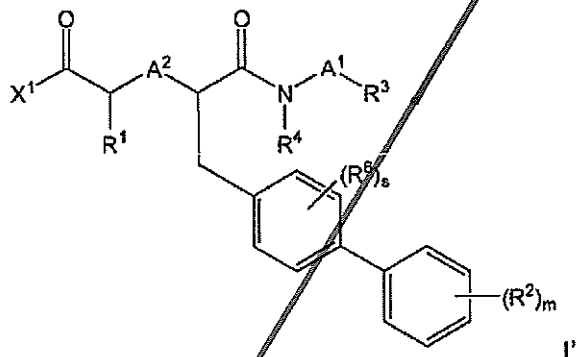
CLAIMS

What is claimed is:

1. The invention therefore provides a compound of the formula (I'):



I'

wherein:

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

R^1 is H, C_{1-6} alkyl or C_{6-10}-aryl-C_{1-6}alkyl, wherein alkyl is optionally substituted with 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^2 is O or NR^5;

R^4 and R^5 are independently H or C_{1-6} alkyl;

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

R^3 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;

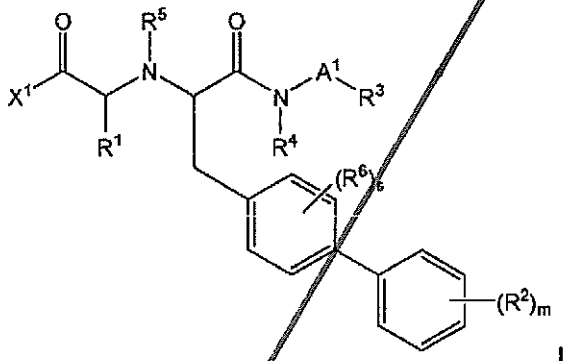
R^6 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; or

R^4, A^1-R^3, together with the nitrogen to which R^4 and A^1-R^3 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

m 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.

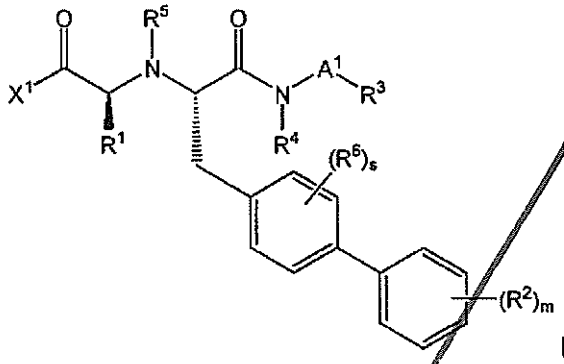
2. The compound according to claim 1 of Formula I:



I

wherein:
X^1 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^4 and R^5 are independently H or C_{1-6} alkyl;
A^1 is a bond or C_{1-3}alkylene chain;
R^3 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^6 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl; or
R^4, A^1-R^3, together with the nitrogen to which R^4 and A^1-R^3 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
m 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.

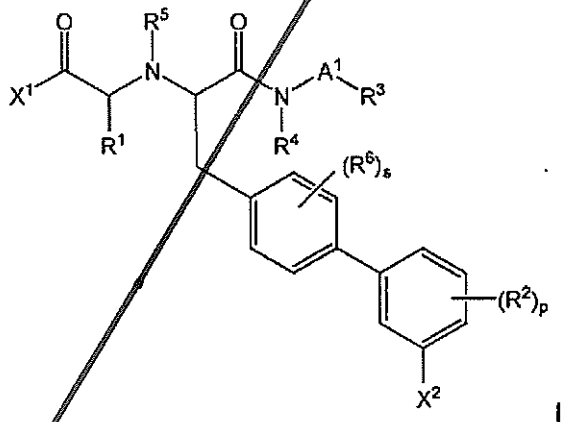
3. The compound according to claim 1 or 2 of Formula II:



II

or a pharmaceutically acceptable salt thereof.

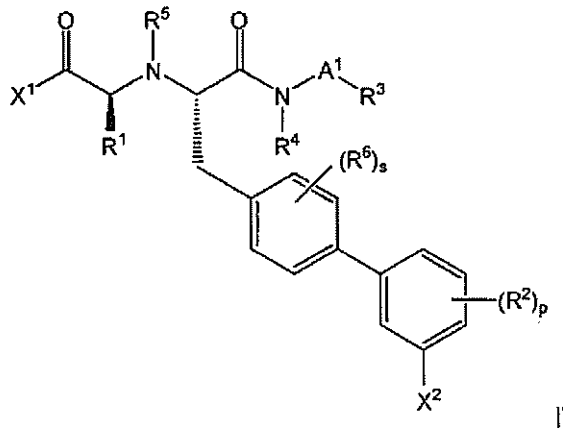
4. The compound according to claim 1 or 2 of Formula III:



III

Wherein X^2 is halo and p is 0 or an integer from 1 to 4, or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 4 of formula IV:



IV

or a pharmaceutically acceptable salt thereof.

6. The compound of any of the preceding claims wherein
X^1 represent OH or O-C_{1-6}-alkyl;
R^1 is H or C_{1-6} alkyl;
R^2 for each occurrence is independently C_{1-6}-alkoxy, hydroxy, halo, C_{1-6}-alkyl, cyano or trifluoromethyl;
R^4 and R^5 are independently H or C_{1-6} alkyl;
A^1 is a bond or C_{1-3}alkylene chain;
R^3 is a 5- or 6-membered heteroaryl optionally substituted with one or more substituents 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^6 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}akyl;
m is 0 or an integer of 1 to 5;
s is 0 or an integer of 1 to 4; or
a pharmaceutically acceptable salt thereof.

7. The compound of any of the preceding claims wherein
A^1 is a bond or CH_2; or a pharmaceutically acceptable salt thereof.

8. The compound of any of the preceding claims wherein
R^1 is methyl or ethyl, R^5 and R^4 are H; or a pharmaceutically acceptable salt thereof.

9. The compound of any of the preceding claims wherein
R^3 is a 5-membered ring heteroaryl selected from the group consisting of oxazole, pyrrole, pyrazole, isooxazole, triazole, tetrazole, oxadiazole, thiazole, isothiazole, thiophene, imidazole and thiadiazole; each of which is optionally substituted with one or more substituents 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;
or a pharmaceutically acceptable salt thereof.

10. The compounds of any of the preceding claims wherein
R^3 is tetrazole; or a pharmaceutically acceptable salt thereof.

11. The compounds of any of claims 4 to 10 wherein X^2 is Cl, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

13. A combination comprising: a compound according to any one of claims 1 to 11 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 phophodiesterase type 5 (PDE5) inhibitor.

14. 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 11 or a pharmaceutically acceptable salt thereof.

15. A method of treating a disorder or a disease associated with 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 11 or a pharmaceutically acceptable salt thereof.

16. The method according to claim 15, wherein the disorder or the disease is selected from hypertension, resistant hypertension, pulmonary hypertension, pulmonary arterial hypertension, isolated systolic 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), 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, 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 11, or a pharmaceutically acceptable salt thereof, for use as a medicament.

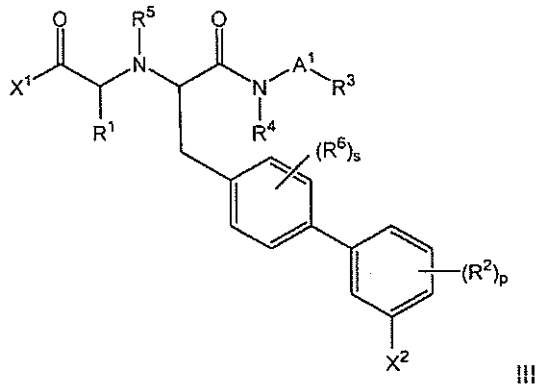
18. Use of the compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for the treatment of a disorder or disease associated with neutral endopeptidase EC. 3.4. 24.11 activity in a subject in need of such treatment.

19. The use of claim 18, wherein the disorder or disease is selected from hypertension, resistant hypertension, pulmonary hypertension, pulmonary arterial hypertension, isolated systolic 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), 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, 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.

Claims

1. A compound of the formula (III):



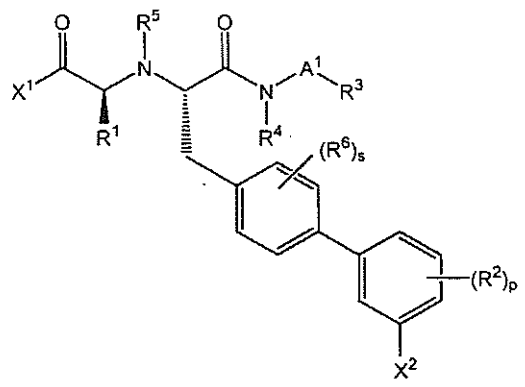
III

I'

wherein:

X^1 is OH, -O-C_{1-7}alkyl, -NR^aR^b, -$NHS(O)_2$-C_{1-7}alkyl or -$NHS(O)_2$-benzyl, wherein R^a and R^b for each occurrence are independently H or C_{1-7}alkyl;
R^1 is C_{1-6} alkyl or C_{6-10}-aryl-C_{1-6} alkyl, wherein alkyl is optionally substituted with 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;
R^4 and R^5 are independently H or C_{1-6} alkyl;
A^1 is a bond or C_{1-3}alkylene chain;
R^3 is a 5- or 6-membered heteroaryl, C_{6-10}-aryl or C_{3-7}-cydoalkyl, 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^6 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{1-7}alkyl; or
R^4, A^1-R^3, together with the nitrogen to which R^4 and A^1-R^3 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
m is 0 or an integer from 1 to 5;
s is 0 or an integer from 1 to 4;
X^2 is halo; and
p is 0 or an integer from 1 to 4; or
a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 of formula IV:



IV

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or claim 2 wherein
X^1 represent OH or O-C_{1-6}-alkyl;
R^1 is C_{1-6} alkyl;
R^2 for each occurrence is independently C_{1-6}-alkoxy, hydroxy, halo, C_{1-6}-alkyl, cyano or trifluoromethyl;
R^4 and R^5 are independently H or C_{1-6} alkyl;
A^1 is a bond or C_{1-3}alkylene chain;
R^3 is a 5- or 6-membered heteroaryl optionally substituted with one or more substituents 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^6 for each occurrence is independently halo, hydroxy, C_{1-7}alkoxy, halo, C_{1-7}alkyl or halo-C_{17}alkyl;
m is 0 or an integer of 1 to 5;
s is 0 or an integer of 1 to 4;
X^2 is halo; and
p is 0 or an integer from 1 to 4; or
a pharmaceutically acceptable salt thereof.

4. The compound of any of the preceding claims wherein
A^1 is a bond or CH_2; or a pharmaceutically acceptable salt thereof.

5. The compound of any of the preceding claims wherein
R^1 is methyl or ethyl, R^5 and R^4 are H; or a pharmaceutically acceptable salt thereof.

6. The compound of any of the preceding claims wherein
R^3 is a 5-membered ring heteroaryl selected from the group consisting of oxazole, pyrrole, pyrazole, isooxazole, triazole, tetrazole, oxadiazole, thiazole, isothiazole, thiophene, imidazole and thiadiazole; each of which is optionally substituted with one or more substituents 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;
or a pharmaceutically acceptable salt thereof.

7. The compounds of any of the preceding claims wherein
R^3 is tetrazole; or a pharmaceutically acceptable salt thereof.

8. The compounds of any of the preceding claims wherein
X^2 is Cl, or a pharmaceutically acceptable salt thereof.

9. The compound according to any of the preceding claims 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)-ethoxy]-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-(3-hydroxy-isoxazol-5-ylcarbamoyl)-ethylamino]-propionic acid;

(S)-2-[(S)-2-(3'-Chloro-biphenyl-4-yl)-1-(1-methyl-1H-tetrazol-5-ylcarbamoyl)-ethylamino]-propionic acid; and
(S)-2-[(S)-2-(3'-chloro-biphenyl-4-yl)-1-(1H-tetrazol-5-ylcarbamoyl)-ethylamino]-3-methoxy-propionic acid;
or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound according to any of the preceding claims or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

11. A combination comprising: a compound according to any one of claims 1 to 9 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 phophodiesterase type 5 (PDE5) inhibitor.

12. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use as a medicament.

13. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in 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.

14. The compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease is selected from hypertension, resistant hypertension, pulmonary hypertension, pulmonary arterial hypertension, isolated systolic 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), 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, 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.