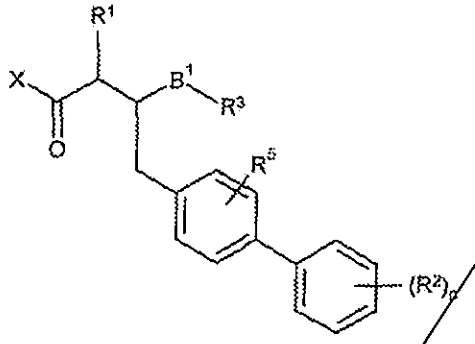
CLAIMS

1. A compound of Formula I':



Formula 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^aR^b;

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^aR^b, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b 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^aR^b, -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^aR^b, -$NHS(O)_2$-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^c; 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^c 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, $-NR^aR^b$, $-OCH_2CO_2H$, 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

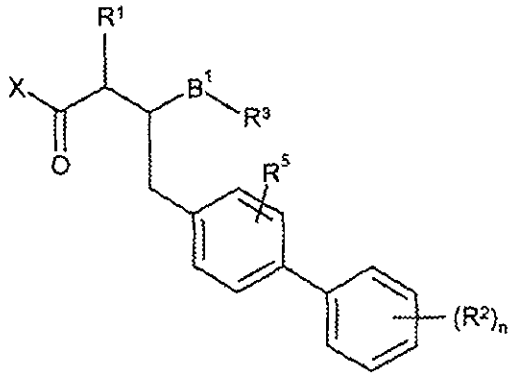
A^2 is a bond or a linear or branched C_{1-7} alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

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.

2. A compound according to claim 1 of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H or C_{1-7}alkyl;
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, $-NR^aR^b$, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b 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, 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; 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^aR^b, 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 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, $-NR^aR^b$, $-OCH_2CO_2H$, 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.

3. The compound of Claim 1 or 2 wherein:

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

R^2 for each occurrence, is independently C_{1-7}alkyl, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, -NR^aR^b, C_{6-20}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b 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_{6-20}aryl or a heteroaryl, each of which can be monocyclic or bicyclic and each of which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, 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; and

X and X^1 are independently OH, -O-C_{1-7}alkyl or NR^aR^b;

B^1 is –C(O)NH- or –NHC(O)-;

A^1 is 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 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^aR^b, -OCH_2CO_2H, and -$OCH_2C(O)NH_2$; 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; and

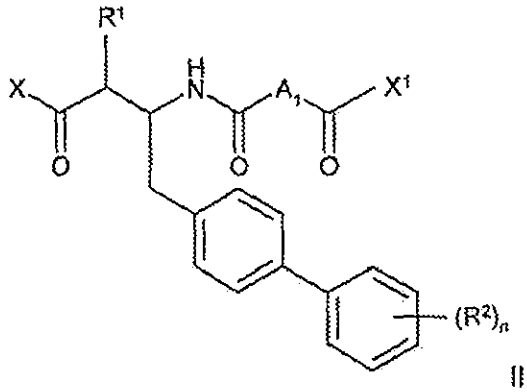
n is 0, 1, 2, 3, 4 or 5;

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

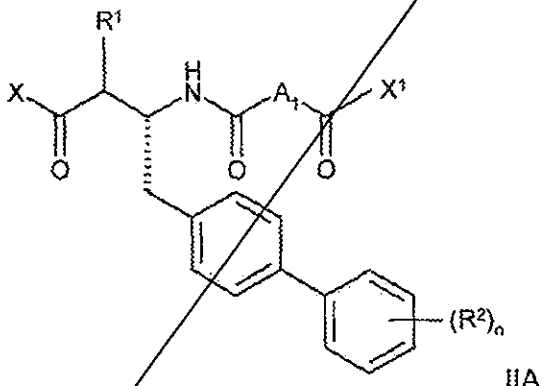
each heterocyclyl is a monocyclic saturated or partially saturated but non-aromatic moiety comprising 4-7 ring atoms selected from carbon atoms and 1-5 heteroatoms, wherein

each heteroatom of a heteroaryl or a heterocyclyl is independently selected from O, N and S, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1, 2 or 3 having Formula II or IIA:



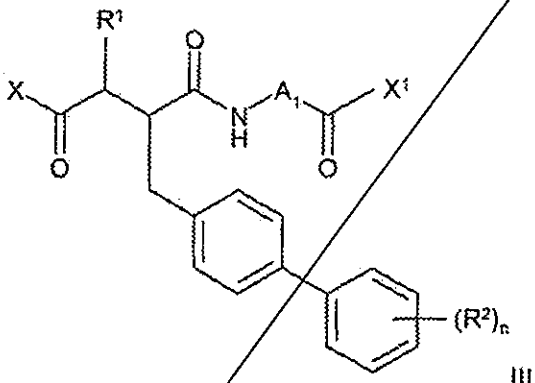
II



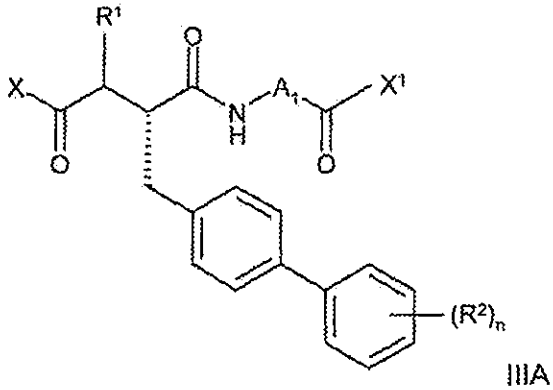
IIA

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, 2 or 3 having formula III or IIIA:



III



IIIA

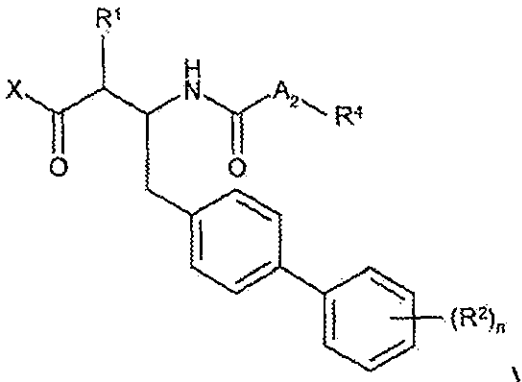
or a pharmaceutically acceptable salt thereof.

6. The compound of any of claims 1 to 5 wherein A^1 is an optionally substituted linear or branched C_{1-7} alkylene, or a pharmaceutically acceptable salt thereof.

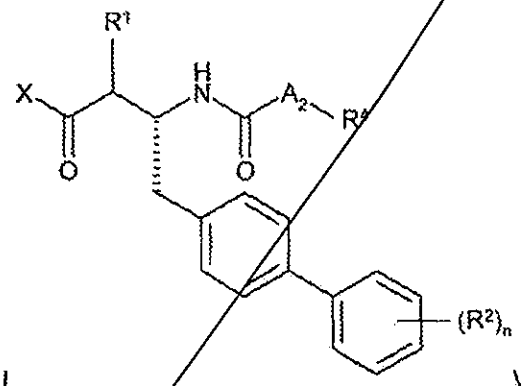
7. The compounds of any of claims 1 to 6 wherein A^1 is CH_2CH_2, or a pharmaceutically acceptable salt thereof.

8. The compound of any of claims 1 to 5 wherein A^1 is an optionally substituted phenyl or heteroaryl, or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, 2 or 3 having Formula VII or VIIA:



VII



VIIA

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 9 wherein A^2 is a bond or CH_2 or CH_2-CH_2, or a pharmaceutically acceptable salt thereof.

11. The compound of any of claims 1 to 10 wherein R^1 is H, R^2 is independently halo, C_{1-7}alkoxy, hydroxy, C_{1-7}alkyl or halo-C_{1-7}alkyl , n is 0, 1 or 2 and X and X^1 are independently OH or -O-C_{1-7}alkyl, or a pharmaceutically acceptable salt thereof.

12. The compounds of any of claims 1 to 11 wherein n is 1 or 2; R^2 is meta-chloro or meta-fluoro and the other optional R^2 group is halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, hydroxy and C_{1-7}alkoxy, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

14. A combination comprising: a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agents selected from HMG-Co-A reductase inhibitor, an anigiotensin receptor blocker, angiotensin converting enzyme inhibitor, a calcium channel blocker, an endothelin antagonist, a renin

inhibitor, a diuretic, an ApoA-I mimic, an anti-diabetic agent, an obesity-reducing agent, an aldosterone receptor blocker, an endothelin receptor blocker, an aldosterone synthase inhibitors, a CETP inhibitor and a phosphodiesterase of type 5 (PDE5) inhibitor.

15. A method of inhibiting neutral endopeptidase EC. 3.4. 24.11. activity in a subject in need thereof, comprising: administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof.

16. The method according to claim 15, wherein the disorder or the disease is selected from hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency, renal failure, diabetic nephropathy, non-diabetic nephropathy, nephroic syndrome, glomerulonephritis, scleroderma, glomerular sclerosis, proteinurea of primary renal disease, renal vascular hypertention, diabetic retinopathy and end-stage renal disease (ESRD), endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation (AF), cardiac fibrosis,atrial flutter, detrimental vascular remodeling, plaque stabilization, myocardial infarction (MI), renal fibrosis, polycystic kidney disease (PKD), pulmonary arterial hypertension, renal failure, cyclical oedema, Menières disease, hyperaldosteroneism hypercalciuria, ascites, glaucoma, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders, asthma, obstructive sleep apnea, inflammation, leukemia, pain, epilepsy, affective disorders, depression, psychotic condition, dementia, geriatric confusion, obesity and gastrointestinal disorders, wound healing, septic shock, gastric acid secretion dysfunction, hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, metabolic syndrome, diabetic complications, atherosclerosis, male and female sexual dysfunction.

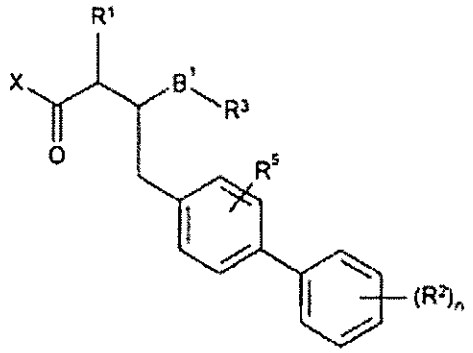
17. The compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.

18. Use of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for the treatment of a disorder or disease associated with neutral endopeptidase EC. 3.4. 24.11. activity in a subject in need of such treatment.

19. The use of claim 18, wherein the disorder or disease is selected from hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency, renal failure, diabetic nephropathy, non-diabetic nephropathy, nephroic syndrome, glomerulonephritis, scleroderma, glomerular sclerosis, proteinurea of primary renal disease, renal vascular hypertention, diabetic retinopathy and end-stage renal disease (ESRD), endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation (AF), cardiac fibrosis, atrial flutter, detrimental vascular remodeling, plaque stabilization, myocardial infarction (MI), renal fibrosis, polycystic kidney disease (PKD), pulmonary arterial hypertension, renal failure, cyclical oedema, Menières disease, hyperaldosteroneism hypercalciuria, ascites, glaucoma, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders, asthma, obstructive sleep apnea, inflammation, leukemia, pain, epilepsy, affective disorders, depression, psychotic condition, dementia, geriatric confusion, obesity and gastrointestinal disorders, wound healing, septic shock, gastric acid secretion dysfunction, hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, metabolic syndrome, diabetic complications, atherosclerosis, male and female sexual dysfunction.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of Formula I':



Formula 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^aR^b;
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^aR^b, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b 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^aR^b, -$C(O)C_{1-7}$alkyl, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, 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}alkyl, 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}alkyl; and
X and **X^1** are independently OH, -O-C_{1-7}alkyl, -NR^aR^b, -$NHS(O)_2$-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^c; 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^c 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, $-NR^aR^b$, $-OCH_2CO_2H$, 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^1may be in either direction; and

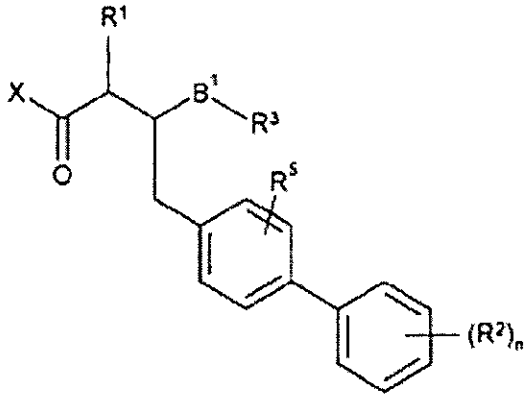
A^2 is a bond or a linear or branched C_{1-7}alkylene; which is optionally substituted with one or more substituents independently selected from the group consisting of halo, C_{1-7}alkoxy, hydroxy, O-Acetate and C_{3-7}cycloalkyl;

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.

2. A compound according to claim 1 of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

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

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, $-NR^aR^b$, C_{6-10}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b 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, amino, C(O)-O-C_{1-7}alkyl, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, 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}alkyl, 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}alkyl; and

X and X^1 are independently OH, -O-C_{1-7}alkyl, NR^aR^b, 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 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, $-NR^aR^b$, $-OCH_2CO_2H$, 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.

3. The compound according to claim 1 or 2 wherein:
R^1 is H or C_{1-7}alkyl;
R^2 for each occurrence, is independently C_{1-7}alkyl, halo, C_{3-7}cycloalkyl, hydroxy, C_{1-7}alkoxy, haloC_{1-7}alkyl, $-NR^aR^b$, C_{6-20}aryl, heteroaryl or heterocyclyl; wherein R^a and R^b 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_{6-20}aryl or a heteroaryl, each of which can be monocyclic or bicyclic and each of which can be optionally substituted with one or more substituents independently selected from the group consisting of hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, C_{6-10}aryl, heteroaryl, $-NHSO_2$-C_{1-7}alkyl and benzyl;
R^5 is H; and
X and X^1 are independently OH, -O-C_{1-7}alkyl or NR^aR^b;
B^1 is –C(O)NH- or –NHC(O)-;
A^1 is 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

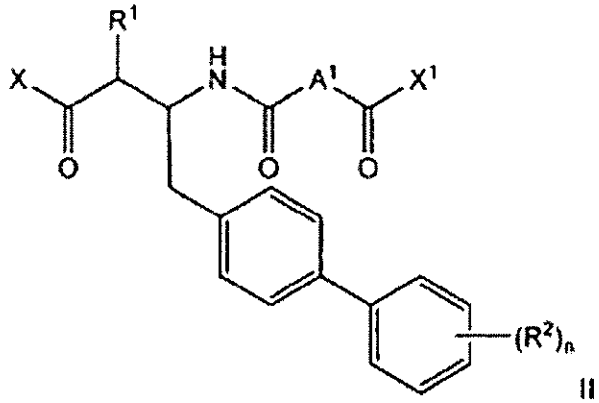
A^1 is a phenyl or a heteroaryl; each of which is optionally substituted with one or more substituents independently selected from the group consisting of C_{1-7}alkyl, C_{3-7}cycloalkyl, halo-C_{1-7}alkyl, hydroxy, C_{1-7}alkoxy, halo, $-NR^aR^b$, $-OCH_2CO_2H$, and $-OCH_2C(O)NH_2$; and A^2 is a bond 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; and

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

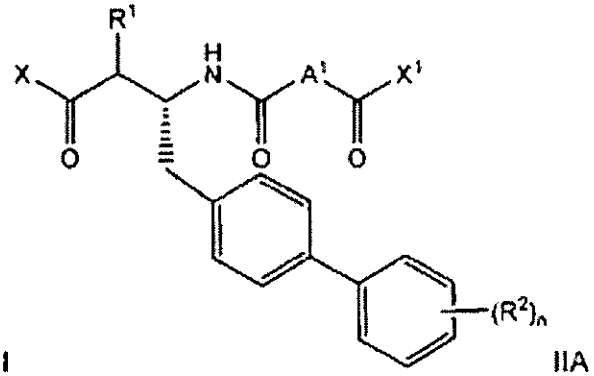
wherein each heteroaryl is a monocyclic or bicyclic aromatic ring comprising 5-10 ring atoms selected from carbon atoms and 1 to 5 heteroatoms, and

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, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1, 2 or 3 having Formula II or IIA:



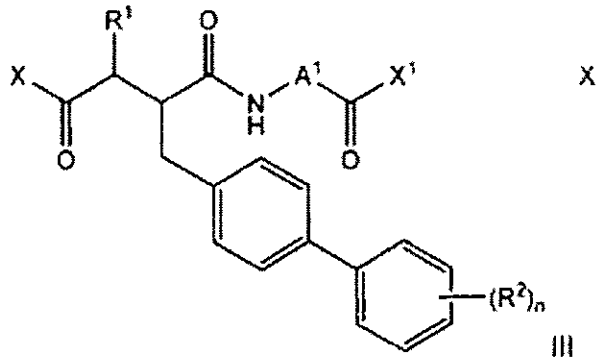
II



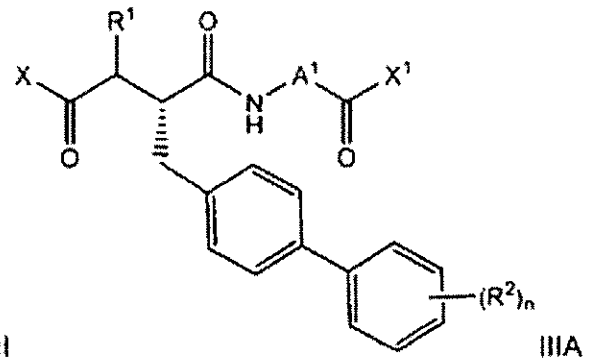
IIA

or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1 to 3 having Formula III or IIIA:



III



IIIA

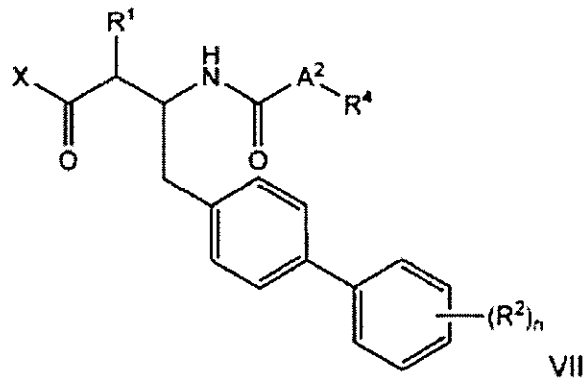
or a pharmaceutically acceptable salt thereof.

6. The compound according to any one of claims 1 to 5 wherein A^1 is an optionally substituted linear or branched C_{1-7}alkylene, or a pharmaceutically acceptable salt thereof.

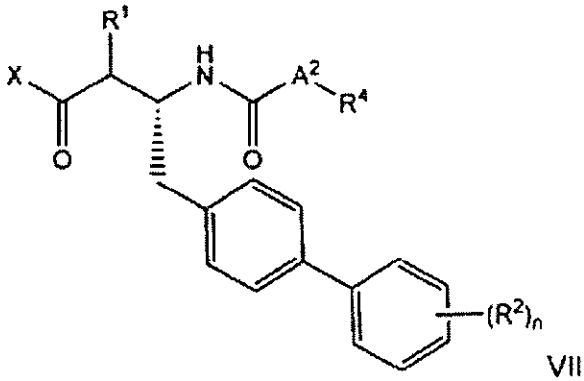
7. The compound according to any one of claims 1 to 6 wherein A^1 is CH_2CH_2, or a pharmaceutically acceptable salt thereof.

8. The compound according to any one of claims 1 to 5 wherein A^1 is an optionally substituted phenyl or heteroaryl, or a pharmaceutically acceptable salt thereof.

9. The compound according to any one of claims 1 to 3 having Formula VII or VIIA:



VII



VII

A

or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 9 wherein A^2 is a bond or CH_2 or CH_2-CH_2, or a pharmaceutically acceptable salt thereof.

11. The compound according to any one of claims 1 to 10 wherein R^1 is H, R^2 is independently halo, C_{1-7}alkoxy, hydroxy, C_{1-7}alkyl or halo-C_{1-7}alkyl, n is 0, 1 or 2 and X and X^1 are independently OH or -O-C_{1-7}alkyl, or a pharmaceutically acceptable salt thereof.

12. The compound according to any one of claims 1 to 11 wherein n is 1 or 2; R^2 is meta-chloro or meta-fluoro and the other optional R^2 group is halo, C_{1-7}alkyl, halo-C_{1-7}alkyl, hydroxy and C_{1-7}alkoxy, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.

14. A combination comprising: a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, and one or more therapeutically active agents selected from HMG-Co-A reductase inhibitor, an angiotensin receptor blocker, angiotensin converting enzyme Inhibitor, a calcium channel blocker, an endothelin antagonist, a renin inhibitor, a diuretic, an ApoA-I mimic, an anti-diabetic agent, an obesity-reducing agent, an aldosterone receptor blocker, an endothelin receptor blocker, an aldosterone synthase inhibitors, a CETP inhibitor and a phosphodiesterase of type 5 (PDE5) inhibitor.

15. The compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.

16. Use of the compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, for the treatment of a disorder or disease associated with neutral endopeptidase EC. 3.4. 24.11. activity in a subject in need of such treatment.

17. The use according to claim 16, wherein the disorder or disease is selected from hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, heart failure, congestive heart failure, left ventricular hypertrophy, angina, renal insufficiency, renal failure, diabetic nephropathy, non-diabetic nephropathy, nephrotic syndrome, glomerulonephritis, scleroderma, glomerular sclerosis, proteinurea of primary renal disease, renal vascular hypertension, diabetic retinopathy and end-stage renal disease (ESRD), endothelial dysfunction, diastolic dysfunction, hypertrophic cardiomyopathy, diabetic cardiac myopathy, supraventricular and ventricular arrhythmias, atrial fibrillation (AF), cardiac fibrosis, atrial flutter, detrimental vascular remodeling, plaque stabilization, myocardial infarction (MI), renal fibrosis, polycystic kidney disease (PKD), pulmonary arterial hypertension, renal failure, cyclical oedema, Menières disease, hyperaldosteroneism hypercalciuria, ascites, glaucoma, menstrual disorders, preterm labour, pre-eclampsia, endometriosis, and reproductive disorders, asthma, obstructive sleep apnea, inflammation, leukemia, pain,

epilepsy, affective disorders, depression, psychotic condition, dementia, geriatric confusion, obesity and gastrointestinal disorders, wound healing, septic shock, gastric acid secretion dysfunction, hyperreninaemia, cystic fibrosis, restenosis, type-2 diabetes, metabolic syndrome, diabetic complications, atherosclerosis, male and female sexual dysfunction.