 and R^{10} are as defined above,
 (x) -NR⁹CO₂R¹⁰, wherein R^9 and R^{10} are as defined above,
25 (xi) -CONR⁹R¹⁰, wherein R^9 and R^{10} are as defined above,
 (xii) -COR⁹, wherein R^9 is as defined above, and
 (xiii) -CO₂R⁹, wherein R^9 is as defined above;
 (b) phenyl, unsubstituted or substituted with one or more
of the substituent(s) selected from:
- 30 (i) hydroxy,
 (ii) C₁₋₆alkoxy,

- (iii) C₁₋₆alkyl,
(iv) C₂₋₅alkenyl,
(v) halo,
(vi) -CN,
5 (vii) -NO₂,
(viii) -CF₃,
(ix) -(CH₂)_m-NR⁹R¹⁰, wherein m, R⁹ and R¹⁰ are as defined
above,
(x) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
10 (xi) -NR⁹CO₂R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(xii) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(xiii) -CO₂NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
(xiv) -COR⁹, wherein R⁹ is as defined above, and
(xv) -CO₂R⁹, wherein R⁹ is as defined above;

15

Z is selected from:

- (1) hydrogen,
(2) C₁₋₄alkyl, and
(3) hydroxy, with the proviso that if Y is -O-, Z is other than
20 hydroxy, or if Y is -CHR¹⁵-, then Z and R¹⁵ may be joined together to form
a double bond.

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

R¹ is selected from the group consisting of:

- (1) C₁₋₆alkyl, substituted with one or more of the substituents
25 selected from:
(a) heterocycle, wherein the heterocycle is selected from
the group consisting of:
(A) benzimidazolyl,
(B) imidazolyl,
30 (C) isoxazolyl,
(D) isothiazolyl,

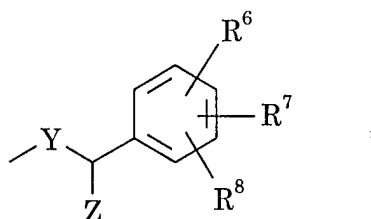
- 25 -

- (E) oxadiazolyl,
(F) pyrazinyl,
(G) pyrazolyl,
(H) pyridyl,
5 (I) pyrrolyl,
(J) tetrazolyl,
(K) thiadiazolyl,
(L) triazolyl, and
(M) piperidinyll,
- 10 and wherein the heterocycle is unsubstituted or substituted with one or more substituent(s) selected from:
- (i) C₁₋₆alkyl, unsubstituted or substituted with halo, -CF₃, -OCH₃, or phenyl,
(ii) C₁₋₆alkoxy,
15 (iii) oxo,
(iv) thioxo,
(v) cyano,
(vi) -SCH₃,
(vii) phenyl,
20 (viii) hydroxy,
(ix) trifluoromethyl,
(x) -(CH₂)_m-NR⁹R¹⁰, wherein m is 0, 1 or 2, and R⁹ and R¹⁰ are independently selected from:
- (I) hydrogen,
25 (II) C₁₋₆alkyl,
(III) hydroxyC₁₋₆alkyl, and
(IV) phenyl,
(xi) -NR⁹COR¹⁰, wherein R⁹ and R¹⁰ are as defined above,
and
30 (xii) -CONR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
R² and R³ are independently selected from the group consisting of:

- (1) hydrogen;
- (2) C₁₋₆alkyl
- (3) C₂₋₆alkenyl, and
- (5) phenyl;

5 X is -O-;

R⁴ is



R⁵ is phenyl, unsubstituted or substituted with halo;

R⁶, R⁷ and R⁸ are independently selected from the group consisting of:

- 10
- (1) hydrogen,
 - (2) C₁₋₆alkyl,
 - (3) halo, and
 - (4) -CF₃;

Y is -O-; and

- 15 Z is hydrogen or C₁₋₄alkyl;

and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of formula (I) are:

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

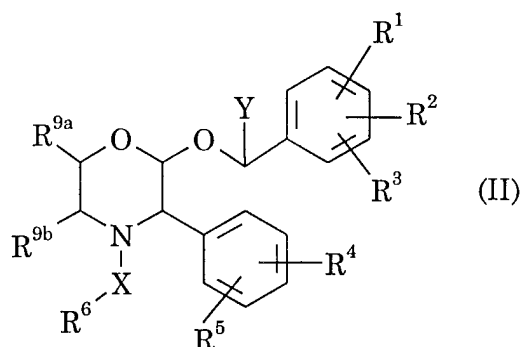
- 20 4-(3-(1,2,4-triazolo)methyl)-2(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3(R)-phenyl-morpholine;

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

2-(R)-(1(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-

- 25 4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine; or a pharmaceutically acceptable salt thereof.

Further preferred NK-1 receptor antagonists are those described in International (PCT) Patent Specification No. WO 95/18124, i.e. compounds of formula (II):



5

or a pharmaceutically acceptable salt or prodrug thereof, wherein

R¹ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, CF₃, NO₂, CN, SR^a, SOR^a, SO₂R^a, CO₂R^a, CONR^aR^b, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₄alkyl substituted by C₁₋₄alkoxy, where R^a and R^b each independently represent hydrogen or C₁₋₄alkyl;

10

R² is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy substituted by C₁₋₄alkoxy or CF₃;

R³ is hydrogen, halogen or CF₃;

R⁴ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy, CF₃, NO₂, CN, SR^a, SOR^a, SO₂R^a, CO₂R^a, CONR^aR^b, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₄alkyl substituted by C₁₋₄alkoxy, where R^a and R^b each independently represent hydrogen or C₁₋₄alkyl;

15

R⁵ is hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy substituted by C₁₋₄alkoxy or CF₃;

20

R⁶ is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C₁₋₄alkyl group, and optionally substituted by a group of the formula ZNR⁷R⁸ where

Z is C₁₋₆alkylene or C₃₋₆cycloalkylene;

R⁷ is hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl or C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by C₁₋₄alkoxy or hydroxyl;

25

R⁸ is hydrogen, C₁₋₄alkyl, C₃₋₇cycloalkyl or C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by one or two substituents selected from C₁₋₄alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

5 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 NR^c moiety where
10 R^c is C₁₋₄alkyl optionally substituted by hydroxy or C₁₋₄alkoxy;

 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
15 oxygen ring atom;

 R^{9a} and R^{9b} are each independently hydrogen or C₁₋₄alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C₅₋₇ ring;

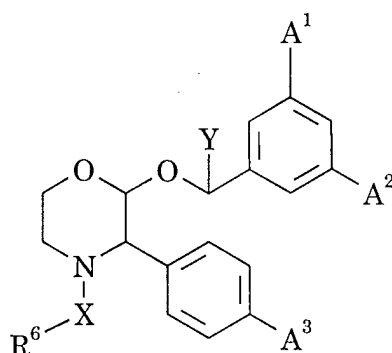
 X is an alkylene chain of 1 to 4 carbon atoms optionally substituted
20 by oxo; and

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

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

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

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(IIa)

wherein:

A¹ is fluorine or CF₃;

A² is fluorine or CF₃;

5 A³ is fluorine or hydrogen;

and X, Y and R⁶ are as defined in relation to formula (II).

Particularly preferred compounds of formula (II) include:

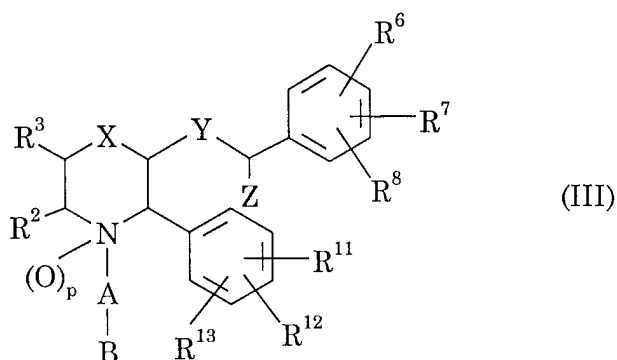
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino) methyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

10 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 NK-1 receptor antagonists are those described in European Patent Specification No. WO 95/23798, i.e. compounds of

15 formula (III):



(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,

15 (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,

20 (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) 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,

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- (h) $-\text{CONR}^9\text{R}^{10}$ wherein R^9 and R^{10} are as defined above,
 - (i) $-\text{COR}^9$ wherein R^9 is as defined above,
 - (j) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above;
- (4) C_{2-6} alkynyl;
- 5 (5) phenyl, unsubstituted or substituted with one or more of the substituent(s) selected from:
- (a) hydroxy,
 - (b) C_{1-6} alkoxy,
 - (c) C_{1-6} alkyl,
 - 10 (d) C_{2-5} alkenyl,
 - (e) halo,
 - (f) $-\text{CN}$,
 - (g) $-\text{NO}_2$,
 - (h) $-\text{CF}_3$,
 - 15 (i) $-(\text{CH}_2)_m-\text{NR}^9\text{R}^{10}$, wherein m , R^9 and R^{10} are as defined above,
 - (j) $-\text{NR}^9\text{COR}^{10}$, wherein R^9 and R^{10} are as defined above,
 - (k) $-\text{NR}^9\text{CO}_2\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
 - (l) $-\text{CONR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
 - 20 (m) $-\text{CO}_2\text{NR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
 - (n) $-\text{COR}^9$, wherein R^9 is as defined above,
 - (o) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above;

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

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

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

- (i) C_{1-6} alkyl,

- 32 -

- (ii) C₁₋₆alkoxy,
- (iii) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (iv) halo, and
- (v) trifluoromethyl;

5

and the groups R² and R³ may be joined together to form a heterocyclic ring selected from the group consisting of:

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

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

- (i) C₁₋₆alkyl,
- 20 (ii) oxo,
- (iii) C₁₋₆alkoxy,
- (iv) -NR⁹R¹⁰, wherein R⁹ and R¹⁰ are as defined above,
- (v) halo, and
- (vi) trifluoromethyl;

25

R⁶, R⁷ and R⁸ 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:

- 30 (a) hydroxy,
- (b) oxo,

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- 5 (c) C₁₋₆alkoxy,
(d) phenyl-C₁₋₃alkoxy,
(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,
10 (l) -COR⁹, wherein R⁹ is as defined above, and
(m) -CO₂R⁹, wherein R⁹ is as defined above;

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

- 15 (a) hydroxy,
(b) oxo,
(c) C₁₋₆alkoxy,
(d) phenyl-C₁₋₃alkoxy,
(e) phenyl,
(f) -CN,
20 (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) C₂₋₆alkynyl;

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

- 30 (a) hydroxy,
(b) C₁₋₆alkoxy,
(c) C₁₋₆alkyl,
(d) C₂₋₅alkenyl,
(e) halo,

- (f) -CN,
(g) -NO₂,
(h) -CF₃,
(i) -(CH₂)_m-NR⁹R¹⁰, wherein m, R⁹ and R¹⁰ are as defined
5 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,
10 (n) -COR⁹, wherein R⁹ is as defined above,
(o) -CO₂R⁹, wherein R⁹ is as defined above;
(6) halo,
(7) -CN,
(8) -CF₃,
15 (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,
20 (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) C₁₋₆alkoxy,
25 (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,
30 (24) 5-tetrazolyl,
(25) 2-oxazolyl, and

(26) 2-thiazolyl;

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

5

A is selected from the group consisting of:

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

- 10
- (a) hydroxy,
 - (b) oxo,
 - (c) C₁₋₆alkoxy,
 - (d) phenyl-C₁₋₃alkoxy,
 - (e) phenyl,
 - (f) -CN,
 - 15 (g) halo, wherein halo is fluoro, chloro, bromo or iodo,
 - (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,
 - 20 (l) -COR⁹, wherein R⁹ is as defined above, and
 - (m) -CO₂R⁹, wherein R⁹ is as defined above;

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

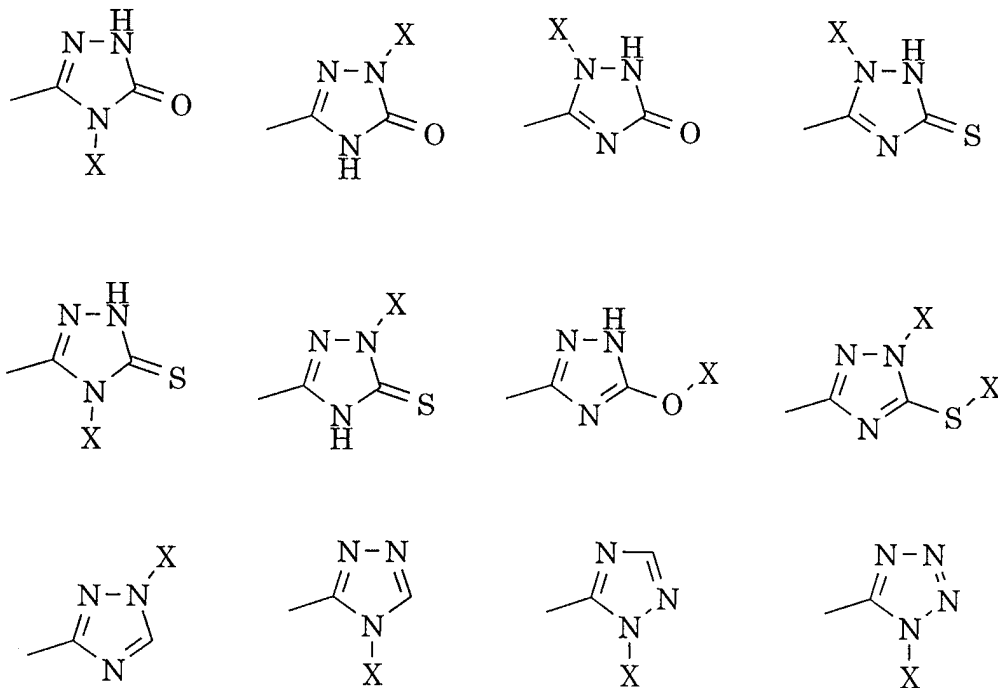
- 25
- (a) hydroxy,
 - (b) oxo,
 - (c) C₁₋₆alkoxy,
 - (d) phenyl-C₁₋₃alkoxy,
 - (e) phenyl,
 - 30 (f) -CN,
 - (g) halo,

- (h) $-\text{CONR}^9\text{R}^{10}$ wherein R^9 and R^{10} are as defined above,
- (i) $-\text{COR}^9$ wherein R^9 is as defined above, and
- (j) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above; and

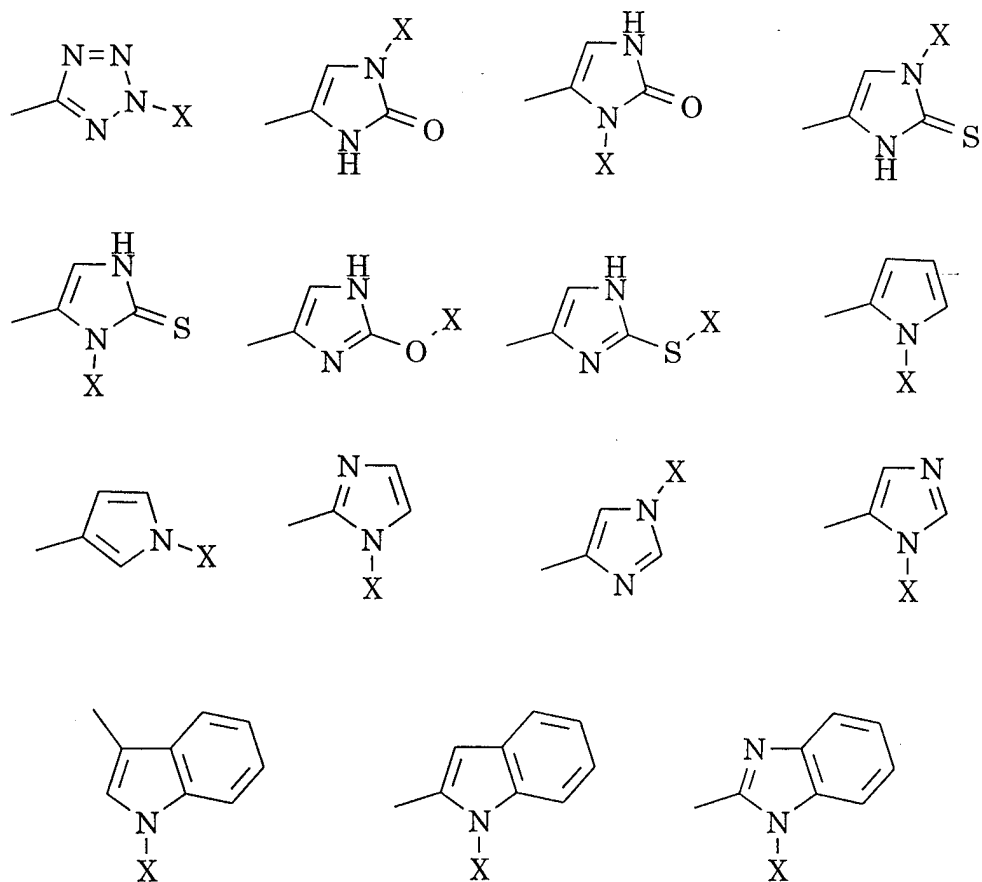
(3) C_{2-6} alkynyl;

5

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



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and wherein the heterocycle may be substituted in addition to -X with one or more substituent(s) selected from:

- (i) C₁₋₆alkyl, unsubstituted or substituted with halo, -CF₃,
5 -OCH₃, or phenyl,
- (ii) C₁₋₆alkoxy,
- (iii) oxo,
- (iv) hydroxy,
- (v) thioxo,
- (vi) -SR⁹, wherein R⁹ is as defined above,
10
- (vii) halo,
- (viii) cyano,
- (ix) phenyl,
- (x) trifluoromethyl,
- (xi) -(CH₂)_m-NR⁹R¹⁰, wherein m is 0, 1 or 2, and R⁹ and R¹⁰
15 are as defined above,

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

5

p is 0 or 1;

X is selected from:

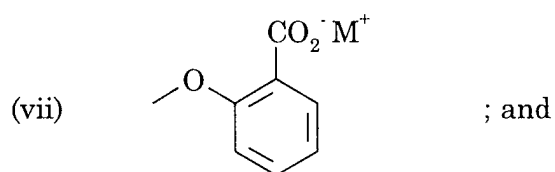
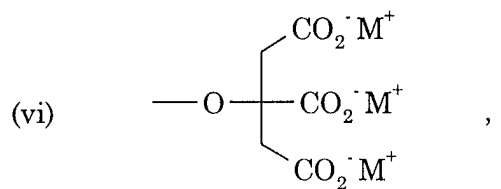
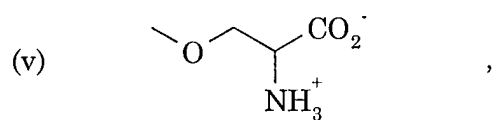
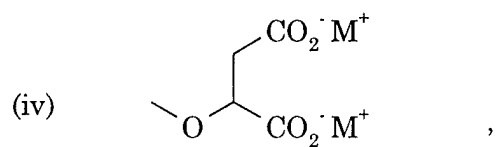
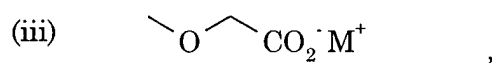
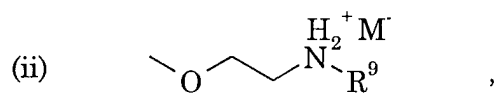
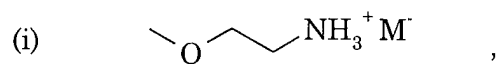
- (a) $-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
- (b) $-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- (c) $-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
- (d) $-\text{CH}(\text{R}^4)-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein R^4 is hydrogen or C_{1-3} alkyl,
- (e) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- (f) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$,
- (g) $-\text{SO}_3^- \cdot \text{M}^+$,
- (h) $-\text{CH}(\text{R}^4)-\text{SO}_3^- \cdot \text{M}^+$,
- (i) $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2^- \cdot \text{M}^+$,
- (j) $-\text{CH}(\text{CH}_3)-\text{O}-\text{CO}-\text{R}^5$, wherein R^5 is selected from the group consisting of:

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15

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(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 R^{15} and R^{16} are independently selected from the group consisting of:

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

(i) hydroxy,

(ii) oxo,

(iii) C_{1-6} alkoxy,

10 (iv) phenyl- C_{1-3} alkoxy,

(v) phenyl,

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

(vii) halo,

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

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

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

(xi) $-\text{CONR}^9\text{R}^{10}$, wherein R^9 and R^{10} 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;

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

(i) hydroxy,

(ii) C_{1-6} alkoxy,

(iii) C_{1-6} alkyl,

25 (iv) C_{2-5} alkenyl,

(v) halo,

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

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

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

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

- (x) $-\text{NR}^9\text{COR}^{10}$, wherein R^9 and R^{10} are as defined above,
(xi) $-\text{NR}^9\text{CO}_2\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
(xii) $-\text{CONR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
(xiii) $-\text{CO}_2\text{NR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,
5 (xiv) $-\text{COR}^9$, wherein R^9 is as defined above, and
(xv) $-\text{CO}_2\text{R}^9$, wherein R^9 is as defined above;

Z is selected from:

- (1) hydrogen,
10 (2) C_{1-6} 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 (III) are those wherein:

- 15 R^2 and R^3 are independently selected from the group consisting of:

- (1) hydrogen,
(2) C_{1-6} alkyl,
(3) C_{2-6} alkenyl, and
(4) phenyl;

- 20 R^6 , R^7 and R^8 are independently selected from the group consisting of:

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

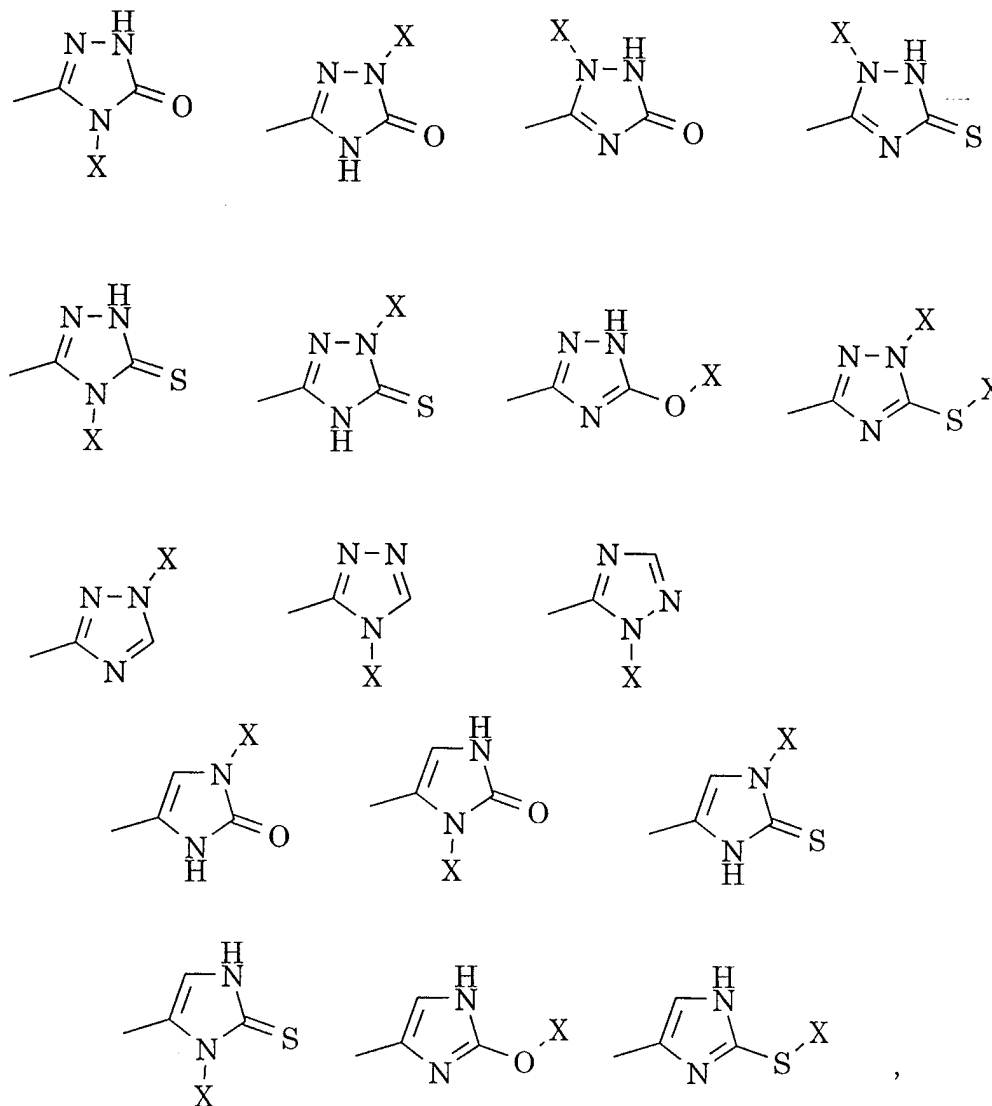
R^{11} , R^{12} and R^{13} are independently selected from the group consisting of:

- (1) fluoro,
30 (2) chloro,
(3) bromo, and

(4) iodo;

A is unsubstituted 1-6alkyl;

B is selected from the group consisting of:



p is 0 or 1;

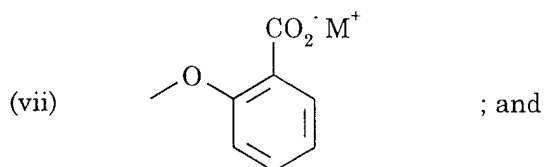
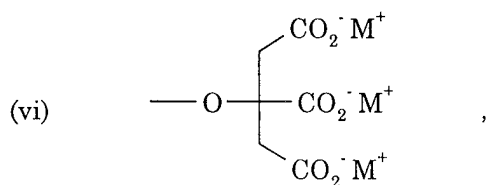
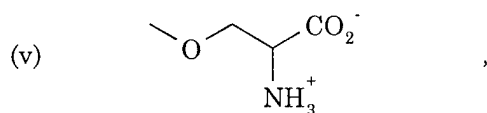
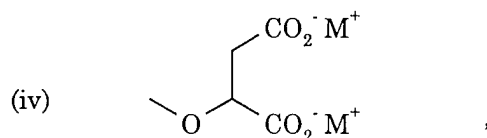
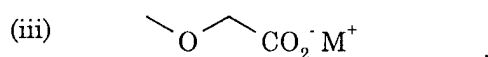
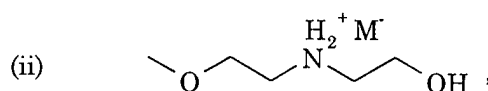
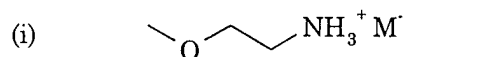
X is selected from:

- (a) $-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
- 10 (b) $-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- (c) $-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
- (d) $-\text{CH}(\text{R}^4)-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein R^4 is hydrogen or C_{1-3} alkyl,

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- (e) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
 (f) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$,
 (i) $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2^- \cdot \text{M}^+$,
 (j) $-\text{CH}(\text{CH}_3)-\text{O}-\text{CO}-\text{R}^5$, wherein R^5 is selected from the group

5 consisting of:



Y is $-\text{O}-$;

Z is hydrogen or C_{1-6} alkyl;

and pharmaceutically acceptable salts thereof.

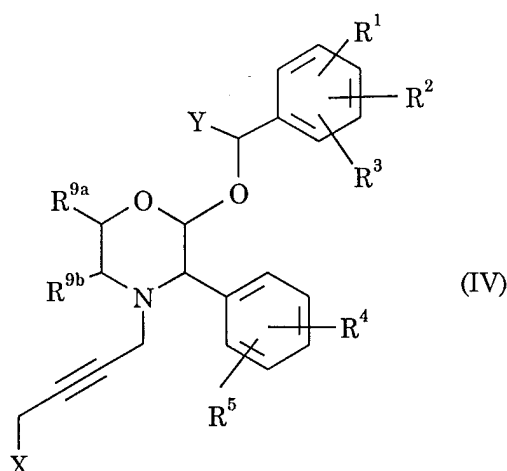
Particularly preferred compounds of formula (III) include:

- (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-
5 (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;
- 10 (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-
15 triazolo)methyl)morpholine;
- (6) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxophosphoryl-1H-1,2,4-triazolo)methyl)morpholine;
- (7) 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-
20 fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;

and pharmaceutically acceptable salts thereof.

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

- 45 -



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 ,
 SOR^a , SO_2R^a , CO_2R^a , CONR^aR^b , C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-4} alkyl
 10 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} cycloalkyl C_{1-4} alkyl,
 phenyl, or C_{2-4} alkyl substituted by C_{1-4} alkoxy or hydroxy;

R^7 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-4} alkyl,
 phenyl, or C_{2-4} alkyl substituted by one or two substituents selected from

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C₁₋₄alkoxy, hydroxy or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

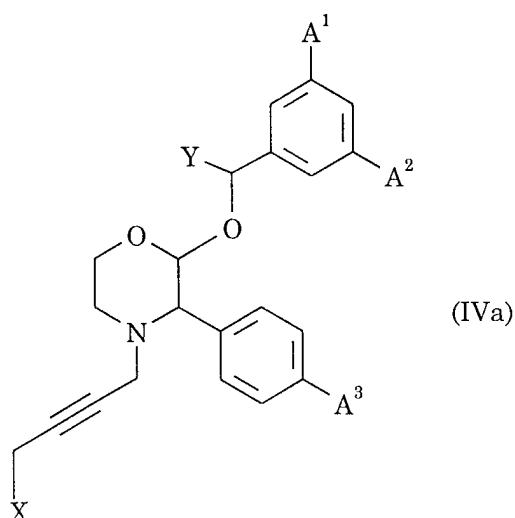
or R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a saturated or partially saturated heterocyclic ring of 4 to 7 ring atoms, which ring may optionally contain in the ring one oxygen or sulphur atom or a group selected from NR⁸, S(O) or S(O)₂ and which ring may be optionally substituted by one or two groups selected from hydroxyc₁₋₄alkyl, C₁₋₄alkoxyc₁₋₄alkyl, oxo, COR^a or CO₂R^a where R^a 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;

R⁸ is hydrogen, C₁₋₄alkyl, hydroxyc₁₋₄alkyl or C₁₋₄alkoxyc₁₋₄alkyl; and

R^{9a} and R^{9b} are each independently hydrogen or C₁₋₄alkyl, or R^{9a} and R^{9b} 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;

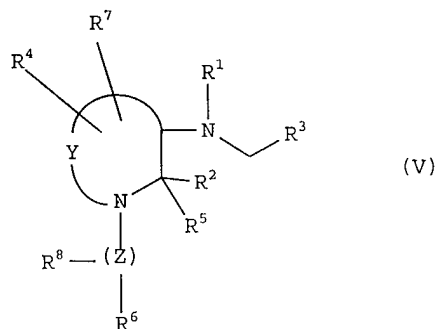
and X and Y are as defined in relation to formula (I).

- Specific compounds of formula (IV) of use in the present invention
- 5 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-azetidinybut-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)-
15 4-(4-(N-methylpiperazinyl)but-2-yn-yl)morpholine;
- 4-(4-bis(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-azetidinybut-2-yn-yl)-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-
25 (trifluoromethyl)phenyl)ethoxy)morpholine;
- 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)amino)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)amino)but-2-yn-yl)-3-(S)-phenylmorpholine;

- 4-(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-azetidinybut-2yn-yl)-3-(S)-(4-fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;
 5 2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-(4-(N,N-dimethylamino)but-2-yn-yl)-3-(S)-(4-fluorophenyl)morpholine;
 4-(4-azetidinybut-2-yn-yl)-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)morpholine;
 4-(4-N-bis(2-methoxy)ethyl-N-methylamino)but-2-yn-yl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;
 10 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-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;
 15 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)-
 20 4-(4-(2-(S)-(hydroxymethyl)pyrrolidino)but-2-yn-yl)morpholine;
 and pharmaceutically acceptable salts thereof.

Another class of NK-1 receptor antagonists of use in the present invention is that described in European Patent Specification No. 0 436 334, i.e. compounds of formula (V):

25



or a pharmaceutically acceptable salt thereof, wherein

Y is $(\text{CH}_2)_n$ wherein n is an integer from 1 to 4, and wherein any one of the carbon-carbon single bonds in said $(\text{CH}_2)_n$ may optionally be replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(\text{CH}_2)_n$ may optionally be substituted with R^4 , and wherein any one of the carbon atoms of said $(\text{CH}_2)_n$ may optionally be substituted with R^7 ;

Z is $(\text{CH}_2)_m$ wherein m is an integer from 0 to 6, and wherein any one of the carbon-carbon single bonds of $(\text{CH}_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(\text{CH}_2)_m$ may optionally be substituted with R^8 ;

R^1 is hydrogen or C_{1-8} alkyl optionally substituted with hydroxy, C_{1-4} alkoxy or fluoro;

R^2 is a radical selected from hydrogen, C_{1-6} straight or branched alkyl, C_3-7 cycloalkyl wherein one of the CH_2 groups in said cycloalkyl may optionally be replaced by NH, oxygen or sulphur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl- C_{2-6} alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl- C_{2-6} alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl, amino, C_{1-6} alkylamino, C_{1-6} alkyl-O-CO, C_{1-6} alkyl-O-CO- C_{1-6} alkyl, C_{1-6} alkyl-CO-O, C_{1-6} alkyl-CO- C_{1-6} alkyl-O-, C_{1-6} alkyl-CO, C_{1-6} alkyl-CO- C_{1-6} alkyl-, di- C_{1-6} alkylamino, -CONH- C_{1-6} alkyl, C_{1-6} alkyl-CO-NH- C_{1-6} alkyl, -NHCOH and -NHCO- C_{1-6} alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^5 is hydrogen, phenyl or C_{1-6} alkyl;

or R² and R⁵ together with the carbon to which they are attached, form a saturated ring having from 3 to 7 carbon atoms wherein one of the CH₂ groups in said ring may optionally be replaced by oxygen, NH or sulfur;

5 R³ is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of the (CH₂) groups in said cycloalkyl may optionally be replaced by NH, oxygen or sulphur;

10 wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said C₃₋₇cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, C₁₋₆alkyl, C₁₋₆alkoxy, trifluoromethyl, amino, C₁₋₆alkylamino, -CO-NH-C₁₋₆alkyl, 15 C₁₋₆alkyl-CO-NH-C₁₋₆alkyl, -NHCOH and -NHCO-C₁₋₆alkyl;

 R⁴ and R⁷ are each independently selected from hydroxy, halogen, halo, amino, oxo, cyano, methylene, hydroxymethyl, halomethyl, C₁₋₆alkylamino, di-C₁₋₆alkylamino, C₁₋₆alkoxy, C₁₋₆alkyl-O-CO, C₁₋₆alkyl-O-CO-C₁₋₆alkyl, C₁₋₆alkyl-CO-O, C₁₋₆alkyl-CO-C₁₋₆alkyl-O-, 20 C₁₋₆alkyl-CO-, C₁₋₆alkyl-CO-C₁₋₆alkyl, and the radicals set forth in the definition of R²;

 R⁶ is -NHCOR⁹, -NHCH₂R⁹, SO₂R⁸ or one of the radicals set forth in any of the definitions of R², R⁴ and R⁷;

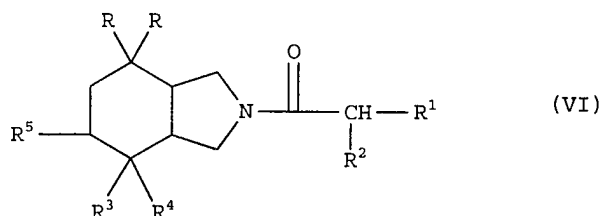
 R⁸ is oximino (=NOH) or one of the radicals set forth in any of the 25 definitions of R², R⁴ and R⁷;

 R⁹ is C₁₋₆alkyl, hydrogen, phenyl or phenylC₁₋₆alkyl; with the proviso that (a) when m is 0, R⁸ is absent, (b) when R⁴, R⁶, R⁷ or R⁸ is as defined in R², it cannot form together with the carbon to which it is attached, a ring with R⁵, and (c) when R⁴ and R⁷ are attached to the 30 same carbon atom, then either each of R⁴ and R⁷ is independently selected from hydrogen, fluoro and C₁₋₆alkyl, or R⁴ and R⁷, together with the carbon

to which they are attached, for a C₃₋₆ saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached.

A particularly preferred compound of formula (V) is (2S,3S)-cis-3-(2-methoxybenzylamino)-2-phenylpiperidine; or a pharmaceutically acceptable salt thereof.

Another class of NK-1 receptor antagonists of use in the present invention is that described in International Patent Specification No. WO 93/21155, i.e. compounds of formula (VI):



or a pharmaceutically acceptable salt thereof, wherein

radicals R are phenyl radicals optionally 2- or 3-substituted by a halogen atom or a methyl radical;

R¹ is optionally substituted phenyl, cyclohexadienyl, naphthyl, indenyl or optionally substituted heterocycle;

R² is H, halogen, OH, alkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkyloxy, alkylthio, acyloxy, carboxy, optionally substituted alkyloxycarbonyl, benzyloxycarbonyl, amino or acylamino;

R³ is optionally 2-substituted phenyl;

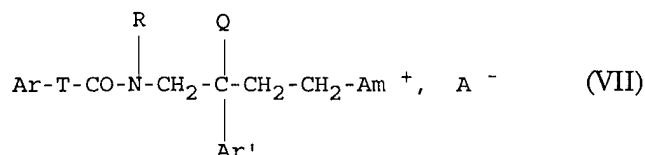
R⁴ is OH or fluorine when R⁵ is H;

or R⁴ and R⁵ are OH ;

or R⁴ and R⁵ together form a bond.

A particularly preferred compound of formula (VI) is (3aS, 4S, 7aS)-7,7-diphenyl-4-(2-methoxyphenyl)-2-[(2S)-(2-methoxyphenyl)propionyl]perhydroisoindol-4-ol; or a pharmaceutically acceptable salt thereof.

Another class of NK-1 receptor antagonists of use in the present invention is that described in European Patent Specification No. 0 591 040, i.e. compounds of formula (VII):



5 wherein

Ar represents an optionally substituted mono-, di- or tricyclic aromatic or heteroaromatic group;

T represents a bond, a hydroxymethylene group, a C₁₋₄alkoxymethylene group or a C₁₋₅alkylene group;

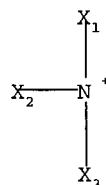
10 Ar' represents a phenyl group which is unsubstituted or substituted by one or more substituents selected from halogen, preferably chlorine or fluorine, trifluoromethyl, C₁₋₄alkoxy, C₁₋₄alkyl where the said substituents may be the same or different; a thienyl group; a benzothienyl group; a naphthyl group; or an indolyl group;

15 R represents hydrogen, C₁₋₄alkyl, ω-C₁₋₄alkoxyC₁₋₄alkyl, or ω-C₂₋₄alkanoyloxyC₂₋₄alkyl;

Q represents hydrogen;

or Q and R together form a 1,2-ethylene, 1,3-propylene or 1,4-butylene group;

20 Am⁺ represents the radical



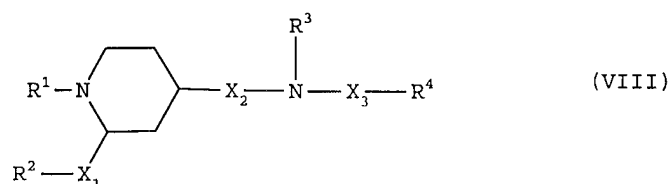
in which X₁, X₂ and X₃, together with the nitrogen atom to which they are attached, form an azabicyclic or azatricyclic ring system optionally substituted by a phenyl or benzyl group; and

25 A⁻ represents a pharmaceutically acceptable anion.

A particularly preferred compound of formula (VII) is (+) 1-[2-[3-(3,4-dichlorophenyl)-1-[(3-isopropoxyphenyl)acetyl]-3-piperidinyl]ethyl]-4-phenyl-1-azabicyclo[2,2,2]octane; or a pharmaceutically acceptable salt, especially the chloride, thereof.

5 Another class of NK-1 receptor antagonists of use in the present invention is that described in European Patent Specification No.

0 532 456, i.e. compounds of formula (VIII):



or a pharmaceutically acceptable salt thereof, wherein

10 R^1 represents an optionally substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl group or the acyl group of an α -amino acid optionally N-substituted by a lower alkanoyl or carbamoyl-lower alkanoyl group;

15 R^2 represents cycloalkyl or an optionally substituted aryl or heteroaryl group;

R^3 represents hydrogen, alkyl, carbamoyl or an alkanoyl or alkenoyl group optionally substituted by carboxy or esterified or amidated carboxy;

20 R^4 represents an optionally substituted aryl group or an optionally partially saturated heteroaryl group;

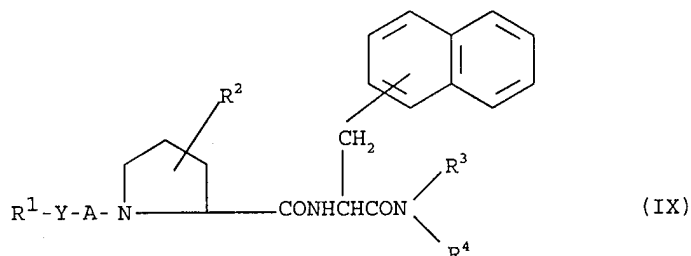
X_1 represents methylene, ethylene, a bond, an optionally ketalised carbonyl group or an optionally etherified hydroxymethylene group;

X_2 represents alkylene, carbonyl or a bond; and

25 X_3 represents carbonyl, oxo-lower alkyl, oxo(aza)-lower alkyl, or an alkyl group optionally substituted by phenyl, hydroxymethyl, optionally esterified or amidated carboxy, or (in other than the α -position) hydroxy.

A particularly preferred compound of formula (VIII) is (2R*, 4S*)-2-benzyl-1-(3,5-dimethylbenzoyl)-N-(4-quinolinylmethyl)-4-piperidineamine; or a pharmaceutically acceptable salt thereof.

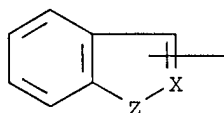
Another class of NK-1 receptor antagonists of use in the present invention is that described in European Patent Specification No. 0 443 132, i.e. compounds of formula (IX)



5

or a pharmaceutically acceptable salt thereof, wherein

R^1 is aryl, or a group of the formula:



X is CH or N; and

10 Z is O or N- R^5 , in which R^5 is hydrogen or lower alkyl;

R^2 is hydroxy or lower alkoxy;

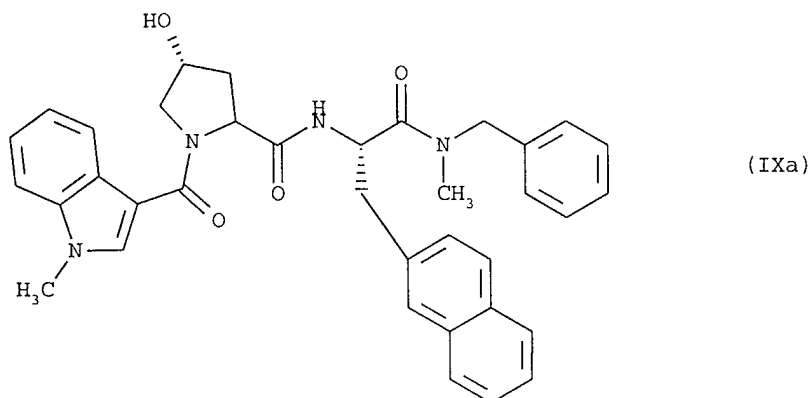
R^3 is hydrogen or optionally substituted lower alkyl;

R^4 is optionally substituted ar(lower)alkyl;

A is carbonyl or sulfonyl; and

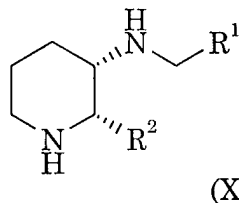
15 Y is a bond or lower alkenylene.

A particularly preferred compound of formula (IX) is the compound of formula (IXa)



or a pharmaceutically acceptable salt thereof.

Another class of NK-1 receptor antagonists of use in the present invention is that described in International Patent Specification No. WO 92/17449, i.e. compounds of the formula (X)



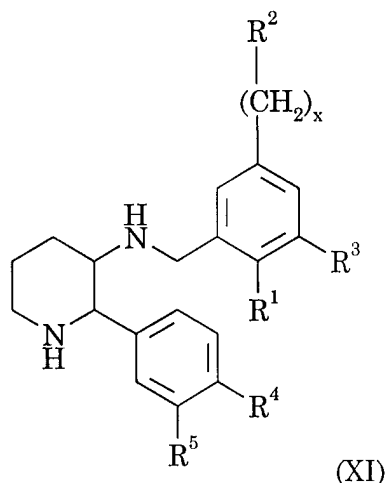
or a pharmaceutically acceptable salt thereof, wherein

R^1 is aryl selected from indanyl, phenyl and naphthyl; heteroaryl selected from thienyl, furyl, pyridyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms, wherein one of said carbon atoms may optionally be replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said C_{3-7} cycloalkyl may optionally be substituted with one or two substituents, said substituents being independently selected from chloro, fluoro, bromo, iodo, nitro, C_{1-10} alkyl optionally substituted with from one to three fluoro groups, C_{1-10} alkoxy optionally substituted with from one to three fluoro groups, amino, C_{1-10} alkyl-S-, C_{1-10} alkyl-S(O)-, C_{1-10} alkyl-SO₂-, phenyl, phenoxy, C_{1-10} alkyl-SO₂NH-, C_{1-10} alkyl-SO₂NH- C_{1-10} alkyl-, C_{1-10} alkylamino-di C_{1-10} alkyl-, cyano, hydroxy, cycloalkoxy having 3 to 7 carbon atoms, C_{1-6} alkylamino, C_{1-6} dialkylamino, HC(O)NH- and C_{1-10} alkyl-C(O)NH-; and

R^2 is thienyl, benzhydryl, naphthyl or phenyl optionally substituted with from one to three substituents independently selected from chloro, bromo, fluoro, iodo, cycloalkoxy having 3 to 7 carbon atoms, C_{1-10} alkyl optionally substituted with from one to three fluoro groups and C_{1-10} alkoxy optionally substituted with from one to three fluoro groups.

A particularly preferred compound of formula (X) is (2*S*,3*S*)-3-(2-methoxy-5-trifluoromethoxybenzyl)-amino-2-phenylpiperidine; or a pharmaceutically acceptable salt thereof.

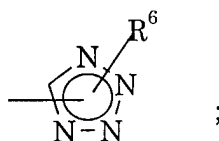
Another class of NK-1 receptor antagonists of use in the present invention is that described in International Patent Specification No. WO 95/08549, i.e. compounds of formula (XI)



5 or a pharmaceutically acceptable salt thereof, wherein

R^1 is a C_{1-4} alkoxy group;

R^2 is



R^3 is a hydrogen or halogen atom;

10 R^4 and R^5 may each independently represent a hydrogen or halogen atom, or a C_{1-4} alkyl, C_{1-4} alkoxy or trifluoromethyl group;

R^6 is a hydrogen atom, a C_{1-4} alkyl, $(CH_2)_m$ cyclopropyl, $-S(O)_n C_{1-4}$ alkyl, phenyl, $NR^7 R^8$, $CH_2C(O)CF_3$ or trifluoromethyl group;

15 R^7 and R^8 may each independently represent a hydrogen atom, or a C_{1-4} alkyl or acyl group;

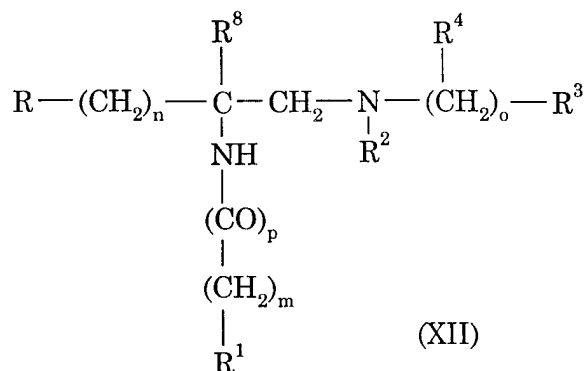
x represents zero or 1;

n represents zero, 1 or 2; and

m represents zero or 1.

Particularly preferred compounds of formula (XI) are (2-methoxy-5-
20 tetrazol-1-yl-benzyl)-([2*S*,3*S*]-2-phenyl-piperidin-3-yl)-amine; and [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-([2*S*,3*S*]-2-phenyl-piperidin-3-yl)-amine; or a pharmaceutically acceptable salt thereof.

Another class of tachykinin antagonists of use in the present invention is that described in International Patent Specification No. WO 95/14017, i.e. compounds of formula (XII)



5 or a pharmaceutically acceptable salt thereof, wherein

m is zero, 1, 2 or 3;

n is zero or 1;

o is zero, 1 or 2;

p is zero or 1;

10 R is phenyl, 2- or 3-indolyl, 2- or 3-indoliny, benzothienyl, benzofuranyl, or naphthyl;

which R groups may be substituted with one or two halo, C₁₋₃alkoxy, trifluoromethyl, C₁₋₄alkyl, phenyl-C₁₋₃alkoxy, or C₁₋₄alkanoyl groups;

15 R¹ is trityl, phenyl, diphenylmethyl, phenoxy, phenylthio, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indoliny, indolyl, benzothienyl, hexamethyleneiminyl, benzofuranyl, tetrahydropyridinyl, quinoliny, isoquinoliny, reduced quinoliny, reduced isoquinoliny, phenyl-(C₁₋₄alkyl)-, phenyl-(C₁₋₄alkoxy)-, quinoliny-(C₁₋₄alkyl)-, isoquinoliny-(C₁₋₄alkyl)-, reduced quinoliny-(C₁₋₄alkyl)-, reduced
20 isoquinoliny-(C₁₋₄alkyl)-, benzoyl-(C₁₋₃alkyl)-, C₁₋₄alkyl, or -NH-CH₂-R⁵;

any one of which R¹ groups may be substituted with halo, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or C₂₋₄alkanoylamino;

25 or any one of which R¹ groups may be substituted with phenyl, piperazinyl, C₃₋₈cycloalkyl, benzyl, C₁₋₄alkyl, piperidinyl, pyridinyl,

pyrimidinyl, C₂₋₆alkanoylamino, pyrrolidinyl, C₂₋₆alkanoyl, or
C₁₋₄alkoxycarbonyl;

any one of which groups may be substituted with halo, C₁₋₄alkyl,
C₁₋₄alkoxy, trifluoromethyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or
5 C₂₋₄alkanoylamino;

or R¹ is amino, a leaving group, hydrogen, C₁₋₄alkylamino, or
di(C₁₋₄alkyl)amino;

R⁵ is pyridyl, anilino-(C₁₋₃alkyl)-, or anilinocarbonyl;

R² is hydrogen, C₁₋₄alkyl, C₁₋₄alkylsulfonyl, carboxy-(C₁₋₃alkyl)-,
10 C₁₋₃alkoxycarbonyl-(C₁₋₃alkyl)-, or -CO-R⁶;

R⁶ is hydrogen, C₁₋₄alkyl, C₁₋₃haloalkyl, phenyl, C₁₋₃alkoxy,
C₁₋₃hydroxyalkyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or -(CH₂)_q-R⁷;
q is zero to 3;

R⁷ is carboxy, C₁₋₄alkoxycarbonyl, C₁₋₄alkylcarbonyloxy, amino,
15 C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₆alkoxycarbonylamino, or phenoxy,
phenylthio, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indolinyl,
indolyl, benzothienyl, benzofuranyl, quinolinyl, phenyl-(C₁₋₄alkyl)-,
quinolinyl-(C₁₋₄alkyl)-, isoquinolinyl-(C₁₋₄alkyl)-, reduced quinolinyl-
(C₁₋₄alkyl)-, reduced isoquinolinyl-(C₁₋₄alkyl)-, benzoyl-C₁₋₃alkyl;

20 any one of which aryl or heterocyclic R⁷ groups may be substituted
with halo, trifluoromethyl, C₁₋₄alkoxy, C₁₋₄alkyl, amino, C₁₋₄alkylamino,
di(C₁₋₄alkyl)amino, or C₂₋₄alkanoylamino;

or any one of which R⁷ groups may be substituted with phenyl,
piperazinyl, C₃₋₈cycloalkyl, benzyl, piperidinyl, pyridinyl, pyrimidinyl,
25 pyrrolidinyl, C₂₋₆alkanoyl, or C₁₋₄alkoxycarbonyl;

any of which groups may be substituted with halo, trifluoromethyl,
amino, C₁₋₄alkoxy, C₁₋₄alkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or
C₂₋₄alkanoylamino;

R⁸ is hydrogen or C₁₋₆alkyl;

30 R³ is phenyl, phenyl-(C₁₋₆alkyl)-, C₃₋₈cycloalkyl, C₅₋₈cycloalkenyl,
C₁₋₈alkyl, naphthyl, C₂₋₈alkenyl, or hydrogen;

any one or which groups except hydrogen may be substituted with one or two halo, C₁₋₃alkoxy, C₁₋₃alkylthio, nitro, trifluoromethyl, or C₁₋₃alkyl groups; and

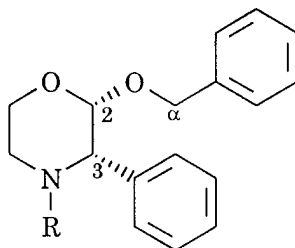
R⁴ is hydrogen or C₁₋₃alkyl;

5 with the proviso that if R¹ is hydrogen or halo, R³ is phenyl, phenyl-(C₁₋₆alkyl)-, C₃₋₈cycloalkyl, C₅₋₈cycloalkenyl, or naphthyl.

A particularly preferred compound of formula (XII) is [N-(2-methoxybenzyl)acetylamino]-3-(1H-indol-3-yl)-2-[N-(2-(4-piperidin-1-yl)piperidin-1-yl)acetylamino]propane; or a pharmaceutically acceptable
10 salt thereof.

The preferred compounds of formulae (I), (II), (III) and (IV) 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:

15



Where the benzyloxy moiety is α -substituted, the preferred stereochemistry of the α -carbon is either (*R*) when the substituent is an
20 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-
25 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.

5 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.

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

A particular aryl-C₁₋₆alkyl, e.g. phenyl-C₁₋₆alkyl, group is benzyl.

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

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

20 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 NK-1 receptor antagonists of use in the present invention include acid addition salts
25 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
30 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 anorectic agent of use in the combinations of the present invention include those salts described above in relation to the salts of NK-1 receptor antagonists.

The present invention accordingly provides the use of a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII), for the manufacture of a medicament for the treatment or prevention of eating disorders.

The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an effective amount of a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII).

In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of eating disorders comprising a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII), together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) may be used in combination with an anorectic agent, present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of eating disorders. 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 NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and an anorectic agent as a combined

preparation for simultaneous, separate or sequential use in the treatment or prevention of eating disorders.

In a preferred aspect, the present invention accordingly provides the use of a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and a halogenated amphetamine derivative for the manufacture of a medicament for the treatment or prevention of eating disorders.

The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an amount of a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and a halogenated amphetamine derivative such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and a halogenated amphetamine derivative 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 NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and a halogenated amphetamine derivative as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of eating disorders.

Particularly preferred halogenated amphetamine derivatives are selected from the group consisting of fenfluramine and dexfenfluramine. Thus in a further preferred aspect, the present invention accordingly provides the use of a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and a halogenated amphetamine derivative selected from

the group consisting of fenfluramine and dexfenfluramine, for the manufacture of a medicament for the treatment or prevention of eating disorders.

The present invention also provides a method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment an amount of a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and an amount of a halogenated amphetamine derivative selected from the group consisting of fenfluramine and dexfenfluramine, such that together they give effective relief.

In a further aspect of the present invention, there is provided a pharmaceutical composition comprising a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and a halogenated amphetamine derivative selected from the group consisting of fenfluramine and dexfenfluramine, 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 NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) and a halogenated amphetamine derivative selected from the group consisting of fenfluramine and dexfenfluramine, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of eating disorders.

As stated above, the NK-1 receptor antagonist and the anorectic 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.

Preferably the compositions according to the present invention are in unit dosage forms such as tablets, pills, capsules, powders, granules,

solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, by inhalation or insufflation or administration by transdermal patches or by buccal cavity absorption wafers. Oral dosage forms are particularly preferred (e.g. tablets, capsules, pills or wafers).

5 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into
10 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
15 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
20 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 or by injection
30 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

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

Preferred compositions for administration by injection include those comprising a NK-1 receptor antagonist as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or

10 in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and

15 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™

20 and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It

25 will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0µm, particularly 0.1 and 0.5µm, and have a pH in the range of 5.5

30 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a NK-1 receptor antagonist selected from the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

Compositions of the present invention may also be presented for administration in the form of trans-dermal patches using conventional technology. The compositions may also be administered via the buccal cavity using, for example, absorption wafers.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a NK-1 receptor antagonist and an anorectic agent, which process comprises bringing a NK-1 receptor antagonist and an anorectic 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 NK-1 receptor antagonist and an anorectic agent, are presented in a ratio which is consistent with the manifestation of the desired effect. In particular, the ratio by weight of

the NK-1 receptor antagonist and the anorectic agent will suitably be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

5 A suitable dosage level for the 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/kg 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 1 or 2 times daily.

10 A suitable dosage level for the anorectic 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 1 or 2 times daily.

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

The compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) 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, EP-A-0 436 334, WO 93/21155, EP-A-0 591 040,
25 EP-A-0 532 456, EP-A-0 443 132, WO 92/17449, WO 95/08549 and WO 95/14017, respectively.

Particularly preferred NK-1 receptor antagonists of the formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI) and (XII) for use in the present invention are compounds which are potent NK-1 receptor
30 antagonists, i.e. compounds with an NK-1 receptor affinity (IC_{50}) of less than 100nM.

Even more preferred NK-1 receptor antagonists of use in the present invention are compounds which are potent NK-1 receptor antagonists with an NK-1 receptor affinity (IC_{50}) of less than 10nM, favourably less than 2nM and preferably less than 1nM.

- 5 Especially preferred NK-1 receptor antagonists of use in the present invention are orally active, long acting, CNS-penetrant NK-1 receptor antagonists, identified using a combination of the following assays:

ASSAY 1: NK-1 Receptor binding

- 10 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 3×10^5 receptors per cell. Cells are grown in monolayer culture,
15 detached from the plate with enzyme-free dissociation solution (Speciality Media Inc.), and washed prior to use in the assay. ^{125}I -Tyr⁸-substance P (0.1nM, 2000Ci/mmol; New England Nuclear) is incubated in the presence or absence of test compounds (dissolved in 5 μ l dimethylsulphoxide, DMSO) with 5×10^4 CHO cells. Ligand binding is performed in 0.25ml of 50mM
20 Tris-HCl, pH7.5, containing 5mM $MnCl_2$, 150mM NaCl, 0.02% bovine serum albumin (Sigma), 50 μ g/ml chymostatin (Peninsula), 0.1nM phenylmethylsulphonyl fluoride, 2 μ g/ml pepstatin, 2 μ g/ml leupeptin and 2.8 μ g/ml furoyl saccharine. The incubation proceeds at room temperature until equilibrium is achieved (>40 minutes) and the receptor-ligand
25 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 (1 μ M) and represents <10% of total binding.

ASSAY 2: Gerbil Foot-Tapping

CNS-penetrant NK-1 receptor antagonists for use in the present invention can be identified by their ability to inhibit foot tapping in gerbils induced by anxiogenic agents (such as pentagastrin) or central infusion of
5 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
10 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
15 selective NK-1 receptor agonist (e.g. GR73632 (d Ala[L-Pro⁹,Me-Leu¹⁰]-substance P-(7-11)) is infused directly into the cerebral ventricles (e.g. 3pmol in 5µl i.c.v., depending on test substance) by vertical insertion of a cuffed 27 gauge needle to a depth of 4.5mm below bregma. The scalp incision is closed and the animal allowed to recover from anaesthesia in a
20 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
25 method of quantification.

ASSAY 3: Ferret Emesis

Individually housed male ferrets (1.0 -2.5 kg) are dosed orally by gavage with test compound. Ten minutes later they are fed with
30 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, after which time the animals are killed humanely. The numbers of retches and vomits occurring during the 4 hours after cisplatin administration are recorded by trained observers.

10 ASSAY 4: Separation-Induced Vocalisation

Male and female guinea-pigs pups are housed in family groups with their mothers and littermates throughout the study. Experiments are commenced after weaning when the pups are 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 are employed for drug challenge studies (approximately 50% of available pups may fail to reach this criterion). On test days each pup receives an oral dose or an s.c. or i.p. injection of test compound or vehicle and is then immediately returned to the home cage with its mother and siblings for 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 receive each test

compound at each dose tested.

A suitable selection cascade for NK₁ antagonists of use according to the present invention is as follows:

5 (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
10 NK₁ agonist (Assay 2); 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
15 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.

20 (iv) Determine oral bioavailability of compounds by pharmacokinetic analysis, activity in gerbil foot tapping assay following oral administration and/or by ability to inhibit cisplatin-induced emesis in ferrets (Assay 3); select compounds with ID₉₀ ≤ 3mg/kg p.o., and preferably ID₉₀ ≤ 1mg/kg p.o.

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

 (v) Determine activity of compounds in assays sensitive to conventional serotonergic drugs (inhibition of pharmacologically evoked foot tapping in gerbils and/or inhibition of distress vocalisations in guinea-

pig pups (Assay 4)). Select compounds with $ID_{50} \leq 20\text{mg/kg}$, and preferably $ID_{50} \leq 10\text{mg/kg}$.

Yet further preferred compounds of use in the present invention may be selected from those compounds which satisfy the NK-1
5 receptor binding criteria of step (i) which, in addition, have ≤ 5 -fold shift in affinity when incubated in the presence of human serum albumin (HSA) to show non-specific protein binding.

One example of a NK-1 receptor antagonist of use in the present invention is the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)-
10 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:	$IC_{50}=0.1\text{nM}$
gerbil foot-tapping (5 mins.):	$ID_{50}=0.36\text{mg/kg i.v.}$
gerbil foot-tapping (24 hrs.):	$ID_{50}=0.33\text{mg/kg i.v.}$
ferret emesis:	$ID_{90}<3\text{mg/kg p.o.}$
guinea-pig vocalisation (4hrs. pretreatment)	$ID_{50}=0.73\text{mg/kg p.o.}$

15

Another example of a NK-1 receptor antagonist of use in the present invention is the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine, the preparation of which is
20 described in International Patent Specification No. WO 95/18124. In the aforementioned assays, this compound has the following activity:

human NK-1 receptor binding:	$IC_{50}=0.25\text{nM}$
gerbil foot-tapping (5 mins.):	$ID_{50}=0.12\text{mg/kg i.v.}$
gerbil foot-tapping (24 hrs.):	$ID_{50}=0.17\text{mg/kg i.v.}$

guinea-pig vocalisation: ID₅₀=0.5mg/kg s.c.

The following assay has been used to demonstrate the potentiation of the anorectic effects of dexfenfluramine in diet-induced obese mice when co-administered with a NK-1 receptor antagonist.

5

Evaluation of the Interaction of NK-1 Antagonists and Anorectic Agents on Food Intake and Body Weight in Diet-Induced Obese Mice.

Mice:

10 Male C57BL/J mice were obtained from Jackson Labs at 3 weeks of age. Half the mice were maintained on a wet diet consisting of sweetened condensed milk and standard ground rodent chow (70%:30%, vol:vol). Fresh wet chow was provided daily. These mice will be referred to as diet-induced obese (DIO). The other half was maintained on just ground rodent
15 chow. These will be referred to as Non-Obese Littermates (NOL). Both food and water were supplied *ad libitum*. Mice were housed with a 12 hour light/dark cycle (4.00am lights on) through out the course of the described studies.

Mice were weighed bi-weekly until a point that both DIO and NOL
20 mice were weight stable (approximately 20 weeks). At this time, DIO mice weighed significantly more than NOL mice ($p < 0.01$). DIO mice also exhibited elevated insulin and glucose levels, as well as polyuria.

Food Intake:

25 (All food intake studies were performed on weight stable DIO mice. Both food and water were available before treatment.)

The effect that the anorectic agent, dexfenfluramine had on food intake in DIO mice was determined previously (ED₅₀ = 3 mg/kg, ip). The combined effect that [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-
30 ([2S,3S]-2-phenyl-piperidin-3-yl)amine (GR205171) and dexfenfluramine

had on food consumption was examined by observing the resulting changes in food intake observed after treatment with dexfenfluramine, GR205171, or combinations of dexfenfluramine with decreasing doses of GR 205171.

5 Mice were randomly assigned to one of the following treatment groups:

- Saline/Saline
- Saline/GR 205171@20 mg/kg
- Dexfenfluramine @ 3 mg/kg/ GR 205171@20 mg/kg
- Dexfenfluramine @ 3 mg/kg/ GR 205171@10 mg/kg
- 10 • Dexfenfluramine @ 3 mg/kg/ GR 205171@ 5 mg/kg

Mice received two injections approximately 30 mins apart. All injections were administered ip., in a volume of 0.2 ml between 3.00pm and 3.30pm. Fresh chow was provided at the time of injection. Food intake was measured 16 hours post-injection for each mouse.

Results shown in Figure 1 are expressed as inhibition of food intake relative to that of saline treated animals.

Body Weight:

20 (All weight studies are performed on DIO mice)

The effect that the combination of anorectic agents and NK-1 antagonists have on weight are examined using a chronic dosing regimen. Mice are treated with dexfenfluramine, GR 205171, or combinations of dexfenfluramine with decreasing doses of GR 205171, similar to those used in the evaluation of food intake. Mice are dosed once daily, for 7 days with body weights being measured at the start and conclusion of the study. Changes in body weight are compared with that of saline treated mice.

Concurrent daily food intake measurements may be taken at this time.

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.

- 5 In such combined preparations, the ratio of the NK-1 receptor antagonist and the anorectic agent will depend upon the choice of active ingredients.

EXAMPLE 1 Tablets containing 50-300mg of NK-1 antagonist and 15mg of dexfenfluramine

	<u>Amount mg</u>		
NK-1 antagonist	50.0	100.0	300.0
dexfenfluramine	15.0	15.0	15.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	174.5	124.5	124.5
Magnesium Stearate	0.5	0.5	0.5

10

EXAMPLE 2 Tablets containing 50-300mg of NK-1 antagonist and 60mg of fenfluramine

	<u>Amount mg</u>		
NK-1 antagonist	50.0	100.0	300.0
fenfluramine	60.0	60.0	60.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	129.5	179.5	129.5
Magnesium Stearate	0.5	0.5	0.5

- 15 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

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then compressed into tablets containing 50mg, 100mg and 300mg of the NK-1 receptor antagonist per tablet.

EXAMPLE 3 Parenteral injection

5		<u>Amount</u>
	Active Ingredients	10 to 300mg
	Citric Acid Monohydrate	0.75mg
	Sodium Phosphate	4.5mg
	Sodium Chloride	9mg
10	Water for injection	to 10ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The active ingredients are dissolved or suspended in the solution and made up to volume.

CLAIMS

1. Use of a NK-1 receptor antagonist for the manufacture of a medicament for the treatment or prevention of eating disorders.

5

2. Use according to claim 1 which further comprises the simultaneous, separate or sequential administration of an anorectic agent.

3. A pharmaceutical composition for the treatment or prevention of eating disorders comprising a NK-1 receptor antagonist, together with at least one pharmaceutically acceptable carrier or excipient.

10

4. A composition according to claim 3 which further comprises an anorectic agent.

15

5. A product comprising a NK-1 receptor antagonist and an anorectic agent as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of eating disorders.

20

6. A method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment of an effective amount of a NK-1 receptor antagonist.

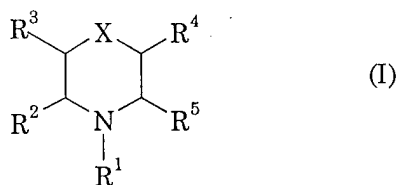
7. A method for the treatment or prevention of eating disorders, which method comprises administration to a patient in need of such treatment of an amount of a NK-1 receptor antagonist and an amount of an anorectic agent, such that together they give effective relief.

25

8. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula I:

30

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wherein

R¹ is selected from the group consisting of:

(1) C₁₋₆alkyl, substituted with one or more of the substituents

5 selected from:

(a) heterocycle, wherein the heterocycle is selected from

the group consisting of:

(A) benzimidazolyl,

(B) imidazolyl,

10 (C) isoxazolyl,

(D) isothiazolyl,

(E) oxadiazolyl,

(F) pyrazinyl,

(G) pyrazolyl,

15 (H) pyridyl,

(I) pyrrolyl,

(J) tetrazolyl,

(K) thiadiazolyl,

(L) triazolyl, and

20 (M) piperidinyll,

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

(i) C₁₋₆alkyl, unsubstituted or substituted with halo, -CF₃,
-OCH₃, or phenyl,

25 (ii) C₁₋₆alkoxy,

(iii) oxo,

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- (iv) thioxo,
- (v) cyano,
- (vi) $-\text{SCH}_3$,
- (vii) phenyl,
- (viii) hydroxy,
- (ix) trifluoromethyl,
- (x) $-(\text{CH}_2)_m-\text{NR}^9\text{R}^{10}$, 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) hydroxy C_{1-6} alkyl, and
- (IV) phenyl,
- (xi) $-\text{NR}^9\text{COR}^{10}$, wherein R^9 and R^{10} are as defined above,

and

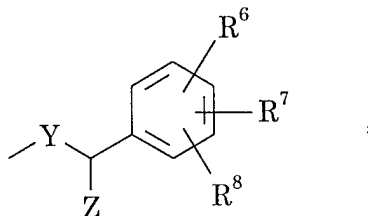
- (xii) $-\text{CONR}^9\text{R}^{10}$, wherein R^9 and R^{10} are as defined above,

R^2 and R^3 are independently selected from the group consisting of:

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

X is $-\text{O}-$;

R^4 is



R^5 is phenyl, unsubstituted or substituted with halo;

R^6 , R^7 and R^8 are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) halo, and

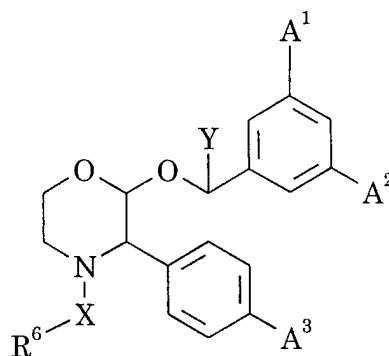
- 80 -

(4) $-\text{CF}_3$;Y is $-\text{O}-$; andZ is hydrogen or C_{1-4} alkyl;

or a pharmaceutically acceptable salt thereof.

5

9. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula IIa:



(IIa)

10

wherein:

 A^1 is fluorine or CF_3 ; A^2 is fluorine or CF_3 ; A^3 is fluorine or hydrogen;

15

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by $=\text{O}$, $=\text{S}$ or a C_{1-4} alkyl group, and optionally substituted by a group of the formula ZNR^7R^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} cycloalkyl C_{1-4} alkyl, or C_{2-4} alkyl substituted by C_{1-4} alkoxy or hydroxyl;

20

R^8 is hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl or C_{3-7} cycloalkyl C_{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;

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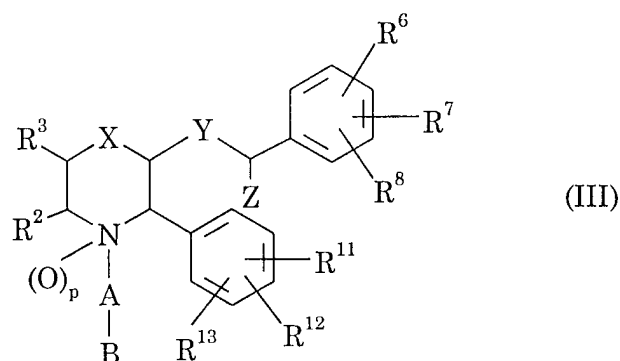
or R^7 , R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by a hydroxy group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group $S(O)$ or $S(O)_2$ or a second 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;

or a pharmaceutically acceptable salt thereof.

10. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula III:



wherein:

R^2 and R^3 are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C_{1-6} alkyl,
- (3) C_{2-6} alkenyl, and
- (4) phenyl;

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R⁶, R⁷ and R⁸ are independently selected from the group consisting of:

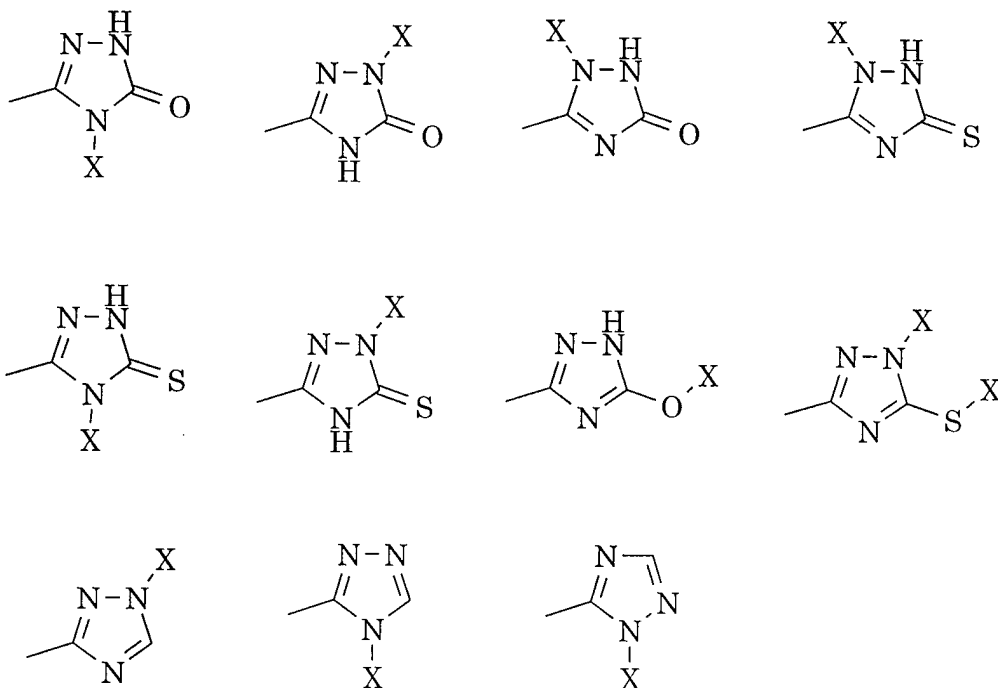
- (1) hydrogen,
- (2) C₁₋₆alkyl,
- (3) fluoro,
- 5 (4) chloro,
- (5) bromo,
- (6) iodo, and
- (7) -CF₃;

R¹¹, R¹² and R¹³ are independently selected from the group consisting of:

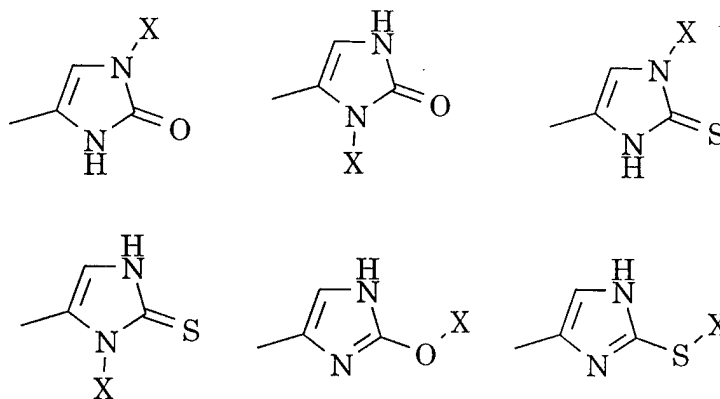
- 10 (1) fluoro,
- (2) chloro,
- (3) bromo, and
- (4) iodo;

A is unsubstituted 1-6alkyl;

- 15 B is selected from the group consisting of:



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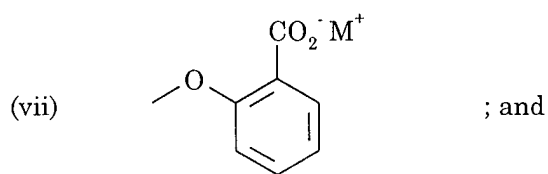
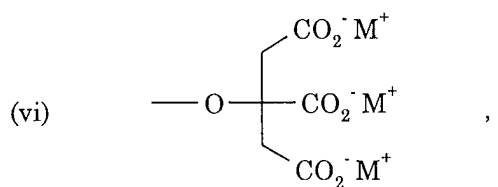
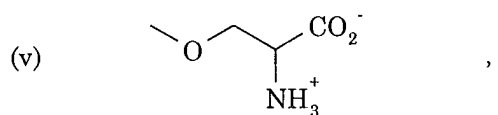
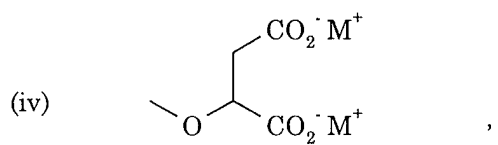
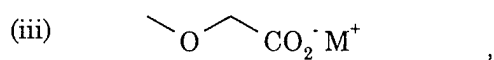
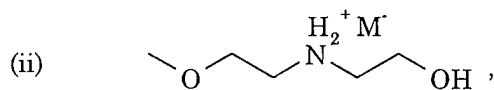
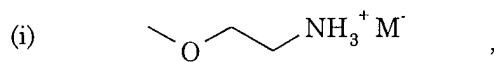


p is 0 or 1;

X is selected from:

- (a) $-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein M^+ is a pharmaceutically acceptable monovalent counterion,
- (b) $-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- (c) $-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$, wherein D^{2+} is a pharmaceutically acceptable divalent counterion,
- (d) $-\text{CH}(\text{R}^4)-\text{PO}(\text{OH})\text{O}^- \cdot \text{M}^+$, wherein R^4 is hydrogen or C_{1-3} alkyl,
- (e) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot 2\text{M}^+$,
- (f) $-\text{CH}(\text{R}^4)-\text{PO}(\text{O}^-)_2 \cdot \text{D}^{2+}$,
- (i) $-\text{CO}-\text{CH}_2\text{CH}_2-\text{CO}_2^- \cdot \text{M}^+$,
- (j) $-\text{CH}(\text{CH}_3)-\text{O}-\text{CO}-\text{R}^5$, wherein R^5 is selected from the group consisting of:

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Y is -O-;

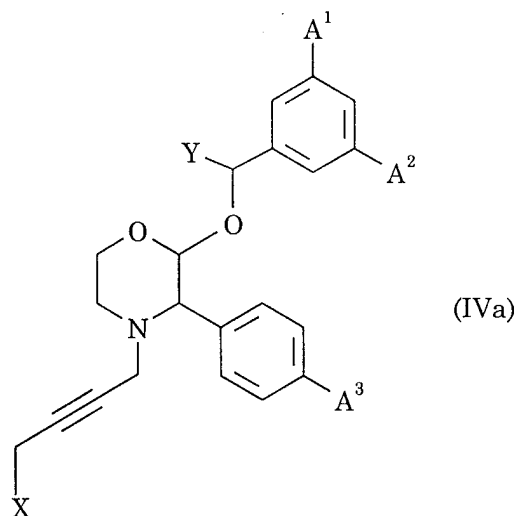
Z is hydrogen or C₁₋₆alkyl;

or a pharmaceutically acceptable salt thereof.

5

11. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula IVa:

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wherein

A¹ is fluorine or CF₃;

5 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;

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

R⁶ is hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, phenyl, or C₂₋₄alkyl substituted by C₁₋₄alkoxy or hydroxy;

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

20 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 hydroxyc₁₋₄alkyl, C₁₋₄alkoxyc₁₋₄alkyl, oxo, COR^a or CO₂R^a where R^a is hydrogen or C₁₋₄alkyl;

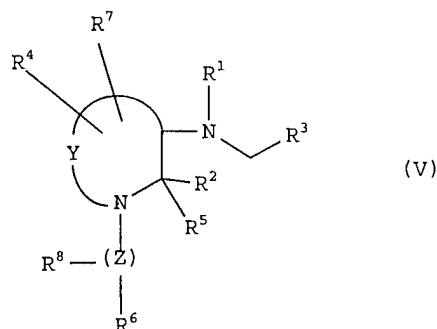
- 86 -

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;
 5 or a pharmaceutically acceptable salt thereof.

12. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula V:

10



wherein:

Y is $(CH_2)_n$ wherein n is an integer from 1 to 4, and wherein any one of the carbon-carbon single bonds in said $(CH_2)_n$ may optionally be
 15 replaced by a carbon-carbon double bond, and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^4 , and wherein any one of the carbon atoms of said $(CH_2)_n$ may optionally be substituted with R^7 ;

Z is $(CH_2)_m$ wherein m is an integer from 0 to 6, and wherein any
 20 one of the carbon-carbon single bonds of $(CH_2)_m$ may optionally be replaced by a carbon-carbon double bond or a carbon-carbon triple bond, and any one of the carbon atoms of said $(CH_2)_m$ may optionally be substituted with R^8 ;

R^1 is hydrogen or C_{1-8} alkyl optionally substituted with hydroxy,
 25 C_{1-4} alkoxy or fluoro;

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R^2 is a radical selected from hydrogen, C_{1-6} straight or branched alkyl, C_{3-7} cycloalkyl wherein one of the CH_2 groups in said cycloalkyl may optionally be replaced by NH, oxygen or sulphur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl- C_{2-6} alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl- C_{2-6} alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl, amino, C_{1-6} alkylamino, C_{1-6} alkyl-O-CO, C_{1-6} alkyl-O-CO- C_{1-6} alkyl, C_{1-6} alkyl-CO-O, C_{1-6} alkyl-CO- C_{1-6} alkyl-O-, C_{1-6} alkyl-CO, C_{1-6} alkyl-CO- C_{1-6} alkyl-, di- C_{1-6} alkylamino, -CONH- C_{1-6} alkyl, C_{1-6} alkyl-CO-NH- C_{1-6} alkyl, -NHCOH and -NHCO- C_{1-6} alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thienyl, furyl or pyridyl;

R^5 is hydrogen, phenyl or C_{1-6} alkyl;

or R^2 and R^5 together with the carbon to which they are attached, form a saturated ring having from 3 to 7 carbon atoms wherein one of the CH_2 groups in said ring may optionally be replaced by oxygen, NH or sulfur;

R^3 is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thienyl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7 carbon atoms wherein one of the (CH_2) groups in said cycloalkyl may optionally be replaced by NH, oxygen or sulphur;

wherein each of said aryl and heteroaryl groups may optionally be substituted with one or more substituents, and said C_{3-7} cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, C_{1-6} alkyl, C_{1-6} alkoxy, trifluoromethyl, amino, C_{1-6} alkylamino, -CO-NH- C_{1-6} alkyl, C_{1-6} alkyl-CO-NH- C_{1-6} alkyl, -NHCOH and -NHCO- C_{1-6} alkyl;

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R^4 and R^7 are each independently selected from hydroxy, halogen, halo, amino, oxo, cyano, methylene, hydroxymethyl, halomethyl, C_{1-6} alkylamino, di- C_{1-6} alkylamino, C_{1-6} alkoxy, C_{1-6} alkyl-O-CO, C_{1-6} alkyl-O-CO- C_{1-6} alkyl, C_{1-6} alkyl-CO-O, C_{1-6} alkyl-CO- C_{1-6} alkyl-O-, C_{1-6} alkyl-CO-, C_{1-6} alkyl-CO- C_{1-6} alkyl, and the radicals set forth in the definition of R^2 ;

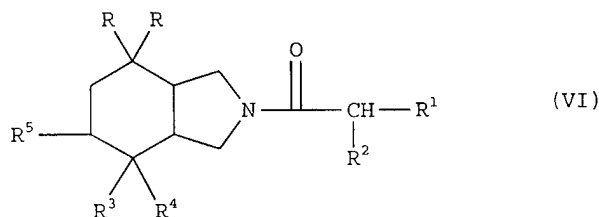
R^6 is -NHCOR⁹, -NHCH₂R⁹, SO₂R⁸ or one of the radicals set forth in any of the definitions of R^2 , R^4 and R^7 ;

R^8 is oximino (=NOH) or one of the radicals set forth in any of the definitions of R^2 , R^4 and R^7 ;

R^9 is C_{1-6} alkyl, hydrogen, phenyl or phenyl C_{1-6} alkyl; with the proviso that (a) when m is 0, R^8 is absent, (b) when R^4 , R^6 , R^7 or R^8 is as defined in R^2 , it cannot form together with the carbon to which it is attached, a ring with R^5 , and (c) when R^4 and R^7 are attached to the same carbon atom, then either each of R^4 and R^7 is independently selected from hydrogen, fluoro and C_{1-6} alkyl, or R^4 and R^7 , together with the carbon to which they are attached, for a C_{3-6} saturated carbocyclic ring that forms a spiro compound with the nitrogen-containing ring to which they are attached;

or a pharmaceutically acceptable salt thereof.

13. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula VI:



wherein:

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radicals R are phenyl radicals optionally 2- or 3-substituted by a halogen atom or a methyl radical;

R¹ is optionally substituted phenyl, cyclohexadienyl, naphthyl, indenyl or optionally substituted heterocycle;

5 R² is H, halogen, OH, alkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkyloxy, alkylthio, acyloxy, carboxy, optionally substituted alkyloxycarbonyl, benzyloxycarbonyl, amino or acylamino;

R³ is optionally 2-substituted phenyl;

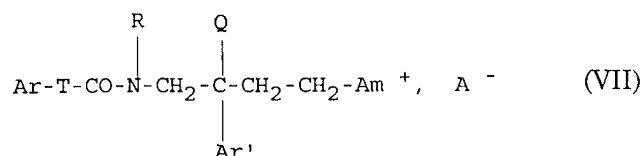
R⁴ is OH or fluorine when R⁵ is H;

10 or R⁴ and R⁵ are OH ;

or R⁴ and R⁵ together form a bond;

or a pharmaceutically acceptable salt thereof.

14. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula VII:



wherein:

20

Ar represents an optionally substituted mono-, di- or tricyclic aromatic or heteroaromatic group;

T represents a bond, a hydroxymethylene group, a C₁₋₄alkoxymethylene group or a C₁₋₅alkylene group;

25 Ar' represents a phenyl group which is unsubstituted or substituted by one or more substituents selected from halogen, preferably chlorine or fluorine, trifluoromethyl, C₁₋₄alkoxy, C₁₋₄alkyl where the said substituents may be the same or different; a thienyl group; a benzothienyl group; a naphthyl group; or an indolyl group;

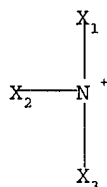
- 90 -

R represents hydrogen, C₁₋₄alkyl, ω-C₁₋₄alkoxyC₁₋₄alkyl, or
ω-C₂₋₄alkanoyloxyC₂₋₄alkyl;

Q represents hydrogen;

or Q and R together form a 1,2-ethylene, 1,3-propylene or 1,4-
5 butylene group;

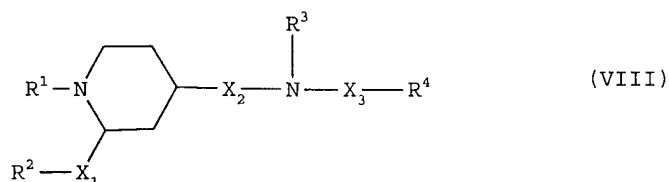
Am⁺ represents the radical



in which X₁, X₂ and X₃, together with the nitrogen atom to which they are
attached, form an azabicyclic or azatricyclic ring system optionally
10 substituted by a phenyl or benzyl group; and

A⁻ represents a pharmaceutically acceptable anion.

15 15. A use according to claim 1 or 2, a composition according to
claim 3 or 4, a product according to claim 5 or a method according to claim
6 or 7 wherein the NK-1 receptor antagonist is a compound of formula VIII



wherein:

R¹ represents an optionally substituted aralkyl, aryloxyalkyl,
heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl,
20 heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl group or the acyl
group of an α-amino acid optionally N-substituted by a lower alkanoyl or
carbamoyl-lower alkanoyl group;

R² represents cycloalkyl or an optionally substituted aryl or
heteroaryl group;

25 R³ represents hydrogen, alkyl, carbamoyl or an alkanoyl or alkenoyl
group optionally substituted by carboxy or esterified or amidated carboxy;

- 91 -

R^4 represents an optionally substituted aryl group or an optionally partially saturated heteroaryl group;

X_1 represents methylene, ethylene, a bond, an optionally ketalised carbonyl group or an optionally etherified hydroxymethylene group;

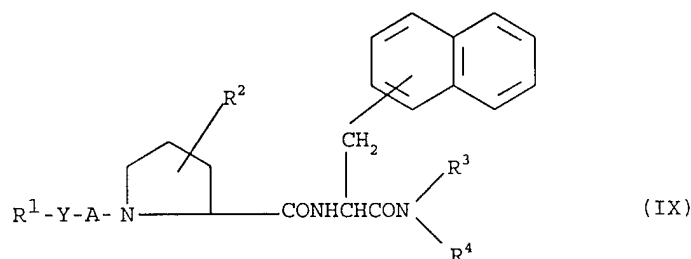
5 X_2 represents alkylene, carbonyl or a bond; and

X_3 represents carbonyl, oxo-lower alkyl, oxo(aza)-lower alkyl, or an alkyl group optionally substituted by phenyl, hydroxymethyl, optionally esterified or amidated carboxy, or (in other than the α -position) hydroxy; or a pharmaceutically acceptable salt thereof.

10

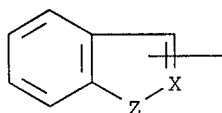
16. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula IX:

15



wherein:

R^1 is aryl, or a group of the formula:



20

X is CH or N; and

Z is O or N- R^5 , in which R^5 is hydrogen or lower alkyl;

R^2 is hydroxy or lower alkoxy;

R^3 is hydrogen or optionally substituted lower alkyl;

R^4 is optionally substituted ar(lower)alkyl;

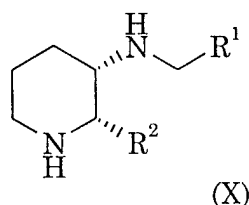
25

A is carbonyl or sulfonyl; and

- 92 -

Y is a bond or lower alkenylene;
or a pharmaceutically acceptable salt thereof.

17. A use according to claim 1 or 2, a composition according to
claim 3 or 4, a product according to claim 5 or a method according to claim
6 or 7 wherein the NK-1 receptor antagonist is a compound of formula X:

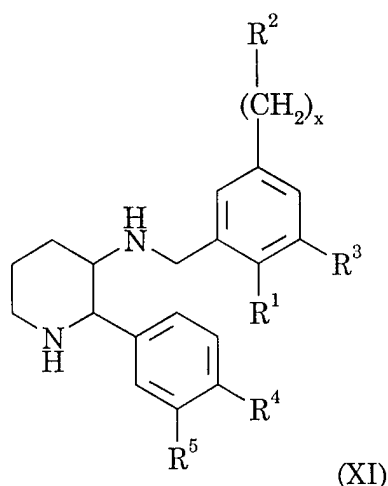


wherein:

- 10 R^1 is aryl selected from indanyl, phenyl and naphthyl; heteroaryl
selected from thienyl, furyl, pyridyl and quinolyl; and cycloalkyl having 3
to 7 carbon atoms, wherein one of said carbon atoms may optionally be
replaced by nitrogen, oxygen or sulfur; wherein each of said aryl and
heteroaryl groups may optionally be substituted with one or more
15 substituents, and said C_{3-7} cycloalkyl may optionally be substituted with
one or two substituents, said substituents being independently selected
from chloro, fluoro, bromo, iodo, nitro, C_{1-10} alkyl optionally substituted
with from one to three fluoro groups, C_{1-10} alkoxy optionally substituted
with from one to three fluoro groups, amino, C_{1-10} alkyl-S-, C_{1-10} alkyl-S(O)-,
20 C_{1-10} alkyl-SO₂-, phenyl, phenoxy, C_{1-10} alkyl-SO₂NH-,
 C_{1-10} alkyl-SO₂NH- C_{1-10} alkyl-, C_{1-10} alkylamino-di C_{1-10} alkyl-, cyano, hydroxy,
cycloalkoxy having 3 to 7 carbon atoms, C_{1-6} alkylamino, C_{1-6} dialkylamino,
HC(O)NH- and C_{1-10} alkyl-C(O)NH-; and
- 25 R^2 is thienyl, benzhydryl, naphthyl or phenyl optionally substituted
with from one to three substituents independently selected from chloro,
bromo, fluoro, iodo, cycloalkoxy having 3 to 7 carbon atoms, C_{1-10} alkyl
optionally substituted with from one to three fluoro groups and C_{1-10} alkoxy
optionally substituted with from one to three fluoro groups;

or a pharmaceutically acceptable salt thereof.

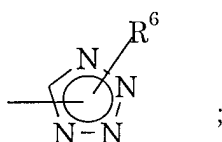
18. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula XI:



wherein:

R¹ is a C₁₋₄alkoxy group;

10 R² is



R³ is a hydrogen or halogen atom;

R⁴ and R⁵ may each independently represent a hydrogen or halogen atom, or a C₁₋₄alkyl, C₁₋₄alkoxy or trifluoromethyl group;

15 R⁶ is a hydrogen atom, a C₁₋₄alkyl, (CH₂)_mcyclopropyl, -S(O)_nC₁₋₄alkyl, phenyl, NR⁷R⁸, CH₂C(O)CF₃ or trifluoromethyl group;

R⁷ and R⁸ may each independently represent a hydrogen atom, or a C₁₋₄alkyl or acyl group;

x represents zero or 1;

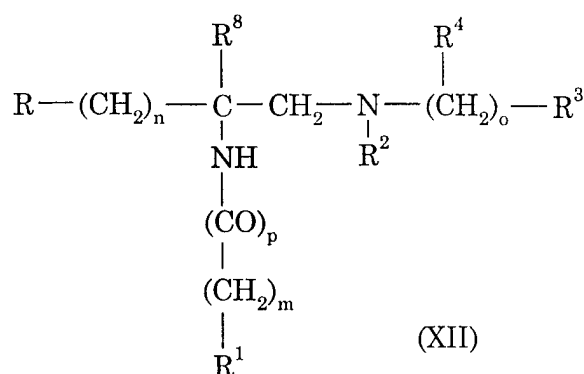
20 n represents zero, 1 or 2; and

m represents zero or 1;

- 94 -

or a pharmaceutically acceptable salt thereof.

19. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is a compound of formula XII:



wherein:

m is zero, 1, 2 or 3;

10 n is zero or 1;

o is zero, 1 or 2;

p is zero or 1;

R is phenyl, 2- or 3-indolyl, 2- or 3-indoliny, benzothienyl, benzofuranyl, or naphthyl;

15 which R groups may be substituted with one or two halo, C₁₋₃alkoxy, trifluoromethyl, C₁₋₄alkyl, phenyl-C₁₋₃alkoxy, or C₁₋₄alkanoyl groups;

R¹ is trityl, phenyl, diphenylmethyl, phenoxy, phenylthio, piperaziny, piperidiny, pyrrolidiny, morpholiny, indoliny, indolyl, benzothienyl, hexamethyleneiminy, benzofuranyl, tetrahydropyridiny, quinoliny, isoquinoliny, reduced quinoliny, reduced isoquinoliny, phenyl-(C₁₋₄alkyl)-, phenyl-(C₁₋₄alkoxy)-, quinoliny-(C₁₋₄alkyl)-, isoquinoliny-(C₁₋₄alkyl)-, reduced quinioliny-(C₁₋₄alkyl)-, reduced isoquinoliny-(C₁₋₄alkyl)-, benzoyl-(C₁₋₃alkyl)-, C₁₋₄alkyl, or -NH-CH₂-R⁵;

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any one of which R¹ groups may be substituted with halo, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or C₂₋₄alkanoylamino;

5 or any one of which R¹ groups may be substituted with phenyl, piperazinyl, C₃₋₈cycloalkyl, benzyl, C₁₋₄alkyl, piperidinyl, pyridinyl, pyrimidinyl, C₂₋₆alkanoylamino, pyrrolidinyl, C₂₋₆alkanoyl, or C₁₋₄alkoxycarbonyl;

any one of which groups may be substituted with halo, C₁₋₄alkyl, C₁₋₄alkoxy, trifluoromethyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or
10 C₂₋₄alkanoylamino;

or R¹ is amino, a leaving group, hydrogen, C₁₋₄alkylamino, or di(C₁₋₄alkyl)amino;

R⁵ is pyridyl, anilino-(C₁₋₃alkyl)-, or anilinocarbonyl;

R² is hydrogen, C₁₋₄alkyl, C₁₋₄alkylsulfonyl, carboxy-(C₁₋₃alkyl)-,
15 C₁₋₃alkoxycarbonyl-(C₁₋₃alkyl)-, or -CO-R⁶;

R⁶ is hydrogen, C₁₋₄alkyl, C₁₋₃haloalkyl, phenyl, C₁₋₃alkoxy, C₁₋₃hydroxyalkyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or -(CH₂)_q-R⁷;
q is zero to 3;

R⁷ is carboxy, C₁₋₄alkoxycarbonyl, C₁₋₄alkylcarbonyloxy, amino,
20 C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₆alkoxycarbonylamino, or phenoxy, phenylthio, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indolinyl, indolyl, benzothienyl, benzofuranyl, quinolinyl, phenyl-(C₁₋₄alkyl)-, quinolinyl-(C₁₋₄alkyl)-, isoquinolinyl-(C₁₋₄alkyl)-, reduced quinolinyl-(C₁₋₄alkyl)-, reduced isoquinolinyl-(C₁₋₄alkyl)-, benzoyl-C₁₋₃alkyl;

25 any one of which aryl or heterocyclic R⁷ groups may be substituted with halo, trifluoromethyl, C₁₋₄alkoxy, C₁₋₄alkyl, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or C₂₋₄alkanoylamino;

or any one of which R⁷ groups may be substituted with phenyl, piperazinyl, C₃₋₈cycloalkyl, benzyl, piperidinyl, pyridinyl, pyrimidinyl,
30 pyrrolidinyl, C₂₋₆alkanoyl, or C₁₋₄alkoxycarbonyl;

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any of which groups may be substituted with halo, trifluoromethyl, amino, C₁₋₄alkoxy, C₁₋₄alkyl, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, or C₂₋₄alkanoylamino;

R⁸ is hydrogen or C₁₋₆alkyl;

5 R³ is phenyl, phenyl-(C₁₋₆alkyl)-, C₃₋₈cycloalkyl, C₅₋₈cycloalkenyl, C₁₋₈alkyl, naphthyl, C₂₋₈alkenyl, or hydrogen;

any one or which groups except hydrogen may be substituted with one or two halo, C₁₋₃alkoxy, C₁₋₃alkylthio, nitro, trifluoromethyl, or C₁₋₃alkyl groups; and

10 R⁴ is hydrogen or C₁₋₃alkyl;

with the proviso that if R¹ is hydrogen or halo, R³ is phenyl, phenyl-(C₁₋₆alkyl)-, C₃₋₈cycloalkyl, C₅₋₈cycloalkenyl, or naphthyl; or a pharmaceutically acceptable salt thereof.

15 20. A use, composition, product or method according to any one of the preceding claims wherein the NK-1 receptor antagonist is orally active, long acting and CNS-penetrant.

20 21. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is selected from the classes of compounds described in EP-A-0577394, WO-A-9508549, WO-A-9518124, WO-A-9523798 and WO-A-9605181.

25 22. A use according to claim 1 or 2, a composition according to claim 3 or 4, a product according to claim 5 or a method according to claim 6 or 7 wherein the NK-1 receptor antagonist is selected from
2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;
30 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;
- 5 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;
- 10 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(2-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
- 15 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxyphosphoryl-1H-1,2,4-triazolo)methyl)morpholine;
- 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;
- 20 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-N,N-dimethylaminobut-2-yn-yl)-3-(S)-(4-fluorophenyl)morpholine;
- or a pharmaceutically acceptable salt thereof.

23. A use, composition, product or method according to any one of
- 25 the preceding claims wherein the anorectic agent is selected from aminorex, amphechloral, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphemethoxidine, *N*-ethylamphetamine, fenbutrazate, fenfluramine,
- 30 fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamfetamine, levophacetoperane, mazindol, mefenorex,

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metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; or a pharmaceutically acceptable salt thereof.

5 24. A use, composition, product or method according to any one of the preceding claims wherein the anorectic agent is a halogenated amphetamine derivative.

10 25. A use, composition, product or method according to claim 24 wherein the amphetamine derivative is selected from chlorphentermine, cloforex, clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; or a pharmaceutically acceptable salt thereof.

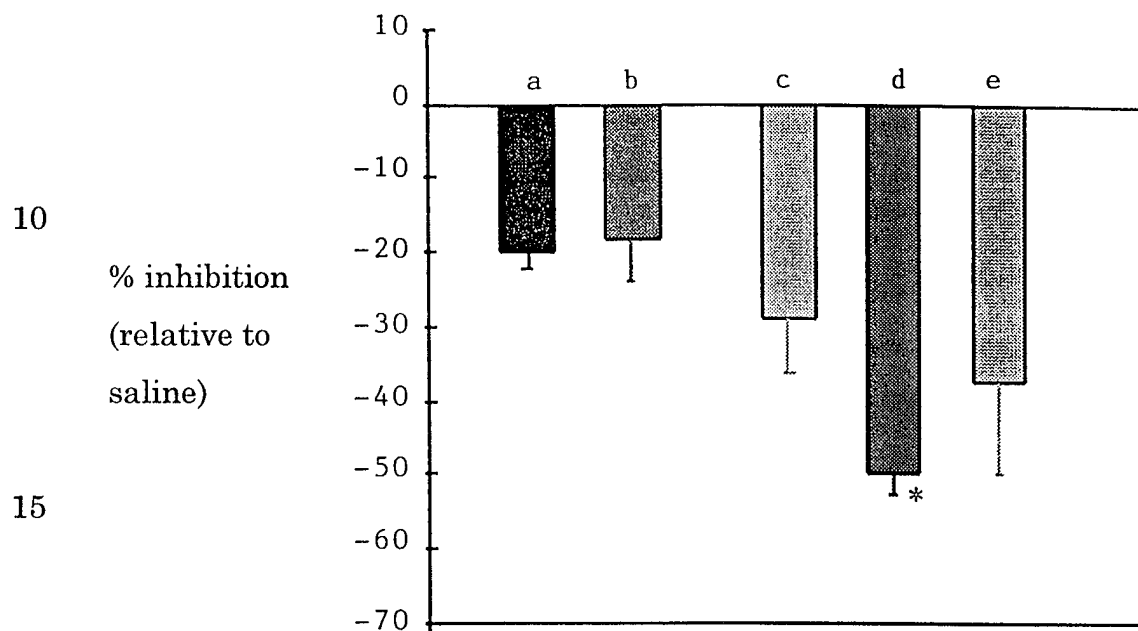
15 26. A use, composition, product or method according to any one of claims 1 to 25 wherein the eating disorder is obesity.

 27. A use, composition, product or method according to any one of claims 1 to 25 wherein the eating disorder is bulimia nervosa.

20 28. A use, composition, product or method according to any one of claims 1 to 25 wherein the eating disorder is a compulsive eating disorder.

FIGURE 1

Effect of dexfenfluramine and GR205171 on food intake in diet-induced
5 obese C57BL6/J mice.



- a dexfenfluramine, 3mg/kg
- 20 b GR205171, 20mg/kg
- c dexfenfluramine, 3mg/kg + GR205171, 5mg/kg
- d dexfenfluramine, 3mg/kg + GR205171, 10mg/kg
- e dexfenfluramine, 3mg/kg + GR205171, 20mg/kg
- 25 * p<0.01 vs. dexfenfluramine, 3mg/kg
p<0.01 vs. GR205171, 20mg/kg

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/01161

A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K31/535 A61K31/675 A61K31/435 A61K31/445 A61K31/40 A61K31/47		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 01450 A (HUSCROFT IAN THOMAS ;KULAGOWSKI JANUSZ JOZEF (GB); MERCK SHARP & D) 15 January 1998 see abstract see page 1, line 1 - line 12 see page 23, line 13 - page 27, line 28 see page 49, line 27 - line 30; claims; examples ---	1-7, 20, 23-28
P, X	WO 97 49710 A (ELLIOTT JASON MATTHEW ;HOLLINGWORTH GREGORY JOHN (GB); KULAGOWSKI) 31 December 1997 see abstract see page 1, line 11 - line 18 see page 23, line 6 - page 27, line 20 see page 48, line 3 - line 15; claims; examples --- -/--	1-7, 20, 23-28
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.		
Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search 20 August 1998		Date of mailing of the international search report 26/08/1998
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Hoff, P

INTERNATIONAL SEARCH REPORT

Int ernational Application No

PCT/GB 98/01161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 38692 A (LILLY CO ELI) 23 October 1997 see abstract see page 5, line 1 - page 6, line 28 see page 51, line 15 - page 52, line 10 see page 61, line 5 - page 62, line 5; claims; examples ---	1,3,6, 20,26-28
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Y	see page 21, line 17 - page 26, line 15 see page 43, line 20 - page 44, line 7 see page 63, line 1 - page 64, line 3; claims ---	8-13, 15-18, 21,22
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Y	see page 1, line 14 - line 24 see page 5, line 5 - line 14 see page 17, line 6 - line 17; example 6; table 1 see claims 1-7,9-23,28 ---	8-13, 15-18
Y	EP 0 577 394 A (MERCK & CO INC) 5 January 1994 cited in the application see abstract	8,21,22
X	see page 18, line 37 - page 21, line 38; claims ---	3
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X	see page 30, line 22 - page 35, line 23; claims ---	3
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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 23798 A (MERCK & CO INC ;DORN CONRAD P (US); HALE JEFFREY J (US); MACCOSS M) 8 September 1995 cited in the application see abstract	10,21,22
X	see page 70, line 10 - line 30 see page 73, line 30 - page 85, line 12; claims	3
Y	WO 96 05181 A (MERCK SHARP & DOHME ;HARRISON TIMOTHY (GB); OWENS ANDREW PATE (GB)) 22 February 1996 cited in the application see abstract	11,21,22
X	see page 16, line 16 - page 22, line 17; claims	3
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X	see page 6, line 35 - page 7, line 16 see page 17, line 50 - page 19, line 22; claims	3
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X	see page 12, line 20 - line 26 see page 55, line 21 - page 56, line 25; claims	3
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X	see page 5, line 11 - line 24; claims	3
Y	EP 0 443 132 A (FUJISAWA PHARMACEUTICAL CO) 28 August 1991 cited in the application see abstract	16
X	see page 11, line 51 - page 12, line 17; claims	3
Y	WO 92 17449 A (PFIZER) 15 October 1992 cited in the application see abstract	17
X	see page 11, line 1 - line 37; claims	3
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/01161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 08549 A (GLAXO GROUP LTD ;ARMOUR DUNCAN ROBERT (GB); EVANS BRIAN (GB); GIBL) 30 March 1995 cited in the application see abstract	18,21
X	see page 9, line 10 - page 11, line 13 see page 15, line 18 - line 29; claims	3
A	WO 95 14017 A (LILLY CO ELI) 26 May 1995 cited in the application see abstract	19
X	see page 111, line 1 - line 32 see page 126, line 4 - page 129, line 14; claims; table II	3
A	EP 0 591 040 A (SANOFI ELF) 6 April 1994 cited in the application see abstract	14
X	see page 14, line 48 - page 15, line 5; claims	3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 98/01161

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 6-28
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 98/01161

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