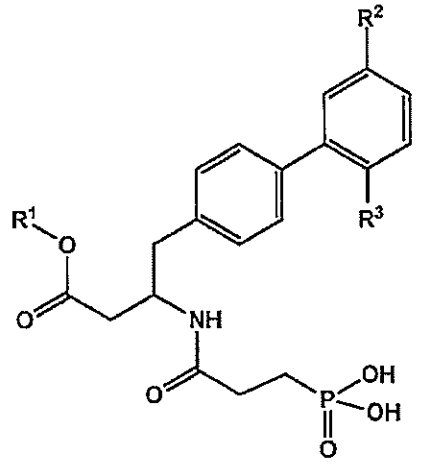
NEW CLAIMS 1 to 19

What is claimed is:

1. A compound of the formula (I):



I

wherein:

$R^1$ is H; -$C_{1-7}$alkyl or $C_{6-10}$aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of -O-C(O)-O-$C_{3-7}$cycloalkyl, -O-C(O)-$C_{3-7}$cycloalkyl, -O-C(O)-$C_{6-10}$aryl, -O-C(O)-O-$C_{6-10}$aryl, -O-C(O)-O-$C_{1-7}$alkyl, -O-C(O)-$C_{1-7}$alkyl, heteroaryl, heterocyclyl, -C(O)-heterocyclyl, -C(O)$NH_2$, -C(O)NH-$C_{1-7}$alkyl, and -C(O)N($C_{1-7}$alkyl)$_2$;

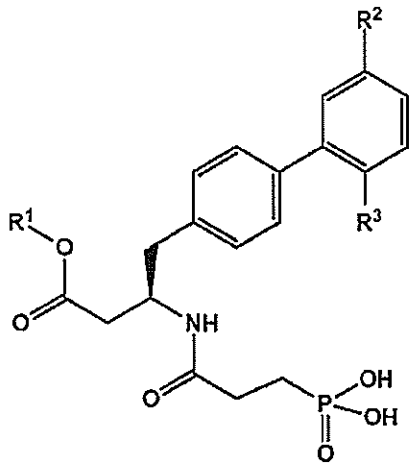
wherein $C_{3-7}$cycloalkyl is a saturated or unsaturated, but non-aromatic, monocyclic, bicyclic or tricyclic $C_{3-7}$ hydrocarbon group,

$R^2$ is Cl, $CH_3$ or F;

$R^3$ is H, F, Cl, $CH_3$ or $OCH_3$, or

a pharmaceutically acceptable salt thereof.

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



II

wherein:

$R^1$ is H; -$C_{1-7}$alkyl or $C_{6-10}$aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of -O-C(O)-O-$C_{3-7}$cycloalkyl, -O-C(O)-$C_{3-7}$cycloalkyl, -O-C(O)-$C_{6-10}$aryl, -O-C(O)-O-$C_{6-10}$aryl, -O-C(O)-O-$C_{1-7}$alkyl, -O-C(O)-$C_{1-7}$alkyl, heteroaryl, heterocyclyl, -C(O)-heterocyclyl, -C(O)$NH_2$, -C(O)NH-$C_{1-7}$alkyl, and -C(O)N($C_{1-7}$alkyl)$_2$;

wherein $C_{3-7}$cycloalkyl is a saturated or unsaturated, but non-aromatic, monocyclic, bicyclic or tricyclic $C_{3-7}$ hydrocarbon group,

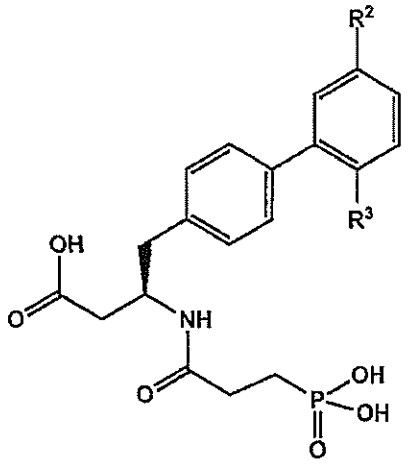
$R^2$ is Cl, $CH_3$ or F;

$R^3$ is H, F, Cl, $CH_3$ or $OCH_3$, or

a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein $R^2$ is Cl and $R^3$ is F; or a pharmaceutically acceptable salt thereof.

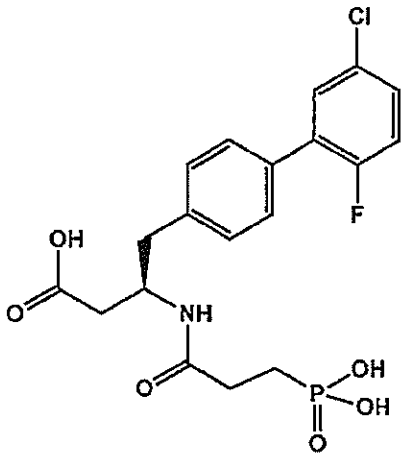
4. The compound according to claim 1, 2 or 3 having Formula III:



III;

or a pharmaceutically acceptable salt thereof.

5. The compound according to any one of claims 1 to 4 having Formula IV:



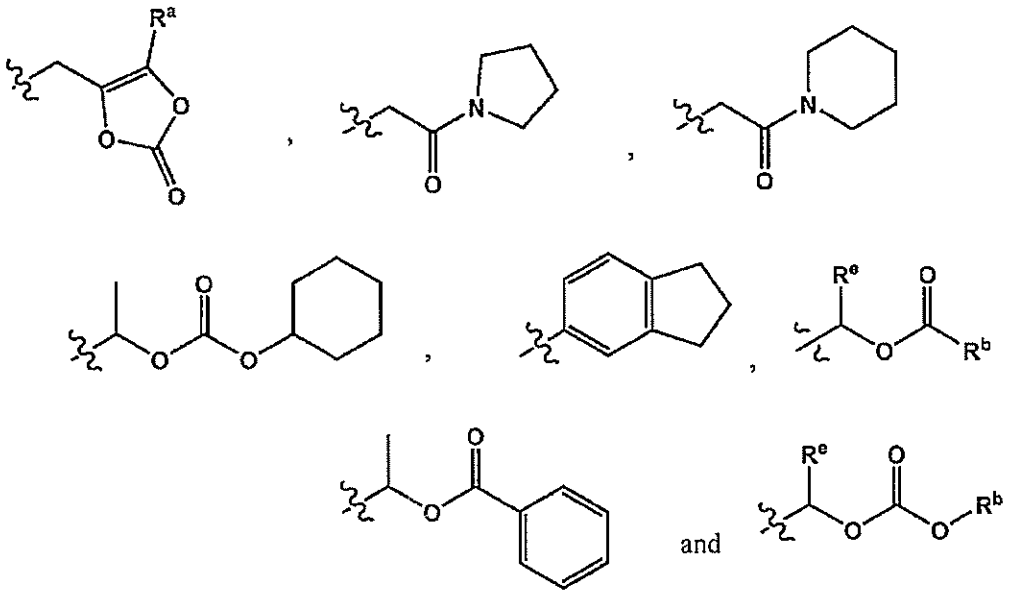
IV;

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, 2 or 3 wherein $R^1$ is -$C_{1-7}$alkyl or $C_{6-10}$aryl; wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of -O-C(O)-O-$C_{3-7}$cycloalkyl, -O-C(O)-$C_{3-7}$cycloalkyl, -O-C(O)-$C_{6-10}$aryl, -O-C(O)-O-$C_{6-10}$aryl, -O-C(O)-O-$C_{1-7}$alkyl, -O-C(O)-$C_{1-7}$alkyl, heteroaryl, heterocyclyl, -C(O)-heterocyclyl, -C(O)$NH_2$, -C(O)NH-$C_{1-7}$alkyl, and -C(O)N($C_{1-7}$alkyl)$_2$;

wherein $C_{3-7}$cycloalkyl is a saturated or unsaturated, but non-aromatic, monocyclic, bicyclic or tricyclic $C_{3-7}$ hydrocarbon group,
or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 1, 2 or 3 wherein $R^1$ is -$C_{1-4}$alkyl or $R^1$ is selected from the following groups:

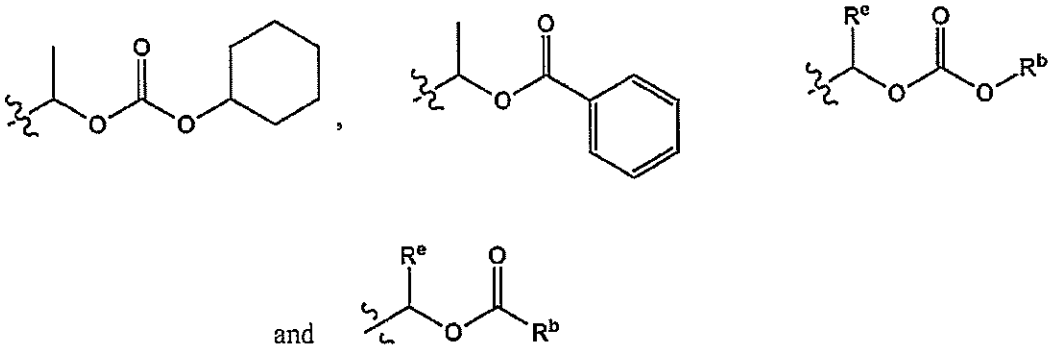



and

wherein $R^a$, $R^c$, $R^d$ and $R^e$ are independently selected from H and $C_{1-4}$alkyl and $R^b$ is $C_{1-4}$alkyl;
or a pharmaceutically acceptable salt thereof.

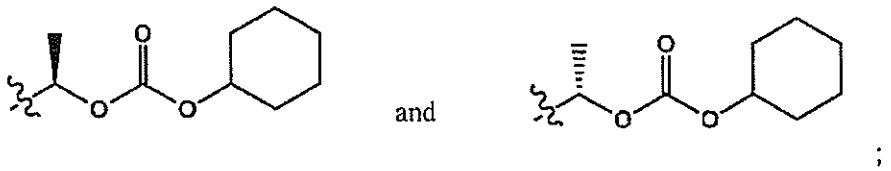
8. The compound according to claim 1, 2 or 3 wherein $R^1$ is -$C_{1-4}$alkyl wherein alkyl is optionally substituted with one or more substituents independently selected from the group consisting of -$C(O)NH_2$, -C(O)NH-$C_{1-7}$alkyl, and -C(O)N($C_{1-7}$alkyl)$_2$;
or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1, 2 or 3 wherein $R^1$ is Me, Et or is selected from a group of the following Formulae:



wherein $R^e$ is H or $C_{1-4}$alkyl, and $R^b$ is $C_{1-4}$alkyl; or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 1, 2 or 3 wherein $R^1$ is Me, Et or is selected from a group of the following Formulae:



or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 1 which is (R)-4-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-3-(3-phosphonopropanamido)butanoic acid or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 1 which is (3-(((2R)-1-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-(1-(((cyclohexyloxy)carbonyl)oxy)ethoxy)-4-oxobutan-2-yl)amino)-3-oxopropyl)phosphonic acid or a pharmaceutically acceptable salt thereof.

13. The compound according to claim 1 which is (3-(((R)-1-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-((S)-1-(((cyclohexyloxy)carbonyl)oxy)ethoxy)-4-oxobutan-2-yl)amino)-3-oxopropyl)phosphonic acid or a pharmaceutically acceptable salt thereof.

14. The crystalline free acid form A of the compound according to claim 1 which is (3-(((R)-1-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-((S)-1-(((cyclohexyloxy)carbonyl)oxy)ethoxy)-4-oxobutan-2-yl)amino)-3-oxopropyl)phosphonic acid characterized by a x-ray powder diffraction pattern comprising four or more 2θ values (CuKα λ=1.5418 Å) selected from the group consisting of 16.5±0.2°, 17.5±0.2°, 17.8±0.2°, 18.7±0.2°, 20.2±0.2°, 20.7±0.2°, 21.7±0.2°, 21.9±0.2°, 24.1±0.2°, 24.6±0.2°, 25.0±0.2°, 25.5±0.2° and 27.4±0.2° measured at a temperature of about 22°C and an x-ray wavelength, λ, of 1.5418 Å.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

16. A combination comprising: a compound according to any one of claims 1 to 14 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 inhibitor, a CETP inhibitor and a phophodiesterase type 5 (PDE5) inhibitor.

17. The compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, for use as a medicament.

18. A compound according to any one of claims 1 to 14, or a pharmaceutically acceptable salt thereof, for use in the treatment of a disorder or disease associated with neutral endopeptidase activity and selected from the group consisting of 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, contrast-induced 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 cardiomyopathy, 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, Menière's disease, hyperaldosteronism, 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, and male and female sexual dysfunction,
in a subject in need of such treatment.

19. The compound according to any one of claims 1 to 14 for use according to claim 18 wherein the disorder or disease is selected from hypertension, pulmonary hypertension, isolated systolic hypertension, resistant hypertension, peripheral vascular disease, congestive heart failure or pulmonary arterial hypertension.