Title: PROLINE DERIVATIVES FOR USE IN THE TREATMENT OF DIABETES

Abstract: The present invention provides novel heterocyclic compounds and methods of preparing such compounds. The compounds of the invention are useful for palliative, curative or prophylactic treatment of diseases or conditions of diabetes and/or hypertension. This invention also relates to pharmaceutical compositions containing the compounds of the present invention, and methods for palliative, curative or prophylactic treatment of diseases or conditions of diabetes and/or hypertension. The present invention also provides pharmaceutical compositions consisting of the heterocyclic compounds along with one or more dyslipidemic agents, antiobesity agents, anti-hyperglycemic agents, antihypertensive agents and anti-inflammatory agents.
Field of the Invention

The present invention provides novel heterocyclic compounds and methods of preparing such compounds. The compounds of the invention are useful for palliative, curative or prophylactic treatment of diseases or conditions of diabetes and/or hypertension. This invention also relates to pharmaceutical compositions containing the compounds of the present invention, and methods for palliative, curative or prophylactic treatment of diseases or conditions of diabetes and/or hypertension. The present invention also provides pharmaceutical compositions consisting of the heterocyclic compounds along with one or more dyslipidemic agents, antiobesity agents, anti-hyperglycemic agents, antihypertensive agents and anti-inflammatory agents.

Background of the Invention

Metabolic syndrome, also called insulin resistance syndrome or syndrome X, is a cluster of risk factors that is responsible for much of the excess cardiovascular disease morbidity, among overweight and obese patients and those persons with type 2 diabetes mellitus. The major characteristics of metabolic syndrome include insulin resistance, abdominal obesity, elevated blood pressure, and lipid abnormalities (i.e., elevated levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol). Initially defined by an expert panel of the World Health Organization in 1998, the NCEP-ATP III has created an operational definition of metabolic syndrome: the co-occurrence of any three of the abnormalities mentioned above. Currently, no study has been carried out which specifically examines the treatment of metabolic syndrome. Although the etiology of the metabolic syndrome has not been established definitively, one hypothesis presumes that the primary cause is insulin resistance. Presently, effective interventions for metabolic disorders include diet, exercise, and judicious use of pharmacologic agents to address individual risk factors. Hence, agents having potential to intervene with the pharmacological processes contributing to more than one risk factor would be desirable.

Type 2 diabetes mellitus also known as "non-insulin dependent diabetes mellitus" (NIDDM), accounts for 90% of all diabetes. This afflicts an estimated 6% of the adult population in western society and is expected to continue to grow at a rate of 6% per
annum worldwide. Type-2 diabetes is a complex metabolic disorder, characterized by hyperglycemia and hyperinsulinemia. This results from contribution of impaired insulin secretion from β-cells in pancreas and insulin resistance, mainly in muscle and liver. Uncontrolled hyperglycemia can further lead to late stage microvascular and macrovascular complications such as nephropathy, neuropathy, retinopathy and premature atherosclerosis. In fact, 80% of diabetic mortality arises from atherosclerotic cardiovascular disease (ASCVD).

Presently, several pharmacological agents are available as antihyperglycemic agents to mitigate the conditions manifested in NIDDM (Lancet, 2005, 365, 1333-1346). These include insulin secretagogues, which increase insulin secretion from pancreatic cells [e.g., sulphonyl urea’s (glimeperide) and non-sulphonyl ureas (repaglinide)], biguanides, which lower hepatic glucose production (e.g., metformin), and a-glucosidase inhibitors, which delay intestinal absorption of carbohydrates [e.g., acarbose] (Lancet, 2005, 365, 1333-1346). The insulin sensitizers like pioglitazone and rosiglitazone (TZDs), which exhibit their effect by PPARy agonism, control hyperglycemia by improving peripheral insulin sensitivity without increasing circulating insulin levels. However, all these agents are associated with one or more of side effects like hypoglycaemia, gastrointestinal side effects including abdominal discomfort, bloating, flatulence, hepatotoxicity, weight gain, dilutional anemia and peripheral edema (Endocrine Rev., 2000, 21, 585-618).

Recently, inhibition of dipeptidyl peptidase IV (DPP-IV, CD26, EC 3.4.14.5) has turned out to be a promising approach for treatment of type 2 diabetes (Proc. Natl. Acad. ScL, 2003, 100, 6825-6830; Expert Opin. Investig. Drugs, 2004, 13, 1091-1102). While the DPP-rV inhibitor, sitagliptin (Januvia®), was approved worldwide as a first-in-class drug, vildagliptin (Galvus®) was approved for EU market. Several other potential gliptins are under various phases of development. DPP-IV diminishes the physiological level of active incretin (stimulating insulin secretion) hormone, glucagon-like peptide-1 (GLP-1) (tin. ~2 min) by proteolytic deactivation. The inhibition of DPP-IV elevates the level of active GLP-1 by 2-3 folds. GLP-1 targets multiple pathways of glucose regulation. It augments insulin secretion in glucose-dependent manner, thereby avoiding hypoglycemic episodes. Importantly, GLP-1 is shown to increase β-cell mass in animal models, which offers the potential to prevent or reverse the progression of the disease. DPP-IV is a
ubiquitous serine protease, which exists as both the soluble and membrane-bound forms with identical structure and function. It is clinically proven that DPP-IV inhibition leads to increase of GLP-1 to therapeutically beneficial levels and thus enhances the body's own normal glucose homeostatic mechanism. (J. Clin. Invest., 2007, 117, 24-32).

Hypertension (HT) or high blood pressure is a common disorder in which blood pressure is abnormally high with undue stress on heart, blood vessels and other organs such as kidney and brain.

Various pharmacological strategies targeting HT are available: (1) ACE inhibitors (ACEIs; e.g., enalapril, captopril, lisinopril, benazepril, quinapril etc.) block the activation of the RAAS thereby reducing the blood pressure; (2) angiotensin receptor blockers (ARBs; e.g., losartan, irbesartan, valsartan, candesartan, olmesartan, etc.) mediate their actions through receptors on the arteries and appear to have the same beneficial effects of ACEIs but without the associated cough; (3) beta-blockers (e.g., atenolol, propranolol, nandolol, etc.) will cause contraction of the smooth muscle of the peripheral arteries and thereby decrease the blood flow to the tissues throughout the body; (4) Diuretics class of compounds (e.g., hydrochlorothiazide, furosemide, torsemide, etc.) are used to treat hypertension. They mediate their action in the tubules of the kidneys to remove salt from the body; (5) calcium channel blockers (CCBs; e.g., amlodipine, nifedipine, felodipine etc.) inhibit the movement of calcium into the muscle cells thereby lowering the heart's pumping action.

It has been established that RAAS plays a pivotal role in the development of hypertension by regulating pressure/volume homeostasis as well as in the development of hypertension. RAAS is activated by the enzyme renin secreted from juxtaglomerular cells in the kidney. Renin releases a decapeptide angiotensin I (ANG I) from angiotensinogen, the naturally occurring substrate of renin, synthesized in the liver. ANG I is cleaved by angiotensin converting enzyme (ACE) to give the octapeptide, angiotensin II (ANG II). ANG II is the active species of the RAAS system, which mediates various physiological functions, which include vasoconstriction, stimulating aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity, stimulating vasopressin secretion, causing cardiac inotropic effect and modulating other hormone system. In addition, ANG II also increases hepatic glucose
production and decreases insulin sensitivity. Therefore, pharmacological inhibition of RAAS may not only exert antihypertensive effects but also improves insulin resistance and glucose metabolism.

Further, experimental evidence suggests that ACEIs improve insulin sensitivity also. (Hypertension, 2002, 40, 329-334; JRAAS, 2008, 9, 75-88). In addition, ACEIs are thought to be beneficial in improving ventricular remodeling following myocardial infarction, reducing mortality in patients with heart failure and prevent the progression of diabetic nephropathy (Diabetes Care, 2003, 26, 2421-2425). The American Heart Association and American College of Cardiology recommend ACEIs as standard therapy in patients with recent myocardial infarction, systolic heart failure and patients at high risk of cardiovascular events.

U.S. Publication No. 2006/0046978 discloses novel compounds that inhibit dipeptidyl peptidase (DPP rV) and/or neprilysin (NEP) and/or angiotensin converting enzyme (ACE).

Summary of the Invention

The present invention provides novel heterocyclic compounds, which can be useful for palliative, curative or prophylactic treatment of diseases or conditions of diabetes and/or hypertension. Also provided herein, are processes for synthesizing such compounds.

Pharmaceutical compositions containing such compounds are provided together with the pharmaceutically acceptable carriers or diluents, which can be used for palliative, curative or prophylactic treatment of diseases or conditions of diabetes and/or hypertension. These pharmaceutical compositions may be administered or co-administered by a wide variety of routes including, for example, oral or parenteral.

Also provided herein are pharmaceutical compositions comprise one or more compound of Formula I and at least one other active ingredient include, but are not limited to, anti-hypertensive agents, dyslipidemic agents, anti-obesity agents, anti-hyperglycemic agents and anti-inflammatory agents.

The racemates, enantiomers, diastereomers, and pharmaceutically acceptable salts as well as pharmaceutical compositions comprising the compounds, their racemates,
enantiomers, pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

Other objects are set forth in the accompanying description which follows and will be apparent from the description or may be learnt by the practice of the invention.

**Detailed Description of the Invention**

In accordance with one aspect of the invention, are provided compounds having the structure of Formula I

![Formula I](image)

and their pharmaceutically acceptable salts, enantiomers, or diastereomers,

wherein

- \( n \) is an integer 0-2;
- \( R \) is hydrogen or alkyl;
- \( X \) is -CH\(_2\)- or -C(=0)-;
- \( Y \) is -CH- or -N-;
- If \( Y \) is -CH then \( R_1 \) is \(-R_a-R_b\), wherein \( R_a \) is a direct bond, -NH-, -O-, -C=O, alkylene, -CO-alkylene, -NRCO-, -CONH-, -OCO- wherein \( R \) is as defined above and \( R_b \) is

![Substituent](image)

wherein \( G \) can independently be hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carbonyl, thiocarbonyl or oxo; \( f \) can be 0-3; \( R_j \) is alkyl, alkenyl,
alkynyl, hydroxy, alkoxy, amino or NRₐRₐ (wherein Rₐ and Rₐ are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl or heterocyclylalkyl); and Rₐ is alkylene or -NH-alkylene;

If Y is -N then Ri is -Rₐ-Rb, wherein Rₐ is a direct bond, -C=0, alkylene, -CO-alkylene, -CONH- and Rₐ is same as defined above;

R₂ is

\[
\begin{align*}
\text{or } & \frac{\text{o}}{\text{C(O)-ORₐ}}
\end{align*}
\]

wherein R₃ is aralkyl, (CH₂)ₖSRₜ,

\[
\begin{align*}
\text{or } & \frac{\text{O}}{\text{OH-ORₜ}}
\end{align*}
\]

wherein Rₜ is hydrogen, alkyl, -CO-alkyl, -CO-aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, cycloalkyl or cycloalkylalkyl; q is an integer 1-3; Rₗ is hydrogen or alkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, C₆₇ alkylamine, aralkyl, heterocyclylalkyl, cycloalkylalkyl, heteroarylalkyl, alkyl-COOR, (CH₂)ₖSRₜ, alkyl-ORₜ;

wherein Rₗ is hydrogen, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl; Rₚ is direct bond, alkylene; Rₚ can be NHCORₑ (wherein Rₑ is aryl, heteroaryl, heterocyclyl, cycloalkyl); Rₛ and Rᵣ are independently hydrogen, alkyl, aralkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl or can join together along with the carbon and nitrogen to which they are attached to form a ring system; Rₐ and Rᵣ can also join together along with the carbon to which they are attached to form a ring system and p is an integer 0-2;

R₄ and R₅ are independently hydrogen, alkyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, aralkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl, C₆₇ alkylamine, alkyl-COR,
alkyl-OR\textsubscript{f}; wherein R\textsubscript{i} is hydroxy, alkoxy, NHR and R\textsubscript{f} and R\textsubscript{f} are as defined earlier or R\textsubscript{f} and R\textsubscript{f} can join together along with the carbon to which they are attached to form a ring system or R\textsubscript{f} and R\textsubscript{f} can join together along with the carbon and nitrogen to which they are attached to form a ring system:

\[
\text{R}_6 \text{ can be } \text{aralkyl or } (\text{CH}_2)_p \text{SR}, \text{ wherein R}_u, \text{R}_d, q \text{ and } p \text{ are as defined above.}
\]

In another aspect of the invention, are provided compounds having the structure of Formula 1a

![Formula 1a](image)

and their pharmaceutically acceptable salts, enantiomers, or diastereomers

wherein

P\textsubscript{q} is N\textsuperscript{-} protecting group;

R, G, f and R\textsubscript{2} is as defined earlier.

In yet another embodiment, the invention encompasses compounds of Formula 1 that include, for example:

(4S')-4-\{[(3\textsuperscript{R})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-\{[(25)-2-methyl-3-sulfanylpropanoyl]-L-proline ditrifluoroacetate salt (Compound No 1);

Methyl (4S)-L-\{[(25)-3-(acetylsulfanyl)-2-methylpropanoyl]-4-\{[(3\textsuperscript{R})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-prolinate ditrifluoroacetate salt (Compound No 2);

(4S)-L-\{[(25)-3-(acetylsulfanyl)-2-methylpropanoyl]-4-\{[(3\textsuperscript{R})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-proline ditrifluoroacetate salt (Compound No. 3);
(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-\{3-[phenylcarbonyl)sulfanyl]propanoyl\}-L-proline difluoroacetate salt (Compound No. 4);

\[N-(15)-l\text{-carboxy-3-phenylpropyl]-L-alanyl-(45)-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline difluoroacetate salt (Compound No. 5);

\[N-(15)-l\text{-carboxy-3-phenylpropyl]-L-alanyl-(45)-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline dilithium salt (Compound No. 5a),

Methyl \[N-(25)-l\text{-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline difluoroacetate salt (Compound No. 6);

\[N-(25)-l\text{-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-valyl-(4S)-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline difluoroacetate salt (Compound No. 8);

\[N-(15)-l\text{-carboxy-3-phenylpropyl]-L-valyl-(45)-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline dilithium salt (Compound No. 9);

\[N-(2S)-l\text{-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-leucyl-(45\text{'})-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline difluoroacetate salt (Compound No. 10);

\[N-(15)-l\text{-carboxy-3-phenylpropyl]-L-leucyl-(45)-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline dilithium salt (Compound No. 11);

\[N-(15)-l\text{-carboxy-2-methylbutyl]-L-alanyl-(45)-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline difluoroacetate salt (Compound No. 12);

\[N-(15\text{'})-l\text{-carboxy-3-phenylpropyl]-L-isoleucyl-(45\text{'})-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline dilithium salt (Compound No. 13);

\[N-(25)-l\text{-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-phenylalanyl-(4S)-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline difluoroacetate salt (Compound No. 14);

\[N-(15\text{'})-l\text{-carboxy-3-phenylpropyl]-L-phenylalanyl-(45\text{'})-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline dilithium salt (Compound No. 15);

\[N-(2S)-l\text{-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-seryl-(45\text{'})-4-\{[(3 }R\text{-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline difluoroacetate salt (Compound No. 16);
\[
\begin{align*}
N\text{-}[\{(15\text{-}l\text{-carboxy}-3\text{-phenylpropyl}\}-L\text{-seryl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline dilithium salt (Compound No. 17)}; \\
N\text{-}[\{(25\text{\prime})\text{-l-ethoxy-l-oxo-4-phenylbutan-2-yl}\}-L\text{-tyrosyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 18)}; \\
N\text{-}[\{(15\text{-})\text{-l-carboxy}-3\text{-phenylpropyl}\}-L\text{-tyrosyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline dilithium salt (Compound No. 19)}; \\
N\text{-}[\{(15\text{-})\text{-l-carboxy}-3\text{-phenylpropyl}\}]\text{-glycyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 20)}; \\
N\text{-}[\{(25\text{\prime})\text{-l-ethoxy-l-oxo-4-phenylbutan-2-yl}\}-L\text{-alanyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 21)}; \\
N\text{-}[\{(15\text{-})\text{-l-carboxy}-3\text{-phenylpropyl}\}-L\text{-alanyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 22)}; \\
N\text{-}[\{(25\text{\prime})\text{-l-ethoxy-l-oxopentan-2-yl}\}-L\text{-alanyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 23)}; \\
N\text{-}[\{(15\text{-})\text{-l-carboxy}-3\text{-methylbutyl}\}-L\text{-alanyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 24)}; \\
N\text{-}[\{(25\text{\prime})\text{-l-ethoxy-l-oxopropan-2-yl}\}-L\text{-alanyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 25)}; \\
N\text{-}[\{(15\text{\prime})\text{-l-cyclohexyl-2-ethoxy-2-oxoethyl}\}-L\text{-alanyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 26)}; \\
N\text{-}[\{(25\text{\prime})\text{-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl}\}-L\text{-alanyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 27)}; \\
N\text{-}[\{(15\text{-})\text{-l-carboxy}-2\text{-methylpropyl}\}-L\text{-alanyl-(45\text{-})}-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-L-proline ditrifluoroacetate salt (Compound No. 28)}; \\
(45\text{-})-4\text{-}[\{(3 \text{ } R)-3\text{-amino}-4\text{-}(2,4,5\text{-trifluorophenyl})\text{butanoyl}] \text{amino}\} \text{-l-(25\text{-})-2\text{-[25\text{-})-2-(methoxy-carbonyl)pyrrolidin-1-yl]}\text{propanoyl} \text{-L-proline ditrifluoroacetate salt (Compound No. 29)};
\end{align*}
\]
(25,45)-4-{[(3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino} -L-proline ditrifluoroacetate salt (Compound No. 42),
N-[(1S)-1-carboxy-3-(methylsulfanyl)propyl]-L-alanyl-(45')-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline dilithium salt (Compound No. 43),

N-[(1S)-1,3-dicarboxypropyl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline dilithium salt (Compound No. 44),

N-(2-carboxypropan-2-yl)-L-alanyl-(45')-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline dilithium salt (Compound No. 45),

N-[(1S)-1-carboxypentyl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 46),

N-[(1S)-1-carboxypropan-2-yl]-L-alanyl-(45')-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 47),

N-[(1S)-1-carboxybutyl]glycyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 48),

N-[(1S)-1-carboxy-2-hydroxyethyl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 49),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-norvalyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 50),

N-[(1S')-1-carboxy-3-phenylpropyl]-L-norvalyl-(45')-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 51),

N-[(25)-6-amino-1-ethoxy-1-oxohexan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 52),

N-[(1S')-5-amino-1-carboxypentyl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 53),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-norleucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 54),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-norleucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 55),

N-[(1S')-1-carboxy-3-phenylpropyl]-L-norleucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 56),

N-[(1S')-1-carboxy-3-phenylpropyl]-L-norleucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline (Compound No. 57),
$N^2$-[(15)-l-carboxy-3-phenylpropyl]-L-lysyl-(45)-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 58),

$N$-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-2-methylalanyl-(45)-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 59),

(45)-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 60),

1-[(25)-l-ethoxy-1-oxo-4-phenylbutan-2-yl] -D-prolyl-(45)-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 61),

$N$-[(15')-l-carboxy-3-phenylpropyl]-2-methylalanyl-(45')-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 62),

(45)-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 63),

1-[(15)-l-carboxy-3-phenylpropyl]-D-prolyl-(45)-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 64),

3-cyclopropyl-$N$-[(2S)-l-ethoxy-l-oxo-4-phenylbutan-2-yl] -L-alanyl-(45')-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 65),

(25,45)-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 66),

$N$-[(15')-l-carboxy-3-phenylpropyl]-L-a-glutamyl-(45')-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 67),

$N^2$-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-asparaginyl-(45')-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 68),

$N^2$-[(15)-l-carboxy-3-phenylpropyl]-L-asparaginyl-(45')-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 69),

$N$-[(l-carboxy-3-phenylpropyl)]-L-threonyl-(45')-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 70),

$N$-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-0-methyl-L-seryl-(45)-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 71),

$N$-[(15)-l-carboxy-3-phenylpropyl]-0-methyl-L-seryl-(45')-4-[[3 $R$)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino} -L-proline (Compound No. 72),
N-[(25')-3-(benzyloxy)-1-ethoxy-1-oxopropan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 73),

N-[(15')-l-carboxy-3-methylbutyl]norleucyl-4-\{[3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 74),

N-[(25')-3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 75),

N-[(25')-3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl]-L-norvalyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 76),

(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 77),

(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 78),

(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 79),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-norvalyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 80),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-norleucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 81),

N-[(15')-l-carboxy-3-phenylpropyl]-L-norvalyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 82),

N-[(15')-l-carboxy-3-phenylpropyl]-L-norleucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 83),

N-[(15')-l-carboxy-3-phenylpropyl]-L-norvalyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 84),

N-[(15')-l-carboxy-3-phenylpropyl]-L-norleucyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 85),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 86),

N-[(15)-l-carboxy-3-phenylpropyl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 87),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-D-norvalyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 88),
In another aspect, there is provided herein a pharmaceutical composition comprising therapeutically effective amount of compound of Formula I described herein together with one or more pharmaceutically acceptable carrier(s), excipients(s) or diluent(s).

In yet another aspect there is provided a method for palliative, curative or prophylactic treatment of diseases or conditions of diabetes and/or hypertension in a mammal by administering at least one compound having the structure of Formula I.

The methods may include one or more of the following embodiments. For example, there is provided a method for palliative, curative or prophylactic treatment of diseases or conditions of a mammal suffering from diabetes and/or hypertension, wherein the diabetes is treated by Dipeptidyl peptidases-IV (DPP-IV) inhibition and also benefited by ACE inhibition and hypertension is treated by angiotensin converting enzyme (ACE) inhibition. The method includes administration of at least one compound having the structure of Formula I.

In another embodiment the diseases or conditions of diabetes are selected from the type 2 diabetes, prediabetes, dyslipidemia, metabolic syndrome, metabolic acidosis,
ketosis, and satiety disorders, diabetic nephropathy and end organ damage such as kidney
and brain and diseases or conditions of hypertension are selected from hypertension with
or without incipient nephropathy, myocardial infarction, stroke, increased collagen
formation, fibrosis, remodeling following hypertension, congestive heart failure, left
ventricular hypertrophy, survival post myocardial infarction (MI), coronary artery
diseases, atherosclerosis, angina pectoris or thrombosis.

In yet another aspect, there are provided methods for palliative, curative or
prophylactic treatment of diseases or conditions of diabetes and/or hypertension
comprising administering to a mammal in need thereof therapeutically effective amounts
of one or more compounds of Formula I in combination with one or more therapeutic
agents selected from anti-hypertensive agents, dyslipidemic agents, anti-obesity agents,
anti-hyperglycemic agents and anti-inflammatory agents.

In yet another aspect there is provided the use of a pharmaceutical composition of
the combination of the compounds of the said invention with various other therapeutic
agents as described above in the manufacture of a medicament for palliative, curative or
prophylactic treatment of diseases or conditions of diabetes and/or hypertension.

In yet another aspect, there are provided processes for preparing the compounds of
Formula I.

Definitions

The following definitions apply to terms as used herein:

The term "alkyl" unless and otherwise specified, refers to a branched or
unbranched saturated hydrocarbon chain having 1 to 20 carbon atoms. This term is
exemplified by groups such as methyl, ethyl, w-propyl, iso-propyl, w-butyl, iso-butyl, t-
butyl, w-hexyl, w-decyl, w-tetradecyl and the like. It may further be substituted with one or
more of the substituents selected from the group consisting of alkenyl, alkynyl, cycloalkyl,
cycloalkenyl, aryl, heterocyclyl, heteroaryl, -OR, -SR, -C(=0)-R₂, -C(=S)-R₄, -0-C(=0)-
R₂, azido, oxo, cyano, halo, -C(=0)O₃, nitro, -NH-C(=0)-R₃, -NH-C(=0)NR₄R₅, -
NHC(=O)NR₆R₇, -0-C(=0)N₃Jl [wherein R₆ and R₇ are independently selected from
hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl;
and R₆ and R₇ may together form a ring with nitrogen], -NHSOIR₉ and -SOIR₉.
(wherein \( R \) is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl or heteroaryl, heteroarylalkyl, heterocyclylalkyl).

The term "alkenyl", unless and otherwise specified, refers to a branched or unbranched unsaturated hydrocarbon group containing at least one double bond with cis or trans geometry and preferably having 2 to 20 carbon atoms. It may further be substituted with one or more of the substituents selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkyl, oxo, cyano, halo, azido, nitro, \(-\text{NR}^2\text{R}^\pi\), \(-\text{O-C(=0)NR}^2\text{R}^\pi\), \(-\text{C(=0)NR}^2\text{R}^\pi\), \(-\text{O-NHC(=0)R}^2\text{R}^\pi\), \(-\text{C(=0)NR}^2\text{R}^\pi\), \(-\text{NHC(=0)R}^2\text{R}^\pi\) [wherein \( R_\alpha \) and \( R_\pi \) are defined as above; \( R_\alpha \) and \( R_\pi \) may together form a ring], \(-\text{NHSO}_2\text{R}_\psi\) and \(-\text{SO}_2\text{R}_\psi\) (wherein \( R_\psi \) is the same as defined above).

The term "alkynyl", unless and otherwise specified, refers to a branched or unbranched unsaturated hydrocarbon group containing at least one triple bond and preferably having 2 to 20 carbon atoms. It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, oxo, cyano, halo, azido, nitro, \(-\text{NR}^2\text{R}^\pi\), \(-\text{O-C(=0)NR}^2\text{R}^\pi\), \(-\text{C(=0)NR}^2\text{R}^\pi\), \(-\text{O-NHC(=0)R}^2\text{R}^\pi\), \(-\text{C(=0)NR}^2\text{R}^\pi\), \(-\text{NHC(=0)R}^2\text{R}^\pi\) [wherein \( R_\alpha \) and \( R_\pi \) are defined as above; \( R_\alpha \) and \( R_\pi \) may together form a ring], \(-\text{NHSO}_2\text{R}_\psi\) and \(-\text{SO}_2\text{R}_\psi\) (wherein \( R_\psi \) is the same as defined above).

The term "alkylene," as used herein, refers to a diradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms and one or more hydrogen can optionally be substituted with alkyl, hydroxy, halogen or oximes. This term can be exemplified by groups such as methylene, ethylene, propylene isomers (e.g., \(-\text{CH}_2\text{CH}_2\text{CH}_2\), \(-\text{CH}_2\text{CH}_2\text{CH}_2\)), and the like. Alkylene may further be substituted with one or more substituents such as alkyl, alkenyl, alkynyl, acyloxy, cyano, halo, hydroxy, oxo, thio, carboxy, arythio, thiol, alkythio, aryloxy, heteroaryl, aminosulfonyl, \(-\text{OR}^2\text{R}^\pi\), \(-\text{SR}^\pi\), \(-\text{C(=0)R}^\pi\), \(-\text{OC(=0)R}^\pi\), \(-\text{COOR}^2\text{R}^\pi\), \(-\text{NHC(=0)R}^2\text{R}^\pi\), \(-\text{NR}^2\text{R}^\pi\), \(-\text{C(=0)NR}^2\text{R}^\pi\), \(-\text{NHC(=0)NR}^2\text{R}^\pi\), \(-\text{C(=0)NHC(=0)R}^2\text{R}^\pi\), \(-\text{NO}_2\) heteroaryl, \(-\text{C(=0)heterocyclyl}\), \(-\text{O-C(=0)NR}^2\text{R}^\pi\), \(-\text{nitro}\), \(-\text{S(=0)}\text{R}^\pi\) [wherein \( R^\alpha \), \( R^\pi \), \( m \) and \( R^\psi \) are the same as defined earlier].
The term "cycloalkyl" refers to a cyclic alkyl group of 3 to 20 carbon atoms having a monocyclic ring or polycyclic (fused, spiro and bridged rings) ring, which may optionally contain one or more olefinic bonds, unless or otherwise constrained by the definition. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, and polycyclic like, and multiple ring structures such as adamantyl and bicyclo[2.2.1]heptanyl. It may further be substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, oxo, -0\(\phi\), cycloalkyl, cycloalkenyl, -C(=O)-R\(^\wedge\), -C(=S)-R\(^\wedge\), -0\(^\phi\)(=0)\(^\wedge\), azido, cyano, halo, -C(=O)C\(\wedge\)\(\wedge\), aryl, heterocyclyl, heteroaryl, -SR\(_\lambda\), nitro, -NHC(=0)R\(_\lambda\), -NR\(_\lambda R\_\pi\), -C(=0)NR\(_\lambda R\_\pi\), -NHC(=0)NR\(_\lambda\), -0-C(=0)NR\(_\lambda\)R\(_\pi\) [wherein R\(_\lambda\) and R\(_\pi\) are defined as above; R\(_\lambda\) and R\(_\pi\) may together form a ring], -NHSOiR\('i'\), and -SOiR\('i'\) (wherein R\(_{i}\) is the same as defined above);

The term "cycloalkylalkyl" refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are the same as defined earlier.

The term "aryl" refers to a carbcyclic group containing 6 to 20 carbon atoms having a single aromatic ring, or polycyclic (fused) ring wherein at least one of the rings is aromatic, optionally substituted with 1 to 3 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, -0R\(_\psi\), -SR\(_\psi\), -C(=O)-R\(_\psi\), -C(=S)-R\(_\psi\), -0-C(=O)-R\(_\psi\), azido, cyano, halo, -C(=O)OR\(_\psi\) nitro, -NHC(=O)R\(_\psi\), -NR\(_\psi R\_\pi\), -C(=O)NR\(_\psi R\_\pi\), -NHC(=O)NR\(_\psi\), -0-C(=O)NR\(_\psi\)R\(_\pi\) [wherein R\(_\lambda\) and R\(_\psi\) are defined as above; R\(_\lambda\) and R\(_\psi\) may together form a ring], -NHSO\(_2\)R\(_\psi\)'i' and -SOiR\(_\psi\)'i' (wherein R\(_{\psi}\) is defined as above). Representative examples of aryl include, but not limited to, phenyl, naphthyl, anthracenyl, azulenyl, and indany.

The term "ar-alkyl" or "arylalkyl" refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-8 carbon atoms and aryl is as defined below.

The term 'heteroaryi" refers to a 5 to 6 membered monocyclic or a 8 to 16 membered polycyclic aromatic group containing at least one heteroatom, independently selected from the group consisting of N, O and S. It may optionally be substituted with 1 to 8 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl,
cycloalkenyl, aryl, heterocyclyl, heteroaryl, oxo, -ORx, -SR, -C(=0)-Rx, -C(=S)-R%,
-0-C(=0)-R^ azido, cyano, halo, -C(=0)OR^ nitro, -NHC(=0)R^ -NR^,
-C(=0)NR_2R_π, -NHC(=0)NR_2R_π, -0-C(=0)NR_2R_π [wherein R_π and R_π are the same as
defined above; R_π and R_π may together form a ring], -NHSO_iR' or -SO_iR' (wherein R_ψ
is the same as defined above). Examples of heteroaryl groups are pyridinyl, quinolinyl,
oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl,
oxadiazolyl, benzimidazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, thienyl, isoxazolyl,
triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, benzoxazolyl, and the like.

The term "heterocyclyl" refers to a non-aromatic monocyclic or polycyclic
(multiple condensed, spiro or bridged) cycloalkyl group of 5 to 16 atoms in which 1 to 4
carbon atoms in the ring are replaced by a heteroatom selected from the group comprising
of O, S and N, wherein the optionally-fused ring may, in turn, be saturated or unsaturated
and may further contain 1-4 heteroatoms selected from the group comprising of N, O, and
S. It may be optionally substituted with one or more of the substituents selected from
alkyl, alkyndy, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, oxo, -0¼, -SR^,
-C(=0)-R^ -C(=S)-R^ -0-C(=0)-R^ azido, cyano, halo, -C(=0)OR^ nitro, -NHC(=0)R^,
-NR^, -C(=O)NR_2R_π, -NHC(=0)NR_2R_π, -0-C(=0)NR_2R_π [wherein R_π and R_π are
defined as above], -NHSO_2R_ψ, and -SO_iR_ψ (wherein R_ψ is defined as above). Also unless
otherwise constrained by the definition, the said heterocyclyl ring may optionally
contain one or more olefinic bonds. Examples of heterocyclyl groups are oxazolidinyl,
tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydroisoxazolyl,
dihydrobenzofuranyl, azabicyclohexyl, dihydroindolyl, piperidinyl or piperazinyl,
tetrahydroquinolinyl, pyrrolidinyl, morpholinyl, piperizinyl, azepinyl, azetidinyl,
azeridinyl, tetrahydropyridinyl, benzthiazinyl, benzoaxazinyl, isoindolinyl, phenoxazine
and the like.

The term "heteroaryalkyl" refers to alkyl-heteroaryl group linked through alkyl portion,
wherein the alkyl and heteroaryl are as defined earlier.

The term "heterocyclylalkyl" refers to alkyl-heterocyclyl group linked through
alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

The term "carboxy" refers to -C(=0)OR.
The term "amino" refers to \(-\text{N}(\text{R}_1)_2\), (wherein \(\text{R}_1\) is the same as defined earlier).

The term 'alkylamine" refers to alkyl-amino group linked through alkyl portion, wherein the alkyl and amino are as defined earlier.

The terms "acyl" and "carbonyl" refer to \(-\text{C} (=\text{O})\text{R}^+\) (wherein \(\text{R}^+\) is the same as defined earlier).

The term "halo" or "halogen" refers to -F, -Cl, -Br, and -I.

The term "thiocarbonyl" refers to \(-\text{C} (=\text{S})\).

The term "leaving group" generally refers to groups that exhibit the desirable properties of being labile under the defined synthetic conditions. The examples of such leaving groups include, but are not limited to, halide (\(\text{F}^-, \text{Cl}^-, \text{Br}^-, \Gamma\)), triflate, tosylate, mesylate radical and the like.

The term "protecting group" is used herein to refer to known moieties which have the desirable property of preventing specific chemical reaction at a site on the molecule undergoing chemical modification intended to be left unaffected by the particular chemical modification. Also the term "protecting group", unless or otherwise specified, may be used with groups such as hydroxy, amino, and carboxy. The examples of such groups are found in T.W. Greene and P.G.M. Wuts, "Protective groups in organic synthesis", 3rd ed., John Wiley and Sons Inc., New York, 1999.

The term "pharmaceutically acceptable salts" refers to the inorganic and organic base or acid addition salts of compounds of present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free form with a suitable organic or inorganic base or acid and isolating the salt thus obtained. Representative salts include, but not limited to, trifluoroacetate, hydrochloride, acetate, fumarate, phosphate, tosylate, hydrobromide, sulfate, bisulfate, nitrate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, citrate, maleate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulfonate and the like. Where the compounds carry acidic moiety, the salts derived from inorganic bases include, but not limited to, lithium, sodium, potassium, calcium, magnesium, zinc, aluminium as well as non-toxic ammonium, quaternary ammonium and amine cations, including, but not limited to
ammonium, tetramethylammonium, tetraethylammonium, methylamine, triethylamine, ethylamine, diethylamine, and the like. The salts derived from organic bases include, but not limited to, salts of natural or synthetic amino acids, betaine, caffeine, 2-diethylaminoethanol, N-ethylmorpholine, glucosamine, dibenzylethylene-diamine, chloroprocaine, choline, diethanolamine, ethylenediamine, piperazine, procaine, purine, tromethamine and the like. The free base form may be regenerated by contacting the salt form with a base. While the free base form may differ from the salt form in terms of physical properties, such as solubility, the salts are equivalent to their respective free bases for the purposes of the present invention.

The term "pharmacetically acceptable carriers" is intended to include non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

The compounds of present invention include stereoisomers.

The term "stereoisomer" refers to compounds, which have identical chemical composition, but differ with regard to arrangement of the atoms and the groups in space. These include enantiomers, diastereomers, geometrical isomers, atropisomers and conformational isomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Racemic mixtures are also encompassed within the scope of this invention.

The enantiomeric compounds of the invention may be obtained by a) the separation of the components of the corresponding racemic mixture, for example, by chiral chromatography, enzymatic resolution methods or preparing and separating suitable diastereoisomers, which can then be converted to required isomer and b) by asymmetric synthesis route either by using chiral starting materials, chiral reagents and catalysts.

"Anti-hypertensive agents" described herein can be selected from, but are not limited to: renin inhibitors, angiotensin receptor blockers, beta blockers, diuretics class of compounds, calcium channel blockers, aldosterone receptor blockers or other antihypertensive agents.

"Dyslipidemic agents" described herein can be selected from, but are not limited to: cholesteroyl ester transfer protein (CETP) inhibitors, fibric acid derivatives/fibrates,
bile acid sequestrants, Acyl CoA-cholesterol acyltransferase inhibitors, HMG CoA reductase inhibitors, cholesterol absorption inhibitors or other dyslipidemic agents.

"Anti-obesity agents" described herein can be selected from, but are not limited to, 5-HT reuptake inhibitors, pancreatic lipase inhibitors, cannabinoid antagonists or recombinant human ciliary neutrotropic factors.

“Anti-hyperglycemic agents” described herein can be selected from, but are not limited to insulin sensitizing agents/PPAR agonists, sulphonyl ureas, hepatic glucose lowering agents like metformin, a glucosidase inhibitors, GLP-1 analogs or receptor agonists, glucagon receptor antagonists, AMPK activators, glucokinase activators, insulin receptor agonists or activators, silence information regulator-1 activators (SIRT-1), stearoyl CoA desaturase inhibitors, fatty acid synthase inhibitors or protein tyrosine phosphatase inhibitors or other anti-hyperglycemic agents.

"Anti-inflammatory agents" described herein can be selected from, but not limited to, β2 agonists, COX-2 inhibitors, 5-lipoxygenase inhibitors, phosphodiesterase IV inhibitors, MMP inhibitors, TNF-oc inhibitors, caspase inhibitors, p38 MAPkinase inhibitors, VLA-4 antagonists, PAF antagonists and other anti-inflammatory agents.

In another aspect, the compounds disclosed herein may be prepared by the following reaction sequences as depicted in Schemes 1-4.
The compound of Formula XI can be prepared following Scheme 1.

Path A: Compound of Formula II can be N-protected to give a compound of Formula III (wherein $R_p$ is carboxy-protecting group, for example, methyl, ethyl i-butyl, benzyl, trimethylsilyl, $R_i$ is a amine-protecting group such as benzyloxy carbonyl, i-Boc and Fmoc).
**Path B:** Compound of Formula IV can be \( N \)-protected to give a compound of Formula V, which is then \( O \)-protected to give a compound of Formula III (wherein \( R_c \) and \( R_{pf} \) are as defined earlier).

Compound of Formula III then undergo \( O \)-activation to give a compound of Formula VI (wherein, \( U \) is an \( O \)-activating group like mesyl, tosyl or triflate), which can undergo azidation to give a compound of Formula VII. The compound of Formula VII can then undergo azide reduction to give a compound of Formula VIII. The compound of Formula VIII can then be coupled with a compound of Formula IX (wherein \( G \) and \( f \) are as defined earlier) to yield the compound of Formula X (wherein \( P_q \) is \( N \)-protecting group).

The compound of Formula X can be \( N \)-deprotected/ hydrogenolyzed to give a compound of Formula XL

\( N \)-protection of compound of Formula II to give a compound of Formula III can be carried out with amine-protecting reagents, for example, benzylchloroformate, Boc anhydride or Fmoc chloride in one or more solvents, for example, dichloromethane, dioxane, water, dichloroethane, chloroform, carbon tetrachloride or tetrahydrofuran in the presence of a base, for example, triethylamine, sodium bicarbonate, \( N,N \)-diisopropylethylamine or potassium carbonate.

\( N \)-protection of compound of Formula IV to give a compound of Formula V can be carried out in the similar way as the conversion of compound of Formula II to compound of Formula III.

Carboxy protection of compound of Formula V to give a compound of Formula III can be carried out with carboxy-protecting reagent, for example, i-butyl bromide in a solvent, for example, \( N,N \)-dimethylacetamide, \( N,N \)-dimethylformamide in presence of a base, for example, potassium carbonate, sodium carbonate, triethylamine, \( N,N \)-diisopropylethylamine or mixtures thereof. The reaction can be carried out in the presence of a phase transfer catalyst, for example, trimethylbenzylammonium chloride, benzethonium chloride, cetrimonium bromide or cetylpyridinium chloride.

\( O \)-activation of compound of Formula III to give a compound of Formula VI can be carried out using suitable sulfonyl chloride, for example, methane sulfonyl chloride, \( p \)-toluene sulfonyl chloride in one or more solvents, for example, dichloromethane,
dichloroethane, chloroform or carbon tetrachloride in presence of one or more base, for example, triethylamine, \(N,N\)-diisopropylethylamine or potassium carbonate.

Azidation of compound of Formula VI to give a compound of Formula VII can be carried out in the presence of sodium azide or lithium azide in one or more solvent, for example, dimethylformamide, 1,4-dioxane, tetrahydrofuran or dimethylsulfoxide.

Reduction of compound of Formula VII to give a compound of Formula VIII can be carried out with a reducing reagent, for example, triphenylphosphine, Fe/AlCl\(_3\), Fe/BiCl\(_3\), sodium amalgam or sodium sulfide hydrate in presence of one or more solvent, for example, tetrahydrofuran, water, ethanol, dioxane, acetonitrile, acetone or dimethylformamide.

Coupling of compound of Formula VIII with a compound of Formula IX to give a compound of Formula X can be carried out using a coupling agent, for example, 1-ethyl-3-(3’-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), 1,3-dicyclohexyl carbodiimide (DCC), \(N\)-((dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridylmethylene)\(N\)-methylmethanaminium hexafluoro-phosphate \(N\)-oxide (HATU) or benzotriazol-1-yl \(N\)-oxytris(pyrrolidino)phosphonium hexafluoro-phosphate (PyBOP) in one or more solvents, for example, dimethylformamide, tetrahydrofuran, dioxane, dichloromethane, acetonitrile or acetone, optionally, with an additive, for example, 1-hydroxybenzotriazole (HOBt), 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine (HODhbt) or 7-aza-l-hydroxybenzotriazole (HOAt) and, optionally, with a base, for example, triethylamine, \(N,N\)-dimethylaminopyridine (DMAP), \(N,N\)-diisopropylethylamine or \(N\)-methylmorpholine. The reaction can also be carried out by any other method well known for amide bond formation.

The hydrogenolysis of compound of Formula X to a compound of Formula XI can be carried out with one or more reducing agent, for example, palladium on carbon or platinum/hydrogen in one or more solvent, for example, methanol, ethanol, 1-propanol, 2-propanol or water.

The compound of Formula XI can react by 3 pathways (Scheme 2, Scheme 3 and Scheme 4).
The compounds of Formula XIV, XI Va and XVI can be prepared following Scheme 2.
Compound of Formula XI can react with a compound of Formula XII to give a compound of Formula XIII (where $R_m$ is sulfur-protecting group selected from the group consisting of acyl, thioacetyl, alkyl, aryl, benzoyl and organothio groups comprising from 1 to about 10 carbon atoms or when taken together with the sulfur atom to be protected, is a hemithioacetal group, for example, tetrahydrofuranyl, 2-methyl tetrahydrofuranyl, tetrahydropyranyl, 2-methyl tetrahydropyranyl, ethoxyethyl, and methoxymethyl groups). The compound of Formula XIII can either be $N$-deprotected directly (Path A) (when $R_{pr}$ is not i-butyl) to give a compound of Formula XIV. Compound of Formula XIII can be hydrolyzed to give a compound of Formula XIVa (Path C) (when $R_{pr}$ is i-butyl and $P_q$ is Boc) or the compound of Formula XIII can be deprotected to give a compound of Formula XV (Path B) (when $R_{pr}$ is not i-butyl), which can then be $N$-deprotected to give a compound of Formula XVI.

The coupling of compound of Formula XI with a compound of Formula XII to give a compound of Formula XIII can be carried out in the similar way as the coupling of compound of Formula VIII to a compound of Formula X.

**Path A:** The $N$-deprotection of compound of Formula XIII to give a compound of XIV can be carried out in one or more solvent, for example, dichloromethane, dichloroethane, chloroform, tetrahydrofuran, water or carbon tetrachloride in the presence of an acid such as trifluoroacetic acid or hydrochloric acid.

**Path B:** The deprotection of compound of Formula XIII to give a compound of Formula XV can be carried out in the presence of base, for example, lithium hydroxide monohydrate, sodium hydroxide or potassium hydroxide in one or more solvent, for example, methanol, tetrahydrofuran, water, acetonitrile, ethanol, propanol or isopropanol.

The $N$-deprotection of compound of Formula XV to give a compound of Formula XVI can be carried out in similar way as the deprotection of compound of Formula XIII to a compound of Formula XIV.

**Path C:** The hydrolysis of compound of Formula XIII to give a compound of Formula XIVa can be carried out in the presence of acid catalysts, for example, trifluoroacetic acid, hydrochloric acid in water, dichloromethane, dichloroethane, chloroform or carbon tetrachloride.
Alternatively, the compound of Formula XI can react via Scheme 3.
Compound of Formula XI can react with a compound of Formula XVII (wherein Rd, Rz, Rs are as defined earlier; Rw is alkyl, arylalkyl, CH2OR, cycloalkylalkyl, heterocyclylalkyl or heteroaryalkyl where Ri is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaryalkyl, heterocyclyl, heterocyclylalkyl, Ci-6 alkylamine, alkyl-COR’ or alkyl-OR’p wherein R’ and Ri are same as defined earlier) to give a compound of Formula XV.

**Path A:** The compound of Formula XVIII (when Rps is not i-butyl) can be hydrolyzed first to give a compound of Formula XIX, which can be then deprotected to give a compound of Formula XX.

**Path B:** The compound of Formula XVIII (when Rps is i-butyl and Pq is Boc) can be deprotected to give a compound of Formula XIXa, which can be hydrolyzed to give a compound of Formula XX.

**Path C:** The compound of Formula XVIII (when Rps is not i-butyl) can be deprotected directly to give a compound of Formula XIXb.

The coupling of compound of Formula XI with a compound of Formula XVII to give a compound of Formula XVIII can be carried out in the similar way as the coupling of compound of Formula VIII to a compound of Formula X.

The hydrolysis of compound of Formula XVIII to give a compound of Formula XIX (Path A) can be carried out in a similar way as the conversion of compound of Formula XIII to a compound of Formula XV.

The deprotection of compound of Formula XIX to a compound of Formula XX can be carried out in a similar manner as the conversion of compound of Formula XIII to a compound of Formula XIV.

The deprotection and hydrolysis of compound of Formula XVIII to give a compound of Formula XIXa (Path B) can be carried out in a similar manner as the conversion of compound of Formula XIII to a compound of Formula XIVa.

The hydrolysis of compound of Formula XIXa to give a compound of Formula XX can be carried out in a similar way as the hydrolysis of compound of Formula XIII to a compound of Formula XV.
The deprotection of compound of Formula XVIII to give a compound of Formula XIXb (Path C) can be carried out in a similar way as the deprotection of a compound of Formula XIII to give a compound of Formula XIV.

Alternatively, the compound of Formula XI can react via Scheme 4.

Scheme 4
Compound of Formula XI (wherein $R_p$ and $P_q$ independently are as defined earlier) can be coupled with a compound of Formula XXI (wherein $R_w$ is as defined earlier) to give a compound of Formula XXII. The compound of Formula XXII can then react with a compound of Formula XXIII (wherein $R_q, R_r$ and $R_s$ are as defined earlier) to give a compound of Formula XXIV.

**Path A:** The compound of Formula XXIV (when $R_{p'}$ is i-butyl and $P_{q'}$ is Boc) can be deprotected and hydrolyzed directly to give a compound of Formula XXVI.

**Path B:** The compound of Formula XXIV (when $R_{p'}$ is i-butyl and $R_{p'}'$ is ethyl) can be deprotected first to give a compound of Formula XXV, which can then be hydrolyzed to give a compound of Formula XXVI.

Coupling of compound of Formula XI with a compound of Formula XXI to give a compound of Formula XXII can be carried out with dicyclohexylcarbodiimide in one or more solvent, for example, dichloromethane, dimethylformamide, tetrahydrofuran, dioxane, acetonitrile or acetone.

Compound of Formula XXII can be alkylated with a compound of Formula XXIII to give a compound of Formula XXIV in one or more solvents, for example, acetonitrile, dichloromethane, dichloroethane, chloroform, tetrahydrofuran, dimethylformamide or acetone in the presence of a base, for example, potassium carbonate, triethylamine, diisopropylethylamine or $N$-methylmorpholine optionally in the presence of a catalyst, for example, potassium iodide.

The deprotection and hydrolysis of compound of Formula XXIV to give a compound of Formula XXVI (Path A) can be carried out in the similar way as conversion of compound of Formula XIII to a compound of Formula XIVa.

The deprotection and hydrolysis of compound of Formula XXIV to give a compound of XXV (Path B) can be carried out in a similar manner as the conversion of compound of Formula XIII to a compound of Formula XIVa.

The hydrolysis of compound of Formula XXV to give a compound of Formula XXVI can be carried out in a similar way as the hydrolysis of compound of Formula XIII to a compound of Formula XV.
In the above schemes, where specific bases, acids, solvents, condensing agents, reducing agents, deprotecting agents, hydrolyzing agents, metal catalysts etc., are mentioned, it is to be understood that other acids, bases, solvents, condensing agents, reducing agent, deprotecting agent, hydrolyzing agents, metal catalysts etc., known to those skilled in the art may also be used. Similarly, the reaction temperature and duration of the reactions may be adjusted according to the requirements that arise during the process.

The following examples are set forth to demonstrate general synthetic procedures for the preparation of representative compounds. The examples are provided to illustrate particular aspect of the disclosure and do not limit the scope of the present invention.

**EXPERIMENTAL**

**Synthetic Procedure for Scheme I:**

**Example 1:** Synthesis of methyl (4S)-4-[(3R)-3-[(tert-butoxycarbonyl) aminol-4-(2A5-trifluoro- phenylbutanoyl)amino]-L-prolinate

**Step 1:** 1-benzyl 2-methyl (2S, 4R)-4-hydroxypyrrolidine-l, 2-dicarboxylate

Benzylicchloroformate (235 ml, 1.7 mol) was added to the chilled solution of trans-4-hydroxy-L-proline methyl ester (120 g, 0.83 mol) (Commercially available) and triethylamine (345 ml, 2.5 mol) in dry dichloromethane (1000 ml) under nitrogen atmosphere over a period of about 15 minutes. After addition, the reaction mixture was stirred at ~ 25°C for about 12 hours and the solvent was recovered under reduced pressure. The crude was purified using column chromatography (Silica gel 100-200 mesh, 0.25% Methanol: dichloromethane) to give title product (Yield: -108 g).

MS (+ve, ion mode); 280.24 (M+l)

**Step 2:** 1-benzyl 2-methyl (25,4R)-4-[(methylsulfonyl)oxy]pyrrolidine-l,2-dicarboxylate

To the solution of 1-benzyl 2-methyl (2S, 4R)-4-hydroxypyrrolidine-l, 2-dicarboxylate (108 g, 0.39 mol) in dry dichloromethane (700 ml) at 0°C, triethylamine (108 ml, 0.77 mol) was added. To this mixture, methane sulfonyl chloride (60 ml, 0.77 mol) was added
over a period of about 30 minutes. After addition, the reaction mixture was stirred at ~ 25°C for about 12 hours. Solvent was recovered under reduced pressure. The crude was purified using column chromatography (Silica gel 100-200 mesh) using 40% ethyl acetate: hexane as eluent to get the title product (Yield: -80 g).

MS (+ve, ion mode); 358.11(M+1)

**Step III: 1-benzyl 2-methyl (2S,4S)-4-azidopyrrolidine-1,2-dicarboxylate**

To the solution of 1-benzyl 2-methyl (2S,4R)-4-[(methylsulfonyl)oxy] pyrrolidine-1,2-dicarboxylate (78 g, 0.22 mol) in dry dimethylformamide (500 ml), sodium azide (71 g, 1.1 mol) was added. The reaction mixture was stirred at 50-60°C for about 5 hours. The reaction mixture was poured in excess of chilled water and the product was extracted out using ethyl acetate. The crude mixture was dried over anhydrous sodium sulphate and concentrated to dryness to get the title compound (Yield: -65 g).

MS (+ve, ion mode); 245.26 (M+l)

**Step IV: 1-Benzyl 2-methyl (2S,4S)-4-aminopyrrolidine-1,2-dicarboxylate**

To the solution of 1-benzyl 2-methyl (2S,4S)-4-azidopyrrolidine-l, 2-dicarboxylate (65 g, 0.22 mol) in dry tetrahydrofuran (500 ml), triphenylphosphene (71 g, 1.1 mol) was added very slowly, over period of about 30 minutes. The reaction mixture was stirred at ~ 25°C for about 1 hour. To this reaction mixture, water (2 ml) was added and heated to reflux temp of 65-70°C for 2-4 hours. The reaction mixture was concentrated and the crude product was purified through column chromatography (silica gel 100-200 mesh) using 10% methanol: dichloromethane as eluent to get the title product (Yield: -35 g).

MS (+ve, ion mode); 278.26(M+1)

**Step V: 1-Benzyl 2-methyl (2S,4S)-4-[[3R]-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino]pyrrolidine-1,2-dicarboxylate**

To the chilled solution of (3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid (4.0 g, 12 mmol) (J. Med. Chem., 2005, 48(1), 141-151), 1-benzyl 2-methyl (2S,4S)-4-azidopyrrolidine-l, 2-dicarboxylate (3.0 g, 12 mmol), 1-ethyl-3-(3′-dimethyl-aminopropyl)carbodiimide hydrochloride (2.8 g, 14.4 mmol) and N-hydroxybenzotriazole (2.8 g, 14.4 mmol) in dry dimethylformamide (20 ml) at about 0°C,
triethylamine (3.4 ml, 24.0 mmol) was added over period of about 15 minutes. The reaction mixture was stirred at ~ 25°C for about 12 hours, decomposed in excess of chilled water and then extracted with ethyl acetate. The organic layer was washed with 5% sodium bicarbonate, 10% citric acid and finally with brine solution. Crude product was dried over anhydrous sodium sulphate, concentrated and then purified through column chromatography (Silica gel 100-200 mesh) using 10% methanol: dichloromethane) as eluent to get the title product (Yield: ~3 g).

MS (+ve, ion mode); 594.25 (M+1)

**Step VI: Methyl (4S)-4-[(3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl) butanoyl]amino]-L-prolinate**

To the solution of 1-benzyl 2-methyl (2S, 4S)-4-[(3R)-3-[(tert-butoxycarbonyl) amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino)pyrrolidine-1,2-dicarboxylate (3.0 g, 5.1 mmol) and ammonium formate (1.6 g, 25.3 mmol) in methanol (10 ml), Pd/C (10%, wet) (3.0 g) was added. The reaction mixture was then heated to reflux at 80°C for about 2 hours. After cooling, it was filtered through celite and the filtrate was concentrated to get the title compound (Yield: ~2.47 g).

MS (+ve, ion mode); 460.22 (M+1)

**NMR:** δ 1.21-1.4 (9H, m); 1.72-1.82 (1H, m), 2.28-2.54(3H, m), 2.6-2.7 (1H, m), 2.8-2.92(2H, m), 3.01-3.11(1H, m), 3.71-3.85(3H, m), 4.05-4.28(2H, m), 7.05-7.22(2H, m)

**HPLC purity:** 81.88%

**Example 2:** Synthesis of tert-Butyl (4S)-4-[(3R)-3-[(tert-butoxycarbonyl)aminol-4-(2A5-trifluorophenyl) butanoyll amino]-L-proline

**Step I: (4R)-l-[benzyloxy] carbonyl]-4-hydroxy-L-proline**

Benzylchloroformate (224 ml, 1.2 mol) was added to the chilled solution of trans-4-hydroxy-L-proline (100 g, 0.76 mol) and sodium bicarbonate (128 g, 1.5 mol) in dioxane: water (1:1) mixture (750 ml) under nitrogen atmosphere over a period of about 15 minutes. After addition, the reaction mixture was stirred at ~ 25°C for about 12 hours and the solvent was recovered under reduced pressure. The aqueous layer was neutralized with
chilled 30% HCl solution. The obtained product was extracted using ethyl acetate, dried over anhydrous sodium sulphate and concentrated. The residue was purified using column chromatography (Silica gel 100-200 mesh) using 10% Methanol: dichloromethane as eluent to give title product (Yield: -170 g).

**Step II: 1-benzyl 2-tert-butyl (IS, 4R)-4-hydroxypyrrolidine-1, 2-dicarboxylate**

To the solution of (4R)-1-[(benzylxoy)carbonyl]-4-hydroxy-L-proline (100 g, 0.8 mol), trimethylbenzylammonium chloride (70 g, 0.37 mol), potassium carbonate (1.1 Kg, 7.31 mol) in N,N-dimethyl acetamide (1500 ml), tert-butyl bromide (1400 ml, 10.5 mol) was added drop wise over a period of 1-1.5 hours. After addition, the reaction mixture was stirred at 50-55°C for about 12 hours. To this, demineralized water was added till it becomes clear and then extracted crude product via ethyl acetate, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude was purified using column chromatography (Silica gel 100-200 mesh) using 40% ethyl acetate: hexane as eluent to get the title product (Yield: -84 g).

**Step-III: 1-benzyl 2-tert-butyl (2S, 4R)-4-[(methylsulfonyl) oxy] pyrrolidine-1, 2-dicarboxylate**

To the solution of 1-benzyl 2-tert-butyl (2S, 4R)-4-hydroxyppyrrrolidine-1, 2-dicarboxylate (74 g, 0.23 mol) in dry dichloromethane (200 ml) at 0°C, triethylamine (65 ml, 0.46 mol) was added. To this mixture, methane sulfonyl chloride (28 ml, 0.39 mol) was added over a period of about 30 minutes. After addition, the reaction mixture was stirred at -25°C for about 12 hours. Solvent was removed under reduced pressure. The crude was purified using column chromatography (Silica gel 100-200 mesh) using 40% ethyl acetate: hexane as eluent to get the title product (Yield: -95 g).

**Step IV: 1-Benzyl 2-tert-butyl (IS, 4S)-4-azidopyrrrolidine-1, 2-dicarboxylate**

To the solution of 1-benzyl 2-tert-butyl (2S, 4R)-4-[(methylsulfonyl)oxy]pyrrolidine-1, 2-dicarboxylate (94 g, 0.23 mol) in dry dimethylformamide (500 ml), sodium azide (70 g,
1.2 mol) was added. The reaction mixture was stirred at 50-60°C for about 5 hours. The reaction mixture was decomposed in excess of chilled water and the product was extracted out using ethyl acetate. The crude mixture was dried over anhydrous sodium sulphate and concentrated to dryness to get the title compound (Yield: -70 g).

MS (+ve, ion mode); 347.07 (M+1)

**Step V: 1-Benzyl 2-tert-butyl (2S, 4S)-4-aminopyrrolidine-1, 2-dicarboxylate**

To the solution of 1-benzyl 2-tert-butyl(2S,4S)-4-azidopyrrolidine-1, 2-dicarboxylate (68 g, 0.20 mol) in dry tetrahydrofuran (500 ml), triphenylphosphene (77 g, 0.29 mol) was added very slowly over period of about 30 minutes. The reaction mixture was stirred at ~ 25°C for about 1 hour. To this reaction mixture, water (70 ml) was added and heated to reflux for about 3 hours. The reaction mixture was concentrated and the crude product was purified through column chromatography (alumina basic) using 10% methanol: dichloromethane as eluent to get the title product (Yield: ~45 g).

MS (+ve, ion mode); 321.17(M+1)

**Step VI: 1-Benzyl 2-tert-butyl (2S,4S)-4-[(3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino]pyrrolidine-1,2-dicarboxylate**

To the chilled solution of (3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid (47 g, 0.14 mol) (J. Med. Chem., 48(1), 141-151 (2005)), 1-benzyl-2-tert-butyl (2S,4S)-4-azidopyrrolidine-1, 2-dicarboxylate (44 g, 0.14 mol), 1-ethyl-3-(3’-dimethylamino- propyl)carbodiimide hydrochloride (30 g, 0.16 mol) and N-hydroxybenzotriazole (28 g, 0.21 mol) in dry dimethylformamide (250 ml) at about 0°C, triethylamine (39 ml, 0.27 mol) was added over period of about 15 minutes. The reaction mixture was stirred at - 25°C for about 12 hours, decomposed in excess of chilled water and then extracted with ethyl acetate. The organic layer was washed with 5% sodium bicarbonate, 10% citric acid and finally with brine solution. Crude product was dried over anhydrous sodium sulphate, concentrated and then purified through column chromatography (Silica gel 100-200 mesh) using 10% methanol: dichloromethane as eluent to get the title product (Yield: ~67g).

MS (+ve, ion mode); 636.35 (M+1)
Step VII: tert-Butyl (45)-4-\([(3R)-3-\{(i-tert-butoxycarbonyl)amino\}-4-(2,4,5-trifluorophenyl)butanoyl]amino\)-L-proline

To the solution of 1-benzyl 2-iert-butyl(25',4S)-4-\([(3R)-3-\{(i-tert-butoxycarbonyl) amino\}-4-(2,4,5-trifluorophenyl)butanoyl] amino \}pyrrolidine-1,2-dicarboxylate (65 g, 0.10 mol) and ammonium formate (32 g, 0.40 mol) in methanol (600 ml), Pd/C (10%, wet) (65 g) was added. The reaction mixture was then heated to reflux at 80°C for about 2 hours. After cooling, it was filtered through celite and the filtrate was concentrated to get the title compound (Yield: ~32 g).

MS (+ve, ion mode); 502.19 (M+1)

NMR: δ 1.24-1.39 (9H, m), 1.45-1.50 (9H, m), 1.69-1.79 (1H, m), 2.28-2.51 (3H, m), 2.60-2.70 (1H, m), 2.80-2.95 (2H, m), 2.99-3.09 (1H, m), 3.60-3.69 (1H, m), 4.05-4.25 (2H, m), 7.00-7.26 (2H,m)

HPLC purity: 93.81%

Synthetic Procedure for Scheme 2:

Path A:

Example 3: Synthesis of methyl (4S)-l-(2S)-3-(acetylsulfanyl)-2-methylpropanoyll-4-\{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound no. 2)

Step I: Methyl (4S)-1-(25)-3-(acetylsulfanyl)-2-methylpropanoyl]-4-\{(3 R)-3-\{(tert-butoxycarbonyl)amino\}-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline

To the solution of methyl (4S)-4-\{(3R)-3-\{(i-tert-butoxycarbonyl)amino\}-4-(2,4,5-trifluorophenyl)butanoyl] amino \}]-L-proline (1.0 g, 2.2 mmol), (S)-(−)-3-acetythio-2-methyl propionic acid (0.4 g, 2.2 mmol), 1-ethyl-3-(3’-dimethylaminopropyl) carbodiimide hydrochloride (0.4 g, 2.6 mmol) and N-hydroxybenzotriazole (0.5 g, 2.6 mmol) in dry dimethylformamide (12 ml) at about 0°C, triethylamine (3.4 ml, 24.0 mmol) was added over period of about 15 minutes. The reaction mixture was stirred at ~ 25°C for about 12 hours, decomposed in excess of chilled water and then extracted out with ethyl acetate. The organic layer was washed with 5% NaHCO₃, 10% citric acid and finally with
brine solution. The organic layer was dried over anhydrous sodium sulphate and concentrated. The crude thus obtained was purified through column chromatography (silica gel 100-200 mesh) using 10% methanol: dichloromethane as eluent to get title product (Yield: ~0.6 g).

MS (+ve, ion mode); 604.26 (M+1)

Step II: Methyl (4S)-l-[(2S)-3-(acetylsulfanyl)-2-methylpropanoyl]-4-{{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino}-L-prolinate

To the solution of methyl (4S)-l-[(2S)-3-(acetylsulfanyl)-2-methylpropanoyl]-4-{{[(3R)-3-{(te/t-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-prolinate (0.067 g, 0.11 mmol) in dry dichloromethane (4.0 ml), trifluoroacetic acid (1.0 ml) was added drop wise at about 0°C. The reaction mixture was stirred at ~ 25°C for about 1 hour, concentrated and hexane was added into it. This mixture was stirred vigorously and hexane layer were decanted. This process was repeated three times and residue was dried under vacuum at ~ 25°C for about 1 hour to get title compound (Yield: ~0.032 g).

NMR (CD$_3$OD; 400MHZ); 51.14-1.18 (m,3H), 1.70-1.85 (m, IH), 2.29 (s, 3H), 2.40-2.50 (m, IH), 2.55-2.70 (m, 2H), 2.80-2.31 (m, 5H), 3.70 (s, 3H), 3.71-3.85 (m, IH), 3.97-4.10 (m, IH), 4.38-4.45 (m, 2H), 7.20-7.35 (m, 2H)

MS (+ve, ion mode); 504.07(M+1)

Path B:

Example 4: Synthesis of (4S)-4-{{1Y3R)-3-amino-4-(2A5-
trifluorophenyl)butanoyl amino}-L-proline ditrifluoroacetate salt (Compound no 1)

Step II: (4S)-4-{{[(3R)-3-{(te/butoxycarbonyl)amino]-4-(2,4,5-
trifluorophenyl)butanoyl] amino}-L-prolinate

To the solution of methyl (4S)-l-[(2S)-3-(acetylsulfanyl)-2-methylpropanoyl]-4-{{[(3R)-3-{(te/butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-prolinate (0.6 g, 1.0 mmol) and lithium hydroxide monohydrate (0.13 g, 3.0 mmol) in methanol: tetrahydrofuran (1:1) ( 5.0 ml) water (0.3 ml) was added. The reaction mixture was stirred at - 25°C for about 1 hour. The reaction mixture was concentrated and neutralized with
1.0 N hydrochloric acid and then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated. The crude compound was purified using prep plate chromatography to get title compound (Yield: -0.2 g).

MS (+ve, ion mode); 548.19(M+1)

### Step III: (4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-[2S]-2-methyl-3-sulfanylpropanoyl]-L-proline trifluoroacetate salt

To the solution of (4S)-4-\{[(3R)-3-[(t-tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-[2S]-2-methyl-3-sulfanylpropanoyl]-L-proline (0.035 g, 0.06 mmol) in dry dichloromethane (2.0 ml), trifluoroacetic acid (0.5 ml) was added drop wise at about 0°C. The reaction mixture was stirred at ~ 25°C for about 1 hour, concentrated and hexane was added into it. It was then stirred vigorously and hexane layer was decanted. This process was repeated three times and residue was dried under vacuum at ~ 25°C for about 1 hour to get title compound. (Yield: -0.012 g)

NMR (CD\textsubscript{3}OD; 400MHz); δ 1.16 (d, J = 6.8Hz, 3H), 1.78-2.00 (m, 1H), 2.35-3.16 (m, 9H), 3.70-3.85 (m, 2H), 4.10-4.21 (m, 1H), 4.39-4.50 (m, 2H), 7.20-7.40 (m, 2H).

MS (+ve, ion mode); 448.13 (M+l)

HPLC Purity: -91.63%

### Path C:

Example 5: Synthesis of (4S)-L-\{r(2S)-3-(acetylsulfanyl)-2-methylpropanoyl\}-4-\{[(3R)-3-[(t-tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline trifluoroacetate salt

(Compound no. 3)

### Step I: t-Butyl (4S)-L-[2S]-3-(acetylsulfanyl)-2-methylpropanoyl]-4-\{[(3 R)-3-(tert-butoxycarbonyl) amino]-4-(2,4,5-trifluorophenyl) butanoyl] amino\]-L-proline

To the solution of t-butyl (4S)-4-\{[(3R)-3-[(t-tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-prolate (0.20 g, 0.4 mmol), (S)-(\(-\))-3-acetylthio-2-methyl propionic acid (0.07 g, 2.2 mmol), 1-ethyl-3-(3’-dimethylaminopropyl) carboadiimide hydrochloride (0.092 g, 0.48 mmol) and N-hydroxybenzotriazole (0.074 g, 0.48 mmol) in dry dimethylformamide (12 ml) at about 0°C, triethylamine (3.4 ml, 24.0 mmol) was added over period of about 15 minutes. The reaction mixture was stirred at -
25°C for about 12 hours, decomposed in excess of chilled water and then extracted out with ethyl acetate. The organic layer was washed with 5% NaHCO₃, 10% citric acid and finally with brine solution. The organic layer was dried over anhydrous sodium sulphate and concentrated. The crude thus obtained was purified through column chromatography (silica gel 100-200 mesh) using 10% methanol: dichloromethane as eluent to get title product (Yield: ~0.11 g).

MS (+ve, ion mode); 646.19(M+1)

Step II: (4S)-l-[(2S)-3-(acetylsulfanyl)-2-methylpropanoyl]-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino}-L-proline ditrifluoroacetate salt (Compound no. 3)

To the solution of t-Butyl (4S)-l-[(25')-3-(acetylsulfanyl)-2-methylpropanoyl]-4-{{(3 R)-3-[(tert-butoxycarbonyl)amino] -4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-prolate (0.1 g, 0.15 mmol) in trifluoroacetic acid: water (95:5) (0.77 ml) was added drop wise at about 0°C. The reaction mixture was stirred at ~25°C for about 1 hour, concentrated and hexane was added into it. This mixture was stirred vigorously and hexane layer were decanted. This process was repeated three times and residue was dried under vacuum at ~25°C for about 1 hour to get title compound (Yield: -0.07 g).

NMR (CD₃OD; 400MHZ); δ 1.14-1.19 (m,3H), 1.90-1.94 (m, 1H), 2.23-2.47 (m, 4H), 2.55-2.62 (m, 2H), 2.86-3.04 (m, 5H), 3.45-3.55 (m, 1H), 3.70-3.75 (m, 1H), 3.95-4.05 (m, 1H), 4.30-4.50 (m, 2H), 7.23-7.34 (m, 2H)

MS (+ve, ion mode); 489.99(M+1)

The following compounds are prepared using the above synthetic route.

(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino}-l-{{3-[(phenylcarbonyl)sulfanyl]propanoyl}-L-proline ditrifluoroacetate salt (Compound no. 4)

MS (+ve, ion mode); 537.97 (M+1)
Synthetic Procedure for Scheme 3

Path A

Example 6: Synthesis of N-((1S)-1-carboxy-3-phenylpropyl)-L-alanyl-(4S)-4-{[(3R)-3-amino-4-(2A5-trifluorophenyl)butanoyl]-amino}-L-proline ditrifluoroacetate salt

(Compound No. 5)

Step I: Methyl N-[(15)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-(4S)-4-{[(3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]-amino}-L-prolinate

To the solution of methyl (4S)-4-{[(3R)-3-[(ieri-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]-amino}-L-prolinate (0.85 g, 1.85 mmol), N-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanine trifluoroacetate (Bioorganic & Medicinal Chemistry Letters 1994, 4, 2673-76) (0.73 g, 1.85 mmol), 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide hydrochloride (0.43 g, 2.2 mmol) and N-hydroxybenzotriazole (0.34 g, 2.2 mmol) in dry dimethylformamide (12 ml) at about 0°C, triethylamine (0.77 ml, 5.5 mmol) was added over a period of about 15 minutes. The reaction mixture was stirred at ~ 25°C for about 12 hours, decomposed in excess of chilled water and extracted out using ethyl acetate. The organic layer was washed with 5% sodium bicarbonate, 10% citric acid and finally with brine solution. The organic layer was dried over anhydrous sodium sulphate and concentrated. The crude was then purified through column chromatography (silica gel 100-200 mesh) using 10% methanol: dichloromethane as eluent to get title product (Yield: ~0.7 g).

MS (+ve, ion mode); 721.38 (M+1)

Step II: N-[(15)-1-carboxy-3-phenylpropyl]-L-alanyl-(4S)-4-{[(3 R)-3-[(tert-butoxy-carbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]-amino}-L-proline

To the solution of Methyl N-[(15)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-(4S)-4-{[(3R)-3-[(ieri-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]-amino}-L-prolinate (0.1 g, 0.14 mmol) and lithium hydroxide monohydrate (0.13 g, 0.3 mmol) in methanol :tetrahydrofuran (1:1) (5.0 ml), water (0.3 ml) was added. The reaction mixture was stirred at ~ 25°C for about 1 hour, concentrated, neutralized with 1.0 N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get title compound (Yield: ~0.072 g).
Step III: \(N\-{[(15)-l\text{-carboxy-3-phenylpropyl}]\text{-L-}alanyl\-(4S\)-4\-\{[(3R\)-3-amino-4\-(2,4,5-trifluorophenyl)butanoyl\]amino\]-L-proline} ditrifluoroacetate salt\) (Compound No. 5)

To the solution of \(N\-{[(15)-l\text{-carboxy-3-phenylpropyl}]\text{-L-}alanyl\-(4S\)-4\-\{[(3R\)-3-amino-4\-(2,4,5-trifluorophenyl)butanoyl\]amino\]-L-proline\) (0.72 g, 0.11 mmol) in dry dichloromethane (4.0 ml), trifluoroacetic acid (1.0 ml) was added dropwise at about 0°C. The reaction mixture was stirred at ~ 25°C for about 1 hour, concentrated and hexane was added into it. This mixture was stirred vigorously and hexane layer were decanted and dried under vacuum at ~ 25°C to get title compound (Yield: 0.032 g).

NMR (CD\(_3\)OD; 400 MHZ): 81.53-1.58 (m, 3H), 1.87-2.00 (m, 1H), 2.4-3.1 (m, 8H), 3.47-3.55 (m, 1H), 3.60-3.70 (m, 1H), 3.75-3.90 (m, 2H), 3.92-4.00 (m, 1H), 4.17-4.27 (m, 2H), 4.29-4.52 (m, 2H), 7.17-7.32 (m, 7H)

MS (+ve, ion mode); 579.21(M+1)

HPLC (purity): -92.11%

Path B

Example 6A: Synthesis of \(N\-\text{r(lS)-l\text{-carboxy-3-phenylpropyl-L-alanyl}\-(4S\)-4\-\{r(3R)-3\-amino-4\-(2,5\text{-trifluorophenyl})butanoyl\]amino\)}-L-proline\) dilithium salt (Compound No. 5)

Step I: \(\text{tert-butyl \-}\text{N\-[\text{25\-l-ethoxy-l-oxo-4-phenylbutan-2-yl}\]L-alanyl\-(4S\)-4\-\{[(3R\)}-3\-amino-4\-(2,4,5\text{-trifluorophenyl})butanoyl\]amino\}L-prolinate\)

To the solution of \(\text{tert-butyl \-(4S\)-4-\{[(3R\)-3\-(fert-butyloxy carbonyl))amino\]-L-prolinate\) (1.27 g, 2.50 mmol), \(N\-\text{r(lS)-l\text{-ethoxy carbonyl})-3-phenylpropyl\]}-L- alanine trifluoroacetate\) (Bioorganic & Medicinal Chemistry Letters 1994, 4, 2673-76) (1.0 g, 2.50 mmol), 1-ethyl-3-(3\'-dimethylaminopropyl) carbodiimide hydrochloride (0.53 g, 2.7 mmol) and \(N\-\text{hydroxybenzotriazole\) (0.42 g, 2.7 mmol) in dry dimethylformamide (12 ml) at about 0°C, triethylamine (1.41 ml, 10.0 mmol) was added over a period of about 15 minutes. The reaction mixture was stirred at - 25°C for about 12 hours, decomposed in excess of chilled water and extracted out using ethyl acetate. The organic layer was washed with 5%
sodium bicarbonate, 10% citric acid and finally with brine solution. The organic layer was dried over anhydrous sodium sulphate and concentrated. The crude was then purified through column chromatography (silica gel 100-200 mesh) using 10% methanol: dichloromethane as eluent to get title product (Yield: -0.8 g).

**Step II:** \(N\)-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 21)

To the solution of tert-butyl \(N\)-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-[(iери-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-prolinate (0.5 g, 6.5 mmol) in dry dichloromethane (15.6 ml), trifluoroacetic acid (4.4 ml) was added drop wise at about 0°C. The reaction mixture was stirred at ~ 25°C for about 1 hour, concentrated and hexane was added into it. This mixture was stirred vigorously and hexane layer were decanted and dried under vacuum at ~ 25°C to get title compound (Yield: -0.321 g).

**Step III:** \(N\)-[(15)-l-carboxy-3-phenylpropyl]-L-alanyl-(45)-4-\{[(3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline dilithium salt (Compound No. 5)

To the solution of \(N\)-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline (0.2 g, 0.27 mmol) and lithium hydroxide monohydrate (0.08 g, 1.8 mmol) in methanol :tetrahydrofuran (1:1) (5.0 ml), water (0.3 ml) was added. The reaction mixture was stirred at - 25°C for about 1 hour, concentrated, neutralized with 1.0 N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated to get title compound (Yield: -0.161 g).

The following compounds are prepared using the above synthetic route

\(N\)-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-norvalyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\}-L-proline(Compound No. 50),

**MS (+ve, ion mode);** 635.38(M+1)
N-[(15')-l-carboxy-3-phenylpropyl]-L-norvalyl-(4S)-4-([(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-proline (Compound No. 51),

MS (+ve, ion mode); 608.09(M+1)

(4S)-4-([(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino }-l-[(25)-2-[(25)-1-ethoxy-l-oxo-4-phenylbutan-2-yl] amino }butanoyl]-L-proline (Compound No. 54),

MS (+ve, ion mode); 622.42(M+1)

N-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-norleucyl-(4S)-4-([(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-proline (Compound No. 55),

MS (+ve, ion mode); 650.45(M+1)

(4S)-4-([(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino }-l-[(15)-l-carboxy-3-phenylpropyl]amino }butanoyl]-L-proline (Compound No. 56),

MS (+ve, ion mode); 593.98(M+1)

N-[(15')-l-carboxy-3-phenylpropyl]-L-norleucyl-(4S)-4-([(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-proline (Compound No. 57),

MS (+ve, ion mode); 621.39(M+1)

N^2-[(15)-l-carboxy-3-phenylpropyl]-L-lysyl-(4S)-4-([(3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-proline (Compound No. 58),

MS (+ve, ion mode); 637.39(M+1)

N-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-2-methylalanyl-(4S)-4-([(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-proline (Compound No. 59),
MS (+ve, ion mode); 622.32(M+1)

(45)-4-[(3R)-3-amino-4(2,4,5-trifluorophenyl)butanoyl]amino]-l-[l-[(25)-ethoxy-l-oxo-4-phenylbutan-2-yl] amino]cyclopentyl]carbonyl]-L-proline (Compound No. 60),

MS (+ve, ion mode); 648.4(M+1)

l-[25]-ethoxy-l-oxo-4-phenylbutan-2-yl]-D-prolyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino]-L-proline (Compound No. 61),

MS (+ve, ion mode); 634.29(M+1)

N-[(15')-l-carboxy-3-phenylpropyl]-2-methylalanyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino]-L-proline (Compound No. 62),

MS (+ve, ion mode); 593.92(M+1)

(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-l-[l-[(1S)-l-carboxy-3-phenylpropyl]amino]cyclopentyl]carbonyl]-L-proline (Compound No. 63),

MS (+ve, ion mode); 620.27(M+1)

l-[(15)-l-carboxy-3-phenylpropyl]-D-prolyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino]-L-proline (Compound No. 64),

MS (+ve, ion mode); 606.25(M+1)

3-cyclopropyl-N-[(25')-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino]-L-proline (Compound No. 65),

MS (+ve, ion mode); 646.95(M+1)
(25,45)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl}amino}-l-[(25)-2-{{(25)-l-
ethoxy-1-oxo-4-phenylbutan-2-yl] amino }-5-methoxy-5-oxopentanoyl}pyrrolidine-2-
carboxylic acid (Compound No. 66),

MS (+ve, ion mode); 679.01(M+1)

N’-[(15’)-l-carboxy-3-phenylpropyl]-L-a-glutamyl-(45)-4-{{(3R)-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl}amino }-L-proline (Compound No. 67),

MS (+ve, ion mode); 637.87(M+1)

N‘2-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-asparaginyl-(45’)-4-{{(3 R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl}amino }-L-proline (Compound No. 68),

MS (+ve, ion mode); 650.91(M+1)

N‘2-[(15)-l-carboxy-3-phenylpropyl]-L-asparaginyl-(45’)-4-{{(3 R)-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl}amino }-L-proline (Compound No. 69),

MS (+ve, ion mode); 622.01(M+1)

N-[(l-carboxy-3-phenylpropyl)-L-threonyl-(45’)-4-{{(3 R)-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl}amino }-L-proline (Compound No. 70),

MS (+ve, ion mode); 610.28(M+1)

N’-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl] O-methyl-L-seryl-(45)-4-{{(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl}amino }-L-proline (Compound No. 71),

MS (+ve, ion mode); 636.93(M+1)

N’-[(15)-l-carboxy-3-phenylpropyl]-0-methyl-L-seryl-(45’)-4-{{(3R)-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl}amino }-L-proline (Compound No. 72),
MS (+ve, ion mode); 608.9(M+1)

(45)-4-[[[(3i?)-3-amino-4^2,4,5-trifluorophenyl]butanoyl](methyl)amino]-l-[(25 \text{ S})-2-\{(2S)-l-ethoxy-l-oxo-4-phenylbutan-2-yl\} amino]butanoyl]-L-proline (Compound No. 80),

MS (+ve, ion mode); 635.44(M+1)

N-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-norvalyl-(45 \text{ S})-4-{{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl](methyl)amino}\}}-L-proline (Compound No. 81),

MS (+ve, ion mode); 649.44(M+1)

N-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-norleucyl-(45 \text{ S})-4-{{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl](methyl)amino}\}}-L-proline (Compound No. 82),

MS (+ve, ion mode); 663.44(M+1)

(4,5)-4-{{[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl](methyl)amino}\}}-l-[(25 \text{ S})-2-\{[(l^-l-carboxy-S-phenylpropyl]aminojbutanoy^-L-proline (Compound No. 83),

MS (+ve, ion mode); 607.36(M+1)

N-[(15)-l-carboxy-3-phenylpropyl]-L-norvalyl-(45)-4-{{[(3 \text{ R})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl](methyl)amino}\}}-L-proline (Compound No. 84),

MS (+ve, ion mode); 621.37(M+1)

N-[(15')-l-carboxy-3-phenylpropyl]-L-norleucyl-(45)-4-{{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl](methyl)amino}\}}-L-proline (Compound No. 85),

MS (+ve, ion mode); 635.42(M+1)
$N$-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-\{[(3 \ R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl](methyl)amino\}-L-proline (Compound No. 86),

MS (+ve, ion mode); 621.19(M+1)

$N$-[(15)-l-carboxy-3-phenylpropyl]-L-alanyl-(45)-4-\{[(3 \ R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl](methyl)amino\}-L-proline (Compound No. 87),

MS (+ve, ion mode); 593.26(M+1)

$N$-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-D-norvalyl-(45)-4-\{[(3 \ R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 88),

MS (+ve, ion mode); 635.43(M+1)

$N$-[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-D-norleucyl-(45)-4-\{[(3 \ R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 89),

MS (+ve, ion mode); 649.4(M+1)

$N$-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-D-alanyl-(45)-4-\{[(3 \ R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 90),

MS (+ve, ion mode); 607.42(M+1)

(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-[2 \ R)-2-\{[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl] amino \}butanoyl]-L-proline (Compound No. 91),

MS (+ve, ion mode); 621.39(M+1)
\[ N'-(15')-l\text{-carboxy-3-phenylpropyl}\]-D-norvalyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl}]amino\}-L-proline \text{ (Compound No. 92)}, \]

MS (+ve, ion mode); 607.43(M+1)

\[ N'-(15')-l\text{-carboxy-3-phenylpropyl}\]-D-norleucyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl}]amino\}-L-proline \text{ (Compound No. 93)}, \]

MS (+ve, ion mode); 621.49(M+1)

\[ N-(15)-l\text{-carboxy-3-phenylpropyl}\]-D-alanyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl}]amino\}-L-proline \text{ (Compound No. 94) and} \]

MS (+ve, ion mode); 579.45(M+1)

\[ (4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl}]amino\}-l-(2R)-2-\{[(15)-l\text{-carboxy-3-phenylpropyl}]amino\}butanoyllamino]-L-prolinate \text{ (Compound No. 95)} \]

MS (+ve, ion mode); 593.44(M+1)

**Path C**

**Example LE 6B: Synthesis of methyl N\{(2S)-l-ethoxy-l-oxo-4-phenylbutan-2-yll-L-alanyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl}]amino\}butanoyllamino]-L-prolinate ditrifluoroacetate salt (Compound No. 6)***

To a solution of methyl \[ N'-(15')-l\text{-ethoxycarbonyl-3-phenylpropyl}\]-L-alanyl-(4S)-4-\{[(3R)-3\text{-([iertoxy carbonyl]amino}]-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-prolinate (0.050 g, 0.07 mmol) in dry dichloromethane (4.0 ml), trifluoroacetic acid (1.0 ml) was added drop wise at about 0°C. This reaction mixture was stirred at ~25°C for about 1 hour, concentrated and hexane was added to it. The obtained residue was dried under vacuum at ~25°C for about 1 hour to get the title compound (Yield: -0.023 g).
NMR (CD$_3$OD; 400MHz); δ 1.28-1.33(m, 3H), 1.51(d, 3H, J = 6.8Hz), 1.80-1.90 (s, 1H), 2.10-2.30(m,2H), 2.40-3. 15( m,8H), 3.24-3.30( m,1H), 3.40-3.52 (m, 1H), 3.65 (s, 3H), 3.70-3.90 (m,3H), 4.22-4.30(m, 4H), 4.35-4.89(m,2H), 7.19-7.32(m,7H).

MS (+ve, ion mode); 621.32(M+1)

HPLC (Purity): 96.62%

The following compounds were prepared employing procedures as provided in Examples 6, Examples 6A or Examples 6B described above:

$N$-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-valyl-(45)-4-[[3 R)-3-amino-4-(2,4,5-trifluoro-phenyl)butanoyl] amino }-L-proline ditrifluoroacetate salt (Compound no. 8)

MS (+ve, ion mode); 635.55 (M+l)

$N$-[(15)-l-carboxy-3-phenylpropyl]-L-valyl-(45)-4-[[3 R)-3-amino-4-(2,4,5-trifluorophenyl) butanoyl] amino }-L-proline dilithium salt (Compound no. 9)

MS (+ve, ion mode); 601.53 (M+l)

$N$-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-leucyl-(45)-4-[[3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-proline ditrifluoroacetate salt (Compound no. 10)

MS (+ve, ion mode); 649.67 (M+l)

$N$-[(15)-l-carboxy-3-phenylpropyl]-L-leucyl-(45)-4-[[3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-proline dilithium salt (Compound no. 11)

MS (+ve, ion mode); 621.57 (M+l)

$N$-[(15)-l-carboxy-2-methylbutyl]-L-alanyl-(45)-4-[[3 R)-3-amino-4-(2,4,5-trifluorophenyl) butanoyl] amino }-L-proline ditrifluoroacetate salt (Compound no. 12)

MS (+ve, ion mode); 649.60 (M+l)
\[ N-\{(15)-l\text{-carboxy-3-phenylpropyl}\}-l\text{-isoleucyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl} \text{amino}\}}-l\text{-proline dilithium salt (Compound no. 13)} \]

MS (+ve, ion mode); 621.51 (M+I)

\[ N-\{(25)-1\text{-ethoxy-1-oxo-4-phenylbutan-2-yl}\}-l\text{-phenylalanyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl} \text{amino}\}}-l\text{-proline ditrifluoroacetate salt (Compound no. 14)} \]

MS (+ve, ion mode); 683.49 (M+I)

\[ N-\{(15)-l\text{-carboxy-3-phenylpropyl}\}-l\text{-phenylalanyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl} \text{amino}\}}-l\text{-proline dilithium salt (Compound no. 15)} \]

MS (+ve, ion mode); 655.63 (M+I)

\[ N-\{(2S)-1\text{-ethoxy-1-oxo-4-phenylbutan-2-yl}\}-l\text{-seryl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl} \text{amino}\}}-l\text{-proline ditrifluoroacetate salt (Compound no. 16)} \]

MS (+ve, ion mode); 624.23 (M+I)

\[ N-\{(15)-l\text{-carboxy-3-phenylpropyl}\}-l\text{-seryl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl} \text{amino}\}}-l\text{-proline dilithium salt (Compound no. 17)} \]

MS (+ve, ion mode); 596.02 (M+I)

\[ N-\{(2S)-1\text{-ethoxy-1-oxo-4-phenylbutan-2-yl}\}-l\text{-tyrosyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl} \text{amino}\}}-l\text{-proline ditrifluoroacetate salt (Compound no. 18)} \]

MS (+ve, ion mode); 700.58 (M+I)

\[ N-\{(15')-l\text{-carboxy-3-phenylpropyl}\}-l\text{-tyrosyl-(4S)-4-\{[(3R)-3\text{-amino-4-(2,4,5-trifluorophenyl)butanoyl} \text{amino}\}}-l\text{-proline dilithium salt (Compound no. 19)} \]
MS (+ve, ion mode); 672.28 (M+l)

N-[(15)-l-carboxy-3-phenylpropyl]glycyl-(45)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino }-L-proline ditrifluoroacetate salt (Compound no. 20)

MS (+ve, ion mode); 565.34 (M+l)

N-[(15)-l-carboxy-3-phenylpropyl]-L-alanyl-(4R)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino }-L-proline ditrifluoroacetate salt (Compound no. 22),

MS (+ve, ion mode); 579.86 (M+l)

This compound was prepared by using cis-4-hydroxy proline as starting material.

**Synthetic Procedure for Scheme 4**

**Path A**

Example 7: Synthesis of N-[(IS)-l-carboxy-3-methylbutyll-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino }-L-proline ditrifluoroacetate salt (Compound no. 24)

**Step I.** tert-butyl (45)-l-(2(R)-bromopropanoyl)-4-{{(3 R)-3-{(tert-butoxycarbonyl)amino}-4-(2,4,5-trifluorophenyl)butanoyl}amino}-L-prolinate

To a solution of tert-butyl (4S)-4-{{(3R)-3-{(tert-butoxycarbonyl)amino}-4-(2,4,5-trifluorophenyl)butanoyl} amino }-L-prolinate (3.0 g, 5.98 mmol) and dicyclohexylcarbodiimide (1.35 g, 6.57 mmol) under inert atmosphere in dry dichloromethane (20 ml), (R)-2-bromopropionic acid (0.65 ml, 7.18 mmol) was added at ~25°C. The reaction mixture was stirred at same temperature for about 18 hours. The reaction mixture was diluted with dichloromethane and then washed with aqueous sodium bicarbonate, chilled hydrochloric acid (1.0 N), brine and finally with demineralized water, dried over anhydrous sodium sulphate, concentrated and then purified through column
chromatography (Silica gel 100-200 mesh) using 45% ethyl acetate:Hexane as eluent to get the title compound (Yield: 3.2 g).

MS (+ve, ion mode); 636.08 (M+) & 638.11 (M+2)

**Step-II:** tert-butyl N-[(15)-1-(tert-butoxycarbonyl)-3-methylbutyl]-L-alanyl-(45)-4-{
(3R)-3-[(tert-butoxycarbonyl) amino]-4-(2,4,5-trifluorophenyl) butanoyl] amino}-L-prolinate

To a solution of hydrochloride salt of L-Leucine tert-butyl ester (0.10 g, 0.47 mmol), potassium carbonate (0.3 g, 0.95 mmol) and potassium iodide (0.01 g) in dry acetonitrile (2.0 ml), tert-butyl(4S)-1-[(2R)-2-bromopropanoyl]-4-{
(3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-prolinate (0.2 g, 0.31 mmol) dissolved in dry acetonitrile (10 ml) was added under inert atmosphere over a period of about 15 minutes. The reaction mixture was stirred at 60-65°C for about 12 hours. The reaction mixture was concentrated and then diluted with dichloromethane, washed with demineralized water and dried over anhydrous sodium sulphate, concentrated and then purified through preparative thin layer chromatography plates (2.0 mm) using 90% ethylacetate: hexane as eluent to get the title compound (Yield: 0.09 g).

MS (+ve, ion mode); 743.27 (M+l)

**Step-III:** N-[(15)-l-carboxy-3-methylbutyl]-L-alanyl-(45)-4-{{(3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino}-L-proline ditrifluoroacetate salt (Compound no. 24)

A mixture of tert-Butyl N-[(IS)-l-benzyl-2-ethoxy-2-oxoethyl]L-alanyl-(4S)-4-{
(3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-prolinate (0.02 g, 0.03 mmol) in trifluoroacetic acid and water (95%) (1.0 ml) was stirred under sonication at 15-20°C in inert atmosphere for about 3 hours. The reaction mixture was concentrated and diethyl ether was added to it, stirred vigorously and ether layer was decanted. This process was repeated 3-4 times and residue was dried under vacuum at with gentle heating for 1-2 hours to get the title compound as ditrifluoroacetate salt (Yield: 15 mg).

NMR (CD$_3$OD, 400MHz); δ 0.9-1.1 (m, 6H), 1.37-1.75 (m,5H), 1.76-2.07 (m, 3H), 2.30-2.75 (m,3H), 2.90-3.10 (m,2H), 3.70-3.90 (m, 2H), 3.91-4.00 (m,1H), 4.21-4.33 (m,1H), 4.35-4.56 (m,2H), 7.20-7.40 (m,2H).
Following compounds are prepared using the similar route of synthesis as above:

\[ N-[(15)-1-carboxy-2-hydroxyethyl]-L-alanyl-(4S)-4-\{[(3 \ R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline \] (Compound No. 49),

\[ MS \ (+ve, \ ion \ mode); \ 505.64 \ (M+1) \]

**Path B**

**Example 7A:** Synthesis of \[ N-[(lS)-1-carboxy-2-cyclopropylethyll-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluoro-phenyl)butanoyl]amino\}-L-proline \] dilithium salt (Compound no. 37)

**Step-I:** \[ tert-butyl \ N-[(2S)-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-prolinate \]

This compound was prepared following the similar procedure as described in step II (Example 6) using \[ L-cyclopropyl \ alanine \ ethyl \ ester \] \(0.070 \, g, \, 0.445 \, mmol), \[ tert-butyl \ (4S)-l-(2-bromopropanoyl)-4-\{[(3 \ R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-prolinate \] \(0.2 \, g, \, 0.296 \, mmol), \[ potassium \ carbonate \] \(0.123 \, g, \, 0.890 \, mmol), \[ potassium \ iodide \] \(0.01 \, g \) in dry acetonitrile \(5.0 \, ml \) (Yield: 0.105 g).

\[ MS \ (+ve, \ ion \ mode); \ 712.79 \ (M+1) \]

**Step-II:** \[ N-[(2S)-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline \]

This compound was prepared following the similar procedure as described in step III (Example 6) using \[ tert-butyl \ N-[(2S)-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-[(tert-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-prolinate \] \(0.045 \, g, \, 0.063 \, mmol) and \[ trifluoroacetic \ acid \] \(0.29 \, ml, \, 3.78 \, mmol \) (Yield: 0.030 g).

\[ MS \ (+ve, \ ion \ mode); \ 557.26 \ (M+1) \]
**Step-III:** \(N\)-[(lS)-l-carboxy-2-cyclopropylethyl]-L-alanyl-(4S)-4-[[3R)-3-amino-4-(2,4,5-trifluoro-phenyl)butanoyl]amino]-L-proline dilithium salt (Compound no. 37)

To a solution of \(N\)-[(2S)-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl]-L-alanyl-(4S)-4-[[3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (0.020 g, 0.036 mmol) in tetrahydrofuran (0.5 ml), lithium hydroxide monohydrate (0.040 g, 0.089 mmol) was added. After about 5 minutes, water (0.1 ml) was added and the reaction mixture was stirred at ~ 25°C for about 18 hours. The reaction mixture was concentrated and diethyl ether was added to it, stirred vigorously and ether layer was decanted. This resulting residue was dried under vacuum at with gentle heating for 1-2 hours to get the title compound as dilithium salt (Yield: 0.015 g).

NMR (D₂O, 400MHz): \(\delta\) 0.07-0.20 (m, 2H), 0.40-0.55 (m, 2H), 0.6-0.9 (m, IH), 1.1-1.3 (m, 4H), 1.4-1.6 (m, 2H), 1.8-1.95 (m, IH), 2.20-2.45 (m, 3H), 2.5-2.80 (m, 3H), 3.0-3.30 (m, IH), 3.40-3.60 (m, 2H), 3.65-3.85 (m, IH), 3.90-4.10 (m, IH), 4.35-4.54 (m, 2H), 7.0-7.35 (m, 2H).

MS (+ve, ion mode); 529.26 (M+l)

The following compounds were prepared employing procedures as provided in Examples 7 or Examples 7a described above:

\(N\)-[(2S)-l-ethoxy-l-oxopentan-2-yl]-L-alanyl-(4S)-4-[[3R)-3-amino-4-(2,4,5-trifluorophenyl) butanoyl] amino}]-L-proline (Compound no. 23) ditrifluoroacetate salt

\(N\)-[(25')-l-ethoxy-l-oxo-3-phenylpropan-2-yl]-L-alanyl-(4S)-4-[[3R)-3-amino-4-(2,4,5-trifluorophenyl) butanoyl] amino}]-L-proline ditrifluoroacetate salt (Compound no. 25),

MS (+ve, ion mode); 593.10 (M+l);

\(N\)-[(15)-l-cyclohexyl-2-ethoxy-2-oxoethyl]-L-alanyl-(4S)-4-[[3R)-3-amino-4-(2,4,5-trifluoro-phenyl)butanoyl] amino}]-L-proline ditrifluoroacetate salt (Compound no. 26),

MS (+ve, ion mode); 585.25 (M+l);
N-[(25)-3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound no. 27)

MS (+ve, ion mode); 551.26(M+1);

N-[(15)-l-carboxy-2-methylpropyl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl) butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound no. 28),

MS (+ve, ion mode); 517.24(M+1);

(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-{(25)-2-[{(25)-2-(methoxy-carbonyl)pyrrolidin-1-yl]propanoyl}\}-L-proline ditrifluoroacetate salt (Compound no. 29),

MS (+ve, ion mode); 529.60(M+1);

N-[(25)-1,4-diethoxy-1,4-dioxobutan-2-yl]-L-alanyl-(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluoro-phenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound no. 30),

MS (+ve, ion mode); 589.48(M+1);

N-[(l-methoxy-2-methyl-l-oxopropan-2-yl)-L-alanyl-(45')-4-\{[(3 R)-3-amino-4-(2,4,5-trifluoro-phenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound no. 31),

MS (+ve, ion mode); 517.38(M+1);

N-(l-carboxypentyl)-L-alanyl-(45')-4-\{[(3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound no. 32)

MS (+ve, ion mode); 621.54(M+1);
\[N-\{(25)-1\text{-ethoxy-1-oxo-4-phenylbutan-2-yl}\}-L\text{-alanyl-}(45)-4\{-[(3\ R)-3\text{-amino-4-(2,4,5-trifluorophenyl)} \text{butanoyl]} \text{ amino }\}L\text{-proline ditrifluoroacetate salt (Compound no. 33)}\]

MS (+ve, ion mode); 607.69(M+1);

\[N-\{(15)-1\text{-carboxybutyl}\}-L\text{-alanyl-}(45)-4\{-[(3\ R)-3\text{-amino-4-(2,4,5-trifluorophenyl)} \text{butanoyl]} \text{ amino }\}L\text{-proline dilithium salt (Compound no. 34)}\]

MS (+ve, ion mode); 517.09(M+1);

\[N-\{(15)-1\text{-carboxy-2-phenylethyl}\}-L\text{-alanyl-}(45)-4\{-[(3\ R)-3\text{-amino-4-(2,4,5-trifluorophenyl)} \text{butanoyl]} \text{ amino }\}L\text{-proline dilithium salt (Compound no. 35)}\]

MS (+ve, ion mode); 565.18(M+1);

\[N-\{(5')-\text{carboxy(cyclohexyl)methyl}\}-L\text{-alanyl-}(45\text{,45})-4\{-[(3\ R)-3\text{-amino-4-(2,4,5-trifluorophenyl)} \text{butanoyl]} \text{ amino }\}L\text{-proline dilithium salt (Compound no. 36)}\]

MS (+ve, ion mode); 557.26(M+1);

\[(25,45)-4\{-[(3\ R)-3\text{-amino-4-(2,4,5-trifluorophenyl)} \text{butanoyl]} \text{amino}\}-1\{-(25)-2\{-[(25)-2\text{-carboxypyrrolidin-1-yl} \text{propanoyl}\} \text{pyrrolidine-2-carboxylic acid dilithium salt (Compound no. 38)}\]

MS (+ve, ion mode); 515.50(M+1);

\[N-\{(15')-1,2\text{-dicarboxyethyl}\}-L\text{-alanyl-}(45\text{,45})-4\{-[(3\ R)-3\text{-amino-4-(2,4,5-trifluorophenyl)} \text{butanoyl]} \text{amino}\}L\text{-proline dilithium salt (Compound no. 39)}\]

MS (+ve, ion mode); 533.42(M+1);

\[N-\{(25)-1\text{-carboxy-2-methylbutyl}\}-L\text{-alanyl-}(45)-4\{-[(3\ R)-3\text{-amino-4-(2,4,5-trifluorophenyl)} \text{butanoyl]} \text{amino}\}L\text{-proline ditrifluoroacetate salt (Compound no. 40)}\]
**MS (+ve, ion mode); 531.21(M+1);**

\[ N\]\-[(15)-l-carboxyethyl]-L-alanyl-(45)-4-\{[(3 \text{ R})-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl] amino }-L-proline ditrifluoroacetate salt (Compound no. 41)

**MS (+ve, ion mode); 531.43(M+1);**

\[ N\]\-[(15)-l-carboxypentyl]-L-alanyl-(45)-4-\{[(3 \text{ R})-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl] amino }-L-proline ditrifluoroacetate salt (Compound no. 46)

\[ N\]\-[(15)-l-carboxyprop-2-yl]-L-alanyl-(45)-4-\{[(3 \text{ R})-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl] amino }-L-proline dilithium salt (Compound no. 45)

**MS (+ve, ion mode); 503.40(M+1);**

\[ N\]\-[(15)-l-carboxypropyl]-L-alanyl-(45)-4-\{[(3 \text{ R})-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl] amino }-L-proline dilithium salt (Compound no. 43)

**MS (+ve, ion mode); 549.27(M+1);**

\[ N\]\-[(15)-l,3-dicarboxypropyl]-L-alanyl-(45)-4-\{[(3 \text{ R})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino }-L-proline dilithium salt (Compound no. 44)

**MS (+ve, ion mode); 547.21(M+1);**
58

\[ N\text{-}\{(15)\text{-}l\text{-}carboxypropyl\}-L\text{-}alanyl}\{(45)\text{-}4-\{(3\text{ }R\text{)}\text{-}3\text{-}amino\text{-}4\text{-}(2,4,5\text{-}trifluorophenyl)butanoyl\} \text{ amino }\} \text{-}L\text{-}proline \text{ ditrilluoroacetate salt (Compound no. 47)} \]

MS (+ve, ion mode); 503.40(M+1);

5

\[ N\text{-}\{(15)\text{-}l\text{-}carboxybutyl\}glycyl\{(45)\text{-}4-\{(3R\text{-}3\text{-}amino\text{-}4\text{-}(2,4,5\text{-}trifluorophenyl)butanoyl\} \text{ amino }\} \text{-}L\text{-}proline \text{ ditrilluoroacetate salt (Compound no. 48)} \]

MS (+ve, ion mode); 503.13 (M+l);

10

\[ N\text{-}\{(25)\text{-}6\text{-}amino\text{-}l\text{-}ethoxy\text{-}l\text{-}oxohexan\text{-}2\text{-}yl\}\text{-}L\text{-}alanyl\{(45)\text{-}4-\{(3R\text{-}3\text{-}amino\text{-}4\text{-}(2,4,5\text{-}trifluorophenyl)butanoyl\} \text{ amino }\} \text{-}L\text{-}proline \text{ (Compound No. 52)}, \]

MS (+ve, ion mode); 574.74(M+1)

15

\[ N\text{-}\{(15')\text{-}5\text{-}amino\text{-}l\text{-}carboxypentyl\}\text{-}L\text{-}alanyl\{(45)\text{-}4-\{(3R\text{-}3\text{-}amino\text{-}4\text{-}(2,4,5\text{-}trifluorophenyl)butanoyl\} \text{ amino }\} \text{-}L\text{-}proline \text{ (Compound No. 53),} \]

MS (+ve, ion mode); 546.76(M+1)

20

\[ N\text{-}\{(25)\text{-}3\text{(benzyloxy)\text{-}l\text{-}ethoxy\text{-}l\text{-}oxopropan\text{-}2\text{-}yl\}\text{-}L\text{-}alanyl\{(45)\text{-}4-\{(3R\text{-}3\text{-}amino\text{-}4\text{-}(2,4,5\text{-}trifluorophenyl)butanoyl\} \text{ amino }\} \text{-}L\text{-}proline \text{ (Compound No. 73),} \]

MS (+ve, ion mode); 622.88(M+1)

25

\[ N\text{-}\{(15')\text{-}l\text{-}carboxy\text{-}3\text{-}methylbutyl\}\text{norleucyl}\text{-}4\text{-}\{(3\text{-}amino\text{-}4\text{-}(2,4,5\text{-}trifluorophenyl)butanoyl}\) \text{ amino }\} \text{-}L\text{-}proline \text{ (Compound No. 74),} \]

MS (+ve, ion mode); 573.41(M+1)

\[ N\text{-}\{(15)\text{-}2\text{(benzyloxy)\text{-}l\text{-}carboxyethyl\}\text{-}L\text{-}alanyl\{(45)\text{-}4-\{(3R\text{-}3\text{-}amino\text{-}4\text{-}(2,4,5\text{-}trifluorophenyl)butanoyl\} \text{ amino }\} \text{-}L\text{-}proline \text{ (Compound No. 75),} \]


MS (νe, ion mode); 595.4(M+1)

N-[(25)-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl]norvalyl-4-[[3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino]praline (Compound No. 76),

MS (+ve, ion mode); 585.34(M+1)

N-[(25)-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl]-L-norleucyl-(45)-4-[[3(R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino]-L-proline (Compound No. 77),

MS (+ve, ion mode); 599.43(M+1)

(45)-4-{{[3(R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino}-l-{[25]-2-{{[25]-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl] amino}butanoyl]-L-proline (Compound No. 78),

MS (+ve, ion mode); 571.39(M+1)

(45)-4-{{[3(R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino}-l-{{[25]-2-{{[25]-l-carboxy-3-methylbutyl] amino}butanoyl]-L-proline (Compound No. 79),

MS (+ve, ion mode); 545.3(M+1)

ASSAY METHODS

DPP IV Assay

Materials:

H-Gly-Pro-7-amido-methyl Coumarine (Gly-Pro-AMC; Cat. # G2761) and 7-amido-methyl Coumarine (AMC; Cat. # A9891) were purchased from Sigma. 1 mM Gly-Pro-AMC stock solution was prepared in 50 mM HEPES buffer, pH 7.8 containing 80 mM MgCl2, 140 mM NaCl and 1% BSA (working buffer). 1 mM AMC was prepared in 10% dimethylsulfoxide (DMSO). Aliquots were stored at -20°C.
Assay: The DPP IV assay was carried out as described earlier with slight modifications (J. Med. Chem. 2003, 46, 2774-2789). The test compounds were dissolved in 100% dimethylsulfoxide (DMSO) to get a final concentration of 10 mM. The compounds were diluted serially in 10% DMSO to get 10X concentrations of 10 nM, 100 nM, 1000 nM, 10 µM, 100 µM, and 1000 µM. The source of DPP IV was human plasma which was procured from local blood bank. DPP IV (10 µl human plasma) was mixed in 96 well fluoroNunc plates with test compounds. The final concentrations of the compounds were 1 nM, 10 nM, 100 nM, 1000 nM, 10 µM and 100 µM in working buffer and pre-incubated at 25°C for 15 minutes. The assay was also carried out without compound and with 1% DMSO (final concentration) as vehicle control. The reaction was started by adding 20 µl of 0.1 mM H-Gly-Pro AMC (40 µM final concentration), mixed and incubated at 25°C for 20 minutes. The reaction was arrested by adding 50 µl of 25% acetic acid and read at 380 nm excitation and 460 nm emissions.

The DPP IV releases AMC from Gly-Pro-AMC which was quantitated as relative fluorescence units (RFU). The percentage of activity was calculated as follows:

\[
\text{activity} = \left( \frac{\text{RFU of test (with compound)}}{\text{RFU of vehicle control}} \right) \times 100
\]

**IC\textsubscript{50} determination**

The IC\textsubscript{50} is defined as the concentration of the inhibitor required to inhibit 50% of the human DPP IV activity under specific assay conditions. The activity obtained at different concentrations of the compound was plotted as log (X) vs % activity in y axis. The data was analysed by GraphPad Prism 4.

The compounds provided herein showed activity (IC\textsubscript{50}) between 0.057 µM - 2.2 µM. More specifically, the compounds showed a range of activity between 0.057 µM - 1 µM.

**ACE Assay:**

The ACE assay was carried out as described earlier with slight modifications (J. Biol. Chem. 2001, 276, 5525-5532) using purified human recombinant enzyme source. The test compounds were dissolved in 100% dimethylsulfoxide (DMSO) to get a final concentration of 10 mM. The compounds were diluted serially in 10% DMSO to get 10X concentrations of 10 nM, 100 nM, 1000 nM, 10 µM, 100 µM, and 1000 µM.
concentrations of 1µM, 10 µM, 100 µM, 400 µM, 800 µM, 1 mM and 10 mM. 20 ng ACE was mixed in 96 well fluronunc plates with test compounds. The final concentrations of the compounds were 100 nM, 1 µM, 10 µM, 40 µM, 80 µM, 100 µM and 1 mM in 50 mM MES working buffer pH 6.5 and pre-incubated at ~25°C for 10 minutes. The standard compound captopril was diluted serially in milliQ to get final concentrations as 100 pM, 1 nM, 10 nM, 100 nM, 1 µM, 10 µM and 100 µM. The assay was also carried out without compound and with 1% DMSO (final concentration) as vehicle control. The reaction was started by adding 10 µl of 100 µM Mca-Arg-Pro-Gly-Phe-Ser-Ala-Phe-Lys (Dnp)-OH (10 µM final concentration) mixed and incubated at ~25°C for 20 minutes. The plate was read immediately after 20 minutes without stopping the reaction at 320 nm excitation and 405 nm emission in Sapphire attached to TECAN.

Calculation: The ACE releases Mca from Mca-Arg-Pro-Gly-Phe-Ser-Ala-Phe-Lys (Dnp)-OH which was quantitated as relative fluorescence units (RFU). The percentage of activity was calculated as follows: = (100/RFU of vehicle control) x RFU of test (with compound).

IC₅₀ determination

The IC₅₀ is defined as the concentration of the inhibitor required to inhibit 50% of the human ACE activity under specific assay conditions. The activity obtained at different concentrations of the compound was plotted as log (X) vs % activity in y axis. The data was analyzed by GraphPad Prism 4.

The compounds provided herein showed activity (IC₅₀) between 0.006 µM -100 µM. More specifically, the compounds showed a range of activity between 0.006 µM - 10 µM.
We claim:

1. Compounds having the structure of Formula I

and their pharmaceutically acceptable salts, enantiomers, or diastereomers

wherein

n is an integer 0-2;

R is hydrogen or alkyl;

X is \(-\text{CH}_2\) or \(-\text{C}(=\text{O})\)-;

Y is \(-\text{CH-}\) or \(-\text{N-}\);

If Y is \(-\text{CH}\) then \(R_i\) is \(\text{-R}_\text{a}-\text{R}_\text{b}\), wherein \(\text{R}_\text{a}\) is a direct bond, \(-\text{NH-}\), \(-0-\), \(-\text{C}=\text{O}\), alkylene, \(-\text{CO-alkylene}\), \(-\text{NRCO-}\), \(-\text{CONH-}\), \(-\text{OCO-}\) wherein \(R\) is as defined above and \(\text{R}_\text{b}\) can be

wherein \(G\) is independently hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carbonyl, thiocarbonyl or oxo; \(f\) can be 0-3; \(R_j\) is alkyl, alkenyl, alkynyl, hydroxy, alkoxy, amino or \(\text{NR}_\text{a}\text{R}_\text{y}\) (wherein \(\text{R}_\text{a}\) and \(\text{R}_\text{y}\) are independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaryalkyl, heterocyclyl or heterocyclylalkyl); and \(\text{R}_k\) is alkylene or \(-\text{NH-alkylene}\);

If Y is \(-\text{N}\) then \(R_i\) is \(\text{-R}_\text{A}-\text{R}_\text{b}\), wherein \(\text{R}_\text{A}\) is a direct bond, \(-\text{C}=\text{O}\), alkylene, \(-\text{CO-alkylene}\), \(-\text{CONH-}\) and \(\text{R}_\text{b}\) is same as defined above;
R₂ is

wherein R₃ can be aralkyl, (CH₂)ₚSRₚ.

wherein R₁ is hydrogen, alkyl, -CO-alkyl, -CO-aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclylalkyl, cycloalkyl or cycloalkylalkyl; q is an integer 1-3; R₄ is hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, cycloalkylalkyl, alkyl-COOR, (CH₂)ₚSRₚ, alkyl-ORₖ; wherein R₅ is hydrogen, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl; R₆ is direct bond, alkyne; Rₗ can be NHCORₑ (wherein Rₑ can be aryl, heteroaryl, heterocyclyl, cycloalkyl); Rₛ and Rᵣ can independently be hydrogen, alkyl, aralkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl or can join together along with the carbon and nitrogen to which they are attached to form a ring system; R₄ and R₅ can also join together along with the carbon to which they are attached to form a ring system and p is an integer 0-2;

R₄ and Rₛ are independently hydrogen, alkyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, aralkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl, alkylamine, alkyl-COR, alkyl-ORₑ; wherein R is hydroxy, alkoxy, NHR and R and Rₑ are as defined earlier or R₄ and Rₛ can join together along with the carbon to which they are attached to form a ring system or Rₛ and Rₛ can join together along with the carbon and nitrogen to which they are attached to form a ring system;

R₆ can be , aralkyl or (CH₂)ₚSRₚ.
2. Compounds having the structure of Formula 1a and their pharmaceutically acceptable salts, enantiomers, or diastereomers wherein

$P_q$ is $N$-protecting group;

$R$ is hydrogen or alkyl;

$G$ are independently hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carbonyl, thiocarbonyl or oxo;

$f$ can be 0-3;

$R_2$ is

$$
\begin{align*}
\text{or } & \\
\text{wherein } R_3 \text{ can be aralkyl, } \left(\text{CH}_2\right)_q\text{SR, } \\
\end{align*}
$$

$R_u$ is hydrogen, alkyl, -CO-alkyl, -CO-aryl, aralkyl, heteroaryl, heteroarylmethyl, heterocyclyl, heterocyclylmethyl, cycloalkyl or cycloalkylalkyl; $q$ is an integer 1-3; $R_d$ is hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkylalkyl, cycloalkylalkylalkylalkyl, alkyl-COOR, (CH$_2$)$_q$SR, alkyl-OR; wherein $R_f$ is hydrogen, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl, heterocyclylmethyl, cycloalkylalkyl, cycloalkylalkylalkyl, alkyl-COOR, (CH$_2$)$_q$SR, alkyl-OR; wherein $R_r$ is hydrogen, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl, heterocyclylalkyl, cycloalkylalkyl, cycloalkylalkylalkyl, alkyl-COOR, (CH$_2$)$_q$SR, alkyl-OR; wherein $R_{sp}$ is direct bond, alkylene; $R_p$ is NHCOR$_e$ (wherein $R_e$ is aryl, heteroaryl, heterocyclyl, cycloalkyl); $R_s$ and $R_r$ is independently hydrogen, alkyl, aralkyl, cycloalkylalkyl, heteroarylalkyl,
heterocyclylalkyl or can join together along with the carbon and nitrogen to which they are attached to form a ring system; \( R_d \) and \( R_r \) can also join together along with the carbon to which they are attached to form a ring system and \( p \) is an integer 0-2;

\( R_d \) and \( R_s \) is independently hydrogen, alkyl, aryl, cycloalkyl, heterocyclyl, heteroaryl, aralkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl, \( C_i \)

\( \alpha \)alkylamine, alkyl-COR,

alkyl-OR; wherein R is hydroxy, alkoxy, NHR and R and \( R_d \) are as defined earlier or \( R_d \) and \( R_s \) can join together along with the carbon to which they are attached to form a ring system or \( R_d \) and \( R_s \) can join together along with the carbon and nitrogen to which they are attached to form a ring system;

\[
\begin{array}{c}
\text{O} \\
\text{OH}
\end{array}
\text{CH}_2_p \underbrace{\text{O}}_{\text{R}_d}
\]

\( R_6 \) can be ..., aralkyl or \( (\text{CH}_2)_q \text{SR}_{u} \).

Compound selected from the group consisting of:

(45)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-\{(25)-2-methyl-3-sulfanylpropanoyl\}-L-proline difluoroacetate salt (Compound No. 1),

Methyl (4S)-l-\{(25')-3-(acetylsulfanyl)-2-methylpropanoyl\}-4-\{ [(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-prolinate difluoroacetate salt (Compound No. 2),

(45)-l-\{(25)-3-(acetylsulfanyl)-2-methylpropanoyl\}-4-\{ [(3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-proline difluoroacetate salt (Compound No. 3),

(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-\{3-(phenylcarbonyl)sulfanyl\}propanoyl\}-L-proline difluoroacetate salt (Compound No. 4),

\( N-[(15)-l\text{-carboxy-3-phenylpropyl}]\text{-L-alanyl-(45)-4-\{[(3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-proline difluoroacetate salt (Compound No. 5),

\( N-[(15)-l\text{-carboxy-3-phenylpropyl}]\text{-L-alanyl-(45)-4-\{[(3 R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-proline dilithium salt (Compound No. 5a),
Methyl N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 6),

N-[(25)- 1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-valyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 8),

N-[(15)-l-carboxy-3-phenylpropyl]-L-valyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 9),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-leucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 10),

N-[(15)-l-carboxy-3-phenylpropyl]-L-leucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline dilithium salt (Compound No. 11),

N-[(15)-l-carboxy-2-methylbutyl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 12),

N-[(15')-l-carboxy-3-phenylpropyl]-L-isoleucyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline dilithium salt (Compound No. 13),

N-[(25)- 1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-phenylalanyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 14),

N-[(15')-l-carboxy-3-phenylpropyl]-L-phenylalanyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline dilithium salt (Compound No. 15),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-seryl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 16),

N-[(15)-l-carboxy-3-phenylpropyl]-L-seryl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline dilithium salt (Compound No. 17),

N-[(25)- 1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-tyrosyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline ditrifluoroacetate salt (Compound No. 18),

N-[(15)-l-carboxy-3-phenylpropyl]-L-tyrosyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino\} -L-proline dilithium salt (Compound No. 19),
N-[(15)-l-carboxy-3-phenylpropyl]glycyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 20),

N-[(2S)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 21),

N-[(15)-l-carboxy-3-phenylpropyl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-(2,4,5-
trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 22),

N-[(2S)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 23),

N-[(15)-l-carboxy-3-methylbutyl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 24),

N-[(2S')-l-ethoxy-l-oxo-3-phenylpropan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 25),

N-[(15)-l-cyclohexyl-2-ethoxy-2-oxoethyl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 26),

N-[(2S')-3-cyclopropyl-L-ethoxy-l-oxopropan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluoropheny]butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 27),

N-[(15)-l-carboxy-2-methylpropyl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 28),

(4S)-4-\{[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoylamino]\}-l-\{(2S)-2-(methoxy-carbonyl)pyrrolidin-1-yl\}-propanoyl]-L-proline ditrifluoroacetate salt (Compound No. 29),

N-[(2S)-l,4-diethoxy-l,4-dioxobutan-2-yl]-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 30),

N-(l-methoxy-2-methyl-l-oxopropan-2-yl)-L-alanyl-(4S)-4-\{[(3R)-3-amino-4-
(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 31),
N-(l-carboxypentyl)-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline ditrifluoroacetate salt (Compound No. 32),

N-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline ditrifluoroacetate salt (Compound No. 33),

N-[(15)-l-carboxybutyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline dilithium salt (Compound No. 34),

N-[(15)-l-carboxy-2-phenylethyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline dilithium salt (Compound No. 35),

N-[(5)-carboxy(cyclohexyl)methyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline dilithium salt (Compound No. 36),

N-[(25)-l-carboxy-2-cyclopropylethyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline dilithium salt (Compound No. 37),

N-[(15)-l,2-dicarboxyethyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline dilithium salt (Compound No. 39),

N-[(25)-l-carboxy-2-methylbutyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline ditrifluoroacetate salt (Compound No. 40),

N-[(1S)-l-carboxyethyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline ditrifluoroacetate salt (Compound No. 41),

N-[(25)-l-methoxy-4-(methylsulfanyl)-l-oxobutan-2-yl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline ditrifluoroacetate salt (Compound No. 42),

N-[(15)-l-carboxy-3-(methylsulfanyl)propyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline dilithium salt (Compound No. 43),

N-[(15)-l,3-dicarboxypropyl]-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline dilithium salt (Compound No. 44),

N-(2-carboxypropan-2-yl)-L-alanyl-(4S)-4-{{(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl} amino}-L-proline dilithium salt (Compound No. 45),
N-\[(15)-l-carboxypentyl\]-L-alanyl-(45)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline ditrifluoroacetate salt (Compound No. 46),

N-\[(15)-l-carboxypropyl\]-L-alanyl-(45)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline ditrifluoroacetate salt (Compound No. 47),

N-\[(15)-l-carboxybutyl\]glycyl-(45)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline ditrifluoroacetate salt (Compound No. 48),

N-\[(15)-l-carboxy-2-hydroxyethyl\]-L-alanyl-(45)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline ditrifluoroacetate salt (Compound No. 49),

N-\[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl\]-L-norvalyl-(4S)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline(Compound No. 50),

N-\[(15)-l-carboxy-3-phenylpropyl\]-L-norvalyl-(45)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline, (Compound No. 51),

N-\[(25)-6-amino-1-ethoxy-1-oxohexan-2-yl\]-L-alanyl-(4S)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline (Compound No. 52),

N-\[(15)-5-amino-l-carboxypentyl\]-L-alanyl-(45)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline (Compound No. 53),

(4S)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-\[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl\] amino Jbutanoyl]-L-proline (Compound No. 54),

(4S)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-\[(15)-l-carboxy-3-phenylpropyl\] amino ]butanoyl]-L-proline (Compound No. 55),

N-/(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-norleucyl-(45')-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline (Compound No. 56),

(4S)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-[\[(15)-l-carboxy-3-phenylpropyl\] amino Jbutanoyl]-L-proline (Compound No. 57),

N\textsuperscript{2}-\[(15)-l-carboxy-3-phenylpropyl\]-L-lysyl-(45)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline (Compound No. 58),

N-\[(25)-l-ethoxy-1-oxo-4-phenylbutan-2-yl\]-2-methylalanyl-(45)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino \}-L-proline (Compound No. 59),

(4S)-4-\{[(\text{\textit{R}})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino \}-L-[\[(25)-l-ethoxy-1-oxo-4-phenylbutan-2-yl] amino Jcyclopentyl]carbonyl]-L-proline (Compound No. 60),
1-{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-D-prolyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 61),

N-{[(15)-l-carboxy-3-phenylpropyl]-2-methylalanyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 62),

(4S)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-l-{[(1S)-l-carboxy-3-phenylpropyl]amino}cyclopentyl]carbonyl]-L-proline (Compound No. 63),

1-{[(15)-l-carboxy-3-phenylpropyl]-D-prolyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 64),

3-cyclopropyl-N-{[(25')-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 65),

(25,45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-l-{[(25)-l-ethoxy-1-oxo-4-phenylbutan-2-yl] amino}-5-methoxy-5-oxopentanoyl]pyrrolidine-2-carboxylic acid (Compound No. 66),

N-{[(15)-l-carboxy-3-phenylpropyl]-L-a-glutamyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 67),

N²-[(25)-l-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-asparaginyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 68),

N²-[(15)-l-carboxy-3-phenylpropyl]-L-asparaginyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 69),

N-{l-carboxy-3-phenylpropyl]-L-threonyl-(45')-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 70),

N-{[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]0-methyl-L-seryl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 71),

N-{[(15)-l-carboxy-3-phenylpropyl]-l-0-methyl-L-seryl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 72),

N-{[(2S)-3-(benzyloxy)-l-ethoxy-l-oxopropan-2-yl]-L-alanyl-(4S)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 73),

N-{[(15')-l-carboxy-3-methylbutyl]norleucyl-4-[(3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino]praline (Compound No. 74),

N-{[(15)-2-(benzyloxy)-l-carboxyethyl]-L-alanyl-(4S)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino}-L-proline (Compound No. 75),

N-{[(2S')-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl]norvalyl-4-[(3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino]praline (Compound No. 76),
N-[(25')-3-cyclopropyl-l-ethoxy-l-oxopropan-2-yl]-L-norleucyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 77),

(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-l-[(25)-2-[(25)-3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl] amino]butanoyl]-L-proline (Compound No. 78),

(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-l-[(25)-2-[(15)-l-carboxy-3-methylbutyl]amino]butanoyl]-L-proline (Compound No. 79),

(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-l-[(25)-2-[(15)-l-carboxy-3-phenylpropyl]amino]butanoyl]-L-proline (Compound No. 80),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] -L-norvalyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 81),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] -L-norleucyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 82),

(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-l-[(25)-2-[(15)-l-carboxy-3-phenylpropyl]amino]butanoyl]-L-proline (Compound No. 83),

N-[(15)-l-carboxy-3-phenylpropyl]-L-norvalyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 84),

N-[(15)-l-carboxy-3-phenylpropyl]-L-norleucyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 85),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 86),

N-[(15)-l-carboxy-3-phenylpropyl]-L-alanyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 87),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-D-norvalyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 88),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-D-norleucyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 89),

N-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-D-alanyl-(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 90),

(45)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-l-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] amino]butanoyl]-L-proline (Compound No. 91),
4. A pharmaceutical composition comprising therapeutically effective amount of
compound of Formula I as defined in claims 1-3 together with one or more
pharmaceutically acceptable carrier, excipients or diluents.

5. A pharmaceutical composition of claim 4 further comprising one or more
therapeutic agents selected from anti-hypertensive agents, dyslipidemic agents,
anti-obesity agents, anti-hyperglycemic agents and anti-inflammatory agents.

6. A method for palliative, curative or prophylactic treatment of diseases or
conditions of diabetes and/or hypertension in a mammal by administering an
effective amount of a compound according to claim 1.

7. A method for palliative, curative or prophylactic treatment of diseases or
conditions of a mammal suffering from diabetes and/or hypertension, wherein the
diabetes is treated by dipeptidyl peptidases -IV (DPP-IV) inhibition and also
benefited by ACE inhibition and hypertension is treated by angiotensin converting
enzyme (ACE) inhibition by administrating an effective amount of a compound
according to claim 1.

8. A method according to claim 7, wherein the diseases or conditions of diabetes are
selected from the type 2 diabetes, prediabetes, dyslipidemia, metabolic syndrome,
metabolic acidosis, ketosis, and satiety disorders, diabetic nephropathy and end
organ damage such as kidney and brain and diseases or conditions of hypertension
are selected from hypertension with or without incipient nephropathy, myocardial
infarction, stroke, increased collagen formation, fibrosis, remodeling following
hypertension, congestive heart failure, left ventricular hypertrophy, survival post
myocardial infarction (MI), coronary artery diseases, atherosclerosis, angina pectoris or thrombosis

9. A process for preparing a compound of Formula XIV, XIVa and XVI comprising

a. reacting compound of Formula XI

\[
\text{Formula XI}
\]

with a compound of Formula XII

\[
\text{Formula XII}
\]

to give a compound of Formula XIII

\[
\text{Formula XIII}
\]

b. IV-deprotection of compound of Formula XIII to give a compound of XIV (when \( R_m \) is COCH\(_3\) and when \( R' \) is not \( t \)-butyl) (Path A)

\[
\text{Formula XIV}
\]

or

a. deprotection of compound of Formula XIII to give a compound of Formula XV (when \( R' \) is not \( t \)-butyl) (Path B),
b. N-deprotection of compound of Formula XV to give a compound of XIV,

or

a. hydrolysis of compound of Formula XIII to give a compound of Formula XIVa (when \( R_p \) is t-butyl and \( P_q \) is Boc) (Path C)

wherein

\( G \) is hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carbonyl, thio carbonyl or oxo;

\( f \) can be 0-3;

\( R_p \) is carboxy-protecting group, for example, methyl, ethyl i-butyl, benzyl, trimethylsilyl;

\( P_q \) is \( N \)-protecting group;
$R_m$ is sulfur-protecting group selected from the group consisting of acyl, thioacyl, alkyl, aryl, benzoyl and organothio groups comprising from 1 to about 10 carbon atoms or when taken together with the sulfur atom to be protected, is a hemithioacetal group, for example, tetrahydrofuranyl, 2-methyl tetrahydrofuranyl, tetrahydropyranyl, 2-methyl tetrahydropyranyl, ethoxyethyl, and methoxymethyl groups.

10. A process for preparing a compound of Formula XX, XIXa and XIXb comprising

a. reacting compound of Formula XI

\[
\begin{array}{c}
\text{(G)}_1 \\
\text{H} \\
\text{N} \\
\text{P} \\
\text{O} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{P} \\
\text{O} \\
\text{O}
\end{array}
\end{array}
\]

\[\text{O} \quad \text{OR}\]

Formula XI

with a compound of Formula XVII

\[
\begin{array}{c}
\text{HC} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\]

\[\text{R}_w \quad \text{R}_s \quad \text{R}_d \quad \text{RO}_\text{Et}
\]

Formula XVII

to give a compound of Formula XVIII

\[
\begin{array}{c}
\text{(G)}_1 \\
\text{H} \\
\text{N} \\
\text{P} \\
\text{O} \\
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{P} \\
\text{O} \\
\text{O}
\end{array}
\end{array}
\]

\[\text{O} \quad \text{OR}\]

Formula XVIII

b. hydrolyzing a compound of Formula XVIII (when $R_{pr}$ is not i-butyl) to give a compound of Formula XIX (Path A)
c. deprotected compound of Formula XIX to give a compound of Formula XX,

or

a. deprotecting compound of Formula XVIII (when $R_p$ is i-butyl and $P_q$ is Boc) to give a compound of Formula XIXa (Path B),

b. hydrolyzing compound of Formula XIXa to give a compound of Formula XX,

or

a. deprotecting compound of Formula XVIII (when $R_p$ is not i-butyl) to give a compound of Formula XIXb (Path C)
wherein

- \( R_d \) is hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, \( C_{1-6} \) alkylamine, aralkyl, heterocyclylalkyl, cycloalkylalkyl, heteroarylalkyl, alkyl-COOR, (CH\(_2\))\(_q\)SR\(_u\), alkyl-OR\(_f\); wherein \( R_f \) is hydrogen, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl; \( R_s \) and \( R_r \) are independently hydrogen, alkyl, aralkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl or can join together along with the carbon and nitrogen to which they are attached to form a ring system;

- \( R_w \) is alkyl, arylalkyl, CH\(_2\)OR\(_t\), cycloalkylalkyl, heterocyclylalkyl or heteroarylalkyl where \( R_f \) is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, \( C_{6}\)alkylamine, alkyl-COR' or alkyl-OR\(_f\), wherein \( R' \) is hydroxy, alkoxy, NHR and R is hydrogen or alkyl;

- \( G_s \) is hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carbonyl, thiocarbonyl or oxo;

- \( f \) can be 0-3;

- \( R_p \) is carboxy-protecting group, for example, methyl, ethyl i-butyl, benzyl, trimethylsilyl;

- \( P_q \) is N-protecting group;

- \( R_m \) is sulfur-protecting group selected from the group consisting of acyl, thioacetyl, alkyl, aryl, benzyol and organothio groups comprising from 1 to about 10 carbon atoms or when taken together with the sulfur atom to be protected, is a hemithioacetal group, for example, tetrahydrofuranyl, 2-
methyl tetrahydrofuranyl, tetrahydropyranyl, 2-methyl tetrahydropyranyl, ethoxyethyl, and methoxymethyl groups.

11. A process for preparing a compound of Formula XXV and XXVI comprising

a. coupling a compound of Formula XI

![Formula XI]

with a compound of Formula XXI

![Formula XXI]

to give a compound of Formula XXII.

![Formula XXII]

b. reacting a compound of Formula XXII with a compound of Formula XXIII

![Formula XXIII]

to give a compound of Formula XXIV,
c. deprotecting and hydrolyzing compound of Formula XXIV (when \( R_p \) is \( t \)-butyl and \( p_q \) is Boc) to give a compound of Formula XXVI

or

a. deprotecting compound of Formula XXIV (when \( R_p' \) is \( i \)-butyl and \( R_p \) is ethyl) to give a compound of Formula XXV (Path B)

b. hydrolyzing a compound of Formula XXV to give a compound of Formula XXVI

wherein
R is hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, C_{1-6} alkyamine, aralkyl, heterocyclylalkyl, cycloalkylalkyl, heteroaryalkyl, alkyl-COOR, (CH2)_qSR, alkyl-OR; wherein R_f is hydrogen, alkyl, arylalkyl, heteroaryalkyl, cycloalkylalkyl, heterocyclylalkyl; R_s and R_r are independently hydrogen, alkyl, aralkyl, cycloalkylalkyl, heteroaryalkyl, heterocyclylalkyl or can join together along with the carbon and nitrogen to which they are attached to form a ring system;

R_w is alkyl, arylalkyl, CH_2OR, cycloalkylalkyl, heterocyclylalkyl or heteroaryalkyl where R_i is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroaryalkyl, heterocyclyl, heterocyclylalkyl, Ci_6alkylamine, alkyl-COR or alkyl-OR, wherein R' is hydroxy, alkoxy, NHR and R is hydrogen or alkyl;

G is hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carbonyl, thiocarbonyl or oxo;

f can be 0-3;

R_p is carboxy-protecting group, for example, methyl, ethyl i-butyl, benzyl, trimethylsilyl;

P_q is N-protecting group;

R_m is sulfur-protecting group selected from the group consisting of acyl, thioacyl, alkyl, aryl, benzoyl and organothio groups comprising from 1 to about 10 carbon atoms or when taken together with the sulfur atom to be protected, is a hemithioacetal group, for example, tetrahydrofuranyl, 2-methyl tetrahydrofuranyl, tetrahydropyranyl, 2-methyl tetrahydropyranyl, ethoxyethyl, and methoxymethyl groups.
1 Compounds having the structure of Formula 1a

[Chemical Structure Image]

and their pharmaceutically acceptable salts, enantiomers, or diastereomers

wherein

Pq is N-protecting group;

R is hydrogen or (Ci-C₈) alkyl;

G are independently hydrogen, halogen, cyano, (C₅-C₈) alkyl, (d-C₈) alkenyl, (d-C₈) alkynyl, hydroxy, alkoxy, carbonyl, thiocarbonyl or oxo;

f can be 0-3;

R₂ is

[Chemical Structure Image]

wherein R₃ can be aralkyl, (CH₂)₉SR, R₄

[Chemical Structure Image]

wherein R₅ is hydrogen, (d-C₈) alkyl, -CO-alkyl(d-C₈), -CO-aryl(C₅-C₁₄), (C₅-C₁₄) aralkyl, (C₅-C₁₄) heteroaryl, (C₅-C₁₄) heterocyclylalkylCd-C₈, (C₅-C₁₄) heterocyclylalkyl(d-C₄), (C₅-C₁₄)cycloalkyl or (C₅-C₁₄) cycloalkylalkyl(d-C₄); q is an integer 1-3; R₆ is hydrogen, (d-C₈) alkyl, (C₅-C₁₄) aryl, (C₅-C₁₄) heteroaryl, (C₅-C₁₄) heterocyclyl, (C₅-C₁₄)cycloalkyl, (C₅-C₁₄)cycloalkylalkyl(d-C₄), (C₅-C₁₄) aralkyl(C₁-C₄), (C₅-C₁₄) heterocyclylalkyl(C₁-C₄), (C₅-C₁₄) alkylamine, (C₅-C₁₄) aralkyl(C₁-C₄), (C₅-C₁₄) heterocyclylalkyl(C₁-C₄), (C₅-C₁₄) heterocyclylalkylalkyl(d-C₄)
20 \( \text{C}_4 \text{C}_i \text{cycloalkylalkyl(C}_4 \text{-C}_5 \text{)} \), (C\text{S}_5 \text{-C}_1 \text{4} \text{)heteroarylalkyl(d-C}_4 \text{)} \), (d-C}_4 \text{) alkyl-COOR, (CH}_2)_q \text{SR}_u \), (C\text{S}_4 \text{-C}_4 \text{) methyl-3-sulfanylpropanoyl]-L-proline \), together with nitrogen which form a ring system; \( \text{R}_d \) and \( \text{R}_e \) can also join together along with the carbon to which they are attached to form a ring system and \( \text{p} \) is an integer 0-2;

21 \( \text{R}_4 \) and \( \text{R}_s \) is independently hydrogen, (d-C\text{S}_8 \text{)alkyl, (C}_5 \text{-C}_1 \text{4} \text{)aryl, (C}_4 \text{-C}_4 \text{cycloalkyl, (C}_5 \text{-C}_1 \text{4)heterocyclylalkyl(d-C}_4 \text{)} \), (C\text{S}_5 \text{-C}_1 \text{4)aralkyl, (C}_4 \text{-C}_4 \text{cycloalkylalkyl(d-C}_4 \text{)} \), (C\text{S}_5 \text{-C}_1 \text{4)heteroarylalkyl(d-C}_4 \text{)} \), (C\text{S}_4 \text{-C}_1 \text{4)heterocyclylalkyl(d-C}_4 \text{)} \) or can join together along with the carbon and nitrogen to which they are attached to form a ring system; \( \text{R}_d \) and \( \text{R}_e \) can also join together along with the carbon to which they are attached to form a ring system;

22 \( \frac{3}{4} \) can be (C\text{S}_5 \text{-C}_1 \text{4)aralkyl(d-C}_4 \text{)} \) or (CH}_2)_q \text{SR}_u \).

23 2. Compound selected from the group consisting of:

24 (45)-4-\{[(3\text{S})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-1-[(2 \text{S})-2-methyl-3-sulfanylpropanoyl]-L-proline ditrifluoroacetate salt (Compound No. 1),

25 Methyl (45)-1-[(2\text{S})-3-(acetylsulfanyl)-2-methylpropanoyl]-4-\{[(3\text{S})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 2),

26 (45)-1-[(2\text{S})-3-(acetylsulfanyl)-2-methylpropanoyl]-4-\{[(3\text{S})-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline ditrifluoroacetate salt (Compound No. 3),

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AMENDED SHEET (ARTICLE 19)
(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 4),

N-[1S]-l-carboxy-3-phenylpropyl-L-alanyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 5),

N-[lS]-l-carboxy-3-phenylpropyl-L-alanyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate dilithium salt (Compound No. 5a),

Methyl N-[2S]-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 6),

N-[lS]-l-carboxy-3-phenylpropyl-L-alanyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 8),

N-[lS]-l-carboxy-3-phenylpropyl-L-phenylalanyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 10),

N-[lS]-l-carboxy-2-methylbutyl-L-alanyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 11),

N-[lS]-l-carboxy-3-phenylpropyl-L-isoleucyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 13),

N-[2S]-1-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-phenylalanyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 14),

N-[lS]-l-carboxy-3-phenylpropyl-L-phenylalanyl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 15),

N-[2S]-1-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-seryl-(4S)-4-[[3(S)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 16),

AMENDED SHEET (ARTICLE 19)
N-[(lS)-l-carboxy-3-phenylpropyl]-L-seryl-(45)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline dilithium salt (Compound No. 17),
N-[(2S)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-tyrosyl-(4 S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 18),
N-[(lS)-l-carboxy-3-phenylpropyl]-L-tyrosyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline dilithium salt (Compound No. 19),
N-[(2S)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 20),
N-[(lS)-l-carboxy-3-phenylpropyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline dilithium salt (Compound No. 21),
N-[(2S)-l-ethoxy-l-oxo-3-phenylpropan-2-yl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 22),
N-[(lS)-l-carboxy-3-methylbutyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 23),
N-[(2S)-1-ethoxy-1-oxopentan-2-yl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 24),
N-[(lS)-1-carboxy-2-methylpropyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 25),
N-[(2S)-l-ethoxy-1-oxo-3-phenylpropan-2-yl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 26),
N-[(1S)-l-cyclohexyl-2-ethoxy-2-oxoethyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 27),
N-[(2S)-3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 28),
N-[(lS)-1-carboxy-2-methylpropyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] -L-proline ditrifluoroacetate salt (Compound No. 29),
(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl] amino] - L-[(2S)-2-[(2S)-2-(methoxy-carbonyl)pyrrolidin-l-yl]propanoyl] -L-proline ditrifluoroacetate salt (Compound No. 29),
N-[(2S)-1,4-dioethoxy-1,4-dioxobutan-2-yl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 30),

N-(1-methoxy-2-methyl-1-oxopropan-2-yl)-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 31),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 32),

N-[(1S)-1-carboxypentyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 33),

N-[(1S)-2-carboxy-2-phenylethyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 34),

N-[(5)-carboxy(cyclohexyl)methyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 35),

N-[(1S)-2-carboxycyclopropylethyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 36),

N-[(15)-l,2-dicarboxyethyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 37),

N-[(15)-l-carboxy-2-oxopropyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 38),

N-[(1S)-1-carboxyethyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 39),

N-[(2S)-1-carboxy-2-methylbutyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 40),

N-[(2S)-1-carboxyethyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 41),

N-[(2S)-1-carboxy-2-oxopropyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 42),

N-[(2S)-1-carboxy-2-oxo-2-(2-carboxypropyl)propanoyl]pyrrolidine-2-carboxylic acid dilithium salt (Compound No. 38),

N-[(15)-l-carboxy-2-cyclopropylethyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 37),

N-[(2S)-1-carboxy-2-oxopropyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 40),

N-[(1S)-1-carboxyethyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 41),

N-[(2S)-1-carboxy-2-oxopropyl]-L-alanyl-(4S)-4-[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 42),

AMENDED SHEET (ARTICLE 19)
N-[(1S)-l-carboxy-3-(methylsulfanyl)propyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 43),

N-[(15)-l-carboxypropyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 44),

N-(2-carboxypropan-2-yl)-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline dilithium salt (Compound No. 45),

N-[(15)-l-carboxypentyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 46),

N-[(15)-l-carboxybutyl]glycyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline ditrifluoroacetate salt (Compound No. 47),

N-[(15)-l-carboxy-2-hydroxyethyl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 49),

N-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-norvalyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 50),

N-[(15)-l-carboxy-3-phenylpropyl]-L-norvalyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 51),

N-[(25)-6-amino-l-ethoxy-l-oxohexan-2-yl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 52),

N-[(1S)-l-carboxy-5-aminocarboxytranyt]-L-alanyl-(4S)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 53),

N-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-norleucyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 54),

N-[(25)-l-ethoxy-l-oxo-4-phenylbutan-2-yl]-L-norleucyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 55),

N-[(15)-l-carboxy-3-phenylpropyl]-L-norleucyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 56),

N-[(15)-l-carboxy-3-phenylpropyl]-L-norleucyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 57),

AMENDED SHEET (ARTICLE 19)
151 $N^2$-[(15)-l-carboxy-3-phenylpropyl]-L-lysyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 58),

153 $N$-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-2-methylalanyl-(4S)-4-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 59),

155 (4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-1-[(1-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino)cyclopentyl]carbonyl]-L-proline (Compound No. 60),

157 1-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-D-prolyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 61),

159 $N$-[(15)-l-carboxy-3-phenylpropyl]-2-methylalanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 62),

161 (4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-1-[(1-[(15)-l-carboxy-3-phenylpropyl]amino)cyclopentyl]carbonyl]-L-proline (Compound No. 63),

163 3-cyclopropyl-$N$-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 65),

165 1-[(15)-l-carboxy-3-phenylpropyl]-D-prolyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 64),

167 3-cyclopropyl-$N$-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 65),

169 (25,45)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-1-[(25)-2-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino]-5-methoxy-5-oxopentanoyl]pyrroldine-2-carboxylic acid (Compound No. 66),

171 $N$-[(15)-l-carboxy-3-phenylpropyl]-L-a-glutamyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 67),

173 $N^2$-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-asparaginyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 68),

175 $N^2$-[(15)-l-carboxy-3-phenylpropyl]-L-asparaginyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 69),

177 $N$-l-carboxy-3-phenylpropyl]-L-threonyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 70),

179 $N$-l-carboxy-3-phenylpropyl]-L-threonyl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 70),

181 $N$-[(25)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-0-methyl-L-seryl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 71),

183 $N$-[(15)-l-carboxy-3-phenylpropyl]-0-methyl-L-seryl-(4S)-4-[(3i?)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino]-L-proline (Compound No. 72),
N-[(2S)-3-(benzyloxy)-1-ethoxy-1-oxopropan-2-yl]-L-alanyl-(4S)-4-\{(QR)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl\}amino\}-L-proline (Compound No. 73),

N-[(15)-l-carboxy-3-methylbutyl]norleucyl-4-\{[3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 74),

N-[(15)-2-(benzyloxy)-l-carboxyethyl]-L-alanyl-(4S)-4-\{[3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 75),

N-[(2S)-3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl]norvalyl-(4S)-4-\{[3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 76),

N-[(2S)-3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl]norleucyl-(4S)-4-\{[3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-L-proline (Compound No. 77),

(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-[(2S)-2-\{[(2S)-3-cyclopropyl-1-ethoxy-1-oxopropan-2-yl]amino\}butanoyl]-L-proline (Compound No. 78),

(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-[(2S)-2-\{[(1S)-1-carboxy-3-methylbutyl]amino\}butanoyl]-L-proline (Compound No. 79),

(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-[(2S)-2-\{[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]amino\}butanoyl]-L-proline (Compound No. 80),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-norvalyl-(45)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-(methyl)amino\}-L-proline (Compound No. 81),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-norleucyl-(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-(methyl)amino\}-L-proline (Compound No. 82),

(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-l-[(2S)-2-\{[(1S)-1-carboxy-3-phenylpropyl]amino\}butanoyl]-L-proline (Compound No. 83),

N-[(2S)-1-carboxy-3-phenylpropyl]-L-norvalyl-(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-(methyl)amino\}-L-proline (Compound No. 84),

N-[(15)-l-carboxy-3-phenylpropyl]-L-norleucyl-(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-(methyl)amino\}-L-proline (Compound No. 85),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl-(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-(methyl)amino\}-L-proline (Compound No. 86),

N-[(1S)-1-carboxy-3-phenylpropyl]-L-alanyl-(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-(methyl)amino\}-L-proline (Compound No. 87),

N-[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl]-D-norvalyl-(4S)-4-\{[(3J)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]amino\}-(methyl)amino\}-L-proline (Compound No. 88),

AMENDED SHEET (ARTICLE 19)
A pharmaceutical composition comprising therapeutically effective amount of a compound of Formula I as defined in claims 1-2 together with one or more pharmaceutically acceptable carrier, excipients or diluents. 

A pharmaceutical composition of claim 3 further comprising one or more therapeutic agents selected from anti-hypertensive agents, dyslipidemic agents, anti-obesity agents, anti-hyperglycemic agents and anti-inflammatory agents.

A method for palliative, curative or prophylactic treatment of diseases or conditions of diabetes and/or hypertension in a mammal by administering an effective amount of a compound according to claim 1.

A method for palliative, curative or prophylactic treatment of diseases or conditions of a mammal suffering from diabetes and/or hypertension, wherein the diabetes is treated by dipeptidyl peptidases -IV (DPP-IV) inhibition and also benefited by ACE inhibition and hypertension is treated by angiotensin converting enzyme (ACE) inhibition by administrating an effective amount of a compound according to claim 1.
7. A method according to claim 6, wherein the diseases or conditions of diabetes are selected from the type 2 diabetes, prediabetes, dyslipidemia, metabolic syndrome, metabolic acidosis, ketosis, and satiety disorders, diabetic nephropathy and end organ damage such as kidney and brain and diseases or conditions of hypertension are selected from hypertension with or without incipient nephropathy, myocardial infarction, stroke, increased collagen formation, fibrosis, remodeling following hypertension, congestive heart failure, left ventricular hypertrophy, survival post myocardial infarction (MI), coronary artery diseases, atherosclerosis, angina pectoris or thrombosis.

8. A process for preparing a compound of Formula XIV, XIVa and XVI comprising

a. reacting compound of Formula XI

\[ \text{Formula XI} \]

with a compound of Formula XII

\[ \text{Formula XII} \]

to give a compound of Formula XIII

\[ \text{Formula XIII} \]

b. \( N\)-deprotection of compound of Formula XIII to give a compound of XIV when \( R_m \) is \( \text{COCH}_3 \) and when \( R_{pr} \) is not \( t\)-butyl (Path A)
or
deprotection of compound of Formula XIII to give a compound of Formula XV (when $R_{pr}$ is not $t$-butyl) (Path B),

$N$-deprotection of compound of Formula XV to give a compound of XIV,

hydrolysis of compound of Formula XIII to give a compound of Formula XIVa (when $R_{pr}$ is $t$-butyl and $P_q$ is Boc) (Path C)

wherein
A process for preparing a compound of Formula XX, XIXa and XIXb comprising

a. reacting compound of Formula XI

with a compound of Formula XVII

to give a compound of Formula XVIII
b. hydrolyzing a compound of Formula XVIII (when R_p is not t-butyl) to give a compound of Formula XIX (Path A)

\[ \text{Formula XIX} \]

\[ \text{Formula XX} \]

c. deprotected compound of Formula XIX to give a compound of Formula XX,

\[ \text{Formula XIXa} \]

or

a. deprotecting compound of Formula XVIII (when R_p is t-butyl and P_q is Boc) to give a compound of Formula XIXa (Path B),

\[ \text{Formula XIXa} \]

b. hydrolyzing compound of Formula XIXa to give a compound of Formula XX,

or

a. deprotecting compound of Formula XVIII (when R_p is not t-butyl) to give a compound of Formula XIXb (Path C)
wherein

\[ \frac{1}{2} \]

is hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, C\textsubscript{1-6} alkyamine, aralkyl, heterocyclylalkyl, cycloalkylalkyl, hetereoarylalkyl, alkyl-COO\textsubscript{R}, (CH\textsubscript{2})\textsubscript{q}SR\textsubscript{R}, alkyl-OR\textsubscript{R}, wherein R\textsubscript{R} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl; R\textsubscript{R} and R\textsubscript{R} are independently hydrogen, alkyl, aralkyl, cycloalkylalkyl, heteroarylalkyl, heterocyclylalkyl or can join together along with the carbon and nitrogen to which they are attached to form a ring system;

R\textsubscript{W} is alkyl, arylalkyl, CH\textsubscript{2}OR, cycloalkylalkyl, heterocyclylalkyl or heteroarylalkyl where R\textsubscript{W} is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heterocyclylalkyl, heterocyclyl alkylamine, alkyl-COR or alkyl-OR\textsubscript{R}, wherein R\textsubscript{R} is hydroxy, alkoxy, NHR and R is hydrogen or alkyl;

G is hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carbonyl, thiocarbonyl or oxo;

f can be 0-3;

R\textsubscript{m} is carboxy-protecting group, for example, methyl, ethyl t-butyl, benzyl, trimethylsilyl;

P\textsubscript{m} is N-protecting group;

R\textsubscript{n} is sulfury protecting group selected from the group consisting of acyl, thioacyl, aryl, benzoyl and organothio groups comprising from 1 to about 10 carbon atoms or when taken together with the sulfur atom to be protected, is a hemithioacetal group, for example, tetrahydrofuranyl, 2-
methyl tetrahydrofuranyl, tetrahydropyranyl, 2-methyl tetrahydropyranyl, ethoxyethyl, and methoxymethyl groups.

10. A process for preparing a compound of Formula XXV and XXVI comprising

a. coupling a compound of Formula XI

```
    (G)    HN                          O
        HN                     O
    O R
```

Formula XI

with a compound of Formula XXI

```
    HO
    O
    Br
```

Formula XXI

to give a compound of Formula XXII.

```
    (G)    HN                          O
        HN                     O
    O R
```

Formula XXII

b. reacting a compound of Formula XXII with a compound of Formula XXIII

```
    R
    O
    R
```

Formula XXIII

to give a compound of Formula XXIV,
c. deprotecting and hydrolyzing compound of Formula XXIV (when \( R_p \) is t-butyl and \( p_q \) is Boc) to give a compound of Formula XXVI

b. hydrolyzing a compound of Formula XXV to give a compound of Formula XXVI

wherein
Rd is hydrogen, alkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, C1,6 alkyamine, aralkyl, heterocyclylalkyl, cycloalkylalkyl, heteroarylalkyl,

alkyl-COO\(_R_1\), \((CH_2)_qSR\_d\)alkyl-OR\(_f\); wherein Rd is hydrogen, alkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heteroarylalkyl, or can join together along with the carbon and nitrogen to which they are attached to form a ring system;

\(R_w\) is alkyl, arylalkyl, \(CH_2OR\_t\), cycloalkylalkyl, heterocyclylalkyl or heteroarylalkyl where \(R_i\) is selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl, heterocyclyl, heteroarylalkyl, \(C_{1-6}\)alkylamine, alkyl-COR or alkyl-OR\(_t\), wherein \(R'\) is hydroxy, alkoxy, NHR and \(R\) is hydrogen or alkyl;

\(G\) is hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, hydroxy, alkoxy, carbonyl, thiocarbonyl or oxo;

\(f\) can be O-3;

\(R_{fr}\) is carboxy-protecting group, for example, methyl, ethyl \(t\)-butyl, benzyl, trimethylsilyl;

\(P_{fr}\) is \(N\)-protecting group;

\(R_{mr}\) is sulfur-protecting group selected from the group consisting of acyl, thioacyl, alkyl, aryl, benzoyl and organothio groups comprising from 1 to about 10 carbon atoms or when taken together with the sulfur atom to be protected, is a hemithioacetal group, for example, tetrahydrofuranyl, \(2\)-methyl tetrahydrofuranyl, tetrahydropyranyl, \(2\)-methyl tetrahydropyranyl, ethoxyethyl, and methoxymethyl groups.

**AMENDED SHEET (ARTICLE 19)**
### A. Classification of Subject Matter

INV. C07D207/16  
C07K5/06  
A61K31/401  
A61P3/10

Adding:

According to International Patent Classification (IPC) or to both national classification and IPC

### B. Fields Searched

Minimum documentation searched (classification system followed by classification symbols):

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<th>Relevant to claim No.</th>
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<td>DE 103 09 005 A1 (MORPHOCHEM AG KOMB CHEMI E [DE]) 9 September 2004 (2004-09-09) the whole document examples; page 6 - page 17; claim 1</td>
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### C. Documents Considered to Be Relevant

Date of the actual completion of the international search: 2 May 2011

Date of mailing of the international search report: 09/05/2011

Authorized officer: Bi ssme re, Stewart
### Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No.
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