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USE OF A NK–1 RECEPTOR ANTAGONIST FOR TREATING OR PREVENTING ABNORMAL BONE RESORPTION

(57) Abstract
The present invention relates to the use of an NK–1 receptor antagonist for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption, optionally in combination with one or more active agents selected from the group consisting of bisphosphonates, estrogen and androgen receptor modulators, and peptide hormones, and to methods of using the same, and to compositions and products containing the same.
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USE OF A NK-1 RECEPTOR ANTAGONIST FOR TREATING OR PREVENTING ABNORMAL BONE RESORPTION

This invention relates to the treatment or prevention of abnormal bone resorption by the administration of a NK-1 receptor antagonist, optionally in combination with one or more active agents from the group consisting of bisphosphonates, estrogen and androgen receptor modulators, and peptide hormones.

The term “abnormal bone resorption”, as used herein means a degree of bone resorption that exceeds the degree of bone formation, either locally, or in the skeleton as a whole. “Abnormal bone resorption” can also be associated with the formation of bone having an abnormal structure.

A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, Paget’s disease, periodontal disease, periprosthetic bone loss or osteolysis, and hypercalcemia of malignancy. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Osteoporotic patients usually experience bone resorption in excess of bone formation, causing chronic bone loss. Because osteoporosis, as well as other disorders associated with ongoing bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

Multinucleated cells called osteoclasts are responsible for a process known as bone resorption. In osteoporosis, the bone resorption rate exceeds the bone formation rate, causing net bone loss. It is well known that bisphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone

At present, a great amount of preclinical and clinical data exists for the potent bisphosphonate compound alendronate. Evidence suggests that other amino-bisphosphonates such as risedronate, ibandronate and zoledronate, have many properties in common with alendronate, including both high bone specificity and potency as inhibitors of osteoclastic bone resorption. An older non-amino-bisphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent bisphosphonates, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization and bone strength. See Boyce, B. F., Fogelman, I., Ralston, S. et al. (1984) *Lancet* 1(8381), pp. 821-824 (1984), and Gibbs, C. J., Aaron, J. E.; Peacock, M. (1986) *Br. Med. J.* 292, pp. 1227-1229 (1986), both of which are incorporated by reference herein in their entirety.

Peak bone mass in women is achieved at around 30-35 years of age.

Bone mass is then relatively stable until the perimenopausal period (usually the late fifth decade of life). The rate of bone loss accelerates markedly during the early post menopausal period to a rate of 3-4% annually, especially at sites with a high component of trabecular bone. After 8-10 years of menopausal life, the bone loss rate slowly stabilizes at about 1% annually.

The average woman has a greater than 40% chance of developing at least one osteoporotic fracture during her lifetime. Osteoporotic fractures, especially of the hip, occur in 16% of all women reaching 80 years of age, and are associated with a marked reduction in the quality of life and high cost of treatment. The total costs and morbidity associated with all
osteoporotic fractures are certain to substantially exceed those of hip fracture alone, although precise estimates are not available.

Apart from bisphosphonates such as alendronate, other generally recognised therapies for prevention of osteoporosis are estrogen replacement therapy, raloxifene, a selective estrogen receptor modulator, and calcitonin. Along with preventing of bone loss associated with reduced endogenous estrogen production, administration of estrogen can help reduce post menopausal symptoms such as vasomotor instability, vaginal atrophy, and increased incidence of cardiovascular problems, possibly associated with a deterioration in the lipid profile. However, at the doses of estrogen commonly employed for bone loss prevention, some women continue to lose bone during treatment. Furthermore, estrogen treatment is also associated with some serious risks, including endometrial carcinoma, symptomatic gall bladder disease, deep vein thrombosis and an increased incidence of breast cancer. Although some of these risks can be lowered by addition of progestins to the therapeutic regimen, a large proportion of women will not accept long-term estrogen treatment mainly because of breakthrough bleeding and safety concerns.

It would be desirable to have an agent other than a bisphosphonate, that prevents osteoporosis without the risks and side effects associated with estrogen.

Neurokinin 1 (NK-1; substance P) receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinins, and in particular substance P. To date, the role of substance P in abnormal bone resorption, and the use of NK-1 receptor antagonists to treat or prevent abnormal bone resorption, has not been elucidated.

We have now found that NK-1 receptor antagonists are effective in the treatment of abnormal bone resorption, as evidenced by their effect on bone density in vivo in an animal model of inflammatory joint disease.
Furthermore, a combination of a NK-1 receptor antagonist with a bisphosphonate may provide enhanced inhibition of bone resorption over that provided by the bisphosphonate alone. They may also allow for a reduced dosage or frequency of dosing with the bisphosphonate which would be particularly advantageous when side-effects are a liability with high dosage or chronic administration regimens.

The present invention accordingly provides the use of a NK-1 receptor antagonist for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.

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

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

In addition to monotherapy, the NK-1 receptor antagonist may be administered in combination with one or more active agents selected from, but not limited to, the group consisting of bisphosphonates, estrogen and androgen receptor modulators, and peptide hormones.

The present invention therefore further provides the use of a NK-1 receptor antagonist and one or more active agents selected from, but not limited to, the group consisting of bisphosphonates, estrogen and androgen receptor modulators, and peptide hormones, for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.

The present invention also provides a method for the treatment or prevention of abnormal bone resorption, which method comprises administration to a patient in need of such treatment a therapeutically effective amount of a NK-1 receptor antagonist and one or more active agents selected from, but not limited to, the group consisting of
biphosphonates, estrogen and androgen receptor modulators and peptide hormones, 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 one or more active agents selected from, but not limited to, the group consisting of biphosphonates, estrogen and androgen receptor modulators, and peptide hormones, together with at least one pharmaceutically acceptable carrier or excipient.

It will be appreciated that the NK-1 receptor antagonist and the additional active agent(s) may be present as a combined preparation for simultaneous, separate or sequential use for the treatment or prevention of abnormal bone resorption. 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 one or more active agents selected from, but not limited to, the group consisting of biphosphonates, estrogen and androgen receptor modulators, and peptide hormones, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of abnormal bone resorption.

The methods and compositions of the present invention are useful for both treating and preventing abnormal bone resorption and conditions associated therewith.

According to a particular aspect of the present invention, when used in combination therapy, the NK-1 receptor antagonist is administered in combination with one or more active agents selected from the group consisting of biphosphonates, estrogen receptor modulators, and peptide hormones.

When used in combination therapy, the NK-1 receptor antagonist is preferably administered in combination with a biphosphonate.
Conditions associated with abnormal bone resorption include both generalized and localized bone loss. The term “generalized bone loss” means bone loss at multiple skeletal sites or throughout the skeletal system. The term “localized bone loss” means bone loss at one or more specific, defined skeletal sites.

Generalized bone loss is usually associated with osteoporosis. Osteoporosis is most common in post-menopausal women, wherein estrogen production has diminished. However, osteoporosis can also be glucocorticoid-induced and has been observed in males due to age and reduced androgen production. Osteoporosis can be induced by disease, e.g. rheumatoid arthritis; by secondary causes, e.g., glucocorticoid therapy; or by no identifiable cause, i.e. idiopathic osteoporosis, possibly of inherited origin. In the present invention, preferred methods include the treatment or prevention of abnormal bone resorption in osteoporotic humans.

Localized bone loss has been associated with periodontal disease and periprosthetic osteolysis where bone resorption has occurred in proximity to a dental or orthopaedic prosthetic implant.

Generalized or localized bone loss can occur from disuse, often a problem for those confined to a bed or a wheelchair, those who have an immobilized limb set in a cast or held in traction, or those who suffer permanently disabling strokes.

The methods and compositions of the present invention are useful for treating and/or preventing the following conditions or disease states: osteoporosis, including post-menopausal osteoporosis, glucocorticoid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, and idiopathic osteoporosis; Paget’s disease; abnormally increased bone turnover; hypercalcemia of malignancy; osteogenesis imperfecta; periodontal disease; periprosthetic osteolysis; and abnormal bone resorption associated with immunosuppressive therapy.

The term “pharmacologically effective amount”, as used herein, means that amount of the NK-1 receptor antagonist and (where present)
the additional active agent(s), that will elicit the desired therapeutic effect or response when administered in accordance with the desired treatment regimen. A preferred pharmaceutically effective amount of the NK-1 receptor antagonist and (where present) the additional active agent(s) is a bone resorption inhibiting amount.

The term “bone resorption inhibiting”, as used herein, means preventing bone resorption by the direct or indirect alteration of osteoclast formation or activity. Inhibition of bone resorption refers to prevention of bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity.

It will be appreciated that the NK-1 receptor antagonist and any additional active agent(s) should be continuously administered, according to the dosing schedule chosen, until the desired therapeutic effect is achieved, i.e. up to the time that the clinical or medical effect sought for the disease or condition being treated is observed by the clinician or researcher. For methods of treatment of the present invention, the NK-1 receptor antagonist and any additional active agent(s) should be continuously administered until the desired change in bone resorption rate, bone mass, or bone structure is observed. In such instances, achieving an increase in bone mass or a replacement of abnormal bone structure with normal bone structure are the desired objectives. For methods of prevention of the present invention, the NK-1 receptor antagonist and any additional active agent(s) should be continuously administered for as long as necessary to prevent the undesired condition. In such instances, maintenance of existing bone mass is often the objective. Non-limiting examples of administration periods can range from about 2 weeks to the remaining lifespan of the mammal. For humans, administration periods can range from about 2 weeks to the remaining lifespan of the human, preferably from about 2 weeks to about 20 years, more preferably from about 1 month to about 20 years, more preferably
from about 6 months to about 10 years, and most preferably from about 1
year to about 10 years.

The term "mammal" as used herein include animals of economic
importance such as bovine, 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 or prevention of abnormal bone resorption where the use of
a bisphosphonate or estrogen replacement therapy is generally prescribed.

By the use of a NK-1 receptor antagonist, optionally in combination with
one or more active agents selected from the group consisting of
bisphosphonates, estrogen and androgen receptor modulators, and peptide
hormones in accordance with the present invention, it is now also possible
to treat or prevent abnormal bone resorption in patients for whom
conventional therapy might not be wholly successful or where patient
compliance with existing therapeutic regimens is problematic.

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,
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,
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,
93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/01402,
94/02461, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843,
94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663,
94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740,
94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 96/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942, 97/21702, 97/22597, 97/24350, 97/30055, 97/38692, 97/49710, 98/01450, 98/13369, 98/49170, 98/54187, 99/00368 and 99/24423; 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, 2 302 689, 2 309 458 and 2 321 058.

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

\[
\begin{align*}
\text{R}^3 & \\
\text{R}^4 & \\
\text{X} & \\
\text{R}^5 & \\
\text{R}^1 & \\
\text{N} & \\
\text{R}^2 & \\
\end{align*}
\]

(I)

or a pharmaceutically acceptable salt thereof, wherein:

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

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

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

- \(\text{benzimidazolyl},\)
- \(\text{imidazolyl},\)
- \(\text{isoxazolyl},\)
- \(\text{isothiazolyl},\)
- \(\text{oxadiazolyl},\)
- \(\text{pyrazolyl},\)
- \(\text{pyrazolinyl},\)
(G) pyrazolyl,

(H) pyridyl,

(I) pyrrolyl,

(J) tetrazolyl,

(K) thiadiazolyl,

(L) triazolyl, and

(M) piperidinyl,

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

(i) $C_{1-6}$-alkyl, unsubstituted or substituted with halo, -CF$_3$, -OCH$_3$, or phenyl,

(ii) $C_{1-6}$-alkoxy,

(iii) oxo,

(iv) thioxo,

(v) cyano,

(vi) -SCH$_3$,

(vii) phenyl,

(viii) hydroxy,

(ix) trifluoromethyl,

(x) -(CH$_2$)$_m$-NR$_2$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) -NR$_2$COR$^{10}$, wherein R$^9$ and R$^{10}$ are as defined above,

and

(xii) -CONR$_2$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 -O-;

R$^4$ is

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

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
(4) -CF$_3$;

Y is -O-; and

Z is hydrogen or C$_{1-4}$alkyl;

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;

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)-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, especially compounds of formula (II) and pharmaceutically acceptable salts thereof:
wherein:

A¹ is fluorine or CF₃;
A² is fluorine or CF₃;
A³ is fluorine or hydrogen;

R⁶ is a 5-membered or 6-membered heterocyclic ring containing 2 or
3 nitrogen atoms optionally substituted by =O, =S or a C₁₄alkyl group, and
optionally substituted by a group of the formula ZNR⁷R⁸ where
Z is C₁₆alkylene or C₂₆cycloalkylene;

R⁷ is hydrogen, C₁₄alkyl, C₃₋₇cycloalkyl or C₃₋₇cycloalkylC₁₄alkyl, or
C₂₋₄alkyl substituted by C₁₄alkoxy or hydroxyl;
R⁸ is hydrogen, C₁₄alkyl, C₃₋₇cycloalkyl or C₃₋₇cycloalkylC₁₄alkyl, or
C₂₋₄alkyl substituted by one or two substituents selected from C₁₄alkoxy,
hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or
two heteroatoms selected from N, O and S;

or R⁷, R⁸ and the nitrogen atom to which they are attached form a
heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by a
hydroxy group, and optionally containing a double bond, which ring may
optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)₂
or a second nitrogen atom which will be part of a NH or NR₆ moiety where
R₆ is C₁₄alkyl optionally substituted by hydroxy or C₁₄alkoxy;

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, 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;

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

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

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

Particularly preferred compounds of formula (II) include:

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

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

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine;

and pharmaceutically acceptable salts thereof.

Further preferred NK-1 receptor antagonists are those described in European Patent Specification No. WO 95/23798, especially compounds of formula (III):

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, 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;

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

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

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

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

A is unsubstituted ₁₋₆alkyl;

B is selected from the group consisting of:

\[
\begin{align*}
\text{N} & \text{N} & \text{N} & \text{N} & \text{N} \\
\text{X} & \text{H} & \text{O} & \text{X} & \text{N} \\
\text{X} & \text{N} & \text{N} & \text{S} & \text{X} \\
\text{X} & \text{N} & \text{S} & \text{X} & \text{N} \\
\text{X} & \text{N} & \text{O} & \text{X} & \text{N} \\
\text{X} & \text{N} & \text{S} & \text{X} & \text{N} \\
\end{align*}
\]
p is 0 or 1;
X is selected from:

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

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

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

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

(e) \(-\text{CH(R}^4)\text{-PO(O)}^-_2 \cdot 2\text{M}^+\),

(f) \(-\text{CH(R}^4)\text{-PO(O)}^-_2 \cdot \text{D}^{2+}\),

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

(h) \(-\text{CH(CH}_3)\text{-O-CO-R}^5\), wherein \(\text{R}^5\) is selected from the group consisting of:
Y is \(-\text{O}\)-;

Z is hydrogen or \(\text{C}_{1-6}\text{alkyl}\);

and pharmaceutically acceptable salts thereof.

- Particularly preferred compounds of formula (III) include:
- (1) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine N-oxide;
Further preferred NK-1 receptor antagonists are those described in International Patent Specification No. WO 97/49710, especially compounds of formula (IV):

wherein
R\(^1\) represents hydrogen, hydroxy, C\(_{1,6}\)alkyl, C\(_{2,6}\)alkenyl, C\(_{3,7}\)cycloalkyl, C\(_{3,7}\)cycloalkylC\(_{1,4}\)alkyl, C\(_{1,6}\)alkoxy, fluoroC\(_{1,6}\)alkoxy, C\(_{1,6}\)alkoxyC\(_{1,4}\)alkyl, C\(_{1,6}\)alkoxyC\(_{1,4}\)alkoxy, fluoroC\(_{1,6}\)alkoxyC\(_{1,4}\)alkyl, C\(_{2,6}\)alkenylxyloxy, C\(_{3,7}\)cycloalkoxy, C\(_{3,7}\)cycloalkylC\(_{1,4}\)alkoxy, phenoxy, benzylxyloxy, cyano, halogen, NR\(^a\)R\(^b\), SR\(^a\), SOR\(^a\), SO\(_2\)R\(^a\), OSO\(_2\)R\(^a\), NR\(^a\)COR\(^14\), COR\(^a\), CO\(_2\)R\(^a\) or CONR\(^a\)R\(^b\) where R\(^a\) and R\(^b\) each independently represent hydrogen, C\(_{1,4}\)alkyl or fluoroC\(_{1,4}\)alkyl;

R\(^2\) represents hydrogen, halogen, C\(_{1,6}\)alkyl or C\(_{1,6}\)alkoxy;

or R\(^1\) and R\(^2\) may be joined together such that there is formed a 5- or 6-membered saturated or unsaturated ring containing one or two atoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by a group selected from C\(_{1,4}\)alkyl, CF\(_3\), =O or =S;

R\(^3\) represents hydrogen, halogen, C\(_{1,6}\)alkyl, fluoroC\(_{1,6}\)alkyl, C\(_{1,6}\)alkoxy, fluoroC\(_{1,6}\)alkoxy, C\(_{3,7}\)cycloalkyl, C\(_{3,7}\)cycloalkylC\(_{1,4}\)alkyl, cyano, SR\(^a\), SOR\(^a\), SO\(_2\)R\(^a\), NR\(^a\)R\(^b\), NR\(^a\)COR\(^14\), COR\(^a\), CO\(_2\)R\(^a\), CONR\(^a\)R\(^b\) or C\(_{1,4}\)alkyl substituted by cyano, CO\(_2\)R\(^a\) or CONR\(^a\)R\(^b\) where R\(^a\) and R\(^b\) are as previously defined;

R\(^4\) represents hydrogen, halogen, C\(_{1,6}\)alkyl, C\(_{1,6}\)alkoxy, CF\(_3\), OCF\(_3\), NO\(_2\), CN, SR\(^a\), SOR\(^a\), SO\(_2\)R\(^a\), CO\(_2\)R\(^a\), CONR\(^a\)R\(^b\), C\(_{2,6}\)alkenyl, C\(_{2,6}\)alkynyl or C\(_{1,4}\)alkyl substituted by C\(_{1,4}\)alkoxy, where R\(^a\) and R\(^b\) are as previously defined; and

the broken line represents an optional double bond;

and pharmaceutically acceptable salts thereof.

Particularly preferred compounds of formula (IV) include:

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

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

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

(3R,5R,6S)-3-(2-methoxy-5-trifluoromethoxyphenyl)-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
spiro[4.5]decane;
(3R,5R,6S)-3,6-bis(phenyl)-1-oxa-7-aza-spiro[4.5]decane;
(3R,5R,6S)-7-benzyl-3-(2-methoxy-5-trifluoromethoxyphenyl)-6-phenyl-1-
oxa-7-aza-spiro[4.5]decane;

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

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

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):

![Diagram](image)

or a pharmaceutically acceptable salt thereof, wherein

Y is (CH₂)ₙ wherein n is an integer from 1 to 4, and wherein any one
of the carbon-carbon single bonds in said (CH₂)ₙ may optionally be
replaced by a carbon-carbon double bond, and wherein any one of the
carbon atoms of said (CH₂)ₙ may optionally be substituted with R⁴, and

wherein any one of the carbon atoms of said (CH₂)ₙ may optionally be
substituted with R⁷;
Z is (CH₂)ₘ wherein m is an integer from 0 to 6, and wherein any one of the carbon-carbon single bonds of (CH₂)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 (CH₂)ₘ may optionally be substituted with R³;

R¹ is hydrogen or C₁₈-alkyl optionally substituted with hydroxy, C₁₄-alkoxy or fluoro;

R² is a radical selected from hydrogen, C₁₆ straight or branched alkyl, C₃-₇-cycloalkyl wherein one of the CH₂ groups in said cycloalkyl may optionally be replaced by NH, oxygen or sulphur; aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thiényl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; phenyl-C₂₆-alkyl, benzhydryl and benzyl, wherein each of said aryl and heteroaryl groups and the phenyl moieties of said benzyl, phenyl-C₂₆-alkyl and benzhydryl may optionally be substituted with one or more substituents independently selected from halo, nitro, C₁₂ alkyl, C₁₈-alkoxy, trifluoromethyl, amino, C₁₈-alkylamino, C₁₈-alkyl-O-CO, C₁₈-alkyl-O-CO-C₁₈-alkyl, C₁₈-alkyl-CO-O-C₁₈-alkyl-C₁₈-alkyl-O-, C₁₈-alkyl-CO-C₁₈-alkyl-, di-C₁₈-alkylamino, -CONH-C₁₈-alkyl, C₁₈-alkyl-CO-NH-C₁₈-alkyl, -NHC(OH) and -NHC(O)-C₁₈-alkyl; and wherein one of the phenyl moieties of said benzhydryl may optionally be replaced by naphthyl, thiényl, furyl or pyridyl;

R⁵ is hydrogen, phenyl or C₁₈-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;

R³ is aryl selected from phenyl and naphthyl; heteroaryl selected from indanyl, thiényl, furyl, pyridyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl and quinolyl; and cycloalkyl having 3 to 7
carbon atoms wherein one of the \((\text{CH}_2)\) 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 \(\text{C}_3-\text{C}_7\)cycloalkyl may optionally be substituted with one or two substituents, each of said substituents being independently selected from halo, nitro, \(\text{C}_1-\text{C}_6\)alkyl, \(\text{C}_1-\text{C}_6\)alkoxy, trifluoromethyl, amino, \(\text{C}_1-\text{C}_6\)alkylamino, \(-\text{CO-NH-}\ \text{C}_1-\text{C}_6\)alkyl, \(\text{C}_1-\text{C}_6\)alkyl-CO-NH-C\(_1\)alkyl, \(-\text{NHOH}\) and \(-\text{NHCOC}_1-\text{C}_6\)alkyl;

\(R^4\) and \(R^7\) are each independently selected from hydroxy, halogen, halo, amino, oxo, cyano, methylene, hydroxymethyl, halomethyl, \(\text{C}_1-\text{C}_6\)alkylamino, di-\(\text{C}_1-\text{C}_6\)alkylamino, \(\text{C}_1-\text{C}_6\)alkoxy, \(\text{C}_1-\text{C}_6\)alkyl-O-CO, \(\text{C}_1-\text{C}_6\)alkyl-O-CO-C\(_1\)alkyl, \(\text{C}_1-\text{C}_6\)alkyl-CO-O, \(\text{C}_1-\text{C}_6\)alkyl-CO-C\(_1\)alkyl-O-, \(\text{C}_1-\text{C}_6\)alkyl-CO-, \(\text{C}_1-\text{C}_6\)alkyl-CO-C\(_1\)alkyl, and the radicals set forth in the definition of \(R^2\);

\(R^6\) is \(-\text{NHCOR}^9\), \(-\text{NHCH}_2\text{R}^9\), \text{SO}_2\text{R}^8\) 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 \(\text{C}_1-\text{C}_6\)alkyl, hydrogen, phenyl or phenyl\(\text{C}_1-\text{C}_6\)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 \(\text{C}_1-\text{C}_6\)alkyl, or \(R^4\) and \(R^7\), together with the carbon to which they are attached, for a \(\text{C}_3-\text{C}_6\) 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 \((\text{2S,3S})\)-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):

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{R}^5 \\
\text{O} \\
\text{N} \\
\text{CH} \\
\text{R}^6 \\
\end{array}
\]  
(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;

R\(^3\) is optionally substituted phenyl, cyclohexadienyl, naphthyl, indenyl or optionally substituted heterocycle;

R\(^2\) is H, halogen, OH, alkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkylthio, acyloxy, carboxy, optionally substituted alkoxy carbonyl, benzyloxycarbonyl, amino or acylamino;

R\(^3\) is optionally 2-substituted phenyl;

R\(^4\) is OH or fluorine when R\(^5\) is H;
or R\(^4\) and R\(^5\) are OH;
or R\(^4\) and R\(^5\) together form a bond.

A particularly preferred compound of formula (VI) is (3\(\alpha\)S, 4\(\alpha\)S, 7\(\alpha\)S)-7,7-diphenyl-4-(2-methoxyphenyl)-2-[(2S)-(2-methoxyphenyl)propionyl]perhydroisindol-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):

\[
\begin{array}{c}
\text{Ar} \\
\text{T} \\
\text{C} \\
\text{N} \\
\text{CH} \\
\text{CH} \\
\text{CH} \\
\text{CH} \\
\text{Am} \\
\end{array}
\] 
\begin{array}{c}
\text{Q} \\
\text{A} \\
\text{Ar}^\prime \\
\end{array}
\] 
(VII)

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

T represents a bond, a hydroxymethylene group, a C₁₄alkoxymethylene group or a C₁₅alkylene group;

Ar' represents a phenyl group which is unsubstituted or substituted by one or more substituents selected from halogen, preferably chlorine or fluorine, trifluoromethyl, C₁₄alkoxy, C₁₄alkyl where the said substituents may be the same or different; a thienyl group; a benzothienyl group; a naphthyl group; or an indolyl group;

R represents hydrogen, C₁₄alkyl, ω-C₁₄alkoxyC₁₄alkyl, or ω-C₂₄alkanoyloxyC₂₄alkyl;

Q represents hydrogen;

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

Am⁺ represents the radical

\[ \begin{array}{c}
\text{X₁} \\
\text{X₂} \\
\text{X₃}
\end{array} \]

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

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.

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

R\textsuperscript{1} represents an optionally substituted aralkyl, aryloxyalkyl, heteroaralkyl, aroyl, heteroaroyl, cycloalkylcarbonyl, aralkanoyl, heteroarylalkanoyl, aralkoxycarbonyl or arylcarbamoyl group or the acyl group of an \(\alpha\)-amino acid optionally N-substituted by a lower alkanoyl or carbamoyl-lower alkanoyl group;

R\textsuperscript{2} represents cycloalkyl or an optionally substituted aryl or heteroaryl group;

R\textsuperscript{3} represents hydrogen, alkyl, carbamoyl or an alkanoyl or alkenoyl group optionally substituted by carboxy or esterified or amidated carboxy;

R\textsuperscript{4} represents an optionally substituted aryl group or an optionally partially saturated heteroaryl group;

X\textsubscript{1} represents methylene, ethylene, a bond, an optionally ketalised carbonyl group or an optionally etherified hydroxymethylene group;

X\textsubscript{2} represents alkylene, carbonyl or a bond; and

X\textsubscript{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 \(\alpha\)-position) hydroxy.

A particularly preferred compound of formula (VIII) is (2R\textsuperscript{*, 4S\textsuperscript{*}})-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)
or a pharmaceutically acceptable salt thereof, wherein

R\textsuperscript{1} is aryl, or a group of the formula:

\[ \text{R}\textsuperscript{2} - \text{Y-A-N} - \text{CONHCHCON} - \text{R}\textsuperscript{3} \]

X is CH or N; and

Z is O or N-R\textsuperscript{5}, in which R\textsuperscript{5} is hydrogen or lower alkyl;

R\textsuperscript{2} is hydroxy or lower alkoxy;

R\textsuperscript{3} is hydrogen or optionally substituted lower alkyl;

R\textsuperscript{4} is optionally substituted ar(lower)alkyl;

A is carbonyl or sulfanyl; and

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)

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
\text{R}^5 \\
\text{R}^6 \\
\text{R}^7 \\
\text{R}^8 \\
\text{R}^9 \\
\text{R}^{10}
\end{array}
\]

(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-SO\(_2\) -, phenyl, phenoxy, C\(_{1-10}\)alkyl-SO\(_2\)NH-, C\(_{1-10}\)alkyl-SO\(_2\)NH-C\(_{1-10}\)alkyl-, C\(_{1-10}\)alkylamino-diC\(_{1-10}\)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 (2S,3S)-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)

\[
\begin{align*}
\text{R}^1 & \text{ is a C}_{1-4}\text{-alkoxy group;} \\
\text{R}^2 & \text{ is} \\
\text{R}^3 & \text{ is a hydrogen or halogen atom;} \\
\text{R}^4 & \text{ and } \text{R}^5 \text{ may each independently represent a hydrogen or halogen atom, or a C}_{1-4}\text{-alkyl, C}_{1-4}\text{-alkoxy or trifluoromethyl group;} \\
\text{R}^6 & \text{ is a hydrogen atom, a C}_{1-4}\text{-alkyl, (CH}_2\text{)}_m\text{cyclopropyl, - S(O)}_n\text{C}_{1-4}\text{-alkyl, phenyl, NR}^7\text{R}^8, \text{CH}_2\text{C(O)CF}_3 \text{ or trifluoromethyl group;} \\
\text{R}^7 & \text{ and } \text{R}^8 \text{ may each independently represent a hydrogen atom, or a C}_{1-4}\text{-alkyl or acyl group;} \\
x & \text{ represents zero or 1;} \\
n & \text{ represents zero, 1 or 2; and} \\
m & \text{ represents zero or 1.}
\end{align*}
\]

Particularly preferred compounds of formula (XI) are (2-methoxy-5-tetrazol-1-yl-benzyl)-([2S,3S]-2-phenyl-piperidin-3-yl)-amine; and [2-methoxy-5-(5-trifluoromethyl-tetrazol-1-yl-benzyl)-([2S,3S]-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)

\[
\begin{align*}
R^8 & \quad R^4 \\
R \quad & (\text{CH}_2)_n \quad \text{C} \quad & \text{CH}_2 \quad & \text{N} \quad & (\text{CH}_2)_o \quad R^3 \\
& \quad \text{NH} \quad & \quad R^2 \\
& & \quad & (\text{CO})_p \\
& & \quad & (\text{CH}_2)_m \\
& & \quad R^1
\end{align*}
\]

(XII)

or a pharmaceutically acceptable salt thereof, wherein

\begin{itemize}
  \item m is zero, 1, 2 or 3;
  \item n is zero or 1;
  \item o is zero, 1 or 2;
  \item p is zero or 1;
  \item R is phenyl, 2- or 3-indolyl, 2- or 3-indoliny1, benzothienyl, benzoafuranyl, or naphthyl;
  \item which R groups may be substituted with one or two halo, C\textsubscript{1-3}alkoxy, trifluoromethyl, C\textsubscript{1-4}alkyl, phenyl-C\textsubscript{1-3}alkoxy, or C\textsubscript{1-4}alkanoyl groups;
  \item R\textsuperscript{1} is trityl, phenyl, diphenylmethyl, phenoxy, phenylthio,
  \item piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indoliny1, indolyl, benzothienyl, hexamethyleniminy1, benzoafuranyl, tetrahydropyridinyl, quinolinyl, isoquinolinyl, reduced quinolinyl, reduced isoquinolinyl, phenyl-(C\textsubscript{1-4}alkyl)-, phenyl-(C\textsubscript{1-4}alkoxy)-, quinolinyl-(C\textsubscript{1-4}alkyl)-, isoquinolinyl-(C\textsubscript{1-4}alkyl)-, reduced quinolinyl-(C\textsubscript{1-4}alkyl)-, reduced isoquinolinyl-(C\textsubscript{1-4}alkyl)-, benzoyl-(C\textsubscript{1-3}alkyl)-, C\textsubscript{1-4}alkyl, or -NH-CH\textsubscript{2}-R\textsuperscript{5};
  \item any one of which R\textsuperscript{1} groups may be substituted with halo, C\textsubscript{1-4}alkyl, C\textsubscript{1-4}alkoxy, trifluoromethyl, amino, C\textsubscript{1-4}alkylamino, di(C\textsubscript{1-4}alkyl)amino, or C\textsubscript{2-4}alkanoylamino;
  \item or any one of which R\textsuperscript{1} groups may be substituted with phenyl, piperazinyl, C\textsubscript{3-8}cycloalkyl, benzyl, C\textsubscript{1-4}alkyl, piperidinyl, pyridinyl,
pyrimidinyl, C$_2$$_6$ alkanoylamino, pyrrolidinyl, C$_2$$_6$ alkanoyl, or C$_4$$_4$ alkoxy carbonyl;

any one of which groups may be substituted with halo, C$_4$$_4$ alkyl, C$_4$$_4$ alkoxy, trifluoromethyl, amino, C$_4$$_4$ alkylamino, di(C$_4$$_4$ alkyl) amino, or C$_4$$_4$ alkanoylamino;

or R$^1$ is amino, a leaving group, hydrogen, C$_4$$_4$ alkylamino, or di(C$_4$$_4$ alkyl) amino;

R$^5$ is pyridyl, anilino-(C$_3$$_3$ alkyl)-, or anilinocarbonyl;

R$^2$ is hydrogen, C$_4$$_4$ alkyl, C$_4$$_4$ alkylsulfonyl, carboxy-(C$_3$$_3$ alkyl)-,

C$_3$$_3$ alkoxy carbonyl-(C$_3$$_3$ alkyl)-, or -CO-R$_6$;

R$^6$ is hydrogen, C$_4$$_4$ alkyl, C$_3$$_3$ haloalkyl, phenyl, C$_4$$_4$ alkoxy,

C$_3$$_3$ hydroxyalkyl, amino, C$_4$$_4$ alkylamino, di(C$_4$$_4$ alkyl) amino, or -(CH$_2$)$_q$-R$^7$;

q is zero to 3;

R$^7$ is carboxy, C$_4$$_4$ alkoxy carbonyl, C$_4$$_4$ alkyl carbonyloxy, amino,

C$_4$$_4$ alkylamino, di(C$_4$$_4$ alkyl) amino, C$_3$$_3$ alkoxy carbonylamino, or phenoxy, phenylthio, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, indolinyl, indolyl, benzothienyl, benzofuranyl, quinolinyl, phenyl-(C$_4$$_4$ alkyl)-,

quinolinyl-(C$_4$$_4$ alkyl)-, isoquinolinyl-(C$_4$$_4$ alkyl)-, reduced quinolinyl-

(C$_4$$_4$ alkyl)-, reduced isoquinolinyl-(C$_4$$_4$ alkyl)-, benzoyl-C$_3$$_3$ alkyl;

any one of which aryl or heterocyclic R$^7$ groups may be substituted with halo, trifluoromethyl, C$_4$$_4$ alkoxy, C$_4$$_4$ alkyl, amino, C$_4$$_4$ alkylamino, di(C$_4$$_4$ alkyl) amino, or C$_4$$_4$ alkanoylamino;

or any one of which R$^7$ groups may be substituted with phenyl, piperazinyl, C$_3$$_3$ cycloalkyl, benzyl, piperidinyl, pyridinyl, pyrimidinyl,

pyrrolidinyl, C$_2$$_6$ alkanoyl, or C$_4$$_4$ alkoxy carbonyl;

any of which groups may be substituted with halo, trifluoromethyl, amino, C$_4$$_4$ alkoxy, C$_4$$_4$ alkyl, C$_4$$_4$ alkylamino, di(C$_4$$_4$ alkyl) amino, or C$_4$$_4$ alkanoylamino;

R$^8$ is hydrogen or C$_4$$_4$ alkyl;

R$^3$ is phenyl, phenyl-(C$_4$$_4$ alkyl)-, C$_3$$_3$ cycloalkyl, C$_5$$_5$ cycloalkenyl,

c$_1$$_1$ alkyl, naphthyl, C$_2$$_2$ alkenyl, or hydrogen;
any one or which groups except hydrogen may be substituted with one or two halo, C₁₃alkoxy, C₁₃alkylthio, nitro, trifluoromethyl, or C₁₃alkyl groups; and

R⁴ is hydrogen or C₁₃alkyl;

with the proviso that if R¹ is hydrogen or halo, R³ is phenyl, phenyl-(C₁₃alkyl)-, C₃₋₅cycloalkyl, C₅₋₇cycloalkenyl, or naphthyl.

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

The bisphosphonates of use in the present invention correspond to the chemical formula (XIII)

\[
\begin{align*}
&\text{PO}_3\text{H}_2 \\
&\text{A-C-X} \\
&\text{PO}_3\text{H}_2
\end{align*}
\]

wherein

A and X are independently selected from the group consisting of H, OH, halogen, NH₂, SH, phenyl, C₁₋₃₀ alkyl, C₃₋₅ cycloalkyl, C₁₋₃₀ substituted alkyl, C₃₋₅ substituted cycloalkyl, C₁₋₁₀ alkyl or C₃₋₁₀ cycloalkyl mono- or di- substituted NH₂, C₁₋₁₀ alkoxy, C₁₋₁₀ alkyl or C₃₋₁₀ cycloalkyl substituted thio, phenyl substituted thio, C₁₋₁₀ alkyl or C₃₋₁₀ cycloalkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

In the foregoing chemical formula (XIII), the alkyl groups can be straight or branched. The C₁₋₃₀ substituted alkyl and C₃₋₅ substituted cycloalkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl,
furanyl, pyrrolidinyl, imidazonyl, NH₂, C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl mono- or di- substituted NH₂, OH, SH, and C₁-C₁₀ alkoxy.

In the foregoing chemical formula (XIII), A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

The foregoing chemical formula (XIII) is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenythio.

Preferred compounds of formula (XIII) are those in which A is selected from the group consisting of H, OH, and halogen, X is selected from the group consisting of C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₁-C₃₀ substituted alkyl, C₃-C₃₀ substituted cycloalkyl, halogen, C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl substituted thio, and phenyl substituted thio.

Particularly preferred compounds of formula (XIII) are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the group consisting of C₁-C₃₀ alkyl, C₃-C₃₀ cycloalkyl, C₁-C₃₀ substituted alkyl, C₃-C₃₀ substituted cycloalkyl, Cl, and chlorophenythio.

Most preferred is when A is OH and X is 4-aminobutyl, i.e.

alendronate.

Non-limiting examples of bisphosphonates useful herein include the following:

Alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid.

Alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate.

Alendronic acid and alendronate are described in U.S. Patents 4,922,007, to Kieczykowski et al., issued May 1, 1990, and 5,019,651, to Kieczykowski, issued May 28, 1991, both of which are incorporated by reference herein in their entirety.
Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (cimadronate), as described in U.S. Patent 4,970,335, to Isomura et al., issued November 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and J. Org. Chem 32, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propyldene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propyldene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropyldene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropyldene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiometane-1,1-disphosphonic acid (tiludronate) as described in U.S. Patent 4,876,248, to Breliere et al., October 24, 1989, which is incorporated by reference herein in its entirety.
1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zoledronate).

Preferred are bisphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

More preferred is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

Most preferred is alendronate monosodium trihydrate.

Estrogen receptor modulators are known for use in hormone replacement therapy and for their anti-bone resorption benefits. Nonlimiting examples of estrogen receptor modulators useful herein include estrogen, progestins, estradiol, raloxifene, and tamoxifene, and their pharmaceutically acceptable salts, and mixtures thereof.

Further examples of estrogen receptor modulators include clomethorone, delmadinone, droloxifene, idoxifene, nafodixidine, nitromifene, ormeloxifene (centchroman), toremifene, trioxifene, BE-25327, CP-336156 and ([2-(4-hydroxyphenyl)-6-hydroxynaphthalen-1-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methane, and their pharmaceutically acceptable salts, and mixtures thereof.

Non-limiting examples of an androgen receptor modulators include danazol, 5a-dihydrotestosterone, testosterone, nandrolone decanoate, methyltestosterone, methanadrostenolone, stanozolol, fluoxymesterone, oxymetholone, oxandrolone, oxymethol, norethandrolone, ethylestranol, 4-androsten-19-al-3,17-dione, 19-nortestosterone, norethandrone, norethisterone, dehydroepiandrosterone, epiandrosterone sulfate, androstenedione and androstenediol, testosterone propionate, testosterone cypionate, and testosterone enanthate.

A peptide hormone useful herein is calcitonin, which is approved for use for treating osteoporosis. Both human and salmon calcitonin are useful herein.
The preferred compounds of formulae (I), (II) and (III) 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:

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

The preferred compounds of formula (IV) will have the stereochemistry of the 5- and 6-positions as shown below (5-(R), 6-(S)). Where the optional double bond shown in formula (IV) is absent, the particularly preferred compounds will have the stereochemistry of the 3-position as shown below (3-(R)):

Unless otherwise defined herein, suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl and tert-butyl.
Unless otherwise defined herein, suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

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

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

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

A particular aryl-C\textsubscript{1-6}alkyl, e.g. phenyl-C\textsubscript{1-6}alkyl, group is benzyl.

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

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

Suitable pharmaceutically acceptable salts of the NK-1 receptor antagonists of use in the present invention include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise the quaternary ammonium salts in which the amino nitrogen atom carries an alkyl, alkenyl, alkynyl or aralkyl group. Where the compound carries an acidic group, for example a carboxylic acid group, the present invention also contemplates salts thereof, preferably non-toxic pharmaceutically acceptable salts thereof, such as the sodium, potassium and calcium salts thereof.
The compounds of use in this invention may have one or more chiral centers and the present compounds may occur as racemates, racemic mixtures and as individual diastereomers or enantiomers with all such isomeric forms and mixtures thereof being included within the scope of this invention. Furthermore, some of the crystalline forms for compounds of the present invention may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates and hydrates, as well as anhydrous compositions, are encompassed within the scope of this invention. Some of the compounds described herein may contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C1-C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts.

Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those or ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis,
unless indicated otherwise herein. For example, the phrase "about 70 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

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

For preparing solid compositions such as tablets, the principal active ingredient can be combined with an oral, non-toxic, pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, croscarmellose sodium and the like; for oral administration in liquid form, e.g., elixirs and syrups, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated. Suitable binders can include starch, gelatin, natural sugars such a glucose, anhydrous lactose, free-flow lactose, beta-lactose, and corn sweeteners, natural and synthetic gums, such as acacia, guar, tragacanth or sodium alginate, carboxymethyl cellulose, polyethylene glycol, waxes, and the like. Lubricants used in
these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. A particularly preferred tablet formulation for alendronate monosodium trihydrate is that described in U.S. Patent No. 5,358,941, to Bechard et al, issued October 25, 1994, which is incorporated by reference herein in its entirety. The compounds used in the present method can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide, and the like.

In the preparation of solid oral dosage forms, a solid preformulation composition containing a homogeneous mixture of one or more compounds of the present invention or a non-toxic pharmaceutically acceptable salt thereof, is conveniently prepared. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.
The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil or soybean oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

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 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 polyoxyethylene sorbitans (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 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™, Intronutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a premixed 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 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 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 a bisphosphonate, which process comprises bringing a NK-1 receptor antagonist and a bisphosphonate, 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
bisphosphonate, 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 bisphosphonate will suitably be between 0.001 to 1 and 1000 to 1, and especially between 0.01 to 1 and 100 to 1.

A suitable dosage level for the NK-1 receptor antagonist about 0.05 to 1500mg per day, preferably about 0.25 to 1500mg per day, and especially about 0.25 to 500mg per day. Preferred oral dosages in humans may include 10mg, 30mg, 100mg and 300mg of the NK-1 receptor antagonist per dose. 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.

A suitable dosage level for the bisphosphonate is between 0.05 mg per kg of body weight per day (mg/kg/day) to about 1.0 mg/kg/day.

Preferred oral dosages in humans may range from daily total dosages of about 2.5-20 mg/day over the effective treatment period, and a preferred prophylactic amount is 2.5, 5, or 10 mg/day.

Alandronate may be administered in a single daily dose or in a divided dose. It is desirable for the dosage to be given in the absence of food, preferably from about 30 minutes to 2 hours prior to a meal, such as breakfast, to permit adequate absorption.

A suitable dosage level for the estrogen or androgen receptor modulator is between about 0.1 and 100 mg/day, and preferably between about 0.1 and 10 mg/day, depending on the potency of the agent.

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

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 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
antagonists, i.e. compounds with an NK-1 receptor affinity (IC50) 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 (IC50) of less than 10nM,
favourably less than 2nM and preferably less than 1nM.

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

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

NK-1 receptor binding assays are performed in intact Chinese
hamster ovary (CHO) cells expressing the human NK-1 receptor using a
modification of the assay conditions described by Cascieri et al, *J.
Pharmacol. Exp. Ther.*, 1992, 42, 458. Typically, the receptor is expressed
at a level of 3x10^6 receptors per cell. Cells are grown in monolayer culture,
detached from the plate with enzyme-free dissociation solution (Speciality
Media Inc.), and washed prior to use in the assay. ^125^I-Tyr^8^-substance P
(0.1nM, 2000Ci/mmol; New England Nuclear) is incubated in the presence
or absence of test compounds (dissolved in 5μl dimethylsulphoxide,
DMSO) with 5x10^4 CHO cells. Ligand binding is performed in 0.25ml of
50mM Tris-HCl, pH7.5, containing 5mM MnCl₂, 150mM NaCl, 0.02%
bovine serum albumin (Sigma), 50μg/ml chymostatin (Peninsula), 0.1nM
phenylmethylsulphonyl fluoride, 2μg/ml pepstatin, 2μg/ml leupeptin and
2.8μg/ml furoyl saccharine. The incubation proceeds at room temperature
until equilibrium is achieved (>40 minutes) and the receptor-ligand
complex is harvested by filtration over GF/C filters pre-soaked in 0.1%
polyethyleneimine using a Tomtek 96-well harvester. Non-specific binding
is determined using excess substance P (1μM) and represents <10% of
total binding.

ASSAY 2: Gerbil Foot-Tapping

Long acting NK-1 receptor antagonists for use in the present
invention can be identified by their ability to inhibit foot tapping in gerbils
induced by central infusion of NK-1 receptor agonists such as GR73632
based on the method of Rupniak & Williams, Eur. J. Pharmacol., 1994,
265, 179.

Male or female Mongolian gerbils (35-70g) are anaesthetised by
inhalation of an isoflurane/oxygen mixture to permit exposure of the
jugular vein in order to permit administration of test compounds or vehicle
in an injection volume of approximately 5ml/kg i.v. Alternatively, test
compounds may be administered orally or by subcutaneous or
intraperitoneal routes. A skin incision is then made in the midline of the
scalp to expose the skull. A selective NK-1 receptor agonist (e.g. GR73632
(d Ala¹-L-Pro⁶,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 clear perspex observation box (approximately 25cm
x 20cm x 20cm). The duration of hind foot tapping is then recorded
continuously for approximately 5 minutes.
Duration of action may be determined by comparing the effect of the test compound on foot tapping when administered five minutes (i.v.) or 1 hour (p.o.) before NK-1 agonist challenge, against the effect when the test compound is administered 24 hours before the NK-1 agonist challenge.

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 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.

ASSAY 4: Ovariectomized Rat

Long acting NK-1 receptor antagonists for use in the present invention can be identified by their ability to inhibit abnormal bone resorption induced by ovariectomy in six-month old rats, as described in Wronski et al. Endocrinology 123:681-686 (1988). Since estrogen deficiency is the main risk factor for post-menopausal osteoporosis in people, abnormal bone resorption in the OVX rat model is extremely relevant to the human condition.

Ovariectomy (OVX) is completed by dorsal or ventral approach; sham-surgery is completed in age/sex-matched rats. Test compounds are administered orally, subcutaneously, or intraperitoneally to OVX rats.
beginning the day after surgery. All rats are killed at four weeks post-surgery.

Bone loss accompanied by accelerated bone resorption and formation in OVX rats is detectable by techniques that are routinely applied in humans. These include measurement of: 1) bone mineral density (BMD) by dual energy x-ray absorptiometry (DXA) in bone regions that contain varying amounts of cortical and trabecular bone (central femur [cortical] and distal femur [trabecular]); 2) urinary deoxypyridinoline crosslinks (uDPD), a biochemical marker of bone turnover; and 3) bone turnover via quantitation of in vivo fluorochrome labelled bone forming surfaces (mineralizing surface; MS/BS) on histologic sections in cancellous bone of the proximal tibia.

BMD significantly above, uDPD significantly below, and MS/BS significantly below that seen in OVX rats after four weeks treatment, are regarded as coordinated signs of test compound efficacy in preventing abnormal bone resorption associated with acute estrogen deficiency.

A typical experimental design using the OVX rat assay in an active pre-clinical development program has six groups:

a) Sham-operation
b) Ovariectomy (OVX)
c) OVX+Low Dose NK-1 Antagonist
d) OVX+Medium Dose NK-1 Antagonist
e) OVX+High Dose NK-1 Antagonist
f) OVX+.003mpk daily alendronate

Alendronate, a known inhibitor of abnormal bone resorption, and a drug already approved for the prevention/treatment of osteoporosis, is used as a positive control.

A suitable selection cascade for NK\textsubscript{1} antagonists of use according to the present invention is as follows:
(i) Determine affinity for human NK₁ receptor in radioligand binding studies (Assay 1); select compounds with IC₅₀ ≤ 10nM, preferably IC₅₀ ≤ 2nM, especially IC₅₀ ≤ 1nM.

(ii) Determine ability of compounds to inhibit foot tapping in gerbils induced by central injection of an 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 duration of action of compounds in gerbil foot tapping assay following intravenous administration 24 hours prior to central NK₁ agonist challenge; select compounds showing ≤ 25-fold loss of potency compared with ID₅₀ determined in step (ii) above with the proviso that ID₅₀ ≤ 10mg/kg i.v., and preferably ≤ 5mg/kg i.v. after 24 hour pre-treatment.

(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 ID₅₀ ≤ 3mg/kg p.o., and preferably ID₅₀ ≤ 1mg/kg p.o.

(v) Determine ability of orally-administered compounds to inhibit abnormal bone resorption induced by ovariectomy in adult female rats (Assay 4); select compounds with ID₉₀ (3mg/kg p.o., and preferably ID₉₀ (1mg/kg p.o.).

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

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

human NK-1 receptor binding: \( IC_{50} = 0.1 \text{nM} \)
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: \( ID_{90} < 3 \text{mg/kg p.o.} \)

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
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.): \( ID_{50} = 0.17 \text{mg/kg i.v.} \)

The following examples illustrate pharmaceutical compositions
according to the invention.

These formulations may be prepared with separate active
ingredients or with a combination of active ingredients in one composition.
In such combined preparations, the ratio of the NK-1 receptor antagonist
and the anorectic agent will depend upon the choice of active ingredients.
**EXAMPLE 1**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount (mg) per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK-1 receptor antagonist</td>
<td>50.0 100.0 300.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>80.0  80.0  80.0</td>
</tr>
<tr>
<td>Modified food corn starch</td>
<td>80.0  80.0  80.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>189.5 139.5 139.5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.5  0.5  0.5</td>
</tr>
</tbody>
</table>

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

**EXAMPLE 2**

Bisphosphonate containing tablets are prepared using standard mixing and formation techniques as described in U.S. Patent No. 5,358,941, to Bechard et al., issued October 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 35 mg of alendronate, on an alendronic acid active basis, are prepared using the following relative weights of ingredients.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Per Tablet</th>
<th>Per 4000 Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate Monosodium Trihydrate</td>
<td>45.68 mg</td>
<td>182.72 g</td>
</tr>
<tr>
<td>Anhydrous Lactose, NF</td>
<td>71.32 mg</td>
<td>285.28 g</td>
</tr>
<tr>
<td>Microcrystalline Cellulose, NF</td>
<td>80.0 mg</td>
<td>320.0 g</td>
</tr>
<tr>
<td>Magnesium Stearate, NF</td>
<td>1.0 mg</td>
<td>4.0 g</td>
</tr>
<tr>
<td>Croscarmellose Sodium, NF</td>
<td>2.0 mg</td>
<td>8.0 g</td>
</tr>
</tbody>
</table>
Tablets comprising other relative weights of alendronate, on an alendronic acid active basis may also be prepared: e.g., about 8.75, 17.5, 70, and 140 mg per tablet. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, clodronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, and pharmaceutically acceptable salts thereof. Also, tablets containing combinations of bisphosphonates are similarly prepared.

**EXAMPLE 3**

<table>
<thead>
<tr>
<th></th>
<th>Amount (mg) per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK-1 Receptor Antagonist</td>
<td>50.0 100.0 300.0</td>
</tr>
<tr>
<td>Alendronate Monosodium</td>
<td>45.0 45.0 45.0</td>
</tr>
<tr>
<td>Trihydrate</td>
<td></td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>80.0 80.0 80.0</td>
</tr>
<tr>
<td>Modified Food Corn Starch</td>
<td>80.0 80.0 80.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>144.5 194.5 144.5</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>0.5 0.5 0.5</td>
</tr>
</tbody>
</table>

The active ingredients cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 50mg, 100mg and 300mg of the NK-1 receptor antagonist and 45mg of alendronate monosodium trihydrate per tablet.
CLAIMS:

1. Use of a NK-1 receptor antagonist of formula (I):

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

(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of:

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

selected from:

10
- (a) heterocycle, wherein the heterocycle is selected from

the group consisting of:

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

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

- (i) C_{1-6}alkyl, unsubstituted or substituted with halo, -CF_3,
-OCH_3, or phenyl,
(ii) C<sub>1-6</sub>alkoxy,
(iii) oxo,
(iv) thioxo,
(v) cyano,
(vi) -SCH<sub>3</sub>,
(vii) phenyl,
(viii) hydroxy,
(ix) trifluoromethyl,
(x) -(CH<sub>2</sub>)<sub>m</sub>-NR<sup>9</sup>R<sup>10</sup>, wherein m is 0, 1 or 2, and R<sup>9</sup> and R<sup>10</sup>

are independently selected from:

(I) hydrogen,
(II) C<sub>1-6</sub>alkyl,
(III) hydroxyC<sub>1-6</sub>alkyl, and
(IV) phenyl,

(xii) -NR<sup>9</sup>COR<sup>10</sup>, wherein R<sup>9</sup> and R<sup>10</sup> are as defined above,
and

(xii) -CONR<sup>9</sup>R<sup>10</sup>, wherein R<sup>9</sup> and R<sup>10</sup> are as defined above,

R<sup>2</sup> and R<sup>3</sup> are independently selected from the group consisting of:

(1) hydrogen;
(2) C<sub>1-6</sub>alkyl
(3) C<sub>2-6</sub>alkenyl, and
(5) phenyl;

X is -O-;
R<sup>4</sup> is

\[
\begin{align*}
\text{R}^5 \text{ is phenyl, unsubstituted or substituted with halo;} \\
\text{R}^6, \text{R}^7 \text{ and } \text{R}^8 \text{ are independently selected from the group consisting of:} \\
(1) \text{ hydrogen,}
\end{align*}
\]
(2) C₁₋₆alkyl,
(3) halo, and
(4) -CF₃;
Y is -O--; and
Z is hydrogen or C₁₋₄alkyl;
or a pharmaceutically acceptable salt thereof,
for the manufacture of a medicament for the treatment or prevention of
abnormal bone resorption.

2. Use as claimed in Claim 1 wherein said compound of formula
(I) is selected from:
4-(3-(1,2,4-triazolo)methyl)-2(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3(S)-
phenyl-morpholine;
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)-
4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine;
or a pharmaceutically acceptable salt thereof.

3. Use of a NK-1 receptor antagonist of formula (II):

![Diagram of formula (II)]
wherein:

A\(^1\) is fluorine or CF\(_3\);
A\(^2\) is fluorine or CF\(_3\);
A\(^3\) is fluorine or hydrogen;

R\(^6\) is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C\(_1\)-alkyl group, and optionally substituted by a group of the formula ZNR\(^7\)R\(^8\) where

Z is C\(_1\)-alkylene or C\(_3\)-cycloalkylene;
R\(^7\) is hydrogen, C\(_1\)-alkyl, C\(_3\)-cycloalkyl or C\(_3\)-cycloalkylC\(_1\)-alkyl, or C\(_2\)-alkyl substituted by C\(_1\)-alkoxy or hydroxyl;
R\(^8\) is hydrogen, C\(_1\)-alkyl, C\(_3\)-cycloalkyl or C\(_3\)-cycloalkylC\(_1\)-alkyl, or C\(_2\)-alkyl substituted by one or two substituents selected from C\(_1\)-alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

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

R\(^e\) is C\(_1\)-alkyl optionally substituted by hydroxy or C\(_1\)-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;

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

Y is a C\(_1\)-alkyl group optionally substituted by a hydroxyl group;

with the proviso that if Y is C\(_1\)-alkyl, R\(^6\) is substituted at least by a group of formula ZNR\(^7\)R\(^8\) as defined above;
or a pharmaceutically acceptable salt thereof;
for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.

4. Use as claimed in Claim 3 wherein said compound of formula (II) is selected from:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino)methyl-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;
2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine;
or a pharmaceutically acceptable salt thereof.

5. Use of a NK-1 receptor antagonist of formula (III):

wherein:
R² and R³ are independently selected from the group consisting of:
(1) hydrogen,
(2) C₁₋₆alkyl,
(3) C₂₋₆alkenyl, and
(4) phenyl;
R⁶, R⁷ and R⁸ are independently selected from the group consisting of:
(1) hydrogen,
(2) C₁₋₆alkyl,
(3) fluoro,
(4) chloro,
(5) bromo,
(6) iodo, and
(7) -CF₃;

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

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

A is unsubstituted 1-alkyl;

B is selected from the group consisting of:

p is 0 or 1;
X is selected from:

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

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

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

(d) \( -\text{CH(R}^4\text{)-PO(OH)}\text{O}^- \cdot M^+ \), wherein \( R^4 \) is hydrogen or \( C_1 \text{-alkyl} \),

(e) \( -\text{CH(R}^4\text{-PO(O)}^-\text{O}_2 \cdot 2M^+ \),

(f) \( -\text{CH(R}^4\text{-PO(O)}^-\text{O}_2 \cdot D^{2+} \),

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

(j) \( -\text{CH(CH}_3\text{-O-CO-}R^5 \), wherein \( R^5 \) is selected from the group consisting of:
Y is -O-;
Z is hydrogen or C_{1-6}alkyl;

or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.

6. Use as claimed in Claim 5 wherein said compound of formula (III) is selected from:
(1) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine N-oxide;
(2) 2-(S)-(3,5-bis(trifluoromethyl)benzyloxy)-3-(S)-phenyl-4-(3-(4-(ethoxycarbonyloxy-1-ethyl)-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
(3) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(4-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
(4) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
(5) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(2-monophosphoryl-5-oxo-1H-1,2,4-triazolo)methyl)morpholine;
(6) 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxyphosphoryl-1H-1,2,4-triazolo)methyl)morpholine;
(7) 2-(S)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(1-monophosphoryl-5-oxo-4H-1,2,4-triazolo)methyl)morpholine;

or a pharmaceutically acceptable salt thereof.

7. Use of a NK-1 receptor antagonist of formula (IV):

\[
\text{Formula (IV)}
\]

wherein
R\textsuperscript{1} represents hydrogen, hydroxy, C\textsubscript{1-6}alkyl, C\textsubscript{2-6}alkenyl, C\textsubscript{3-7}cycloalkyl, C\textsubscript{3-7}cycloalkylC\textsubscript{1-4}alkyl, C\textsubscript{1-6}alkoxy, fluoroC\textsubscript{1-6}alkoxy, C\textsubscript{1-6}alkoxyC\textsubscript{1-4}alkyl, C\textsubscript{1-6}alkoxyC\textsubscript{1-4}alkoxy, fluoroC\textsubscript{1-6}alkoxyC\textsubscript{1-4}alkyl, C\textsubscript{2-6}alkenylxnyloxy, C\textsubscript{3-7}cycloalkoxy, C\textsubscript{3-7}cycloalkylC\textsubscript{1-4}alkoxy, phenoxy, benzyloxy, cyano, halogen, NR\textsuperscript{a}R\textsuperscript{b}, SR\textsuperscript{a}, SOR\textsuperscript{a}, SO\textsubscript{2}R\textsuperscript{a}, OSO\textsubscript{2}R\textsuperscript{a}, NR\textsuperscript{a}COR\textsuperscript{14}, COR\textsuperscript{a}, CO\textsubscript{2}R\textsuperscript{a} or CONR\textsuperscript{a}R\textsuperscript{b} where R\textsuperscript{a} and R\textsuperscript{b} each independently represent hydrogen, C\textsubscript{1-4}alkyl or fluoroC\textsubscript{1-4}alkyl;

R\textsuperscript{2} represents hydrogen, halogen, C\textsubscript{1-6}alkyl or C\textsubscript{1-6}alkoxy;

or R\textsuperscript{1} and R\textsuperscript{2} may be joined together such that there is formed a 5- or 6-membered saturated or unsaturated ring containing one or two atoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by a group selected from C\textsubscript{1-4}alkyl, CF\textsubscript{3}, =O or =S;

R\textsuperscript{3} represents hydrogen, halogen, C\textsubscript{1-6}alkyl, fluoroC\textsubscript{1-6}alkyl, C\textsubscript{1-6}alkoxy, fluoroC\textsubscript{1-6}alkoxy, C\textsubscript{3-7}cycloalkyl, C\textsubscript{3-7}cycloalkylC\textsubscript{1-4}alkyl, cyano, SR\textsuperscript{a}, SOR\textsuperscript{a}, SO\textsubscript{2}R\textsuperscript{a}, NR\textsuperscript{a}R\textsuperscript{b}, NR\textsuperscript{a}COR\textsuperscript{14}, COR\textsuperscript{a}, CO\textsubscript{2}R\textsuperscript{a}, CONR\textsuperscript{a}R\textsuperscript{b} or C\textsubscript{1-4}alkyl substituted by cyano, CO\textsubscript{2}R\textsuperscript{a} or CONR\textsuperscript{a}R\textsuperscript{b} where R\textsuperscript{a} and R\textsuperscript{b} are as previously defined;

R\textsuperscript{4} represents hydrogen, halogen, C\textsubscript{1-6}alkyl, C\textsubscript{1-6}alkoxy, CF\textsubscript{3}, OCF\textsubscript{3}, NO\textsubscript{2}, CN, SR\textsuperscript{a}, SOR\textsuperscript{a}, SO\textsubscript{2}R\textsuperscript{a}, CO\textsubscript{2}R\textsuperscript{a}, CONR\textsuperscript{a}R\textsuperscript{b}, C\textsubscript{2-6}alkenyl, C\textsubscript{2-6}alkynyl or C\textsubscript{1-4}alkyl substituted by C\textsubscript{1-4}alkoxy, where R\textsuperscript{a} and R\textsuperscript{b} are as previously defined; and

the broken line represents an optional double bond;

or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.

8. Use as claimed in Claim 7 wherein said compound of formula (IV) is selected from:

(3R,5R,6S)-3-(2-methoxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
(3R,5R,6S)-3-(2-methoxy-5-(trifluoromethyl)phenyl)-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
(3R,5R,6S)-7-benzyl-3-[2-methoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
(3R,5R,6S)-3-(2-methoxy-5-trifluoromethoxyphenyl)-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
(3R,5R,6S)-3,6-bis(phenyl)-1-oxa-7-aza-spiro[4.5]decane;
(3R,5R,6S)-7-benzyl-3-(2-methoxy-5-trifluoromethoxyphenyl)-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
(±)-(3R*,5R*,6S*)-3-(2-methoxyphenyl)-6-phenyl-1-oxa-7-(phenylmethoxycarbonyl)aza-spiro[4.5]decane;
(3R,5R,6S)-3-(2-methoxyphenyl)-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
(3S,5R,6S)-3-(2-cyclopropoxy-5-(trifluoromethoxy)phenyl)-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
(3R,5R,6S)-3-[2-cyclopropoxy-5-(trifluoromethoxy)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;
(3S,5R,6S)-3-[2-cyclopropoxy-5-(trifluoromethyl)phenyl]-6-phenyl-1-oxa-7-aza-spiro[4.5]decane;

or a pharmaceutically acceptable salt thereof.

9. Use of a NK-1 receptor antagonist of formulae (V), (VI), (VII), (VIII), (IX), (X), (XI) or (XII) as defined herein, for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.

10. Use of a NK-1 receptor antagonist as defined in any one of Claims 1 to 9 in combination with one or more active agents selected from the group consisting of bisphosphonates, estrogen and androgen receptor modulators, and peptide hormones, for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.
11. Use as claimed in Claim 10 wherein said bisphosphonate is a compound of formula (XIII):

\[
\begin{align*}
\text{PO}_3\text{H}_2 \\
\mid \\
\text{A-C-X} \\
\mid \\
\text{PO}_3\text{H}_2
\end{align*}
\]

(XIII)

wherein

A and X are independently selected from the group consisting of H, OH, halogen, NH\textsubscript{2}, SH, phenyl, C\textsubscript{1}-C\textsubscript{30} alkyl, C\textsubscript{3}-C\textsubscript{30} cycloalkyl, C\textsubscript{1}-C\textsubscript{30} substituted alkyl, C\textsubscript{3}-C\textsubscript{30} substituted cycloalkyl, C\textsubscript{1}-C\textsubscript{10} alkyl or C\textsubscript{3}-C\textsubscript{10} cycloalkyl mono- or di- substituted NH\textsubscript{2}, C\textsubscript{1}-C\textsubscript{10} alkoxy, C\textsubscript{1}-C\textsubscript{10} alkyl or C\textsubscript{3}-C\textsubscript{10} cycloalkyl substituted thio, phenyl substituted thio, C\textsubscript{1}-C\textsubscript{10} alkyl or C\textsubscript{3}-C\textsubscript{10} cycloalkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazony1, and benzyl.

12. Use as claimed in Claim 11 wherein said bisphosphonate is selected from the group consisting of alendronate, cimadronate, clodronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

13. Use as claimed in Claim 21 wherein said bisphosphonate is alendronate monosodium trihydrate.

14. Use as claimed in Claim 10 wherein said estrogen receptor modulator is selected from the group consisting of estrogen, progestins, estradiol, raloxifene, tamoxifene, clometherone, delmadinone, droloxifene, idoxifene, nafoxidine, nitromifene, ormeloxyfene, toremifene, trioxifene,
BE-25327, CP-336156 and ([2-(4-hydroxyphenyl)-6-hydroxynaphthalen-1-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methane and their pharmaceutically acceptable salts, and mixtures thereof.

15. Use as claimed in Claim 10 wherein said androgen receptor modulator is selected from the group consisting of danazol, 5α-dihydrotestosterone, testosterone, nandrolane decanoate, methyltestosterone, methandrostrenolone, stanozolol, fluoxymesterone, oxymetholone, oxandrolone, oxymeth, norethandrolone, ethylestranol, 4-androsten-19-al-3,17-dione, 19-nortestosterone, norethandrone, norethisterone, dehydroepiandrosterone, epiandrosterone sulfate, androstenedione and androstenediol, testosterone propionate, testosterone cytopionate, and testosterone enanthate.

16. Use as claimed in Claim 10 wherein said peptide hormone is calcitonin.

17. Use of a NK-1 receptor antagonist for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.

18. A method for the treatment or prevention of abnormal bone resorption, which method comprises administration to a patient in need of such treatment an effective amount of a NK-1 receptor antagonist.

19. A pharmaceutical composition for the treatment or prevention of abnormal bone resorption comprising a NK-1 receptor antagonist, together with at least one pharmaceutically acceptable carrier or excipient.

20. Use of a NK-1 receptor antagonist and one or more active agents selected from the group consisting of bisphosphonates, estrogen
and androgen receptor modulators, and peptide hormones, for the manufacture of a medicament for the treatment or prevention of abnormal bone resorption.

21. A method for the treatment or prevention of abnormal bone resorption, which method comprises administration to a patient in need of such treatment a therapeutically effective amount of a NK-1 receptor antagonist and one or more active agents selected from the group consisting of bisphosphonates, estrogen and androgen receptor modulators and peptide hormones, such that together they give effective relief.

22. A pharmaceutical composition comprising a NK-1 receptor antagonist and one or more active agents selected from the group consisting of bisphosphonates, estrogen and androgen receptor modulators, and peptide hormones, together with at least one pharmaceutically acceptable carrier or excipient.

23. A product comprising a NK-1 receptor antagonist and one or more active agents selected from the group consisting of bisphosphonates, estrogen and androgen receptor modulators, and peptide hormones, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of abnormal bone resorption.

24. A use, method, composition or product as claimed in any one of Claims 1 to 23 wherein the condition associated with abnormal bone resorption is selected from the group consisting of generalized bone loss, localized bone loss, and the creation of bone having an abnormal structure.

25. A use, method, composition or product as claimed in Claim 24 wherein the condition associated with abnormal bone resorption is selected from the group consisting of the following conditions or disease
states: osteoporosis, post-menopausal osteoporosis, glucocorticoid-induced osteoporosis, male osteoporosis, disease-induced osteoporosis, idiopathic osteoporosis, Paget's disease, abnormally increased bone turnover, hypercalcemia of malignancy, osteogenesis imperfecta, periodontal disease, periprosthetic osteolysis, and abnormal bone resorption associated with immunosuppressive therapy.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

<table>
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</tr>
</tbody>
</table>

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 7 | A61K |

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>WO 98 43639 A (GITTER BRUCE DONALD ; LILLY CO ELI (US) ; GALVIN RACHELLE JEANETTE ()) 8 October 1998 (1998-10-08)</td>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

"S" 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**

19 January 2000

**Date of mailing of the international search report**

25/01/2000

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: +31-70 340-3018

Authorized officer

Hoff, P
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<td>WO 94 22822 A (RHONE POULENC RORER SA ; CRESPO ANDRE (FR); FARDIN VERONIQUE (FR)); 13 October 1994 (1994-10-13) abstract page 28, line 17 - page 29, line 19; claims; examples</td>
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<td>WO 94 16697 A (RHONE POULENC RORER SA ; GARRET CLAUDE (FR); MONTIER FRANCOIS (FR)); 4 August 1994 (1994-08-04) whole document, in particular page 48, line 17-line 22</td>
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**INTERNATIONAL SEARCH REPORT**

**C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>EP 0 577 394 A (MERCK &amp; CO INC) 5 January 1994 (1994-01-05) cited in the application abstract page 18, line 37 -page 21, line 38; claims; examples</td>
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<td>WO 95 18124 A (MERCK SHARP &amp; DOHME ;BAKER RAYMOND (GB); HARRISON TIMOTHY (GB); MA) 6 July 1995 (1995-07-06) cited in the application abstract page 30, line 22 -page 35, line 23; claims; examples</td>
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<td>WO 97 49710 A (ELLIOTT JASON MATTHEW ;HOLLINGWORTH GREGORY JOHN (GB); KULAGOWSKI) 31 December 1997 (1997-12-31) cited in the application abstract page 1, line 11 - line 18 page 17, line 16 -page 33, line 29 page 48, line 3 - line 15; claims; examples</td>
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<td>EP 0 591 040 A (SANOFI ELF) 6 April 1994 (1994-04-06) cited in the application abstract page 14, line 48 -page 15, line 10; claims</td>
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*Form PCT/GB/210 (continuation of second sheet) (July 1992) page 3 of 4*
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| Y        | EP 0 532 456 A (CIBA GEIGY AG)  
           | 17 March 1993 (1993-03-17)  
           | cited in the application  
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           | page 5, line 11 - line 24; claims | 9 |
| X        | page 11, line 1 - line 37; claims  
           | examples | 19,24,25 |
           | cited in the application  
           | abstract  
           | page 11, line 11 - page 12, line 17; claims | 19,24,25 |
| Y        | WO 92 17449 A (PFIZER)  
           | cited in the application  
           | abstract  
           | page 9, line 10 - page 12, line 31; claims  
           | examples | 19,24,25 |
INTERNATIONAL SEARCH REPORT

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. X Claims Nos.: 18, 21, 24, 25
   because they relate to subject matter not required to be searched by this Authority, namely:
   Remark: Although claims 18, 21, 24, 25 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. X 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.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1996)
Continuation of Box I.2

Present claims 1,3,5,7,9,10 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Furthermore, present claims 17-25 relate to a compound defined by reference to a desirable characteristic or property, namely "NK-1 receptor antagonist". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to their pharmacological profiles. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified and specifically mentioned in the description and in claims 2,4,6,8 and to the general idea underlying the present invention.

Claims searched completely: 2,4,6,8
Claims searched incompletely: 1,3,5,7,9-25

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.
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