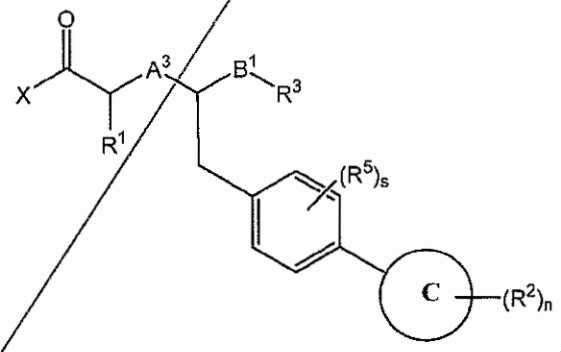
CLAIMS

What is claimed is:

1. A method of treating, preventing or ameliorating contrast-induced nephropathy in a subject in need thereof, comprising administering to the subject a neutral endopeptidase EC. 3.4. 24.11. inhibitor.

2. The method of claim 1 wherein the neutral endopeptidase inhibitor is selected from the group consisting of Candoxatril, Candoxatrilat, Dexecadotril, Ecadotril, Racecadotril, Sampatrilat, Fasidotril, Omapatrilat, Gemopatrilat, Daglutril, SCH-42495, SCH-32615, UK-447841, AVE-0848, PL-37 and (2R,4S)-5-Biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester.

3. The method of treating, preventing or ameliorating contrast-induced nephropathy in a subject in need thereof, according the claim 1, comprising administering to the subject a therapeutically effective amount of a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c; wherein alkyl is optionally substituted with C_{6-10}-aryl, benzyloxy, hydroxy, C_{3-7}cycloalkyl or C_{1-6} alkoxy;

R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl;

R^3 is A^1-$C(O)X^1$ or A^2-R^4;

R^4 is C_{6-10}aryl, C_{3-7}cycloalkyl, or a heteroaryl, which can be monocyclic or bicyclic, each of which can be optionally substituted with one or more substituents independently selected

from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, nitro, -NR^bR^c, -C(O)C_{1-7}alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl, $S(O)_2$-C_{1-7}alkyl, C(O)-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and C(O)N(C_{1-6}alkyl)$_2$;

B^1 is –C(O)NR^d- or –NR^dC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a linear or branched C_{1-7}alkenylene; or

A^1 is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl, -C(O)-O-C_{1-7}alkyl or -$CH_2C(O)OH$; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, -NR^bR^c, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; or

A^1 is a C_{3-7}cycloalkyl or heterocyclyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

A^3 is CH_2, O, NR^e or is absent; and when A^3 is O or NR^e then B^1 is C(O)NR^d;

R^b and R^c for each occurrence are independently H, C_{6-10}aryl or C_{1-7}alkyl;

R^d and R^e are independently H or C_{1-7}alkyl;

Ring C is a phenyl or a monocyclic heteroaryl;

n is 0, 1, 2, 3, 4 or 5;

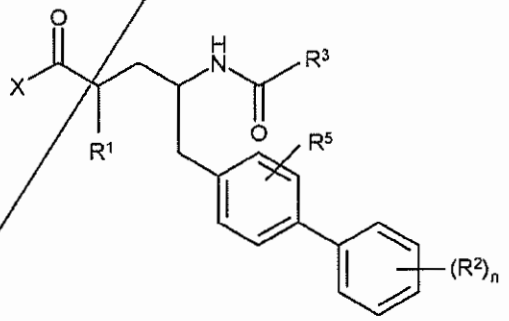
s is 0, 1, 2, 3 or 4; and

when B^1 is $C(O)NR^d$ and R^3 is A^2-R^4, then R^d and A^2-R^4, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of $C_{1\text{-}6}$alkyl, halo, halo$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, hydroxy, CO_2H and $CO_2C_{1\text{-}6}$alkyl;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms unless otherwise specified, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

4. The method of treating, preventing or ameliorating contrast-induced nephropathy in a subject in need thereof, according to claim 1 or 3, comprising administering to the subject a therapeutically effective amount of a compound of Formula II:



Formula II

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $C_{1\text{-}7}$alkyl;

for each occurrence, R^2 is independently $C_{1\text{-}7}$alkyl, NO_2, CN, halo, $C_{3\text{-}7}$cycloalkyl, hydroxy, $C_{1\text{-}7}$alkoxy, halo-$C_{1\text{-}7}$alkyl, NR^bR^c, $C_{6\text{-}10}$aryl, heteroaryl or heterocyclyl; wherein R^b and R^c for each occurrence, are independently H or $C_{1\text{-}7}$alkyl;

R^3 is $A^1C(O)X^1$ or A^2-R^4;

R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic and which can be optionally substituted with one or more substituents independently selected from hydroxy, hydroxy-C_{1-7}alkyl, NR^bR^c, nitro, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$C(O)C_{1-7}$alkyl , -$NHS(O)_2$-C_{1-7}alkyl, -SO_2C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, $-NR^bR^c$, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O-C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of aryl, heteroaryl, heterocyclyl, -$C(O)NH_2$, -C(O)NH- C_{1-6}alkyl, and -$C(O)N(C_{1-6}alkyl)_2$;

A^1 is a bond or a linear C_{1-4}alkylene substituted with one or more substituents independently selected from the group consisting of halo, O-acetate, C_{1-7} alkyl and C_{3-7}cycloalkyl; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a linear or branched C_{2-6}alkenylene; or

A^1 is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl or $CH_2C(O)OH$; or

A^1 is a C_{3-7}cycloalkyl, a heterocyclyl, a phenyl or a heteroaryl in which phenyl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H, and $OCH_2C(O)NH_2$; or

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

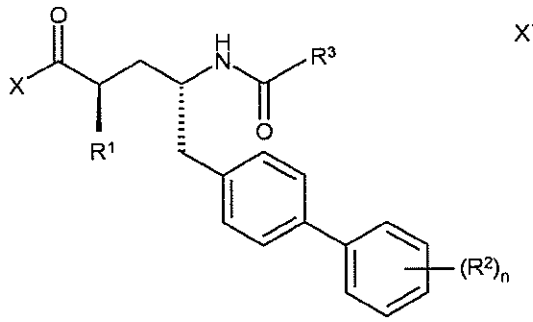
A^2 is a bond or a linear or branched C_{1-7}alkylene which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

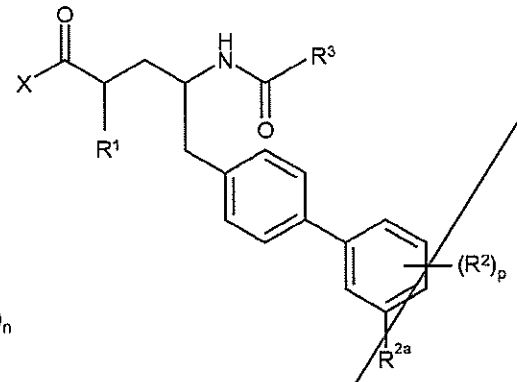
wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

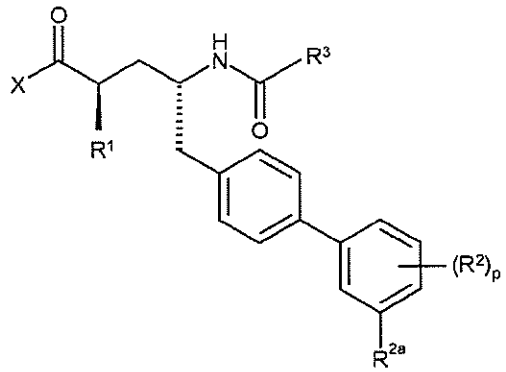
5. The method of claim 4 wherein the compounds has the Formulae:



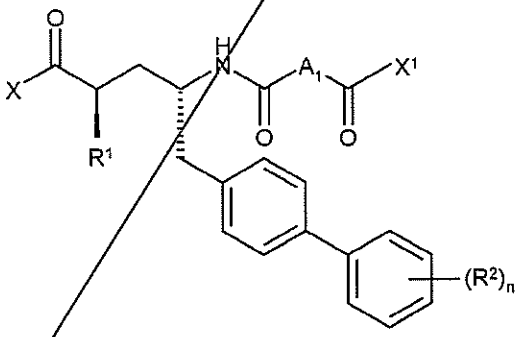
Formula II-A



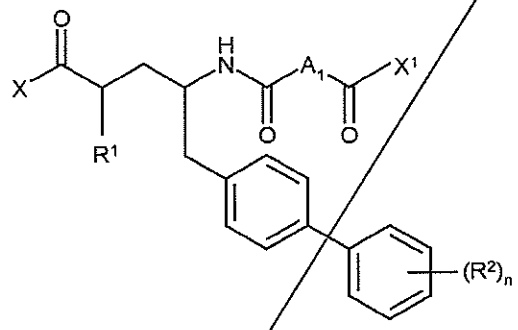
Formula II-B



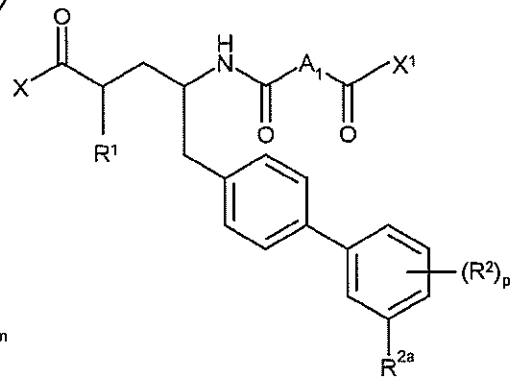
Formula II-C



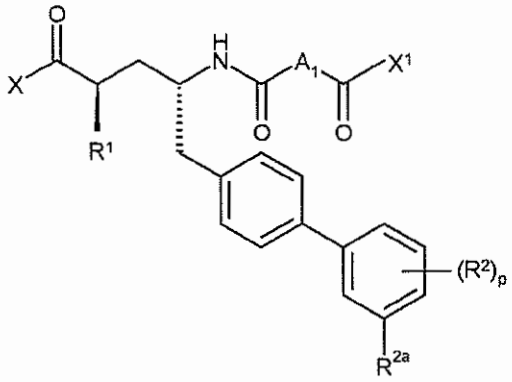
Formula II-D



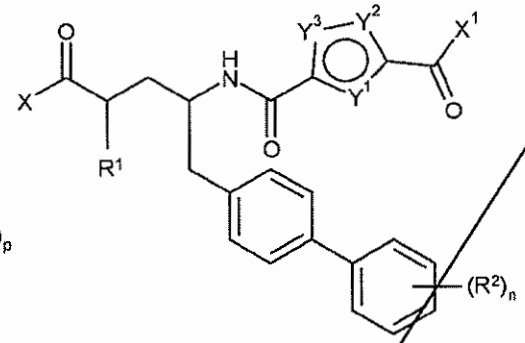
Formula II-E



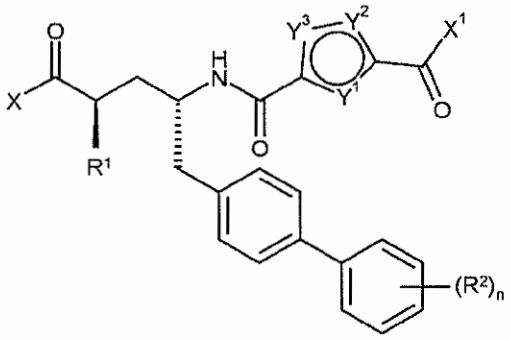
Formula II-F



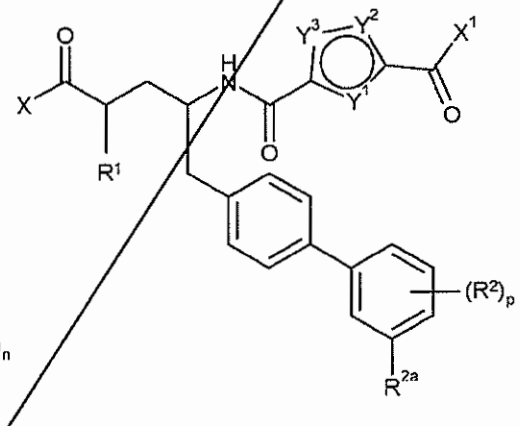
Formula II-G



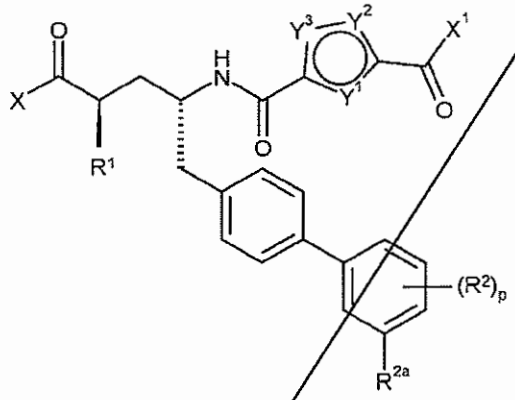
Formula II-H



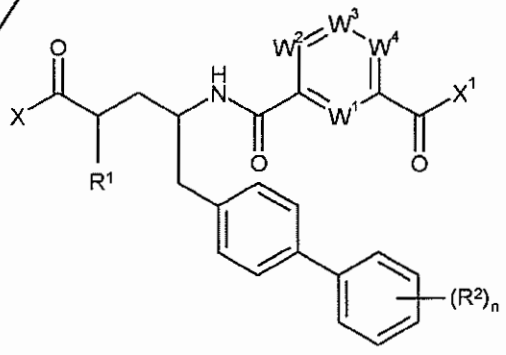
Formula II-I



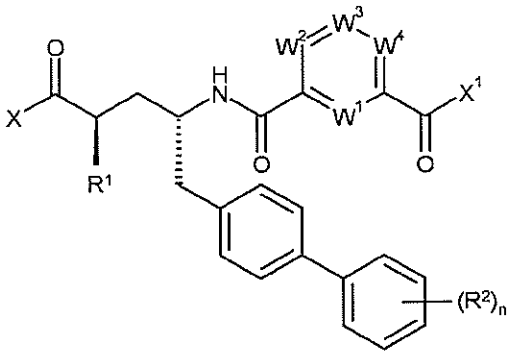
Formula II-J



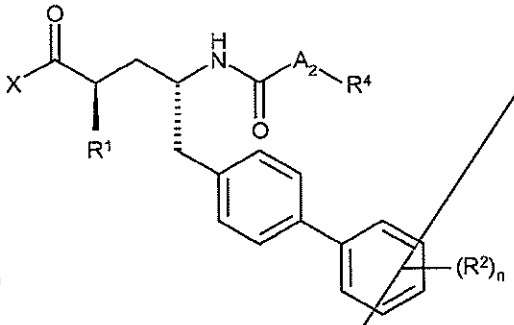
Formula II-K



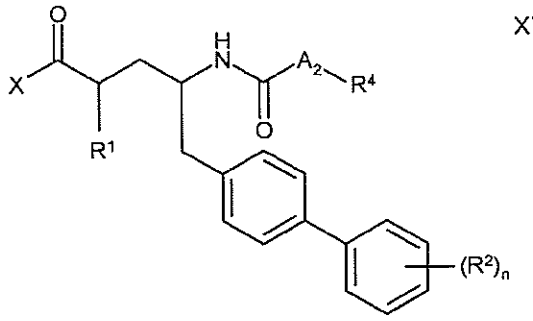
Formula II-L



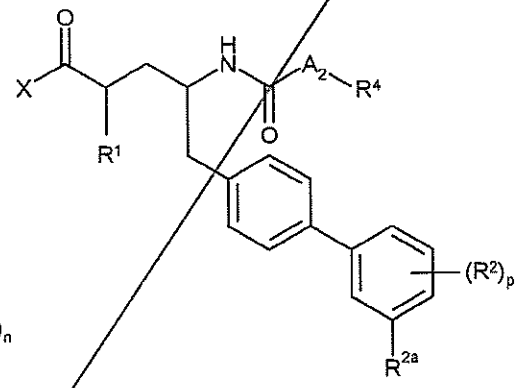
Formula II-M



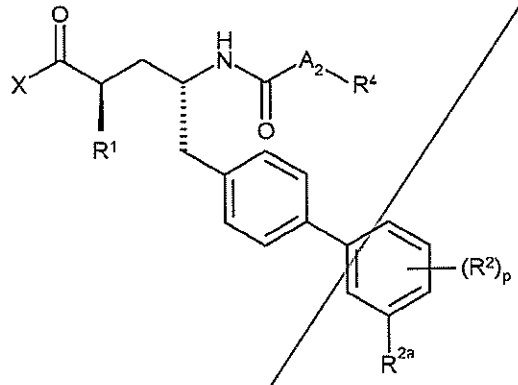
Formula II-N



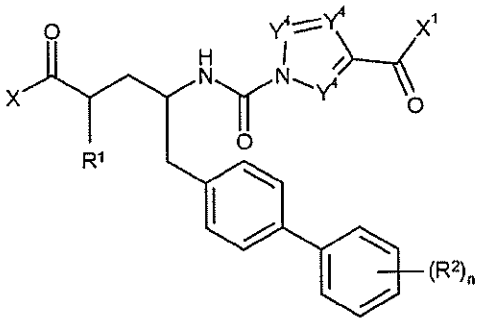
Formula II-O



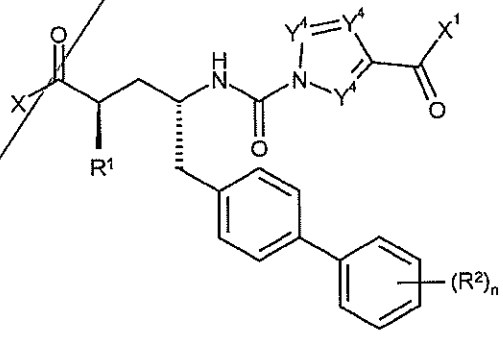
Formula II-P



Formula II-Q



Formula II-R

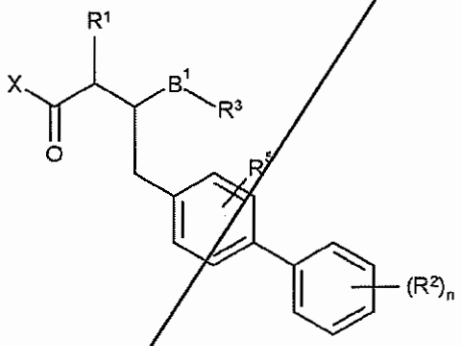


or

Formula II-S

or a pharmaceutically acceptable salt thereof, wherein p is 0, 1, 2, 3 or 4; R^{2a} is halo; W^1, W^2, W^3 and W^4 are independently N or CR^f, in which each R^f is independently selected from H, C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H and $OCH_2C(O)NH_2$; R^b and R^c for each occurrence, are independently H or C_{1-7}alkyl; and Y^1, Y^2 and Y^3 are independently N, NH, S, O or CH and form together with the ring atoms to which they are attached a 5-membered heteroaryl ring, and each Y^4 is independently N, S, O or CH.

6. The method of treating, preventing or ameliorating contrast-induced nephropathy in a subject in need thereof, according to claim 1 or 3, comprising administering to the subject a therapeutically effective amount of a compound of Formula III:



Formula III

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c;
R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^b and R^c for each occurrence are independently H or C_{1-7}alkyl;
R^3 is A^1-$C(O)X^1$ or A^2-R^4;
R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic, and which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, nitro, -NR^bR^c, -$C(O)C_{1-7}$alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more

substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and $C(O)N(C_{1-6}alkyl)_2$;

B^1 is –C(O)NH- or –NHC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a linear or branched C_{1-7}alkenylene; or

A^1 is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl, -C(O)-O-C_{1-7}alkyl or -$CH_2C(O)OH$; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, -NR^bR^c, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; or

A^1 is a C_{3-7}cycloalkyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

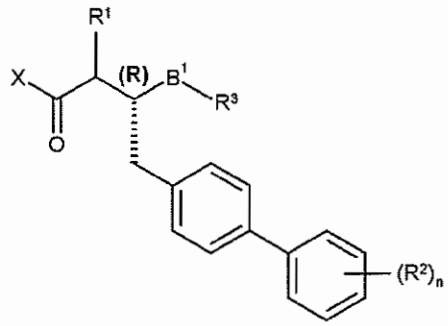
A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

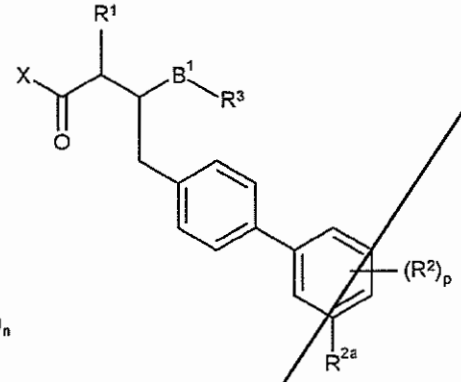
wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

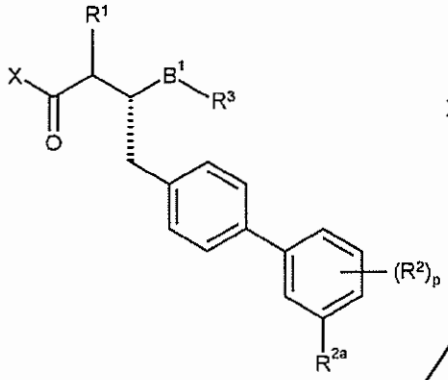
7. The method of claim 6 wherein the compound of the following Formula:



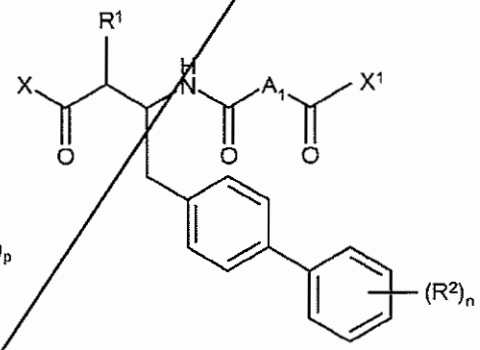
Formula III-A



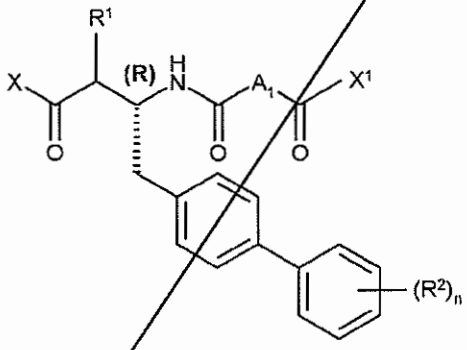
Formula III-B



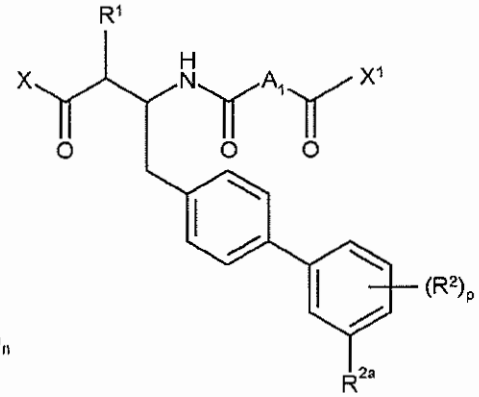
Formula III-C



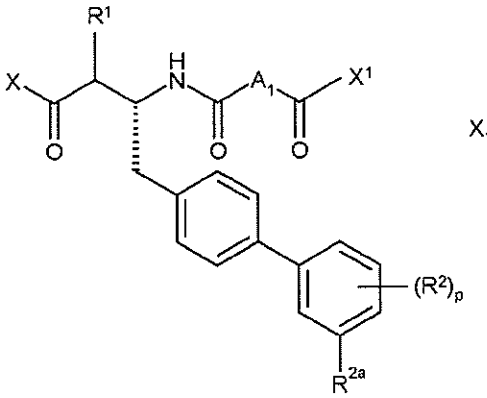
Formula III-D



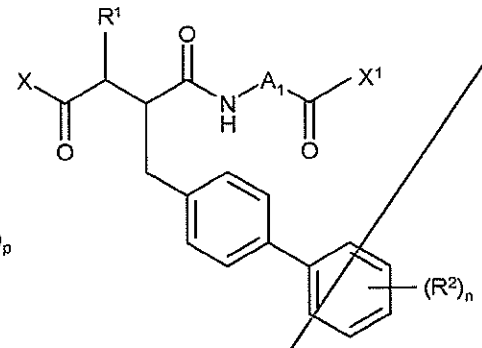
Formula III-E



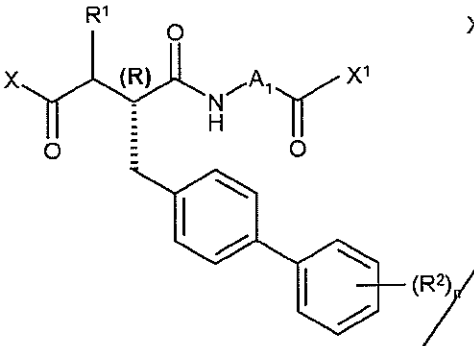
Formula III-F



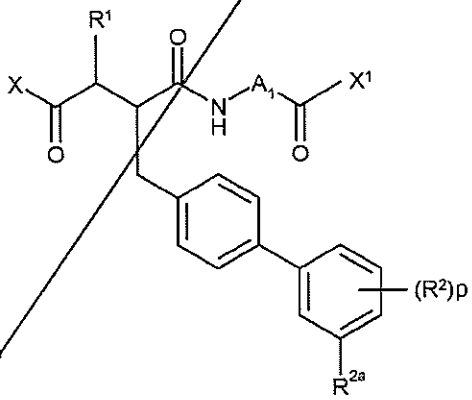
Formula III-G



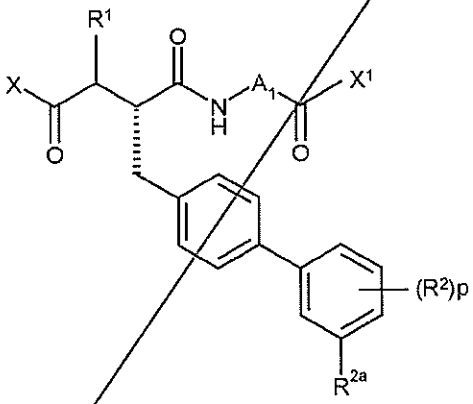
Formula III-H



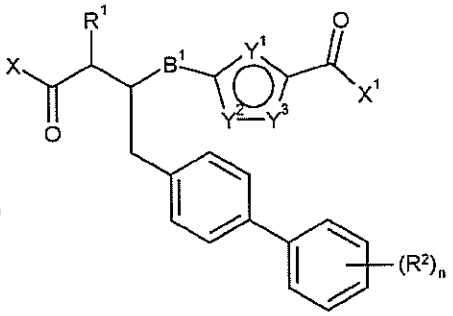
Formula III-I



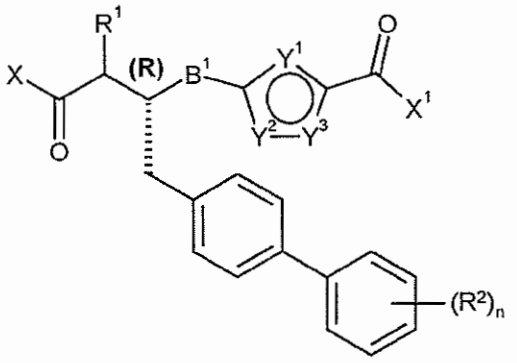
Formula III-J



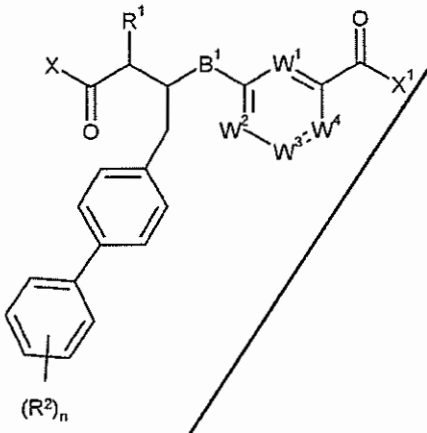
Formula III-K



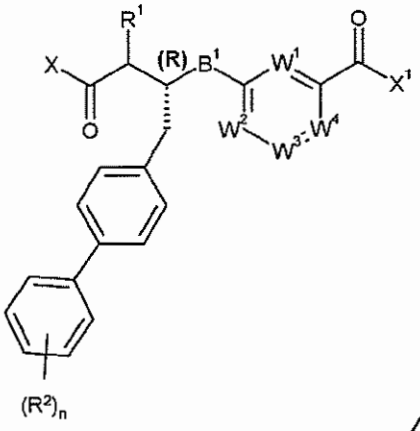
Formula III-L



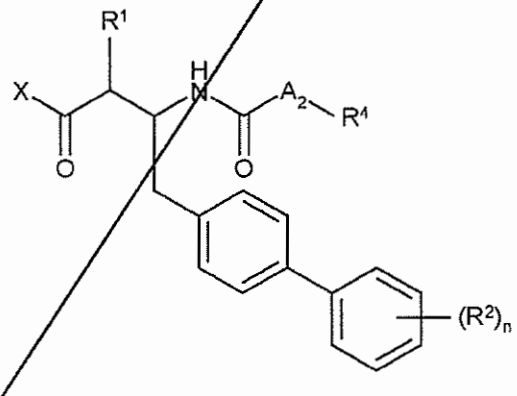
Formula III-M



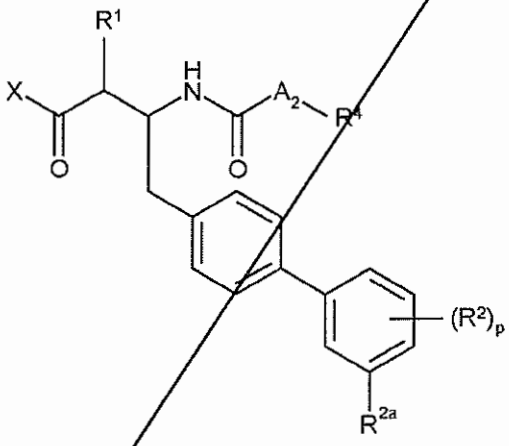
Formula III-N



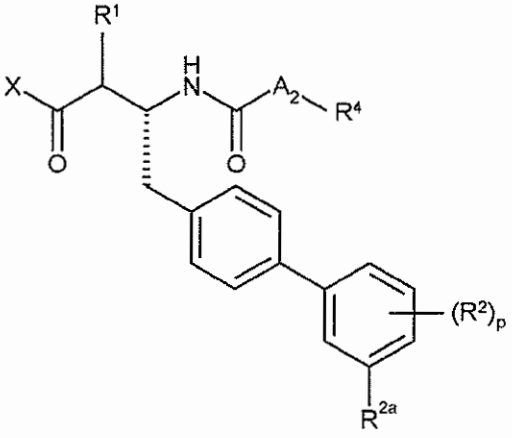
Formula III-O



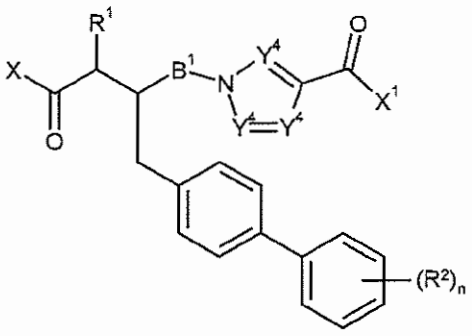
Formula III-P



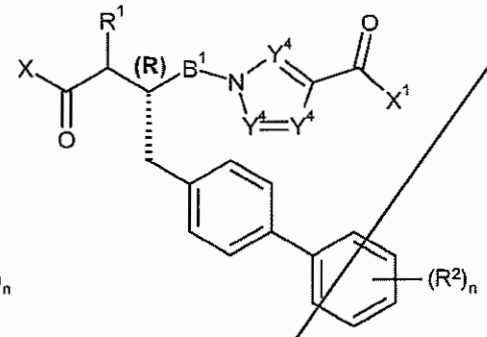
Formula III-Q



Formula III-R



Formula III-S



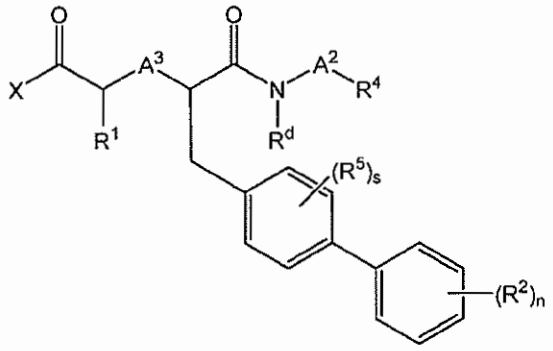
Formula III-T

or a pharmaceutically acceptable salt thereof, wherein p is 0, 1, 2, 3 or 4; R^{2a} is halo; W^1, W^2, W^3 and W^4 are independently N or CR^f, in which each R^f is independently selected from H, C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H and $OCH_2C(O)NH_2$; R^b and R^c for each occurrence are independently H or C_{1-7}alkyl; and Y^1, Y^2 and Y^3 are independently N, NH, S, O or CH and form together with the ring atoms to which they are attached a 5-membered heteroaryl ring, and each Y^4 is independently N, S, O or CH.

8. The method of claim 7 wherein the compound is of Formula III-F or III-G, wherein A^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2$, or a pharmaceutically acceptable salt thereof.

9. The method of claim 8, wherein R^1 is H, p is 0; X and X^1 are independently OH or -O-C_{1-7}alkyl, R^{2a} is chloro; or a pharmaceutically acceptable salt thereof.

10. The method of treating, preventing or ameliorating contrast-induced nephropathy in a subject in need thereof, according to claim 1 or 3, comprising administering to the subject a therapeutically effective amount of a compound of Formula IV:



IV

wherein:

X is OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl or -$NHS(O)_2$-benzyl; wherein R^b and R^c for each occurrence are independently H or C_{1-7}alkyl;

R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c; wherein alkyl is optionally substituted with C_{6-10}-aryl, benzyloxy, hydroxy or C_{1-6} alkoxy;

for each occurence, R^2 is independently C_{1-6}-alkoxy, hydroxy, halo, C_{1-6}-alkyl, cyano or trifluoromethyl;

A^3 is O or NR^e;

R^d and R^e are independently H or C_{1-6} alkyl;

A^2 is a bond or C_{1-3}alkylene chain;

R^4 is a 5- or 6-membered heteroaryl, C_{6-10}-aryl or C_{3-7}-cycloalkyl, wherein each heteroaryl, aryl or cycloalkyl are optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl;

R^5 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; or

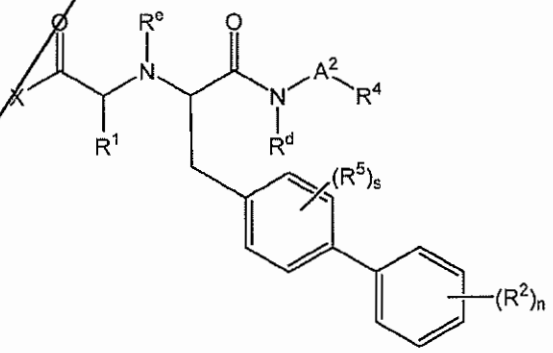
R^d, A^2-R^4, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl; and

n is 0 or an integer from 1 to 5;

s is 0 or an integer from 1 to 4; or

a pharmaceutically acceptable salt thereof.

11. The method of claim 10 wherein the compound is of Formula IV-A:



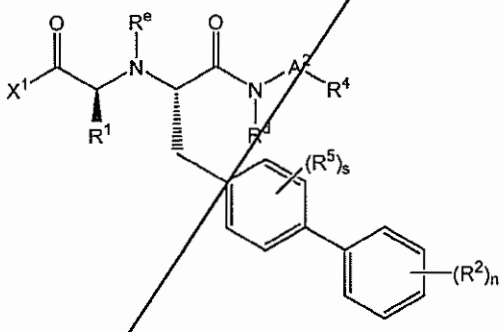
IV-A

Wherein:

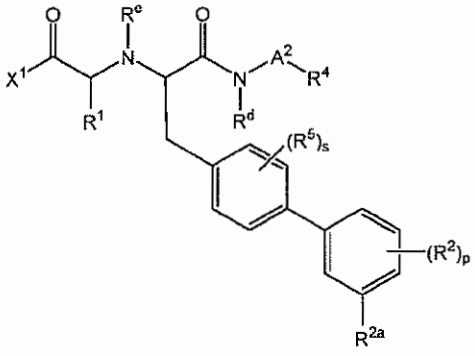
X represent OH or O-C_{1-6}-alkyl;

R^1 is H, C_{1-6} alkyl or C_{6-10}-aryl-C_{1-6} alkyl;
for each occurence, R^2 is independently C_{1-6}-alkoxy, hydroxy, halo, C_{1-6}-alkyl, cyano or trifluoromethyl;
R^d and R^e are independently H or C_{1-6} alkyl;
A^2 is a bond or C_{1-3}alkylene chain;
R^4 is a 5- or 6-membered heteroaryl, C_{6-10}-aryl or C_{3-7}-cycloalkyl, wherein each heteroaryl, aryl or cycloalkyl are optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl;
R^5 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; or
R^d, A^2-R^4, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl; and
n is 0 or an integer from 1 to 5;
s is 0 or an integer from 1 to 4; or
a pharmaceutically acceptable salt thereof.

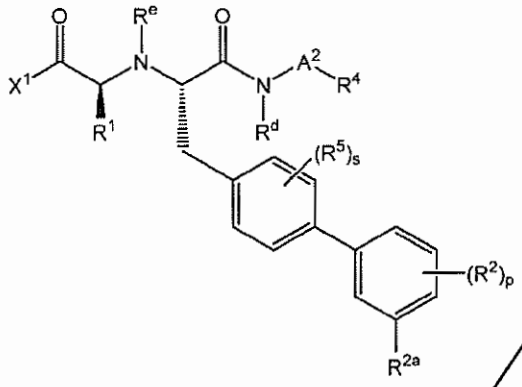
12. The method of claim 10 or 11 wherein the compound is of Formula:



Formula IV-B



Formula IV-C



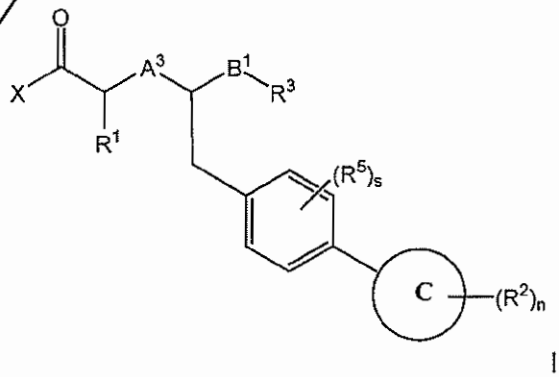
or Formula IV-D

or a pharmaceutically acceptable salt therof, wherein p is 0, 1, 2, 3 or 4 and R^{2a} is halo.

13. Use of a neutral endopeptidase EC. 3.4. 24.11. inhibitor, in the manufacture of a medicament for the treatment, amelioration or prevention of contrast-induced nephropathy in a subject in need of such treatment.

14. Use of claim 13 wherein the neutral endopeptidase inhibitor is selected from the group consisting of Candoxatril, Candoxatrilat, Dexecadotril, Ecadotril, Racecadotril, Sampatrilat, Fasidotril, Omapatrilat, Gemopatrilat, Daglutril, SCH-42495, SCH-32615, UK-447841, AVE-0848, PL-37 and (2R,4S)-5-Biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester.

15. Use of claim 13 wherein the neutral endopeptidase inhibitor is a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

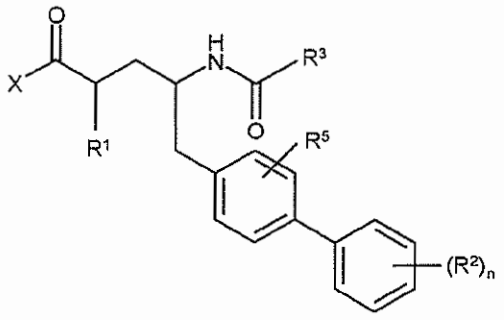
R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c; wherein alkyl is optionally substituted with C_{6-10}-aryl, benzyloxy, hydroxy, C_{3-7}cycloalkyl or C_{1-6} alkoxy;
R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl;
R^3 is A^1-C(O)X^1 or A^2-R^4;
R^4 is C_{6-10}aryl, C_{3-7}cycloalkyl, or a heteroaryl, which can be monocyclic or bicyclic, each of which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, nitro, -NR^bR^c, -C(O)C_{1-7}alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl, $S(O)_2$-C_{1-7}alkyl, C(O)-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;
R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and
X and X^1 are independently OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and $C(O)N(C_{1-6}alkyl)_2$;
B^1 is –C(O)NR^d- or –NR^dC(O)-;
A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or
A^1 is a linear or branched C_{1-7}alkenylene; or
A^1 is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl, -C(O)-O-C_{1-7}alkyl or -$CH_2C(O)OH$; or
A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, -NR^bR^c, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; or
A^1 is a C_{3-7}cycloalkyl or heterocyclyl;
A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;
A^3 is CH_2, O, NR^e or is absent; and when A^3 is O or NR^e then B^1 is $C(O)NR^d$;
R^b and R^c for each occurrence are independently H, C_{6-10}aryl or C_{1-7}alkyl;
R^d and R^e are independently H or C_{1-7}alkyl;
Ring C is a phenyl or a monocyclic heteroaryl;
n is 0, 1, 2, 3, 4 or 5;
s is 0, 1, 2, 3 or 4; and
when B^1 is $C(O)NR^d$ and R^3 is A^2-R^4, then R^d and A^2-R^4, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms unless otherwise specified, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

16. Use of claim 13 or 15, wherein the neutral endopeptidase inhibitor is a compound of Formula II:



Formula II

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is C_{1-7}alkyl;

for each occurrence, R^2 is independently C_{1-7}alkyl, NO_2, CN, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, halo-C_{1-7}alkyl, NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^b and R^c for each occurrence, are independently H or C_{1-7}alkyl;

R^3 is $A^1C(O)X^1$ or A^2-R^4;

R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic and which can be optionally substituted with one or more substituents independently selected from hydroxy, hydroxy-C_{1-7}alkyl, NR^bR^c, nitro, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$C(O)C_{1-7}$alkyl , -$NHS(O)_2$-C_{1-7}alkyl, -SO_2C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, $-NR^bR^c$, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O-C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of aryl, heteroaryl, heterocyclyl, -$C(O)NH_2$, -C(O)NH- C_{1-6}alkyl, and -$C(O)N(C_{1-6}alkyl)_2$;

A^1 is a bond or a linear C_{1-4}alkylene substituted with one or more substituents independently selected from the group consisting of halo, O-acetate, C_{1-7} alkyl and C_{3-7}cycloalkyl; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a linear or branched C_{2-6}alkenylene; or

A^1 is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl or $CH_2C(O)OH$; or

A^1 is a C_{3-7}cycloalkyl, a heterocyclyl, a phenyl or a heteroaryl in which phenyl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H, and $OCH_2C(O)NH_2$; or

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

A^2 is a bond or a linear or branched C_{1-7}alkylene which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

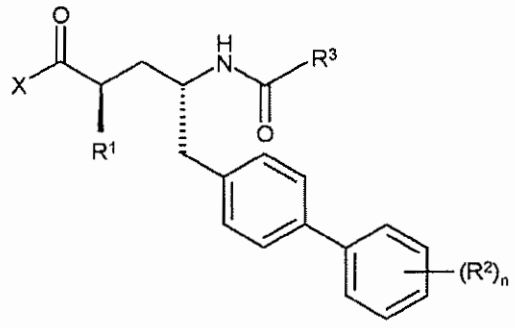
n is 0, 1, 2, 3, 4 or 5;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10

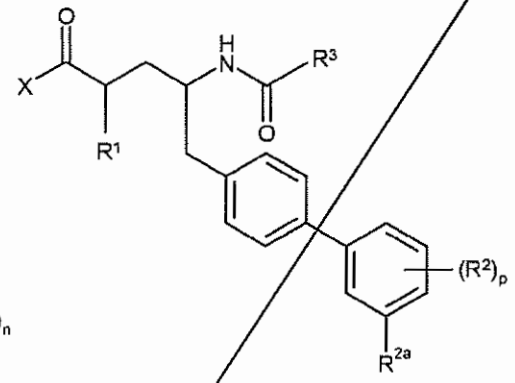
ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

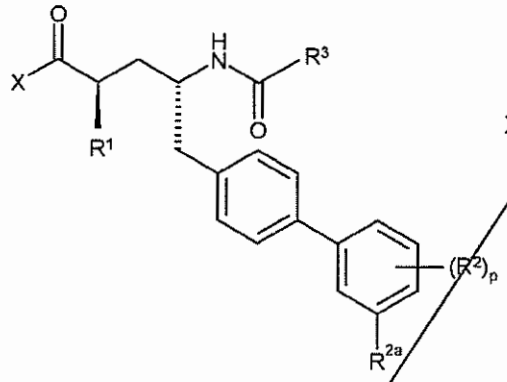
17. Use of claim 16 wherein the compound has the Formula:



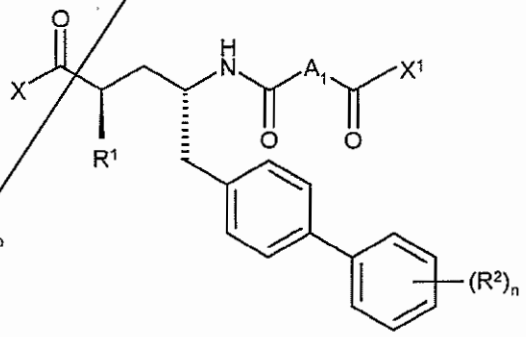
Formula II-A



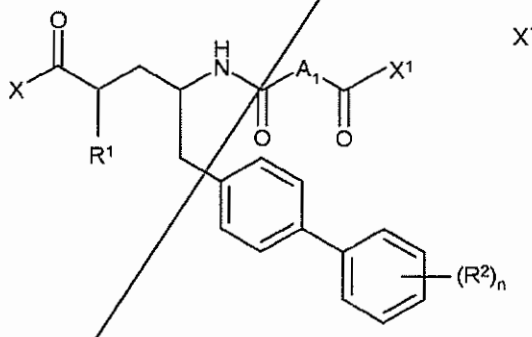
Formula II-B



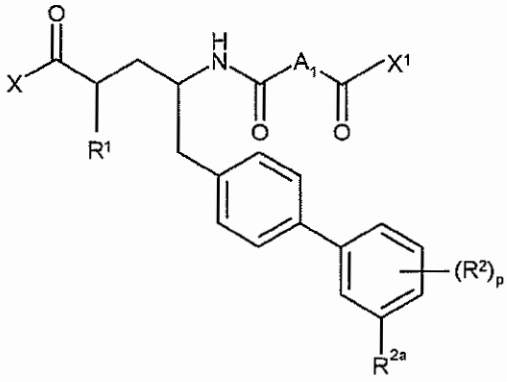
Formula II-C



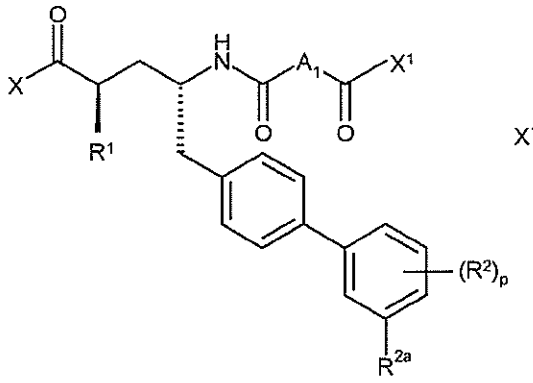
Formula II-D



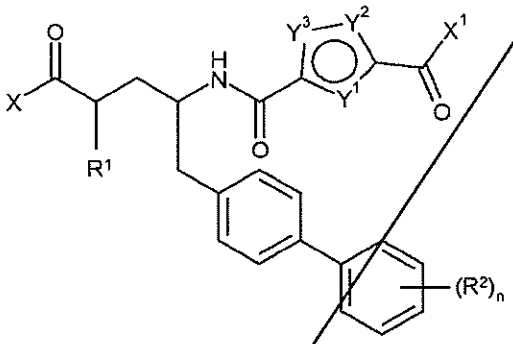
Formula II-E



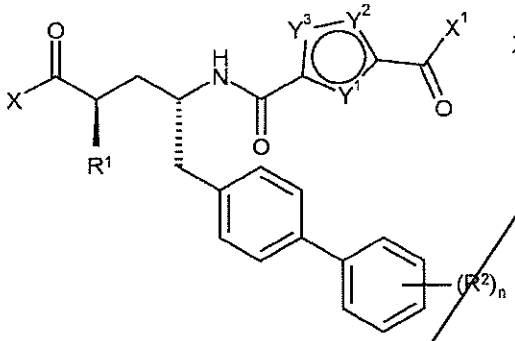
Formula II-F



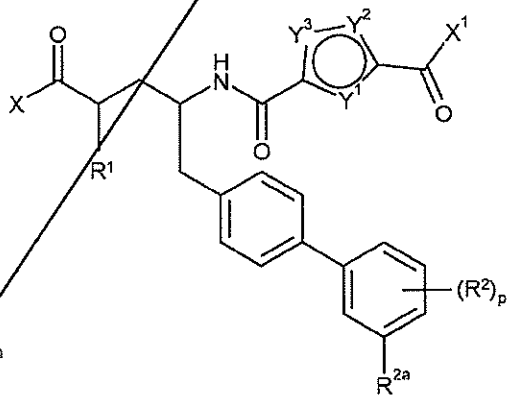
Formula II-G



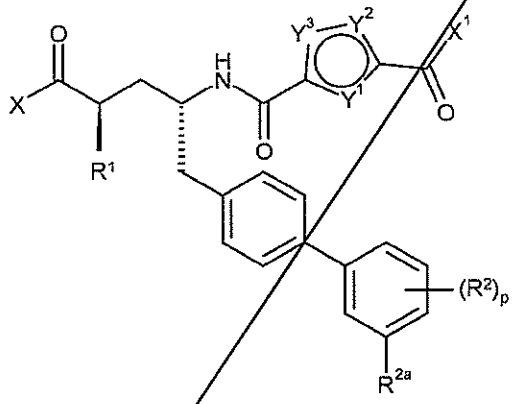
Formula II-H



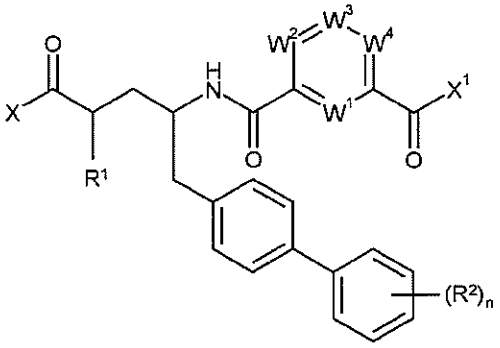
Formula II-I



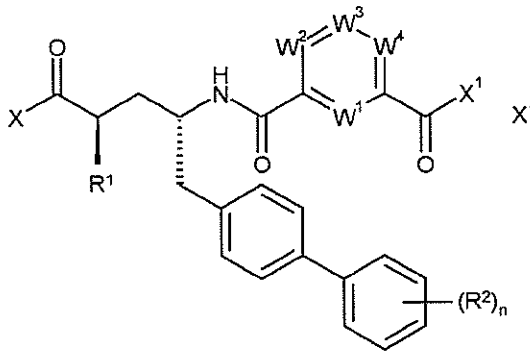
Formula II-J



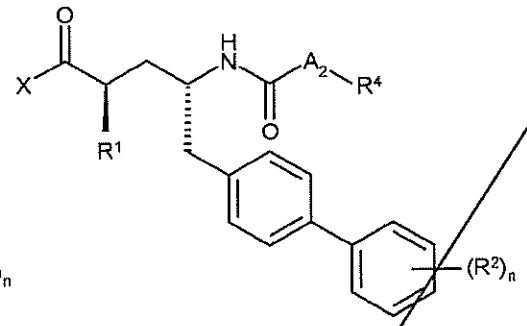
Formula II-K



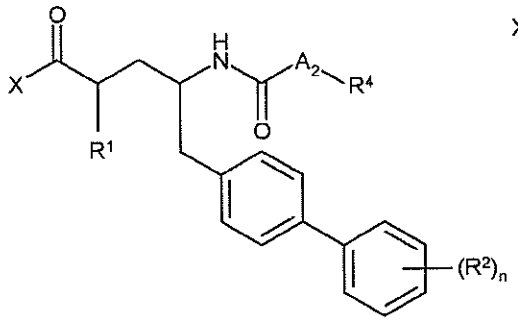
Formula II-L



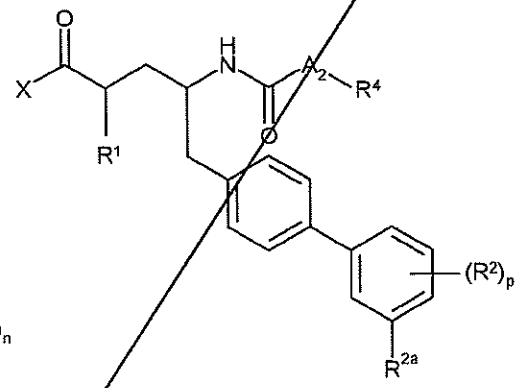
Formula II-M



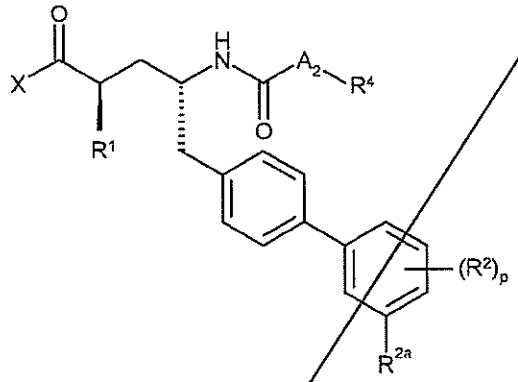
Formula II-N



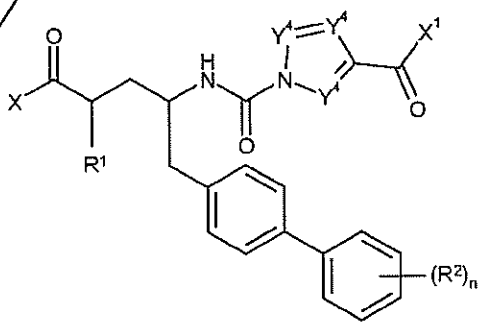
Formula II-O



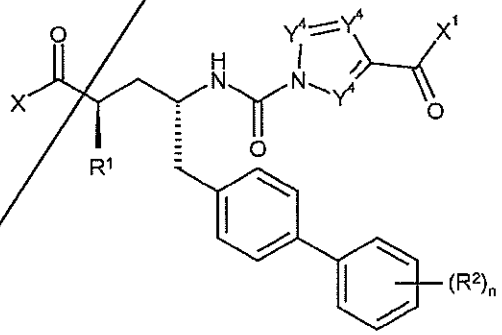
Formula II-P



Formula II-Q



Formula II-R

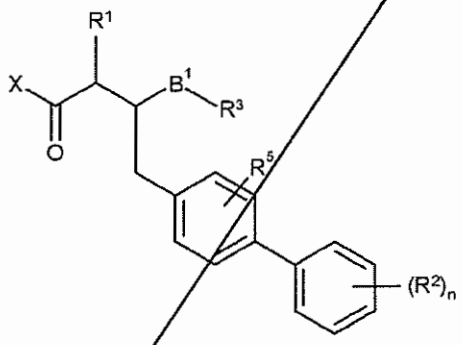


or

Formula II-S

or a pharmaceutically acceptable salt thereof, wherein p is 0, 1, 2, 3 or 4; R^{2a} is halo; W^1, W^2, W^3 and W^4 are independently N or CR^f, in which each R^f is independently selected from H, C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H and $OCH_2C(O)NH_2$; R^b and R^c for each occurrence, are independently H or C_{1-7}alkyl; and Y^1, Y^2 and Y^3 are independently N, NH, S, O or CH and form together with the ring atoms to which they are attached a 5-membered heteroaryl ring, and each Y^4 is independently N, S, O or CH.

18. Use of claim 13 or 15, wherein the neutral endopeptidase inhibitor is a compound of Formula III:



Formula III

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c;
R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^b and R^c for each occurrence are independently H or C_{1-7}alkyl;
R^3 is A^1-$C(O)X^1$ or A^2-R^4;
R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic, and which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, nitro, -NR^bR^c, -$C(O)C_{1-7}$alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-}

$_{7}$alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and $C(O)N(C_{1-6}alkyl)_2$;

B^1 is –C(O)NH- or –NHC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a linear or branched C_{1-7}alkenylene; or

A^1 is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl, -C(O)-O-C_{1-7}alkyl or -$CH_2C(O)OH$; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, -NR^bR^c, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; or

A^1 is a C_{3-7}cycloalkyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

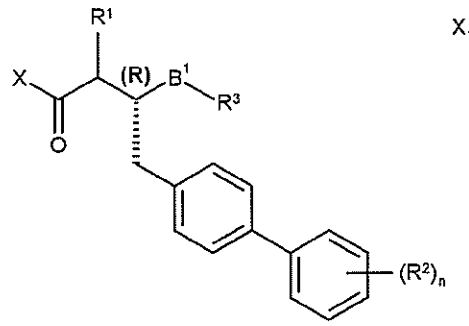
A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

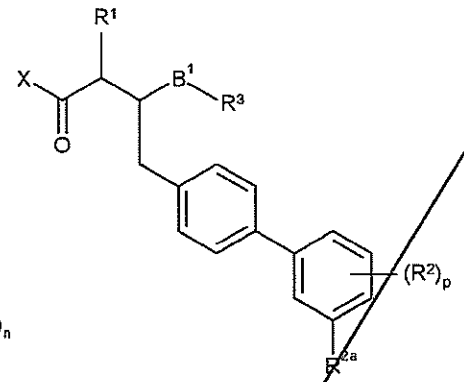
wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

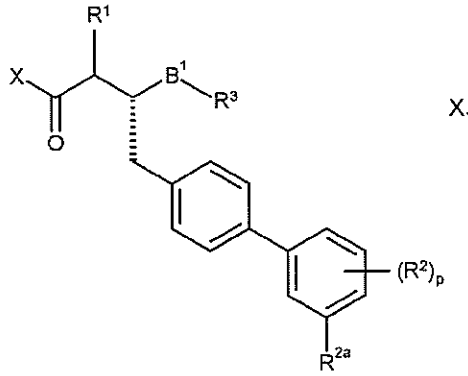
19. Use of claim 18, wherein the compound of the following Formulae:



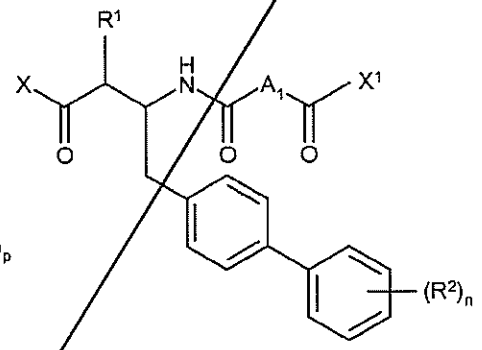
Formula III-A



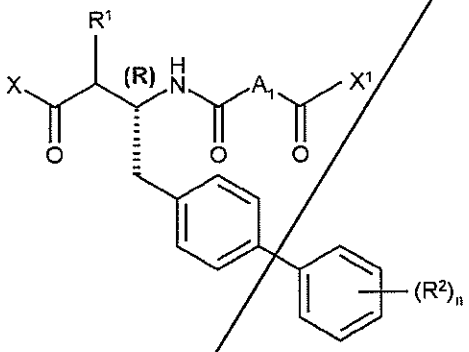
Formula III-B



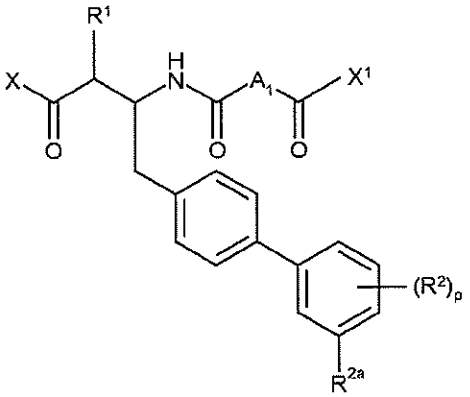
Formula III-C



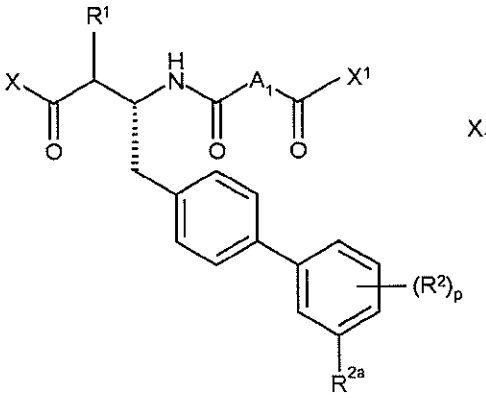
Formula III-D



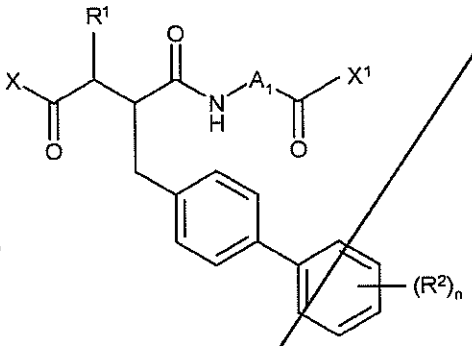
Formula III-E



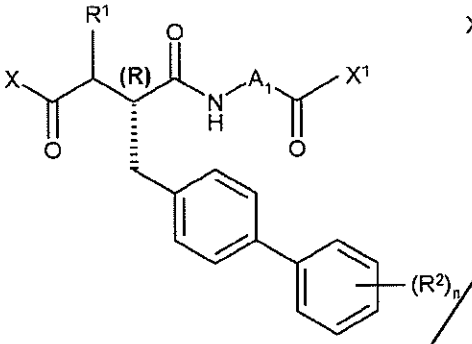
Formula III-F



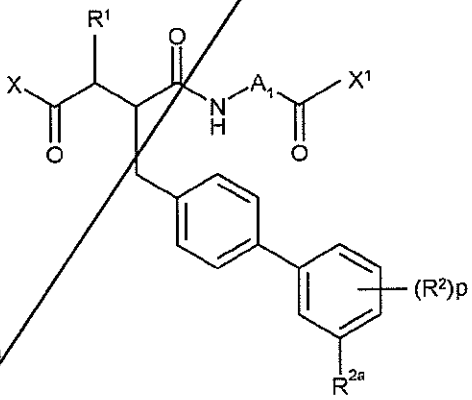
Formula III-G



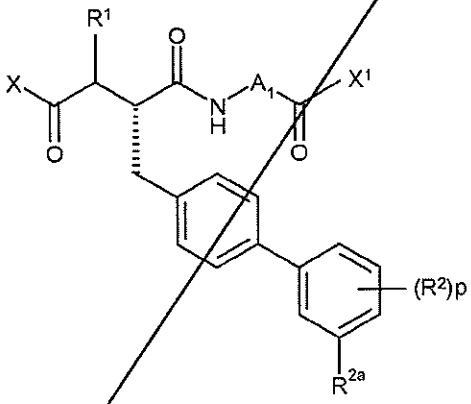
Formula III-H



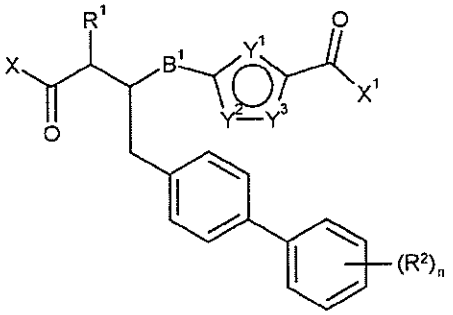
Formula III-I



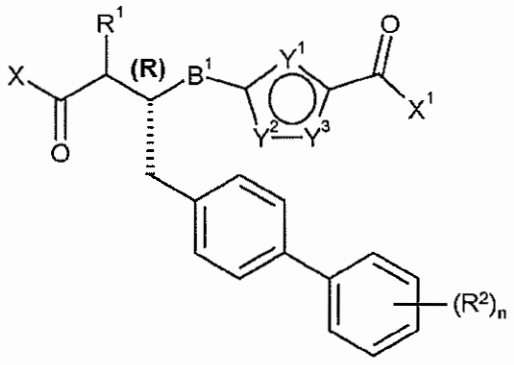
Formula III-J



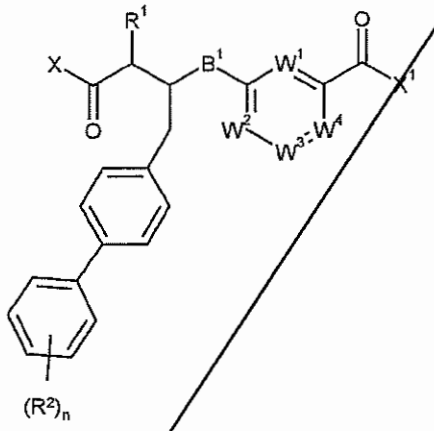
Formula III-K



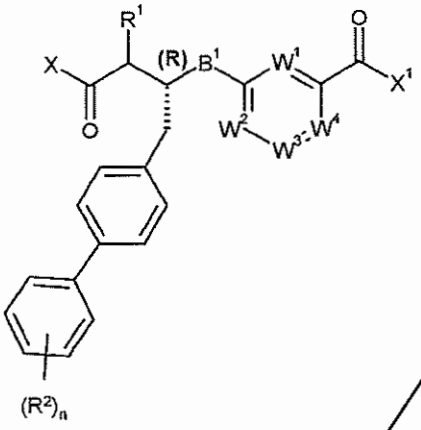
Formula III-L



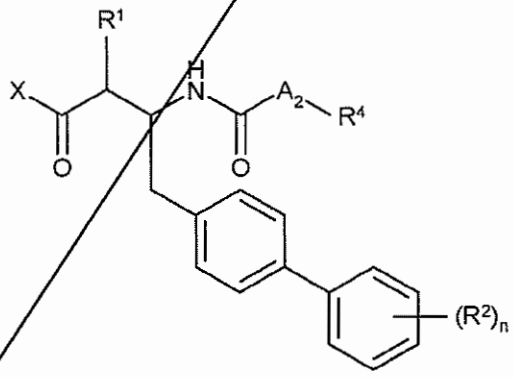
Formula III-M



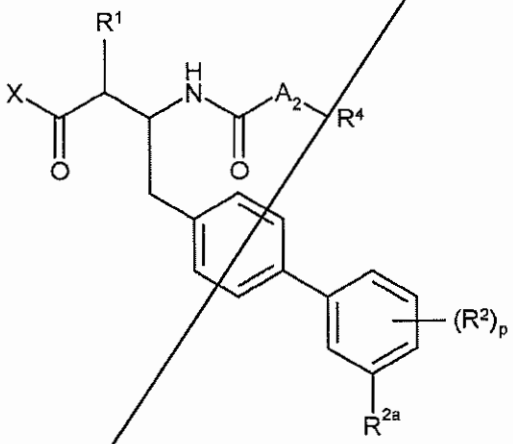
Formula III-N



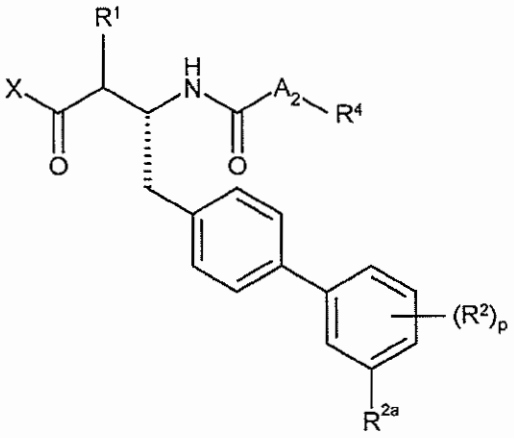
Formula III-O



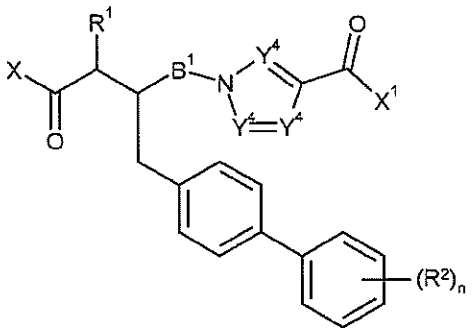
Formula III-P



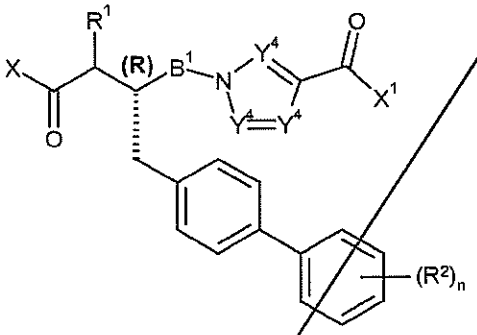
Formula III-Q



Formula III-R



Formula III-S



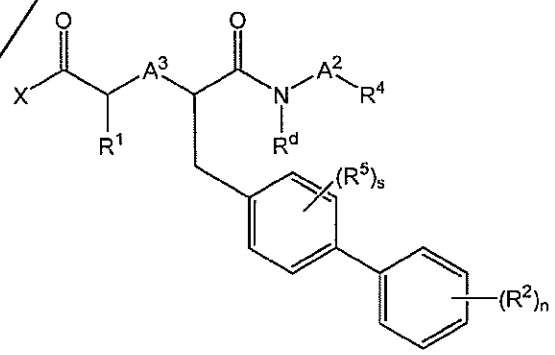
Formula III-T

or a pharmaceutically acceptable salt thereof, wherein p is 0, 1, 2, 3 or 4; R^{2a} is halo; W^1, W^2, W^3 and W^4 are independently N or CR^f, in which each R^f is independently selected from H, C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H and $OCH_2C(O)NH_2$; R^b and R^c for each occurrence are independently H or C_{1-7}alkyl; and Y^1, Y^2 and Y^3 are independently N, NH, S, O or CH and form together with the ring atoms to which they are attached a 5-membered heteroaryl ring, and each Y^4 is independently N, S, O or CH.

20. Use of claim 19, wherein the compound is of Formula III-F, or III-G, wherein A^1 is –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$, or a pharmaceutically acceptable salt thereof.

21. Use according to claim 20, wherein R^1 is H, p is 0; X and X^1 are independently OH or -O-C_{1-7}alkyl, R^{2a} is chloro; or a pharmaceutically acceptable salt thereof.

22. Use according to claim 13 or 15, wherein the neutral endopeptidase inhibitor is a compound of Formula IV:



IV

wherein:

X is OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl or -$NHS(O)_2$-benzyl; wherein R^b and R^c for each occurrence are independently H or C_{1-7}alkyl;

R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c; wherein alkyl is optionally substituted with C_{6-10}-aryl, benzyloxy, hydroxy or C_{1-6} alkoxy;

for each occurence, R^2 is independently C_{1-6}-alkoxy, hydroxy, halo, C_{1-6}-alkyl, cyano or trifluoromethyl;

A^3 is O or NR^e;

R^d and R^e are independently H or C_{1-6} alkyl;

A^2 is a bond or C_{1-3}alkylene chain;

R^4 is a 5- or 6-membered heteroaryl, C_{6-10}-aryl or C_{3-7}-cycloalkyl, wherein each heteroaryl, aryl or cycloalkyl are optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl;

R^5 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; or

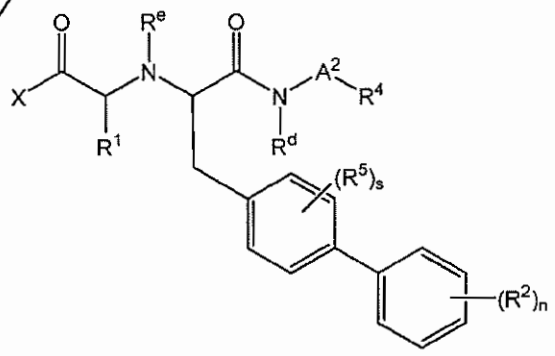
R^d, A^2-R^4, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl; and

n is 0 or an integer from 1 to 5;

s is 0 or an integer from 1 to 4; or

a pharmaceutically acceptable salt thereof.

23. Use of claim 22 wherein the compound is of Formula IV-A:



IV-A

wherein:

X represent OH or O-C_{1-6}-alkyl;

R^1 is H, C_{1-6} alkyl or C_{6-10}-aryl-C_{1-6} alkyl;

for each occurence, R^2 is independently C_{1-6}-alkoxy, hydroxy, halo, C_{1-6}-alkyl, cyano or trifluoromethyl;

R^d and R^e are independently H or C_{1-6} alkyl;

A^2 is a bond or C_{1-3}alkylene chain;

R^4 is a 5- or 6-membered heteroaryl, C_{6-10}-aryl or C_{3-7}-cycloalkyl, wherein each heteroaryl, aryl or cycloalkyl are optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl;

R^5 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; or

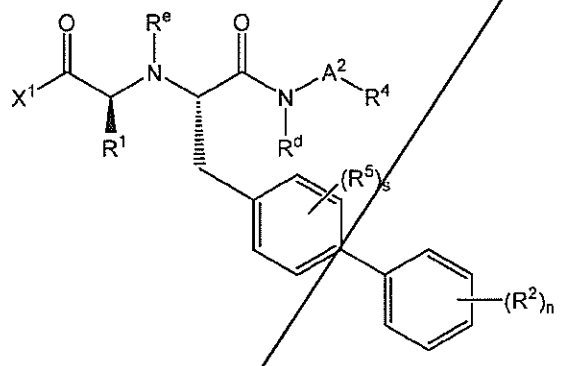
R^d, A^2-R^4, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl; and

n is 0 or an integer from 1 to 5;

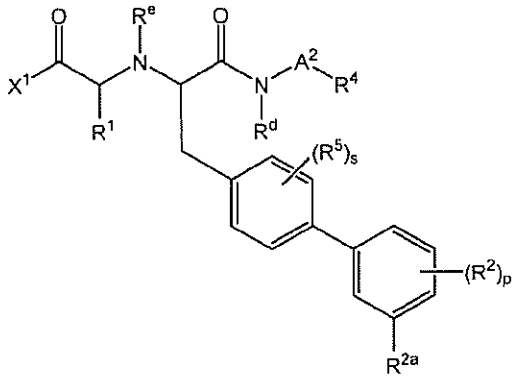
s is 0 or an integer from 1 to 4; or

a pharmaceutically acceptable salt thereof.

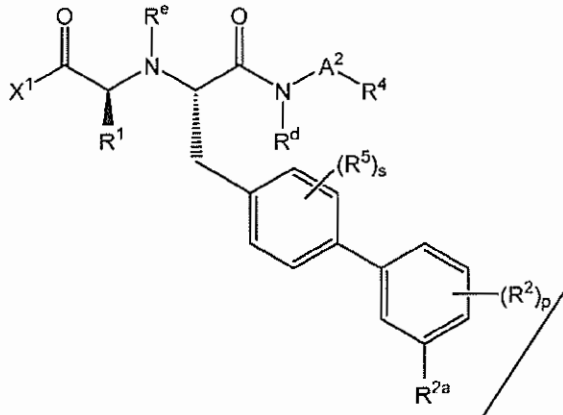
24. Use according to claim 22 or 23 wherein the compound is of Formula:



Formula IV-B



Formula IV-C



or Formula IV-D

or a pharmaceutically acceptable salt therof, wherein p is 0, 1, 2, 3 or 4 and R^{2a} is halo.

25. The method of treating, ameliorating or preventing contrast-induced nephropathy in a subject, according to anyone of claims 1 to 12, further comprising at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy.

26. The method of claim 25 wherein the other therapeutic agent is selected from adenosine-receptor antagonist, a calcium channel blocker, an anti-apoptotic agent, an antioxidant, a MAP kinase inhibitor, a prostacyclin or prostacyclin analogue, endothelin antagonist, an ion chelator and a dopamine receptor agonist, or a pharmaceutically acceptable salt thereof.

27. Use of a neutral endopeptidase inhibitor according to claim 13 to 24, in combination with at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy.

28. Use of claim 27 wherein the other therapeutic agent is selected from adenosine-receptor antagonist, a calcium channel blocker, an anti-apoptotic agent, an antioxidant, a MAP kinase inhibitor, a prostacyclin or prostacyclin analogue, endothelin antagonist, an ion chelator and a dopamine receptor agonist or a pharmaceutically acceptable salt thereof.

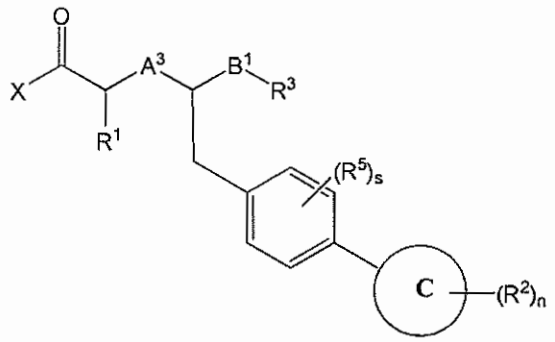
CLAIMS

What is claimed is:

1. Use of a neutral endopeptidase EC. 3.4. 24.11. inhibitor, in the manufacture of a medicament for the treatment, amelioration or prevention of contrast-induced nephropathy in a subject in need of such treatment.

2. Use of claim 1 wherein the neutral endopeptidase inhibitor is selected from the group consisting of Candoxatril, Candoxatrilat, Dexecadotril, Ecadotril, Racecadotril, Sampatrilat, Fasidotril, Omapatrilat, Gemopatrilat, Daglutril, SCH-42495, SCH-32615, UK-447841, AVE-0848, PL-37 and (2R,4S)-5-Biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester.

3. Use of claim 2 wherein the neutral endopeptidase inhibitor is a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c; wherein alkyl is optionally substituted with C_{6-10}-aryl, benzyloxy, hydroxy, C_{3-7}cycloalkyl or C_{1-6} alkoxy;

R2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl;

R3 is A^1-C(O)X^1 or A^2-R^4;

R4 is C_{6-10}aryl, C_{3-7}cycloalkyl, or a heteroaryl, which can be monocyclic or bicyclic, each of which can be optionally substituted with one or more substituents independently selected

from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, nitro, -NR^bR^c, -C(O)C_{1-7}alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl, $S(O)_2$-C_{1-7}alkyl, C(O)-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-7}alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and **X^1** are independently OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and C(O)N(C_{1-6}alkyl)$_2$;

$B^1$is –C(O)NR^d- or –NR^dC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

$A^1$is a linear or branched C_{1-7}alkenylene; or

$A^1$is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl, -C(O)-O-C_{1-7}alkyl or -$CH_2C(O)OH$; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, -NR^bR^c, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; or

$A^1$is a C_{3-7}cycloalkyl or heterocyclyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein **A^1**may be in either direction; and

$A^2$is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

$A^3$is CH_2, O, NR^e or is absent; and when A^3 is O or NR^e then B^1 is C(O)NR^d;

R^b and **R^c**for each occurrence are independently H, C_{6-10}aryl or C_{1-7}alkyl;

$R^d$and **R^e** are independentlyH or C_{1-7}alkyl;

Ring C is a phenyl or a monocyclic heteroaryl;

n is 0, 1, 2, 3, 4 or 5;

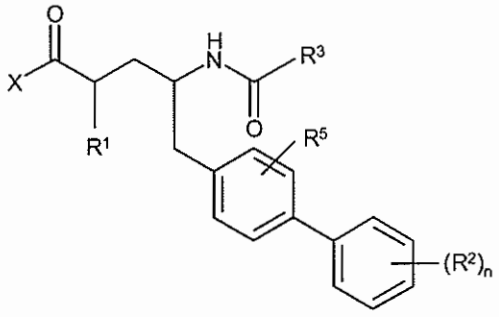
s is 0, 1, 2, 3 or 4; and

when $\mathbf{B^1}$ is $C(O)NR^d$ and R^3 is A^2-R^4, then $\mathbf{R^d}$ and $\mathbf{A^2}$-$\mathbf{R^4}$, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl;

wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms unless otherwise specified, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

4. Use of claim 2 or 3, wherein the neutral endopeptidase inhibitor is a compound of Formula II:



Formula II

or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{R^1}$is C_{1-7}alkyl;

for each occurrence, $\mathbf{R^2}$ is independently C_{1-7}alkyl, NO_2, CN, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, halo-C_{1-7}alkyl, NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^b and R^c for each occurrence, are independently H or C_{1-7}alkyl;

$\mathbf{R^3}$ is $A^1C(O)X^1$ or A^2-R^4;

R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic and which can be optionally substituted with one or more substituents independently selected from hydroxy, hydroxy-C_{1-7}alkyl, NR^bR^c, nitro, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -C(O)C_{1-7}alkyl , -NHS(O)$_2$-C_{1-7}alkyl, -SO_2C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, -NR^bR^c, -NHS(O)$_2$-C_{1-7}alkyl, -NHS(O)$_2$-benzyl or -O-C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of aryl, heteroaryl, heterocyclyl, -$C(O)NH_2$, -C(O)NH- C_{1-6}alkyl, and -C(O)N(C_{1-6}alkyl)$_2$;

A^1 is a bond or a linear C_{1-4}alkylene substituted with one or more substituents independently selected from the group consisting of halo, O-acetate, C_{1-7} alkyl and C_{3-7}cycloalkyl; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

A^1 is a linear or branched C_{2-6}alkenylene; or

$A^1$is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl or $CH_2C(O)OH$; or

A^1 is a C_{3-7}cycloalkyl, a heterocyclyl, a phenyl or a heteroaryl in which phenyl and heteroaryl are optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H, and $OCH_2C(O)NH_2$; or

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein A^1 may be in either direction; and

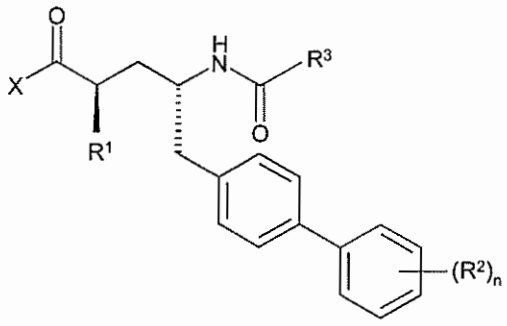
$A^2$is a bond or a linear or branched C_{1-7}alkylene which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

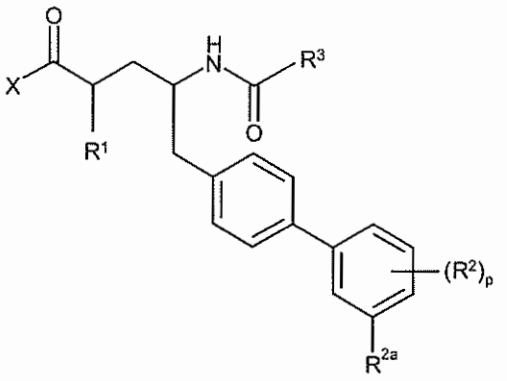
wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

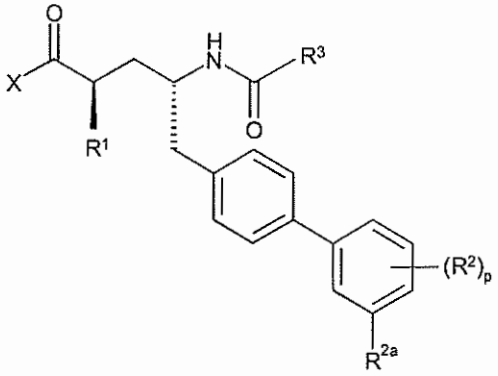
5. Use of claim 4 wherein the compound has the Formula:



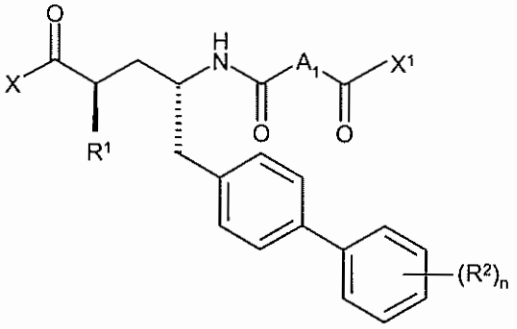
Formula II-A



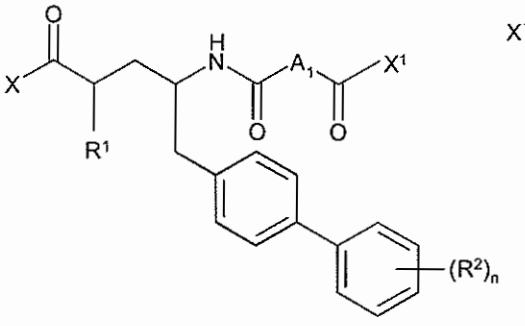
Formula II-B



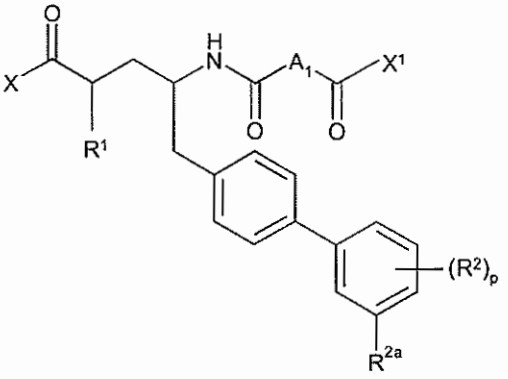
Formula II-C



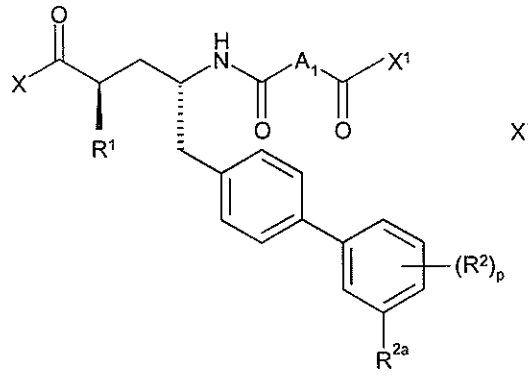
Formula II-D



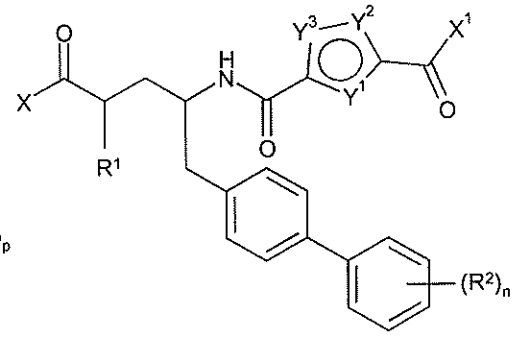
Formula II-E



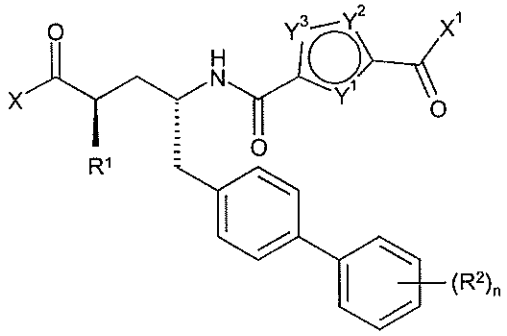
Formula II-F



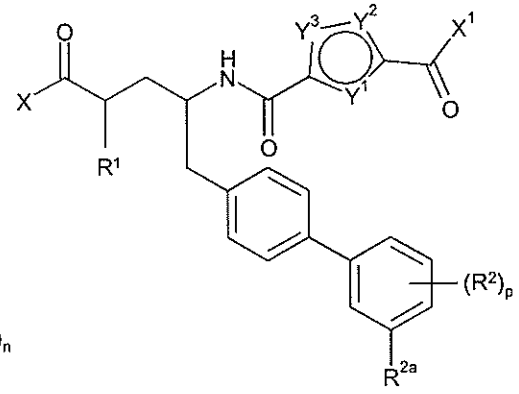
Formula II-G



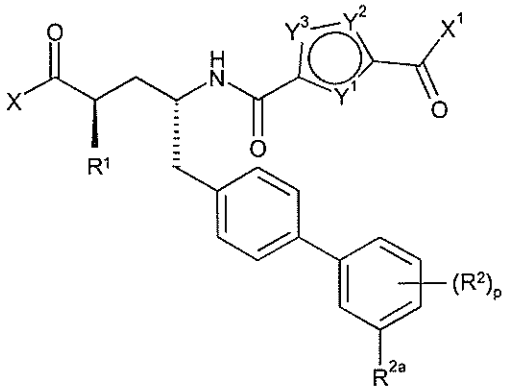
Formula II-H



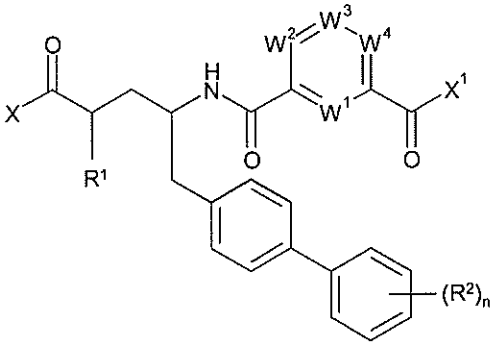
Formula II-I



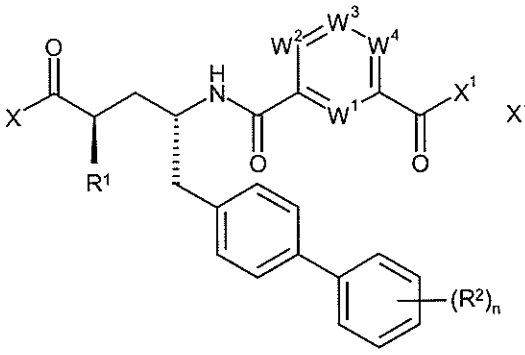
Formula II-J



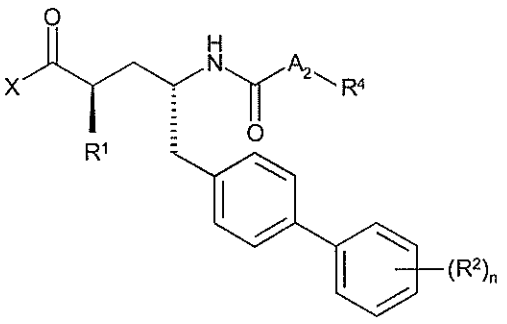
Formula II-K



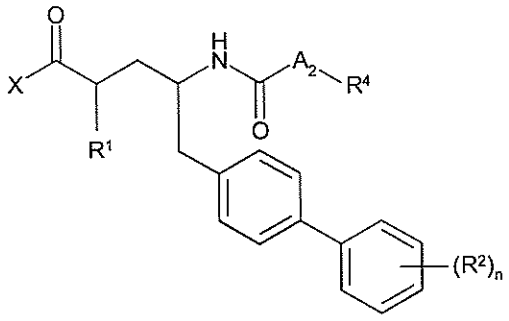
Formula II-L



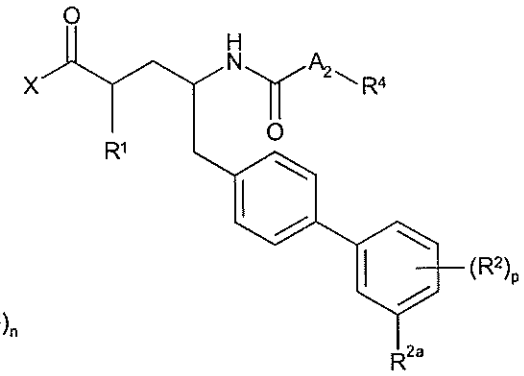
Formula II-M



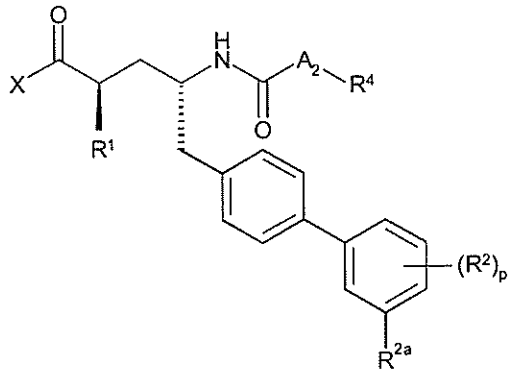
Formula II-N



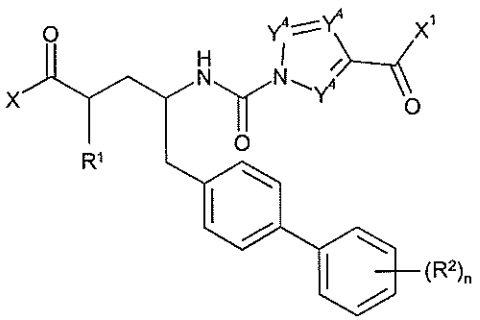
Formula II-O



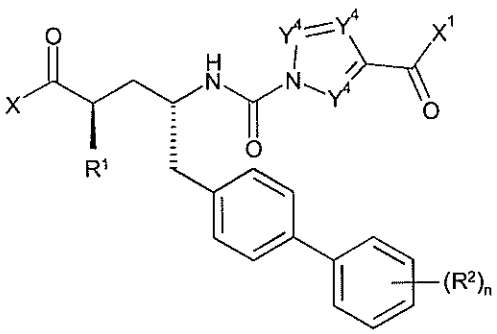
Formula II-P



Formula II-Q



Formula II-R

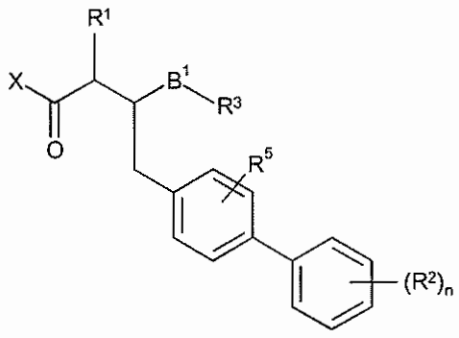


or

Formula II-S

or a pharmaceutically acceptable salt thereof, wherein p is 0, 1, 2, 3 or 4; R^{2a} is halo; W^1, W^2, W^3 and W^4 are independently N or CR^f, in which each R^f is independently selected from H, C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H and $OCH_2C(O)NH_2$; R^b and R^c for each occurrence, are independently H or C_{1-7}alkyl; andY^1, Y^2 and Y^3 are independently N, NH, S, O or CH and form together with the ring atoms to which they are attached a 5-membered heteroaryl ring, and each Y^4 is independently N, S, O or CH.

6. Use of claim 2 or 4, wherein the neutral endopeptidase inhibitor is a compound of Formula III:



Formula III

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c;
R^2 for each occurence, is independently C_{1-7}alkyl, halo, NO_2, CN, C_{1-7}alkanoylamino, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^bR^c, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^b and R^c for each occurrence are independently H or C_{1-7}alkyl;
R^3 is A^1-$C(O)X^1$ or A^2-R^4;
R^4 is C_{6-10}aryl or a heteroaryl, which can be monocyclic or bicyclic, and which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, hydroxyC_{1-7}alkyl, nitro, -NR^bR^c, -$C(O)C_{1-7}$alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{2-7}alkenyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl; or R^4 is a heterocyclyl which can be optionally substituted with one or more substituents independently selected from the group consisting of oxo, hydroxy, hydroxyC_{1-}

$_{7}$alkyl, amino, C(O)-O- C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}akyl, C_{6-10}aryl, heteroaryl, -$NHSO_2$-C_{1-7}alkyl and benzyl;

R^5 is H, halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; and

X and **X^1** are independently OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl, -$NHS(O)_2$-benzyl or -O- C_{6-10}aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of C_{6-10}aryl, heteroaryl, heterocyclyl, $C(O)NH_2$, C(O)NH- C_{1-6}alkyl, and $C(O)N(C_{1-6}alkyl)_2$;

$B^1$is –C(O)NH- or –NHC(O)-;

A^1 is a bond or a linear or branched C_{1-7}alkylene ; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{3-7}cycloalkyl, C_{1-7}alkoxy, hydroxy and O-acetate; in which two geminal alkyl can optionally combine to form a C_{3-7}cycloalkyl; or

$A^1$is a linear or branched C_{1-7}alkenylene; or

$A^1$is a linear C_{1-4} alkylene wherein one or more carbon atom(s) is/are replaced with an heteroatom selected from O, NR^a; and A^1 is optionally substituted with one or more substituents independently selected from the group consisting of halo and C_{1-7}alkyl; in which R^a for each occurrence, is independently H, C_{1-7}alkyl, -C(O)-O-C_{1-7}alkyl or -$CH_2C(O)OH$; or

A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, -NR^bR^c, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; or

$A^1$is a C_{3-7}cycloalkyl;

A^1 is -C_{1-4}alkylene-C_{6-10}-aryl-, -C_{1-4}alkylene-heteroaryl- or -C_{1-4}alkylene-heterocyclyl-, wherein **A^1**may be in either direction; and

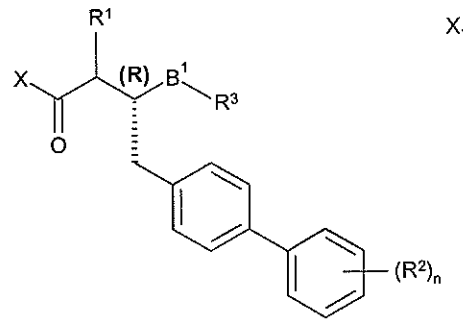
$A^2$is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

n is 0, 1, 2, 3, 4 or 5;

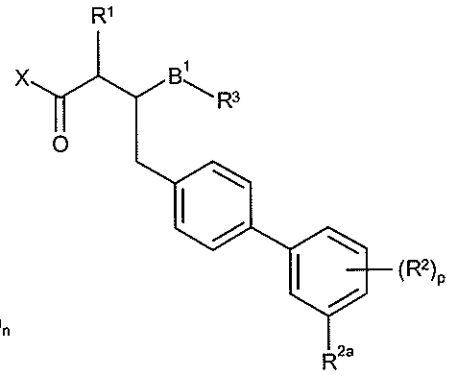
wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S.

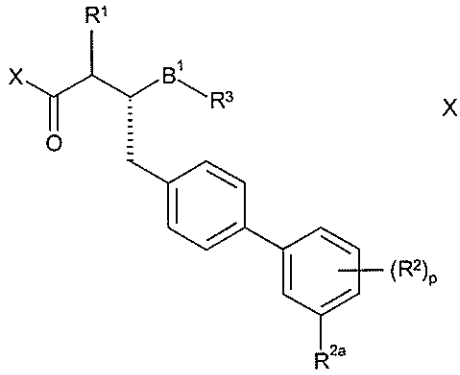
7. Use of claim 6, wherein the compound of the following Formulae:



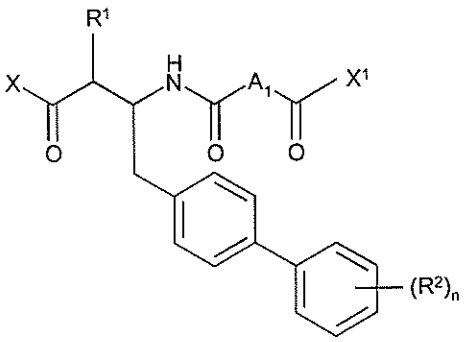
Formula III-A



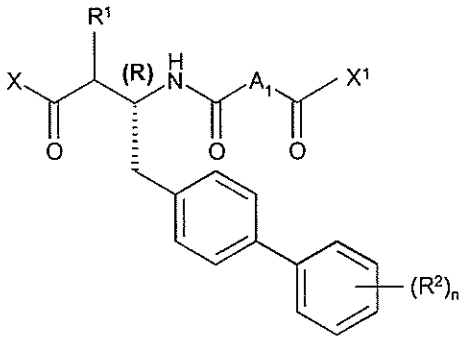
Formula III-B



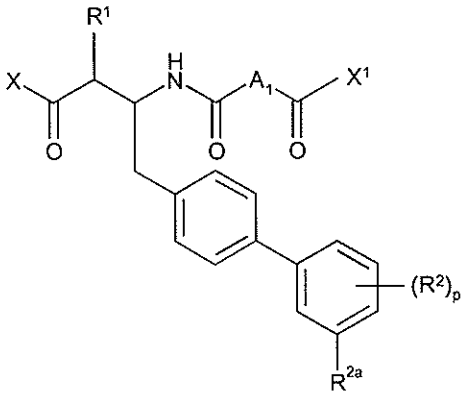
Formula III-C



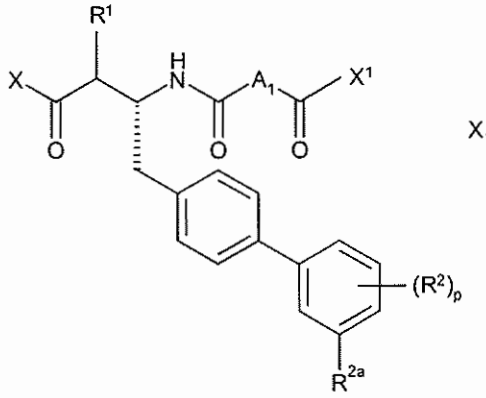
Formula III-D



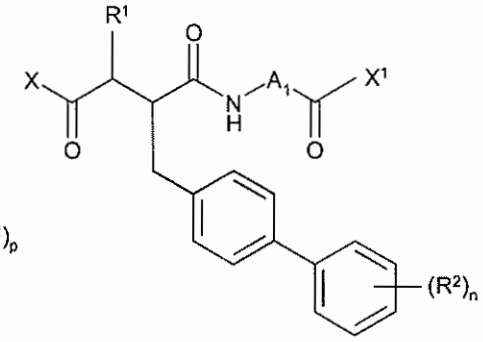
Formula III-E



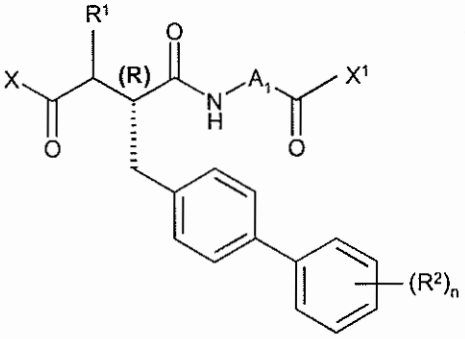
Formula III-F



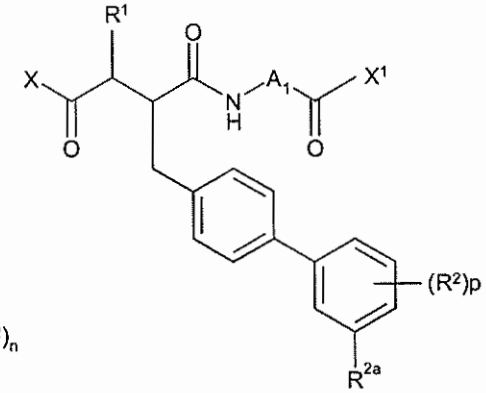
Formula III-G



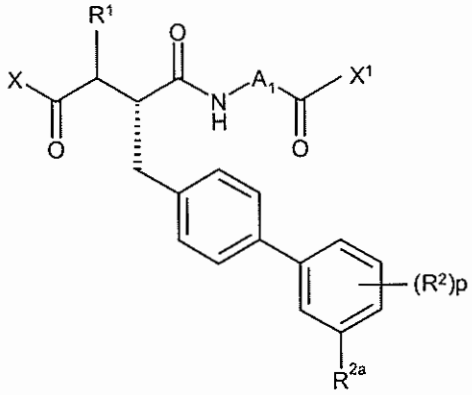
Formula III-H



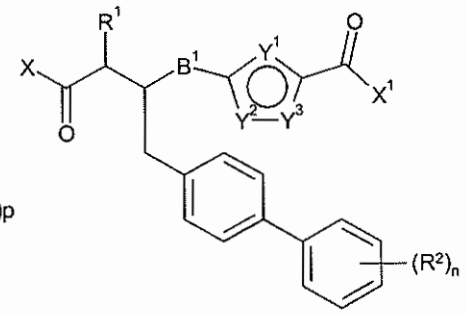
Formula III-I



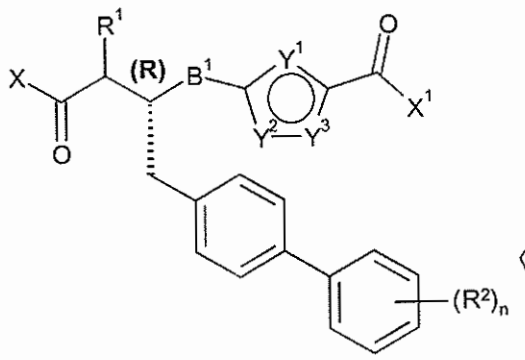
Formula III-J



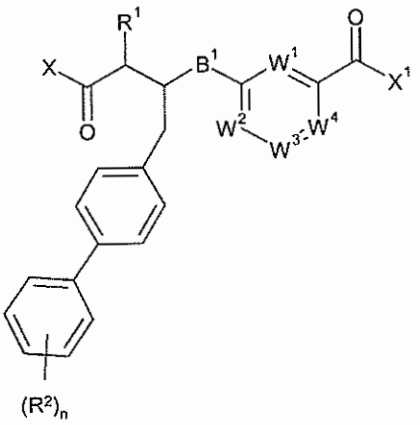
Formula III-K



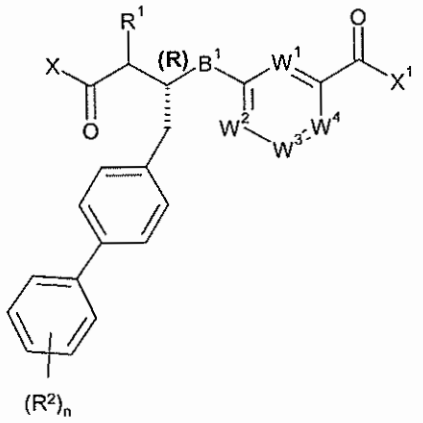
Formula III-L



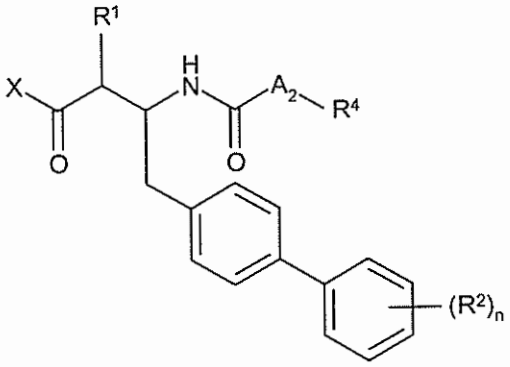
Formula III-M



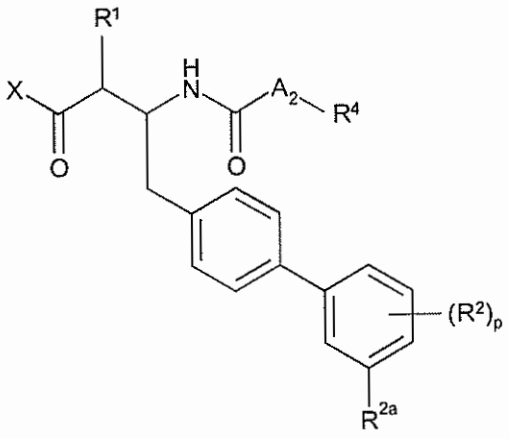
Formula III-N



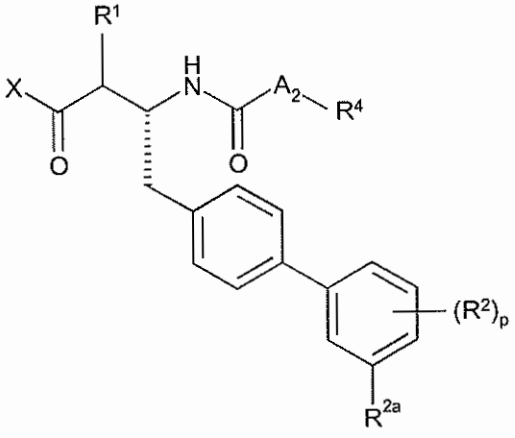
Formula III-O



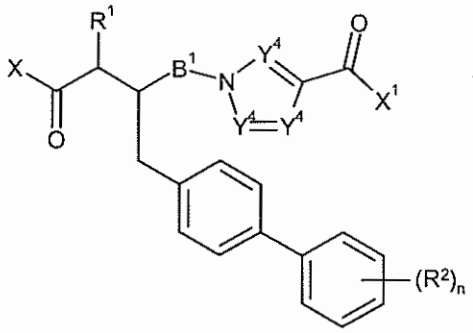
Formula III-P



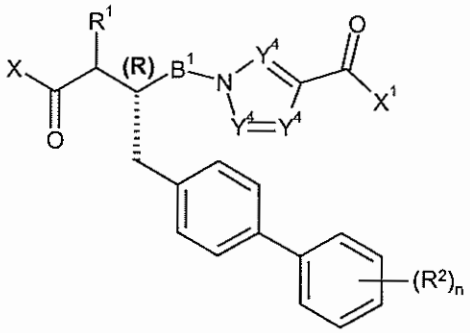
Formula III-Q



Formula III-R



Formula III-S



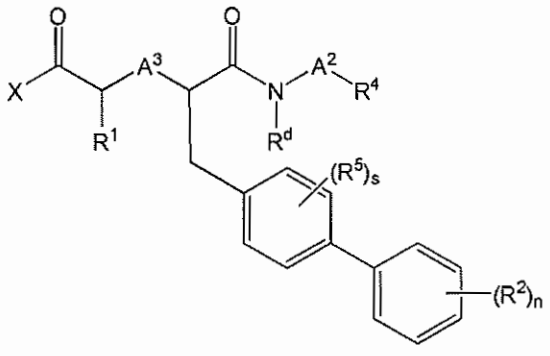
Formula III-T

or a pharmaceutically acceptable salt thereof, wherein p is 0, 1, 2, 3 or 4; R^{2a} is halo; W^1, W^2, W^3 and W^4 are independently N or CR^f, in which each R^f is independently selected from H, C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, NR^bR^c, OCH_2CO_2H and $OCH_2C(O)NH_2$; R^b and R^c for each occurrence are independently H or C_{1-7}alkyl; andY^1, Y^2 and Y^3 are independently N, NH, S, O or CH and form together with the ring atoms to which they are attached a 5-membered heteroaryl ring, and each Y^4 is independently N, S, O or CH.

8. Use of claim 7, wherein the compound is of Formula III-F, or III-G, wherein A^1 is –CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$, or a pharmaceutically acceptable salt thereof.

9. Use according to claim 8, wherein R^1 is H, p is 0; X and X^1 are independently OH or -O-C_{1-7}alkyl, $R^{2a}$is chloro; or a pharmaceutically acceptable salt thereof.

10. Use according to claim 2 or 4, wherein the neutral endopeptidase inhibitor is a compound of Formula IV:



IV

wherein:

X is OH, -O-C_{1-7}alkyl, -NR^bR^c, -$NHS(O)_2$-C_{1-7}alkyl or -$NHS(O)_2$-benzyl; wherein $\mathbf{R^b}$ and $\mathbf{R^c}$for each occurrence are independently H or C_{1-7}alkyl;

$\mathbf{R^1}$is H, C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halogen, -SH, -S-C_{1-7}alkyl or NR^bR^c; wherein alkyl is optionally substituted with C_{6-10}-aryl, benzyloxy, hydroxy or C_{1-6} alkoxy;

for each occurence, $\mathbf{R^2}$is independently C_{1-6}-alkoxy, hydroxy, halo, C_{1-6}-alkyl, cyano or trifluoromethyl;

$\mathbf{A^3}$is O or NR^e;

$\mathbf{R^d}$ and $\mathbf{R^e}$are independently H or C_{1-6} alkyl;

$\mathbf{A^2}$ is a bond or C_{1-3}alkylene chain;

$\mathbf{R^4}$is a 5- or 6-membered heteroaryl, C_{6-10}-aryl or C_{3-7}-cycloalkyl, wherein each heteroaryl, aryl or cycloalkyl are optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl;

$\mathbf{R^5}$ for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; or

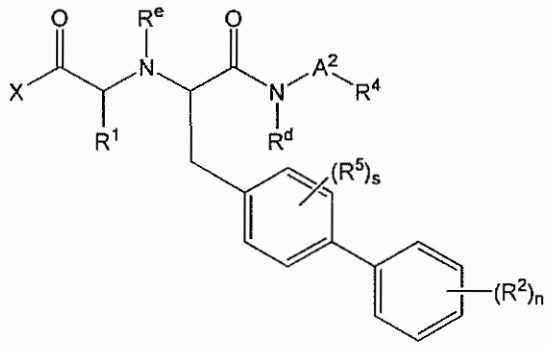
$\mathbf{R^d}$, $\mathbf{A^2}$-$\mathbf{R^4}$, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl; and

n is 0 or an integer from 1 to 5;

s is 0 or an integer from 1 to 4; or

a pharmaceutically acceptable salt thereof.

11. Use of claim 10 wherein the compound is of Formula IV-A:



IV-A

wherein:

X represent OH or O-C_{1-6}-alkyl;

$\mathbf{R^1}$ is H, C_{1-6} alkyl or C_{6-10}-aryl-C_{1-6} alkyl;

for each occurence, $\mathbf{R^2}$is independently C_{1-6}-alkoxy, hydroxy, halo, C_{1-6}-alkyl, cyano or trifluoromethyl;

$\mathbf{R^d}$and $\mathbf{R^e}$ are independently H or C_{1-6} alkyl;

$\mathbf{A^2}$ is a bond or C_{1-3}alkylene chain;

$\mathbf{R^4}$ is a 5- or 6-membered heteroaryl, C_{6-10}-aryl or C_{3-7}-cycloalkyl, wherein each heteroaryl, aryl or cycloalkyl are optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, halo-C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl;

$\mathbf{R^5}$for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; or

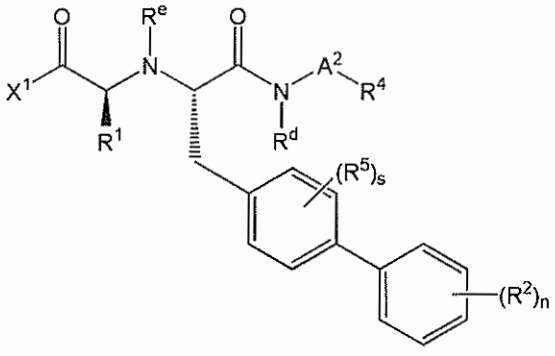
$\mathbf{R^d}$, $\mathbf{A^2}$-$\mathbf{R^4}$, together with the nitrogen to which R^d and A^2-R^4 are attached, form a 4- to 7-membered heterocyclyl or a 5- to 6- membered heteroaryl , each of which is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6}alkyl, halo, haloC_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, CO_2H and CO_2C_{1-6}alkyl; and

n is 0 or an integer from 1 to 5;

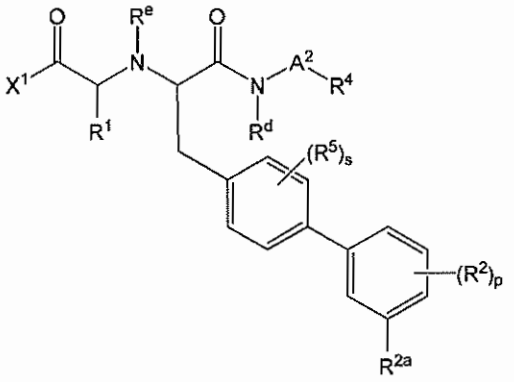
s is 0 or an integer from 1 to 4; or

a pharmaceutically acceptable salt thereof.

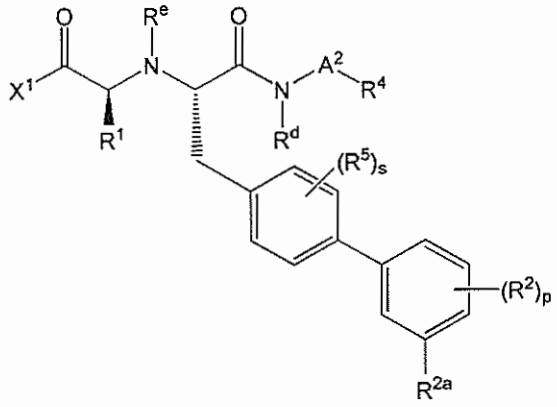
12. Use according to claim 10 or 11 wherein the compound is of Formula:



Formula IV-B



Formula IV-C



or Formula IV-D

or a pharmaceutically acceptable salt therof, wherein p is 0, 1, 2, 3 or 4 and R^{2a} is halo.

13. Use according to claim 12 wherein the compound is selected from:
(*S*)-2-[(*S*)-2-(3'-chloro-biphenyl-4-yl)-1-(1H-tetrazol-5-ylcarbamoyl)-ethylamino]-propionic acid ethyl ester;
(*S*)-2-[(*S*)-2-(3'-chloro-biphenyl-4-yl)-1-(1H-tetrazol-5-ylcarbamoyl)-ethylamino]-propionic acid;
(S)-2-[(S)-2-(3'-chloro-biphenyl-4-yl)-1-(1H-tetrazol-5-ylcarbamoyl)-ethoxy]-propionic acid ethyl ester; and
(S)-2-[(S)-2-(3'-Chloro-biphenyl-4-yl)-1-(1H-tetrazol-5-ylcarbamoyl)-ethylamino]-4-phenyl-butyric acid ethyl ester; or a pharmaceutically acceptable salt thereof.