N-TERMINALLY MODIFIED GLP-1 RECEPTOR MODULATORS

[0001] This application claims priority to United States Provisional Patent Application Serial No. 60/684,805, filed May 26, 2005, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The subject matter disclosed and claimed herein provides novel human glucagon-like peptide-1 (GLP-1) peptide receptor modulators, agonists or partial agonists, which exhibit superior biological properties of the native peptide, GLP-1, and exhibit increased stability to proteolytic cleavage as compared to GLP-1 native sequences, and thus are useful for the amelioration of the diabetic condition.

BACKGROUND OF THE INVENTION

[0003] GLP-1 is an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism. Human GLP-1 is a 30 amino acid peptide originating from preproglucagon, which is synthesized for example, in the L-cells in the distal ileum, in the pancreas and in the brain. Processing of preproglucagon to yield GLP-1 (7-36)amide and GLP-2 occurs mainly in the L-cells. GLP-1 is normally secreted in response to food intake, in particular carbohydrates and lipids stimulate GLP-1 secretion. GLP-1 has been identified as a very potent and efficacious stimulator for insulin release. GLP-1 lowers plasma glucagon concentrations, slows gastric emptying, stimulates insulin biosynthesis and enhances insulin sensitivity (Nauck, 1997, Horm. Metab.Res. 47:1253-1258). GLP-1 also enhances the ability of the B-cells to sense and respond to glucose in subjects with impaired glucose tolerance (Byrne, Eur. J. Clin. Invest., 28:72-78, 1998). The insulinotropic effect of GLP-1 in humans increases the rate of glucose metabolism partly due to increased insulin levels and partly due to enhanced insulin sensitivity (D'Alessio, Eur. J. Clin. Invest., 28:72-78, 1994). The above stated pharmacological properties of GLP-1 make it a highly desirable therapeutic agent for the treatment of type-II diabetes.

[0004] Additionally, recent studies have shown that infusions of slightly supraphysiological amounts of GLP-1 significantly enhance satiety and reduce food intake in normal subjects (Flint, A., Raben, A., Astrup, A. and Holst, J.J., J.Clin.Invest, 101:515-520, 1998; Gutswiller, J.P., Goke, B., Drewe, J., Hildebrand, P., Ketterer, S., Handschin, D., Winterhaider, R., Conen, D and Beglinger, C. Gut 44:81-86, 1999;). The effect on food intake and satiety has also been reported to be preserved in obese subjects (Naslund, E., Barkeling, B., King, N., Gutniak, M., Blundell, J.E., Holst, J.J., Rossner, S., and Hellstrom, P.M., Int. J. Obes. Relat. Metab. Disord., 23:304-311, 1999).

[0005] In the above-cited studies a pronounced effect of GLP-1 on gastric emptying was also suspected to occur. Gastric emptying results in post-prandial glucose excursions. It has also been shown that in addition to stimulation of insulin secretion, GLP-1 stimulates the expression of the transcription factor, islet-duodenal homeobox-1 (IDX-1), while stimulating B-cell neogenesis and may thereby be an effective treatment and/or preventive agent for diabetes (Stoffers, D.A., Kieffer, T.J. Hussain, M.A.,Drucker, D.J., Bonner-Weir, S., Habener, J.F. and Egan, J.M. Diabetes, 40:741-748, 2000). GLP-1 has also been shown to inhibit gastric acid secretion (Wettergren, A., Schjoldager, B., Mortensen, P.E., Myhre, J., Christiansen, J., Holst, J.J., Dig. Dis. Sci., 38:665-673, 1993), which may provide protection against gastric ulcers.

[0006] GLP-1 is an incretin hormone, for example, an intestinal hormone that enhances meal-induced insulin secretion (Holst, J.J., Curr. Med. Chem., 6:1005-1017, 1999). It is a product of the glucagon gene encoding proglucagon. This gene is expressed not only in the A-cells of the pancreas but also in the endocrine L-cells of the intestinal mucosa. Proglucagon is a peptide (protein) containing 160 amino acids. Further processing of proglucagon results in the generation of a) glucagon, b) an N-terminal, presumably inactive fragment, and c) a large C-terminal fragment commonly referred as "the major proglucagon fragment". This fragment is considered to be biologically inactive. Even though this fragment is present in both pancreas and in the L-cells of the gut, it is only in the intestines the breakdown products of the "the major proglucagon fragment" resulting in two highly homologous peptides commonly referred as GLP-1 and GLP-2 are observed. These two peptides have important

biological activities. As such, the amino acid sequence of GLP-1, which is present in the L-cells, is identical to the 78-107 portion of proglucagon.

[0007] Presently, therapy involving the use of GLP-1-type molecules has presented a significant problem because the serum half-life of such peptides is quite short. For example, GLP-1(7-37) has a serum half-life of less than 5 minutes. Thus there exists a critical need for biologically active GLP-1 receptor modulators, agonists or antagonists, that possess extended pharmacodynamic profiles. It is to this and other needs that the disclosed and claimed subject matter is directed.

[0008] Disclosed herein are novel peptides that act as GLP-1 receptor modulators, agonists or partial agonists, which exhibit similar or superior biological properties of the native peptide, GLP-1, and thus are useful for the amelioration of the diabetic and related conditions.

SUMMARY OF THE INVENTION

[0009] The synthetic isolated peptides described herein are capable of modulating the GLP-1 receptor, desirably as agonists or partial agonists of the GLP-1 receptor. These synthetic peptides exhibit superior *in vivo* efficacy and pharmacokinetic properties relative to GLP-1, including postprandial plasma glucose lowering and concomitant increase in plasma insulin levels, thus making them ideal therapeutic candidates for subcutaneous, pulmonary, nasal, buccal or sustained release formulations.

[0010] In a first embodiment of the subject matter described herein, is an isolated polypeptide comprising a sequence of Formula I:

$$X_{aa1}\text{-}X_{aa2}\text{-}X_{aa3}\text{-}X_{aa4}\text{-}X_{aa5}\text{-}X_{aa6}\text{-}X_{aa7}\text{-}X_{aa8}\text{-}X_{aa9}\text{-}X_{aa10}\text{-}X_{aa11}$$

wherein,

X_{aa1} is a naturally or nonnaturally occurring amino acid comprising an imidazole or thiazole ring, such as histidine or thiazolylalanine; wherein any of the carbon atoms of said amino acid are optionally substituted with hydrogen or with one or more alkyl groups, or with one or more halo groups; wherein the free amino group of said amino acid may be replaced with a hydroxyl group or is optionally substituted with hydrogen, alkyl, acyl, benzoyl, alkyloxycarbonyl (*e.g.*, methyloxycarbonyl), aryloxycarbonyl, aralkyloxycarbonyl, heterocyclyloxycarbonyl,

heteroarylalkyloxycarbonyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, heterocyclylsulfonyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, heteroarylalkylsulfonyl or heteroarylsulfonyl;

and wherein the amino group of X_{aa1} is optionally absent, such that X_{aa1} is des-amino acid of histidine or thiazolylalanine in which any of the carbon atoms are optionally substituted with alkyl, halo, or hydroxyl groups;

X_{aa2} is a naturally or nonnaturally occurring amino acid selected from the group consisting of α-amino-isobutryic acid (Aib); (D)-alanine, (L)-alanine, N-methyl-L-Alanine, N-methyl-D-Alanine, (L)-proline, (S)-α-methyl-proline, (L)-azetidine (Azt), (S)-α-methyl-azetidine (α-Me-Azt), (L)-valine, and (R)- or (S)-isovaline, and wherein the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

X_{aa3} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which contains a carboxylic acid, for example aspartic acid or glutamic acid; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

X_{aa4} is glycine;

X_{aa5} is a naturally or nonnaturally occurring amino acid selected from the group consisting of (L)-threonine, (L)-allo-threonine, (L)-serine, (L)-norvaline, (L)-norleucine; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

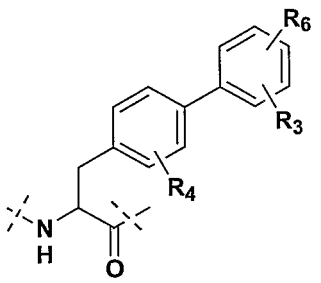
X_{aa6} is a naturally or nonnaturally occurring amino acid comprising an alpha carbon which is disubstituted; wherein one of the side chains of said amino acid contains an aromatic or heteroaromatic ring, for example alpha-methyl-phenylalanine, alpha-methyl-2-fluorophenylalanine, and alpha-methyl-2,6-difluorophenylalanine, wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more halo groups;

X_{aa7} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which is substituted with a hydroxyl group, for example L-threonine or L-allo-threonine; wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl or halo groups;

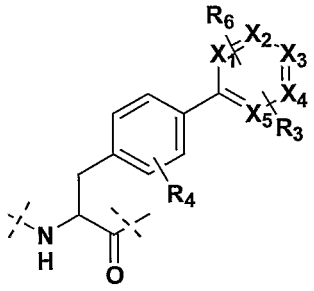
X_{aa8} is a naturally or nonnaturally occurring amino acid selected from the group consisting of L-serine, L-histidine and L-asparagine; wherein one or more of the carbon atoms of said amino acid is optionally substituted with one or more alkyl groups or halo groups;

X_{aa9} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which contains a carboxylic acid, for example L-aspartic acid or L-glutamic acid; wherein one or more of the carbon atoms of said amino acid is optionally substituted with one or more alkyl or halo groups;

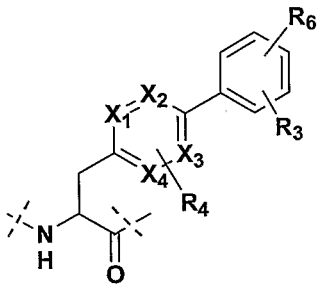
X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II, III, or IV:



Formula II



Formula III



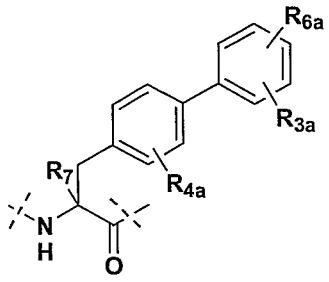
Formula IV

wherein R_3, R_4 and R_6 are each selected from the group consisting of hydrogen, alkyl (*e.g.*, methyl, ethyl), aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxyalkyl, cyano, amino, aminoalkyl, carboxyl, carboxyalkyl, alkoxy (*e.g.*,methoxy) , aryloxy, carboxamides, substituted carboxamides, alkyl esters, aryl esters, alkyl sulfonyl, and aryl sulfonyl;

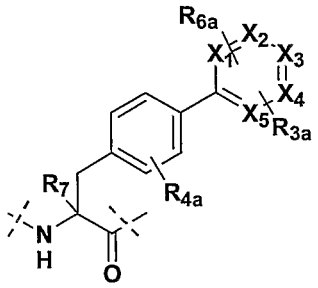
and

wherein X_1, X_2, X_3, X_4, and X_5 are each C or N, with the proviso that at least one of X_1, X_2, X_3, X_4, and X_5 is N;

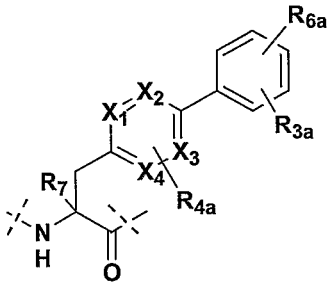
X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IIa, IIIa, or IVa:



Formula IIa



Formula IIIa



Formula IVa

wherein the C-terminal carbonyl carbon of said amino acid is attached to a nitrogen to form a carboxamide (NH_2), an alkyl carboxamide (NHR_1), or a dialkylcarboxamide (NR_1R_2);

wherein each of R_1 and R_2 is an alkyl or arylalkyl group;

wherein R_{3a}, R_{4a} and R_{6a} are each selected from the group consisting of hydrogen, alkyl (*e.g.*, methyl, ethyl), aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxyalkyl, cyano, amino, aminoalkyl, carboxyl, carboxyalkyl, alkoxy, aryloxy, carboxamides, substituted carboxamides, alkyl esters, aryl esters, alkyl sulfonyl, and aryl sulfonyl;

wherein R_7 is selected from the group consisting of hydrogen, methyl, and ethyl; and

wherein X_1, X_2, X_3, X_4, and X_5 are each C or N, with the proviso that at least one of X_1, X_2, X_3, X_4, and X_5 is N;

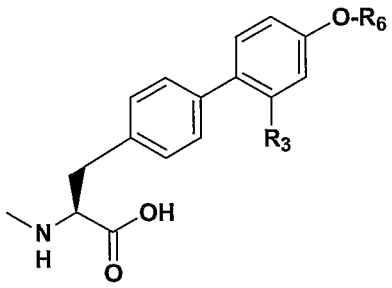
wherein X_{aa11} is not an amino acid of Formula IIa when X_{aa10} is an amino acid of Formula II.

[0011] The naturally or nonnaturally occurring amino acid of Formula II may further comprise more than one R_3, R_4 or R_6 groups. The naturally or nonnaturally

occurring amino acid of Formula III may further comprise more than one R_3, R_4 or R_6 groups. The naturally or nonnaturally occurring amino acid of Formula IV may further comprise more than one R_3, R_4 or R_6 groups. The naturally or nonnaturally occurring amino acid of Formula V may further comprise one or more R_4 or R_5 groups.

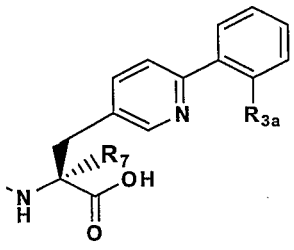
[0012] The naturally or nonnaturally occurring amino acid of Formula IIa may further comprise more than one R_{3a}, R_{4a} or R_{6a} groups. The naturally or nonnaturally occurring amino acid of Formula IIIa may further comprise more than one R_{3a}, R_{4a} or R_{6a} groups. The naturally or nonnaturally occurring amino acid of Formula IVa may further comprise more than one R_{3a}, R_{4a} or R_{6a} groups.

[0013] X_{aa10} of the first embodiment of Formula I, may also be a compound of Formula VI:



wherein, R_3 is selected from the group consisting of alkyl (*e.g.*, methyl, ethyl) and halogen (*e.g.*, fluoro, chloro) and R_6 is selected from the group consisting of hydroxyl and methoxy.

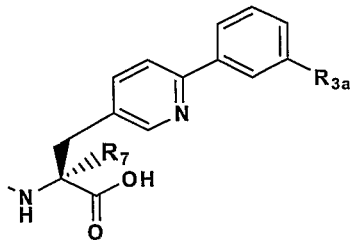
[0014] X_{aa11} of the first embodiment of Formula I, may also be a compound of Formula VIa:



Formula VIa

wherein, R_{3a} is selected from the group consisting of methyl, ethyl and fluoro; and wherein R_7 is selected from the group consisting of hydrogen and methyl.

[0015] X_{aa11} of the first embodiment of Formula I, may also be a compound of Formula VIIa:



Formula VIIa

wherein R_{3a} is methoxy; and wherein R_7 is selected from the group consisting of hydrogen and methyl.

[0016] In another embodiment,

X_{aa1} is selected from the group consisting of L-His, D-His, L-N-Methyl-His, D-N-Methyl-His, L-4-ThiazolylAla, D-4-ThiazolylAla, des-amino-His, des-amino-thiazolylAla, 3-(1H-imidazol-4-yl)-2-methylpropanoyl, (S)-3-(1H-imidazol-4-yl)-2-hydroxypropanoyl (L-β-imidazolelactyl), and

wherein if a terminal amino group is present, said terminal amino group is optionally substituted with hydrogen, alkyl, dialkyl, acyl, benzoyl, alkyloxycarbonyl (e.g. methyloxycarbonyl), aryloxycarbonyl, aralkyloxycarbonyl, heterocyclyloxycarbonyl, heteroarylalkyloxycarbonyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, heterocyclylsulfonyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, heteroarylalkylsulfonyl or heteroarylsulfonyl.

[0017] X_{aa2} is selected from the group consisting of L-Ala, D-Ala, N-methyl-L-Ala, N-methyl-D-Ala, L-Pro, (S)-α-methyl-L-Pro, (L)-azetidine (Azt), (S)-α-methyl-azetidine (α-Me-Azt) and α-aminoisobutyric (Aib).

[0018] X_{aa3} is selected from the group consisting of L-Glu, L-Asp, and L-Gla.

[0019] X_{aa4} is Gly.

[0020] X_{aa5} is selected from the group consisting of L-Thr, L-Nle, L-Nva, L-Aoc and L-allo-Thr.

[0021] X_{aa6} is selected from the group consisting of L-α-Me-Phe, L-α-Et-Phe, L-α-Me-2-fluoroPhe, L-α-Me-3-fluoroPhe, L-α-Me-2,3-di-fluoroPhe, L-α-Me-2,6-di-fluoroPhe, L-α-Me-Phe(penta-Fluoro), and

X_{aa7} is L-Thr or L-allo-threonine.

[0022] X_{aa8} is selected from the group consisting of L-Ser, L-His, and L-Asn.

[0023] X_{aa9} is L-Asp.

[0024] X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II.

[0025] The naturally or nonnaturally occurring amino acid of Formula II is selected from the group consisting of 4-[(4'-methoxy-2'-ethyl)-phenyl]phenylalanine; 4-[(4'-ethoxy-2'-ethyl)phenyl]phenylalanine; 4-[(4'-methoxy-2'-methyl) phenyl] phenylalanine; 4-[(4'-ethoxy-2'-methyl)phenyl]phenylalanine; 4-(2'-ethylphenyl)phenylalanine; 4-(2'-methylphenyl)phenylalanine; 4-[(3',5'-dimethyl)phenyl]phenylalanine, 4-[(3',4'-dimethoxy)phenyl]phenylalanine; 4-[(2'-ethyl-4'-hydroxy)phenyl]phenylalanine;

X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula III.

[0026] The naturally or nonnaturally occurring amino acid of Formula III is selected from the group consisting of 4-[2'-(4'-methoxy-6'-ethyl)pyridyl]phenylalanine; 4-[2'-(4'-methoxy-6'-methyl)pyridyl]-4-phenylalanine; 4-[2'-(6'-ethyl) pyridyl] phenylalanine; 4-[2'-(6'-methyl)pyridyl]phenylalanine; 4-[2'-(3',5'-dimethyl)pyridyl]phenylalanine; 4-[2'-(4'-methoxy-6'-ethyl)pyridyl]phenylalanine; 4-[3'-(4'-methoxy-6'-methyl)pyridyl]phenylalanine; 4-[3'-(2'-ethyl)pyridyl]phenylalanine; and 4-[3'(6'-methyl)pyridyl)phenylalanine;

X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula IV.

[0027] The naturally or nonnaturally occurring amino acid of Formula IV is selected from the group consisting of 4-[(4'-methoxy-2'-ethyl)phenyl]-3-pyridylalanine; 4-[(4'-methoxy-2'-methyl)phenyl]-3-pyridylalanine; 4-(2'-ethylphenyl)-3-pyridylalanine; 4-(2'-methylphenyl)-3-pyridylalanine;4-[(3',5'-dimethyl)phenyl]-3-pyridylalanine; and 4-[(2'-ethyl-4'-hydroxy)phenyl]-3-pyridylalanine;

X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IIa.

[0028] The naturally or nonnaturally occurring amino acid of Formula IIa is selected from the group consisting of 4-(2'-methylphenyl)phenylalanine; 4-(2'-fluorophenyl)phenylalanine; and 4-[(3',5'-dimethyl)phenyl]phenylalanine;

X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IIIa.

[0029] The naturally or nonnaturally occurring amino acid of Formula IIIa is selected from the group consisting of 4-[(6'-methyl)-2'-pyridyl]phenylalanine; 4-[(6'-methyl)-3'-pyridyl]phenylalanine; 4-[(6'-ethyl)-2'-pyridyl)]phenylalanine; and 4-[(6'-ethyl)-3'-pyridyl)]phenylalanine;

X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IVa.

[0030] The naturally or nonnaturally occurring amino acid of Formula IVa is selected from the group consisting of 4-(2'-methylphenyl)-3-pyridylalanine; 4-(2'-fluorophenyl)-3-pyridylalanine; 4-[(3',5'-dimethyl)phenyl]-3-pyridylalanine; 4-(4'-trifluoromethylphenyl)-3-pyridylalanine; and 4-(2'-ethylphenyl)-3-pyridylalanine,

and

wherein the C-terminal carbonyl carbon of said amino acid is attached to a nitrogen to form a carboxamide (NH_2), an alkyl carboxamide (NHR_1) or a dialkylcarboxamide (NR_1R_2), where each of R_1 and R_2 is an alkyl or arylalkyl group.

[0031] In another aspect,

X_{aa1} is an amino acid selected from the group consisting of L-His, D-His, L-N-Methyl-His, D-N-Methyl-His, L-4-ThiazolylAla, D-4-ThiazolylAla, des-amino-His, des-amino-thiazolylAla, 3-(1H-imidazol-4-yl)-2-methylpropanoyl, (S)-3-(1H-imidazol-4-yl)-2-hydroxypropanoyl (L-β-imidazolelactyl);

wherein if a terminal amino group is present, said terminal amino group is optionally substituted with hydrogen, alkyl, acyl, benzoyl, alkyloxycarbonyl (e.g. methyloxycarbonyl), aryloxycarbonyl, aralkyloxycarbonyl, heterocyclyloxycarbonyl, heteroarylalkyloxycarbonyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, heterocyclylsulfonyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, heteroarylalkylsulfonyl or heteroarylsulfonyl;

X_{aa2} is an amino acid selected from the group consisting of L-Alanine, D-Alanine, N-methyl-L-Alanine, N-methyl-D-Alanine, L-Proline,(S)-α-methyl-Proline, (L)-azetidine (Azt), (S)-α-methyl-azetidine (α-Me-Azt) and α-aminoisobutyric (Aib);

X_{aa3} is an amino acid selected from the group consisting of L-Glu, L-Asp, and L-Gla;

X_{aa4} is an amino acid selected from the group consisting of Gly;

X_{aa5} is an amino acid selected from the group consisting of L-Thr, L-Nle, L-Nva, L-Aoc and L-allo-Thr;

X_{aa6} is an amino acid selected from the group consisting of L-α-Me-Phe, L-α-Et-Phe, L-α-Me-2-fluoroPhe, L-α-Me-3-fluoroPhe, L-α-Me-2,3-di-fluoroPhe, L-α-Me-2,6-di-fluoroPhe, and L-α-Me- Phe (penta-Fluoro);

X_{aa7} is an amino acid selected from the group consisting of L-Thr and L-allo-threonine;

X_{aa8} is an amino acid selected from the group consisting of L-Ser, L-His, and L-Asn;

X_{aa9} is L-Asp;

X_{aa10} is a naturally or nonnaturally occurring amino acid selected from the group consisting of amino acids of Formulas II, III, IV, and V;

wherein Formula II is an amino acid selected from the group consisting of 4-[(2'-ethyl-4'-hydroxy)phenyl]phenylalanine; 4-[(4'-methoxy-2'-ethyl)phenyl]phenylalanine; 4-[(4'-methoxy-2'-methyl)phenyl] phenylalanine; 4-(2'-ethylphenyl)phenylalanine; 4-(2'-methylphenyl)phenylalanine; 4-[(3',5'-dimethyl)phenyl]phenylalanine, and 4-[(3',4'-dimethoxy) phenyl] phenylalanine;

wherein Formula III is an amino acid selected from the group consisting of 4-[2'-(4'-methoxy-6'-ethyl)pyridyl]phenylalanine; 4-[2'-(4'-methoxy-6'-methyl)pyridyl]-4-phenylalanine; 4-[2'-(6'-ethyl)pyridyl]phenylalanine; 4-[2'-(6'-methyl)pyridyl]phenylalanine; 4-[2'-(3',5'-dimethyl)pyridyl]phenylalanine; 4-[2'-(4'-methoxy-6'-ethyl)pyridyl]phenylalanine; 4-[3'-(4'-methoxy-6'-methyl)pyridyl]phenylalanine; 4-[3'-(2'-ethyl)pyridyl]phenylalanine; and 4-[3'-(6'-methyl)pyridyl)phenylalanine;

wherein Formula IV is an amino acid selected from the group consisting of 4-[(2'-ethyl-4'-hydroxy)phenyl]-3-pyridylalanine, 4-[(4'-methoxy-2'-ethyl)phenyl]-3-pyridylalanine; 4-[(4'-methoxy-2'-methyl)phenyl]-3-pyridylalanine; 4-(2'-ethylphenyl)-3-pyridylalanine; 4-(2'-methylphenyl)-3-pyridylalanine; and 4-[(3',5'-dimethyl)phenyl]-3-pyridylalanine;

and

X_{aa11} is a naturally or nonnaturally occurring amino acid selected from the group consisting amino acids of Formulas IIa, IIIa, and IVa;

wherein Formula IIa is an amino acid selected from the group consisting of 4-(2'-methylphenyl)phenylalanine; 4-(2'-fluorophenyl)phenylalanine; and 4-[(3',5'-dimethyl)phenyl]phenylalanine;

wherein Formula IIIa is an amino acid selected from the group consisting of 4-[2'-(6'-methyl)pyridyl]phenylalanine; 4-[2'-(6'-methyl)pyridyl] phenylalanine; 4-[2'-(6'-ethyl)pyridyl]phenylalanine; and 4-[3'-(6'-ethyl)pyridyl]phenylalanine;

wherein Formula IVa is an amino acid selected from the group consisting of 4-(2'-methylphenyl)-3-pyridylalanine; 4-(2'-fluorophenyl)-3-pyridylalanine; 4-[(3',5'-dimethyl)phenyl]-3-pyridylalanine; 4-(4'-trifluoromethylphenyl)-3-pyridylalanine; and 4-(2'-ethylphenyl)-3-pyridylalanine;

wherein X_{aa11} is not an amino acid of formula IIa when X_{aa10} is an amino acid of Formula II;

wherein the C-terminal carbonyl carbon is attached to a nitrogen to form a carboxamide (NH_2), an alkyl carboxamide (NHR_1), or a dialkylcarboxamide (NR_1R_2), where each of R_1 and R_2 is an alkyl or arylalkyl group; and

wherein X_{aa10} and X_{aa11} are not both simultaneously an amino acid of Formula II.

[0032] Other embodiments are isolated polypeptides selected from the group consisting of:

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
1.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me)	4-(2'-pyridyl)Phenylalanine-NH_2
2.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(3',5'-di-Me)	4-(2'-pyridyl)Phenylalanine-NH_2
3.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-OBu)	4-(2'-pyridyl)Phenylalanine-NH_2
4.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me)	4-(4'-pyridyl)Phenylalanine-NH_2
5.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Cl)	4-(4'-pyridyl)Phenylalanine-NH_2
6.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-methoxy-5'-iso-propyl)	4-(4'-pyridyl)Phenylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
7.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(2'-Ethylphenyl)-3-pyridylalanine	Bip(2'-Me)-NH_2
8.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[(2'-Ethyl-4'-methoxy)phenyl]-3-pyridylalanine	Bip(2'-Me)-NH_2
9.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
10.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
11.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
12.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
13.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
14.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
15.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Methyl)pyridyl)]phenylalanine-NH_2
16.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Methyl)pyridyl)]phenylalanine-NH_2
17.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-Pyridazyl)phenylalanine-NH_2
18.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-Pyridazyl)phenylalanine-NH_2
19.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Me,6-OMe)pyridyl)]phenylalanine-NH_2
20.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3-(4'-Methyl)pyridyl)]phenylalanine	Bip(2'-Me)-NH_2
21.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me)-NH_2
22.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me)-NH_2
23.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[2(1H)Pyridonyl]phenylalanine-NH_2
24.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(8-Quinoline)-NH_2
25.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(3-Quinoline)-NH_2
26.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(6-Quinoline)-NH_2
27.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(5-Quinoline)-NH_2
28.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-(6-OMe)pyridyl)phenylalanine-NH_2
29.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-(2-Methoxy)pyridyl)phenylalanine-NH_2
30.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-pyridyl)phenylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
31.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
32.	H .	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(5-Quinoline)phenylalanine	Bip(2'-Me)-NH_2
33.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[3-(2'-OMe)pyridyl]phenylalanine	Bip(2'-Me)-NH_2
34.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(6-Quinoline)phenylalanine	Bip(2'-Me)-NH_2
35.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(4'-pyridyl)phenylalanine	Bip(2'-Me)-NH_2
36.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[4'-(3',5'-dimethylisoxazole)]phenylalanine	Bip(2'-Me)-NH_2
37.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2-trifluoromethylphenyl)-3-pyridylalanine-NH_2
38.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2-methyl-5-fluorophenyl)-3-pyridylalanine-NH_2
39.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4-methanesulfonylphenyl)-3-pyridylalanine-NH_2
40.	H	Aib	E	G	T	L-α-Me-Phe	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
41.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
42.	H	Aib	E	G	Nle	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
43.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-Cl, 4'-CF3)-3'-pyridyl]phenylalanine-NH_2
44.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3'-(2'-CN-6'-Me)pyridyl]phenylalanine-NH_2
45.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Cl)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
46.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2',4'-di-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
47.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(3'-pyridyl)phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
48.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(4'-pyridyl)phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
49.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Me-3'-F)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
50.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-F)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
51.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(2'-Cl-6'-CF3)pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
52.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(2'-Cl)-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
53.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(3'-Cl-4'-F)-NH_2
54.	H	Aib	E	G	Nva	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
55.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(3',5'-di-Me)-NH_2
56.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2',3'-pyridazyl)phenylalanine-NH_2
57.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-ethylphenyl)-3-pyridylalanine-NH_2
58.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-[3'-(2'-Cl-6'-CF3)pyridyl]phenylalanine-NH_2
59.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-[3'-(2'-CN-6'-Me)pyridyl]phenylalanine-NH_2
60.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Cl)-NH_2
61.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(3'-Cl-4'-F)-NH_2
62.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(3',5'-di-Me)-NH_2
63.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Me-4'-OMe)-NH_2
64.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Me-3'-F)-NH_2
65.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-F)-NH_2
66.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Cl)-NH_2
67.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(3',4'-di-OMe)-NH_2
68.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	4-(2'-pyridyl)phenylalanine-NH_2
69.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me-4'-OMe)-NH_2
70.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
71.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-ethylphenyl)-3-pyridylalanine-NH_2
72.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Methyl)pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
73.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-pyridyl)-phenylalanine-NH_2
74.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-quinoline)phenylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
75.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-(2'-Methoxy)pyridyl)phenylalanine-NH_2
76.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-phenyl-3-pyridylalanine-NH_2
77.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-dimethylphenyl)-3-pyridylalanine-NH_2
78.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3'-chloro-4'-fluoro)phenyl]-3-pyridylalanine-NH_2
79.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3',4'-dimethoxy)phenyl]-3-pyridylalanine-NH_2
80.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-ethyl-4'-methoxy)phenyl)]-3-pyridylalanine-NH_2
81.	L-β-Imidazole-lactyl	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
82.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-(5-o-Tolyl)thienylalanine-NH_2
83.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3'-Methoxy)phenyl]thienylalanine-NH_2
84.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3',5'-di-Methyl)phenyl]thienylalanine-NH_2
85.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3'-Cl,5'-F)phenyl]thienylalanine-NH_2
86.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Isopropoxyphenyl)-3-pyridylalanine-NH_2
87.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 5'-Fluoro)phenyl)-3-pyridylalanine-NH_2
88.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Isopropoxyphenyl)-3-pyridylalanine-NH_2
89.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	3-(4-Br)pyridylalanine-NH_2
90.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Methoxyphenyl)-3-pyridylalanine-NH_2
91.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 4'-Fluoro)phenyl)-3-pyridylalanine-NH_2
92.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
93.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Trifluoromethoxyphenyl)-3-pyridylalanine-NH_2
94.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Trifluoromethoxyphenyl)-3-pyridylalanine-NH_2
95.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	3-pyridylalanine-NH_2

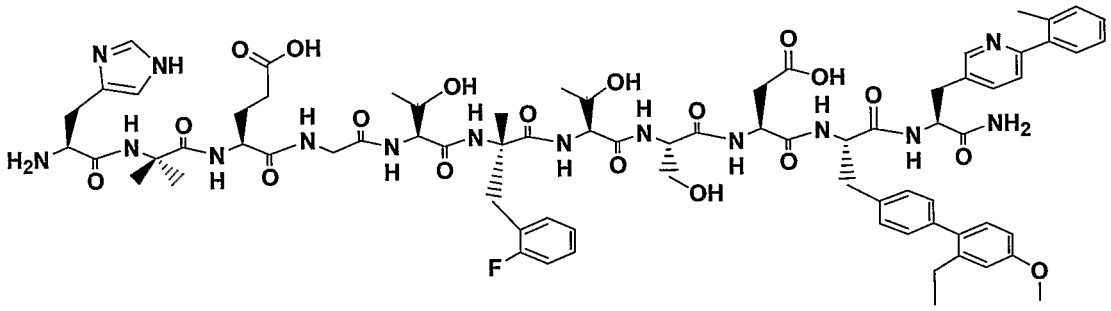
SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
96.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 4'-Chloro)phenyl)-3-pyridylalanine-NH_2
97.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
98.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
99.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Fluorophenyl)-3-pyridylalanine-NH_2
100.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
101.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Chlorophenyl)-3-pyridylalanine-NH_2
102.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Chlorophenyl)-3-pyridylalanine-NH_2
103.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Isopropylphenyl)-3-pyridylalanine-NH_2
104.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-dimethylisoxazol-4'-yl)-3-pyridylalanine-NH_2
105.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-Methyl-4'-methoxy)phenyl)-3-pyridylalanine-NH_2
106.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
107.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Chlorophenyl)-3-pyridylalanine-NH_2
108.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Pyridyl)-3-pyridylalanine-NH_2
109.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
110.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(6'-Methoxypyridin-3'-yl)-3-pyridylalanine-NH_2
111.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Isopropylphenyl)-3-pyridylalanine-NH_2
112.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methoxyphenyl)-3-pyridylalanine-NH_2
113.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3',5'-di-Fluoro-2'-methoxy)phenyl]-3-pyridylalanine-NH_2
114.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-methylphenyl)-3-pyridylalanine-NH_2
115.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-fluorophenyl)-3-pyridylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
116.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-fluorophenyl)-3-pyridylalanine-NH_2
117.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
118.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
119.	H	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
120.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
121.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	(S)-4-(2'-Methylphenyl)-α-Me-3-pyridylalanine-NH_2
122.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	(S)-4-(2'-Methylphenyl)-α-Me-3-pyridylalanine-NH_2
123.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
124.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
125.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
126.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
127.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2
128.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2
129.	H	N-Me-(L)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
130.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3,5-pyrimidylalanine-NH_2
131.	H	(S)-α-Me-Pro	D	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
132.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Ethylphenyl)-3-pyridylalanine-NH_2
133.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
134.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
135.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
136.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
137.	(R)-Imp	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
138.	(S)-Imp	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
139.	CH3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
140.	CH3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
141.	CH3O-CO-His	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
142.	CH3O-CO-His	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
143.	CH3 SO2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
144.	CH3 SO2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
145.	L-Lactyl-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
146.	L-Lactyl-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
147.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-di-Me)phenyl-3-pyridylalanine-NH_2
148.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
149.	H	D-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
150.	H	Aib	H	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
151.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-O-Me)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
152.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-O-Me)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
153.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
154.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
155.	L-β-Imidazole-lactyl	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-O-Me)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2

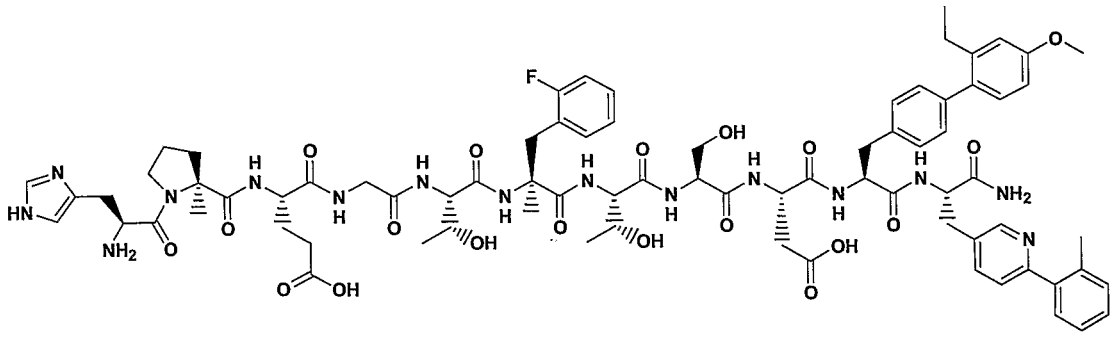
SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
156.	L-β-Imidazole-lactyl	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-O-Me)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
157.	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
158.	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
159.	CH_3O-CO-His	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
160.	CH_3O-CO-His	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
161.	CH_3O-CO-His	Aib	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
162.	CH_3O-CO-His	Aib	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2

[0033] Other embodiments include isolated polypeptides having the structures:



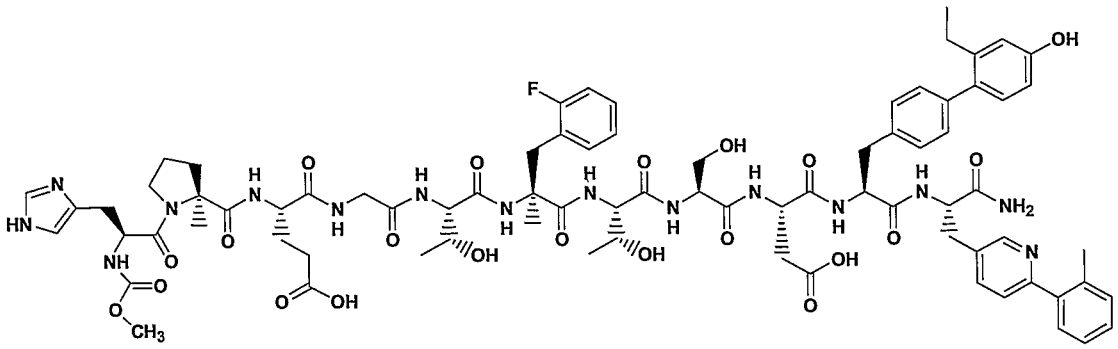
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or



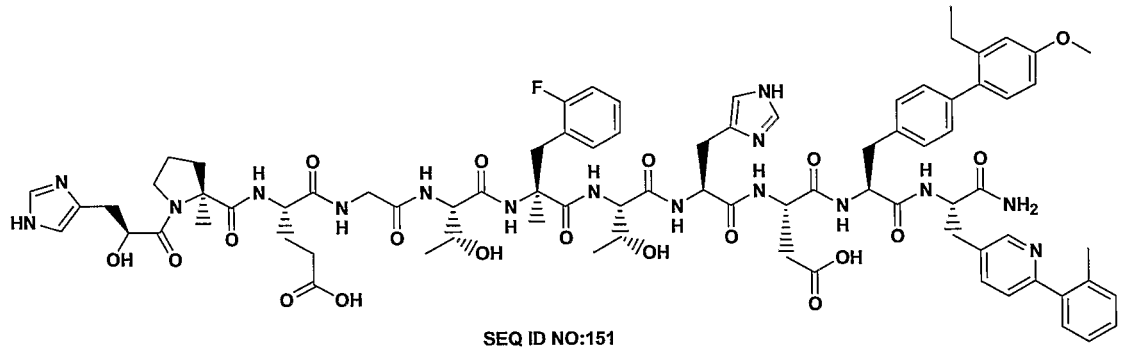
SEQ ID NO:118

or



SEQ ID NO:158

or



SEQ ID NO:151

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[0034] Another embodiment is a pharmaceutical composition comprising an isolated polypeptide of any of the above.

[0035] Another embodiment is directed to a pharmaceutical combination comprising an isolated polypeptide of any of the above and at least one therapeutic agent selected from the group consisting of an antidiabetic agent, an anti-obesity agent, an anti-hypertensive agent, an anti-atherosclerotic agent and a lipid-lowering agent.

[0036] Another embodiment is directed to a pharmaceutical combination of the above, wherein the antidiabetic agent is selected from the group consisting of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an aP2 inhibitor, a DPP4 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and a meglitinide.

[0037] Another embodiment is directed to a pharmaceutical combination of the above, wherein the antidiabetic agent is selected from the group consisting of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, muraglitazar, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677,

repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, and NVP-DPP-728A.

[0038] Another embodiment is directed to a pharmaceutical combination of the above, wherein the anti-obesity agent is selected from the group consisting of a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta compound, and an anorectic agent.

[0039] Another embodiment is directed to a pharmaceutical combination of the above, wherein the anti-obesity agent is selected from the group consisting of orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine and mazindol.

[0040] Another embodiment is directed to a pharmaceutical combination of the above, wherein the lipid lowering agent is selected from the group consisting of an MTP inhibitor, cholesterol ester transfer protein, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, and an ACAT inhibitor.

[0041] Another embodiment is directed to a pharmaceutical combination of the above, wherein the lipid lowering agent is selected from the group consisting of pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, CP-529414, and LY295427.

[0042] Another embodiment is directed to a method for treating or delaying the progression or onset of diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, Syndrome X, diabetic complications, elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, atherosclerosis or hypertension, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of any of the isolated polypeptides above.

[0043] Another embodiment is directed to a method of such treating or delaying of, further comprising administering, concurrently or sequentially, a therapeutically effective amount of one or more therapeutic agents selected from the group consisting

of an antidiabetic agent, an anti-obesity agent, a anti-hypertensive agent, and an anti-atherosclerotic agent and a lipid-lowering agent.

[0044] Another embodiment is directed to a method for treating or delaying the progression or onset of diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, Syndrome X, diabetic complications, elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, atherosclerosis or hypertension, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of any of the pharmaceutical combinations above.

BRIEF DESCRIPTION OF THE DRAWINGS

[0045] Figure 1 illustrates the effects of subcutaneous injection of Compound I on plasma glucose in an ipGTT in ob/ob mice.

[0046] Figure 2 illustrates the effects of subcutaneous injection of Compound I on plasma insulin in an ipGTT in ob/ob mice.

[0047] Figure 3 illustrates the effects of subcutaneous injection of a compound of SEQ ID NO: 9 on plasma glucose in an ipGTT in ob/ob mice.

[0048] Figure 4 illustrates the effects of subcutaneous injection of a compound of SEQ ID NO: 9 on plasma insulin in an ipGTT in ob/ob mice.

[0049] Figure 5 illustrates the effects of subcutaneous injection of a compound of SEQ ID NO: 118 on plasma glucose in an ipGTT in ob/ob mice.

[0050] Figure 6 illustrates the effects of subcutaneous injection of a compound of SEQ ID NO: 151 on plasma glucose in an ipGTT in ob/ob mice.

[0051] Figure 7 illustrates the effects of subcutaneous injection of a compound of SEQ ID NO: 151 on plasma insulin in an ipGTT in ob/ob mice.

[0052] Figure 8 illustrates the effects of subcutaneous injection of a compound of SEQ ID NO: 158 on plasma glucose in an ipGTT in ob/ob mice.

[0053] Figure 9 illustrates the effects of subcutaneous injection of a compound of SEQ ID NO: 158 on plasma insulin in an ipGTT in ob/ob mice.

DETAILED DESCRIPTION OF THE INVENTION

[0054] The synthetic isolated peptides described herein are capable of modulating the GLP-1 receptor, desirably as agonists or partial agonists of the GLP-1 receptor. These synthetic peptide exhibit superior in-vivo efficacy and pharmacokinetic properties relative to GLP-1, including postprandial plasma glucose lowering and concomitant increase in plasma insulin levels, thus making them ideal therapeutic candidates for subcutaneous, pulmonary, nasal, buccal or sustained release.

[0055] The subject matter described and claimed herein includes an isolated polypeptide comprising a sequence of Formula I:

$$X_{aa1}\text{-}X_{aa2}\text{-}X_{aa3}\text{-}X_{aa4}\text{-}X_{aa5}\text{-}X_{aa6}\text{-}X_{aa7}\text{-}X_{aa8}\text{-}X_{aa9}\text{-}X_{aa10}\text{-}X_{aa11}$$

Formula I

wherein,

X_{aa1} is naturally or nonnaturally occurring amino acid comprising an imidazole or thiazole ring, such as histidine or thiazolylalanine; wherein any of the carbon atoms of said amino acid are optionally substituted with hydrogen, with one or more alkyl groups, or with one or more halo groups; wherein the free amino group of said amino acid is optionally substituted hydrogen, hydroxyl, alkyl, acyl, benzoyl, alkyloxycarbonyl (e.g. methyloxycarbonyl), aryloxycarbonyl, aralkyloxycarbonyl, heterocyclyloxycarbonyl, heteroarylalkyloxycarbonyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, heterocyclylsulfonyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, heteroarylalkylsulfonyl or heteroarylsulfonyl;

and wherein the amino group of X_{aa1} is optionally absent, such that X_{aa1} is the des-amino acid of histidine or thiazolylalanine in which any of the carbon atoms are optionally substituted with alkyl, halo, or hydroxyl groups;

X_{aa2} is naturally or nonnaturally occurring amino acid selected from the group consisting of α-amino-isobutryic acid; L-alanine, D-Alanine, N-methyl-L-Alanine, N-methyl-D-Alanine, L-proline, (S)-α-methyl-proline, L-azetidine (Azt), (L)-α-methyl-azetidine (α-Me-Azt), L-valine, and (R)- or (S)-isovaline, and wherein the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

X_{aa3} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which contains a carboxylic acid, for example aspartic acid or

glutamic acid; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

X_{aa4} is glycine;

X_{aa5} is a naturally or nonnaturally occurring amino acid selected from the group consisting of L-threonine, L-allo-threonine, L-serine, L-norvaline, L-norleucine; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

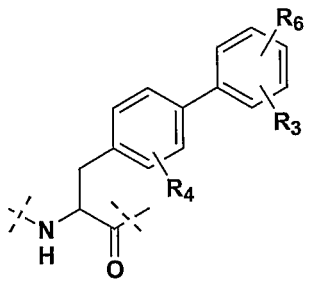
X_{aa6} is a naturally or nonnaturally occurring amino acid comprising an alpha carbon which is disubstituted; wherein one of the side chains of said amino acid contains an aromatic or heteroaromatic ring, for example alpha-methyl-phenylalanine, alpha-methyl-2-fluorophenylalanine, alpha-methyl-2,6-difluorophenylalanine, wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more halo groups;

X_{aa7} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which is substituted with a hydroxyl group, for example L-threonine or L-allo-threonine; wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl or halo groups;

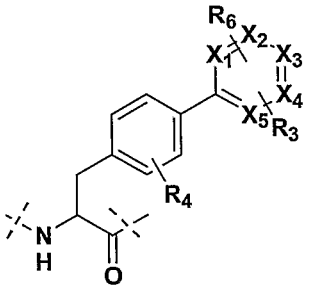
X_{aa8} is a naturally or nonnaturally occurring amino acid selected from the group consisting of L-serine, L-histidine and L-asparagine; wherein one or more of the carbon atoms of said amino acid is optionally substituted with one or more alkyl groups or halo groups;

X_{aa9} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which contains a carboxylic acid, for example L-aspartic acid or L-glutamic acid; wherein one or more of the carbon atoms of said amino acid is optionally substituted with one or more alkyl or halo groups;

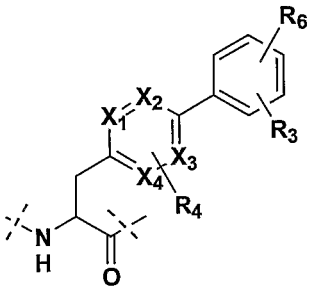
X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II, III, or IV:



Formula II



Formula III

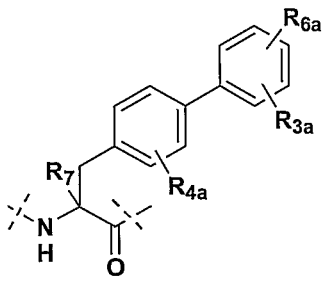


Formula IV

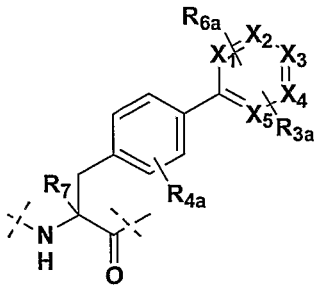
wherein R_3, R_4 and R_6 are each selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxyalkyl, cyano, amino, aminoalkyl, alkoxy, aryloxy, carboxyl, carboxyalkyl, carboxamides, substituted carboxamides, alkyl esters, aryl esters, alkyl sulfonyl, and aryl sulfonyl; and

wherein X_1, X_2, X_3, X_4, and X_5 are each C or N, with the proviso that one of X_1, X_2, X_3, X_4, and X_5 is N;

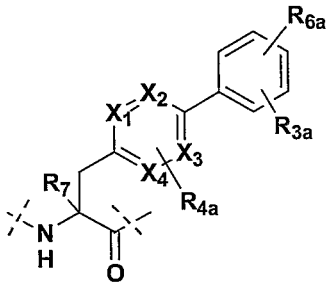
X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IIa, IIIa, or IVa:



Formula IIa



Formula IIIa



Formula IVa

wherein the C-terminus carbonyl carbon of said amino acid is attached to a nitrogen to form a carboxamide (NH_2), an alkyl carboxamide (NHR_1), or a dialkylcarboxamide (NR_1R_2);

wherein each of R_1 and R_2 is an alkyl or arylalkyl group;

wherein R_{3a}, R_{4a} and R_{6a} are each selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxyalkyl, cyano, amino, aminoalkyl, alkoxy, aryloxy, carboxyl, carboxyalkyl, carboxamides, substituted carboxamides, alkyl esters, aryl esters, alkyl sulfonyl, and aryl sulfonyl;

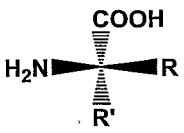
wherein R_7 is selected from the group consisting of hydrogen, methyl, and ethyl; and

wherein X_1, X_2, X_3, X_4, and X_5 are each C or N, with the proviso that one of X_1, X_2, X_3, X_4, and X_5 is N;

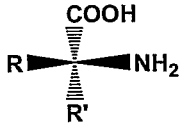
wherein X_{aa11} is not an amino acid of formula IIa when X_{aa10} is an amino acid of Formula II.

[0056] The definitions provided herein apply, without limitation, to the terms as used throughout this specification, unless otherwise limited in specific instances.

[0057] Those of ordinary skill in the art of amino acid and peptide chemistry are aware that an amino acid includes a compound represented by the general structure:



L- or S-α-amino acid
(if R=H)



D- or R-α-amino acid
(if R=H)

where R and R' are as discussed herein.

[0058] Unless otherwise indicated, the term "amino acid" as employed herein, alone or as part of another group, includes, without limitation, an amino group and a carboxyl group linked to the same carbon, referred to as "α" carbon, where R and/or R' can be a natural or an un-natural side chain, including hydrogen. The absolute "S" configuration at the "α" carbon is commonly referred to as the "L" or "natural" configuration. In the case where both the "R" and the "R'"(prime) substituents equal hydrogen, the amino acid is glycine and is not chiral.

[0059] Unless otherwise indicated, the term "amino-alcohol" as employed herein alone or as part of another group includes, without limitation, a natural or un-natural amino acid in which the carboxy group is replaced (reduced) to a methyl alcohol such as valinol, glycinol, alaninol, arylalaninol, heteroarylalaninol.

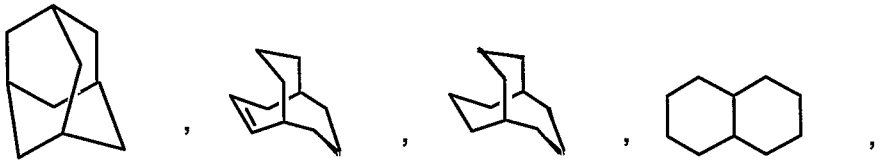
[0060] Unless otherwise indicated, the term "alkyl" as employed herein alone or as part of another group includes, without limitation, both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like. Further, alkyl groups, as defined herein, may optionally be substituted on any available carbon atom with one or more functional groups commonly attached to such chains, such as, but not limited to alkyl, aryl, alkenyl, alkynyl, hydroxy, arylalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, arylalkyloxy, heteroaryloxy, heteroarylalkyloxy, alkanoyl, halo, hydroxyl, thio, nitro, cyano, carboxyl, carbonyl ($\overset{O}{\overset{\|}{}}$), carboxamido, amino, alkylamino, dialkylamino, amido, alkylamino, arylamido, heterarylamido, azido, guanidino, amidino, phosphonic, phosphinic, sulfonic, sulfonamido, haloaryl, CF3, OCF2, OCF3, aryloxy, heteroaryl, cycloalkylalkoxyalkyl, cycloheteroalkyl and the like to form alkyl groups such as

trifluoro methyl, 3-hydroxyhexyl, 2-carboxypropyl, 2-fluoroethyl, carboxymethyl, cyanobutyl and the like.

[0061] Unless otherwise indicated, the term "alkenyl" as employed herein alone or as part of another group includes, without limitation, both straight and branched chain hydrocarbons, containing 2 to 40 carbons with one or more double bonds, preferably 2 to 20 carbons with one to three double bonds, more preferably 2 to 8 carbons with one to two double bonds, in the normal chain, such that any carbon may be optionally substituted as described above for "alkyl".

[0062] Unless otherwise indicated, the term "alkynyl" as employed herein alone or as part of another group includes, without limitation, both straight and branched chain hydrocarbons, containing 2 to 40 carbons with one or more triple bonds, preferably 2 to 20 carbons with one to three triple bonds, more preferably 2 to 8 carbons with one to two triple bonds, in the normal chain, such that any carbon may be optionally substituted as described above for "alkyl".

[0063] Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes, without limitation, saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, appended or fused, including monocyclic alkyl, bicyclic alkyl and tricyclic alkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 7 carbons, forming each ring; which may be fused to 1 aromatic ring as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted through any available carbon atoms with 1 or more groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, fluorenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, oxo, cyano,

carboxyl, carbonyl ($\overset{O}{\overset{\|}{\text{C}}}$), carboxamido, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), amido, azido, guanidino, amidino, phosphonic, phosphinic, sulfonic, sulfonamido, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl, or any of alkyl substituents as set out above.

[0064] The term "aryl" as employed herein alone or as part of another group refers, without limitation, to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to "aryl" (such as aryl, cycloalkyl, heteroaryl or heterocycloalkyl rings) and may be optionally substituted through any available carbon atoms with 1 or more groups selected from hydrogen, alkyl, halo, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, fluorenyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hetroarylalkyloxy, hetroarylalkyloxyalkyl, hydroxy, nitro, oxo, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, cycloalkyl, heterocycloalkyl, heteroaryl, or aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, cycloalyklaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, heteroarylalkylaminocarbonyl alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl, or any of alkyl substituents as set out above.

[0065] The term "arylalkyl" as used herein alone or as part of another group refers, without limitation, to alkyl groups as defined above having an aryl substituent,

such as benzyl, phenethyl or naphthylpropyl, wherein said aryl and/or alkyl groups may optionally be substituted as defined above.

[0066] The term "alkoxy", "aryloxy", "heteroaryloxy" "arylalkyloxy", or "heteroarylalkyloxy" as employed herein alone or as part of another group includes, without limitation, an alkyl or aryl group as defined above linked through an oxygen atom.

[0067] The term "heterocyclo", "heterocycle" "heterocyclyl" or "heterocyclic", as used herein, represents, without limitation, an unsubstituted or substituted stable 4-, 5-, 6-, or 7-membered monocyclic ring system which may be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from nitrogen, sulfur, oxygen and/or a SO or SO_2 group, wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but is not limited to, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, piperazinyl, oxopyrrolidinyl, oxopiperazinyl, oxopiperidinyl and oxadiazolyl. Optionally a heterocyclo group may be substituted with one or more functional groups, such as those described for "alkyl" or "aryl".

[0068] The term "heterocycloalkyl" as used herein alone or as part of another group refers, without limitation, to alkyl groups as defined above having a heterocycloalkyl substituent, wherein said "heterocyclo" and/or alkyl groups may optionally be substituted as defined above.

[0069] The term "heteroaryl" as used herein refers, without limitation, to a 5-, 6- or 7-membered aromatic heterocyclic ring which contains one or more heteroatoms selected from nitrogen, sulfur, oxygen and/or a SO or SO_2 group. Such rings may be fused to another aryl or heteroaryl ring and include possible N-oxides; Examples of such heteroaryl groups include, but are not limited to, furan, pyrrole, thiophene, pyridine,pyrimidine, pyrazine, pyridazine, isoxazole, oxazole, imidazole and the like. Optionally a heteroaryl group may be substituted with one or more functional groups commonly attached to such chains, such as those described for "alkyl" or "aryl".

[0070] The term "heteroarylalkyl" as used herein alone or as part of another group refers, without limitation, to alkyl groups as defined above having a heteroaryl substituent, wherein said heteroaryl and/or alkyl groups may optionally be substituted as defined above.

[0071] The term "receptor modulator" refers to a compound that acts at the GLP-1 receptor to alter its ability to regulate downstream signaling events. Examples of receptor modulators include agonists, antagonists, partial agonists, inverse agonists, allosteric antagonists and allosteric potentiators as defined in standard pharmacology textbooks (*e.g.,* E.M. Ross and T.P. Kenakin in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 10th edition (2001) McGraw Hill, Chapter 2, pp. 31-43).

[0072] One of ordinary skill in the art will readily appreciate the meaning of such terms as provided in the present case and in the art.

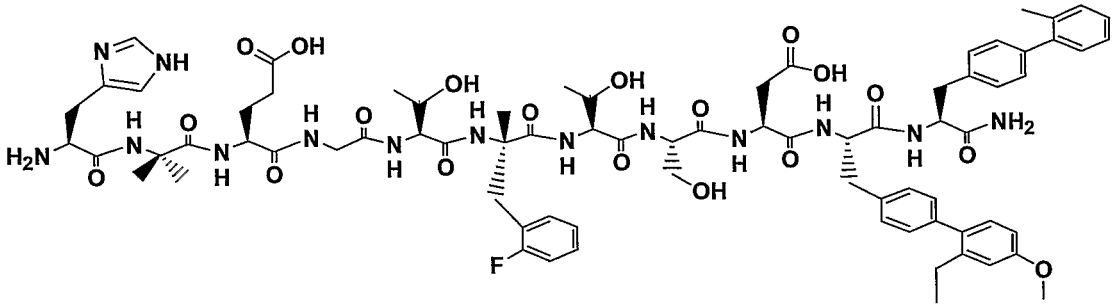
[0073] The term "diabetes and related diseases or related conditions" refers, without limitation, to Type II diabetes, Type I diabetes, impaired glucose tolerance, obesity, hyperglycemia, Syndrome X, dysmetabolic syndrome, diabetic complications, and hyperinsulinemia.

[0074] The term "lipid-modulating" or " lipid lowering" agent as employed herein refers, without limitation, to agents that lower LDL and/or raise HDL and/or lower triglycerides and/or lower total cholesterol and/or other known mechanisms for therapeutically treating lipid disorders.

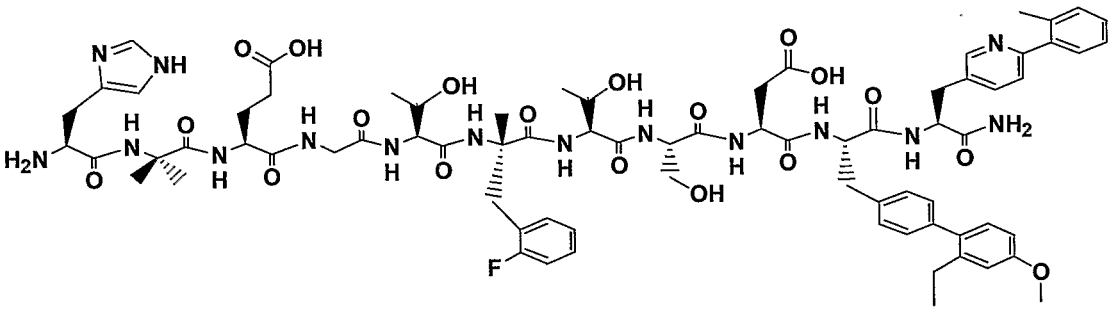
[0075] Administration of a therapeutic agent described herein includes, without limitation, administration of a therapeutically effective amount of the therapeutic agent. The term "therapeutically effective amount" as used herein refers, without limitation, to an amount of a therapeutic agent to treat or prevent a condition treatable by administration of a composition of the GLP-1 receptor modulators described herein. That amount is the amount sufficient to exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example and without limitation, treatment or prevention of the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating

physician, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance.

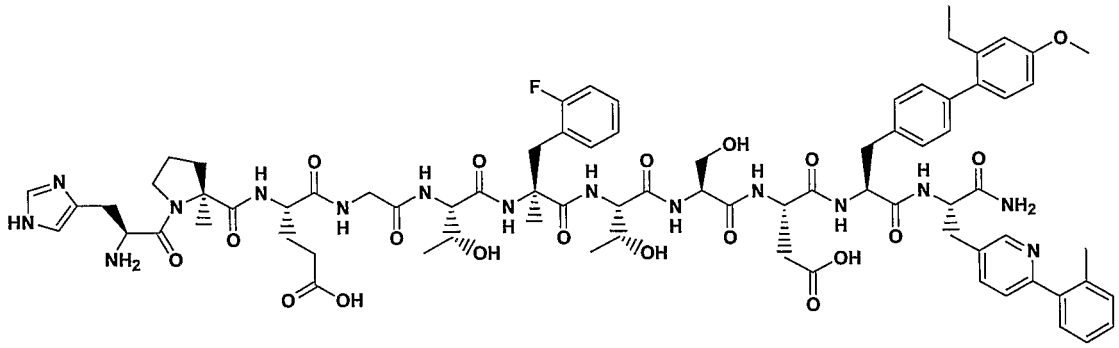
[0076] The peptides disclosed and claimed herein show superior potency, with comparable exposures, in an efficacy model of glucose lowering (ob/ob mouse model) and superior pharmacokinetics (as measured by subcutaneous injection in dogs), as illustrated in the tables and figures provided.



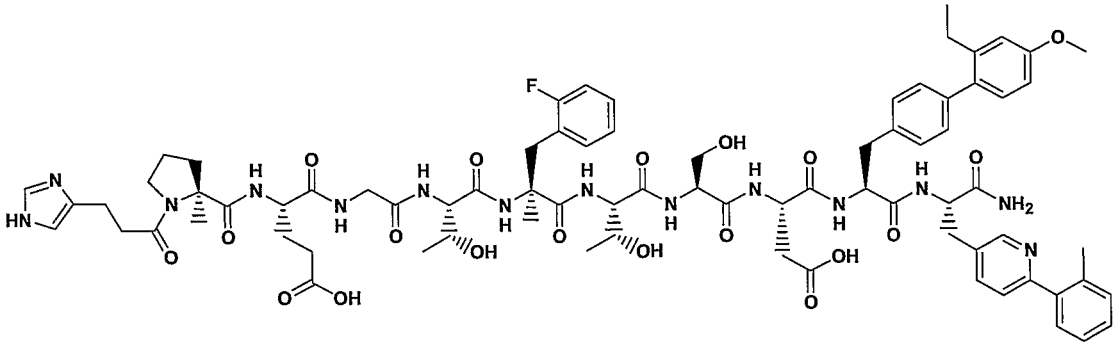
Compound I



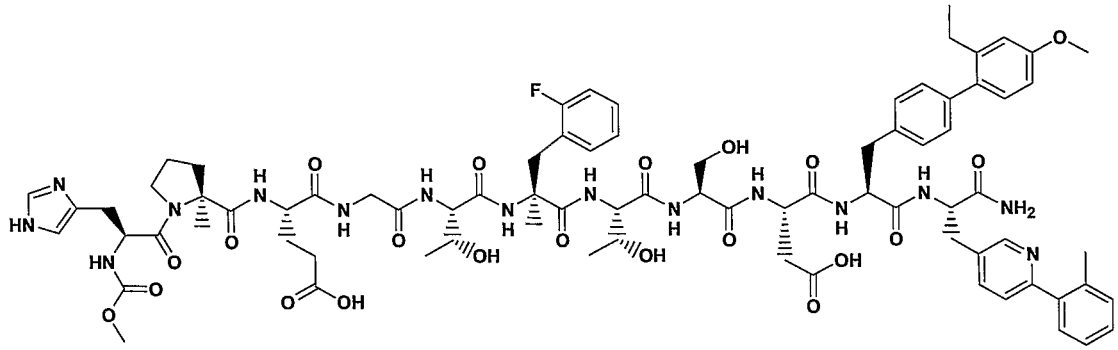
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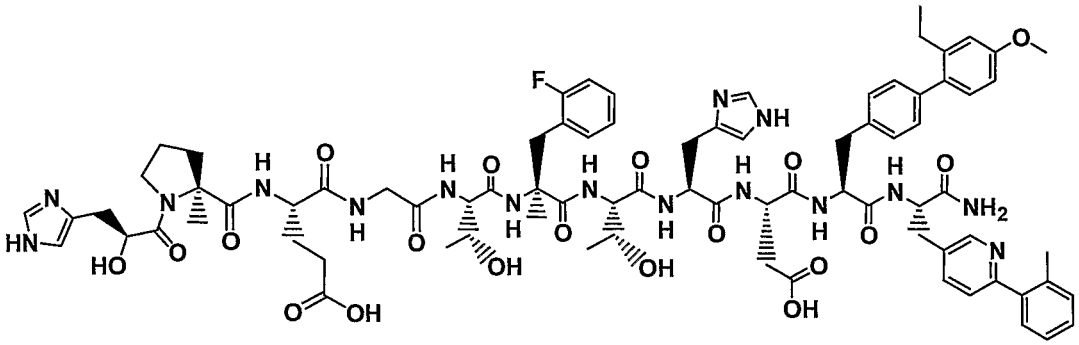
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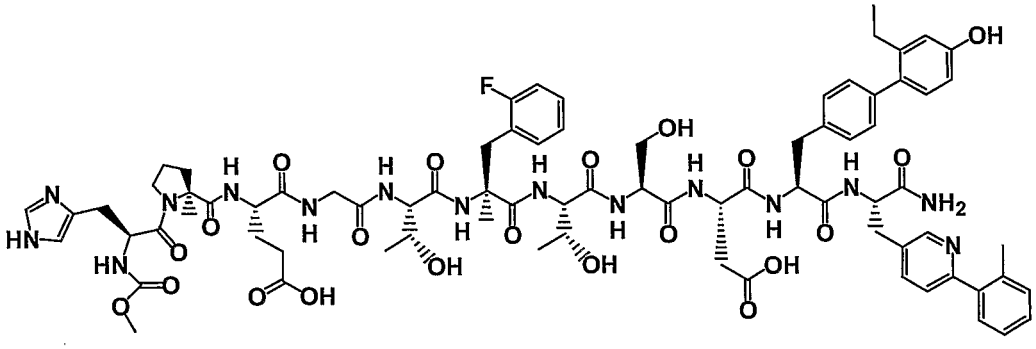
SEQ ID NO: 133



SEQ ID NO: 139



SEQ. ID NO: 151



SEQ ID NO: 158

5

Table I

Compound/ SEQ ID NO:	Potency in ob/ob mice	Exposure/dose during ipGTT in ob/ob mice (nM*h/nmol/kg)	Exposure in dogs* (sc@67μg/kg)
Compound I	ED50 = 50 nmoles/kg	22	89 nM*h
9	ED50 = 5 nmoles/kg	18	452 nM*h
118	ED50 = 2.5 nmoles/kg	4.4	4020 nM*h
151	ED50 = 1 nmoles/kg	16	1566 nM*h
158	ED50 = 2 nmoles/kg	11	1467 nM*h

*Compound I and the compound of SEQ ID NO: 118 were dosed in propylene glycol/pH 7.4 phosphate buffer (1:1); Compounds of SEQ ID Nos: 9, 151 and 158 were dosed in 0.2 M Tris buffer (pH 8.0).

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Table II

Compound/ SEQ ID NO	Potency in ob/ob mice: % AUC Reduction in Plasma Glucose in an IP Glucose Tolerance Test after SC Injection of Compound*	Exposure in dogs***(sc@67μg/kg)
Compound I	-15% (p=0.247, NS) (10 nmol/kg)	89 nM*h
9	-68% (p<0.0001) (10 nmol/kg)	1230 nM*h
118	-70% (p<0.001) (10 nmol/kg)	4020 nM*h
130	-72% (p<0.0001) (10 nmol/kg)	541 nM*h
149	-54%(p<0.0001) (10 nmol/kg)	940 nM*h
140	-73% (p<0.001) (10 nmol/kg)	283 nM*h
120	-68% (p<0.0001) (10 nmol/kg)	1116 nM*h
139	-63% (p<0.01) (10 nmol/kg)	1603 nM*h
119	-61% (p<0.0001) (5 nmol/kg)	1257 nM*h
150	-38% (p<0.05) (10 nmol/kg)	979 nM*h

* AUC = area under the curve. AUC values are calculated using the fasting plasma glucose value as the baseline in each individual animal. The percentage change in the AUC is calculated relative to the AUC for the vehicle-treated group in the same study.

The p values given are determined by comparison to the vehicle-treated group using analysis of variance (ANOVA) followed by Fisher's post-hoc test, **NS = non-statistically significant. *** Dosing vehicle: propylene glycol/pH 7.4 phosphate buffer (1:1).

[0077] The peptides and analogs thereof described herein may be produced by chemical synthesis using various solid-phase techniques such as those described in G. Barany and R.B. Merrifield, "The Peptides: Analysis, Synthesis, Biology"; Volume 2 -"Special Methods in Peptide Synthesis, Part A",, pp. 3-284, E. Gross and J. Meienhofer, Eds., Academic Press, New York, 1980; and in J. M. Stewart and J. D. Young, "Solid-Phase Peptide Synthesis", 2nd Ed., Pierce Chemical Co., Rockford, IL, 1984. The desired strategy is based on the Fmoc (9-Fluorenylmethyl methyl-oxycarbonyl) group for temporary protection of the α-amino group, in combination with the tert-butyl group for temporary protection of the amino acid side chains (see for example E. Atherton and R. C. Sheppard, "The Fluorenylmethoxycarbonyl Amino Protecting Group", in "The Peptides: Analysis, Synthesis, Biology"; Volume 9 - "Special Methods in Peptide Synthesis, Part C", pp. 1-38, S. Undenfriend and J. Meienhofer, Eds., Academic Press, San Diego, 1987.

[0078] The peptides can be synthesized in a stepwise manner on an insoluble polymer support (also referred to as "resin") starting from the C-terminus of the peptide. A synthesis is begun by appending the C-terminal amino acid of the peptide to the resin through formation of an amide or ester linkage. This allows the eventual release of the resulting peptide as a C-terminal amide or carboxylic acid, respectively. Alternatively, in cases where a C-terminal amino alcohol is present, the C-terminal residue may be attached to 2-Methoxy-4-alkoxybenzyl alcohol resin (SASRIN™, Bachem Bioscience, Inc., King of Prussia, PA) as described herein and, after completion of the peptide sequence assembly, the resulting peptide alcohol is released with LiBH4 in THF (see J. M. Stewart and J. D. Young, supra, p. 92).

[0079] The C-terminal amino acid and all other amino acids used in the synthesis are required to have their α-amino groups and side chain functionalities (if present) differentially protected such that the α-amino protecting group may be selectively

removed during the synthesis. The coupling of an amino acid is performed by activation of its carboxyl group as an active ester and reaction thereof with the unblocked α-amino group of the N-terminal amino acid appended to the resin. The sequence of α-amino group deprotection and coupling is repeated until the entire peptide sequence is assembled. The peptide is then released from the resin with concomitant deprotection of the side chain functionalities, usually in the presence of appropriate scavengers to limit side reactions. The resulting peptide is finally purified by reverse phase HPLC.

[0080] The synthesis of the peptidyl-resins required as precursors to the final peptides utilizes commercially available cross-linked polystyrene polymer resins (Novabiochem, San Diego, CA; Applied Biosystems, Foster City, CA). Preferred solid supports are: 4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxyacetyl-p-methyl benzhydrylamine resin (Rink amide MBHA resin); 9-Fmoc-amino-xanthen-3-yloxy-Merrifield resin (Sieber amide resin); 4-(9-Fmoc)aminomethyl-3,5-dimethoxyphenoxy)valeryl-aminomethyl-Merrifield resin (PAL resin), for C-terminal carboxamides. Coupling of first and subsequent amino acids can be accomplished using HOBT or HOAT active esters produced from DIC/HOBT, HBTU/HOBT, BOP, PyBOP, or from DIC/HOAT, HATU/HOAT, respectively. Preferred solid supports are: 2-Chlorotrityl chloride resin and 9-Fmoc-amino-xanthen-3-yloxy-Merrifield resin (Sieber amide resin) for protected peptide fragments. Loading of the first amino acid onto the 2-chlorotrityl chloride resin is best achieved by reacting the Fmoc-protected amino acid with the resin in dichloromethane and DIEA. If necessary, a small amount of DMF may be added to facilitate dissolution of the amino acid.

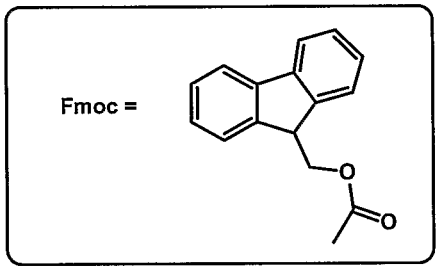
[0081] The syntheses of the 11-mer peptide analogs described herein can be carried out by using a peptide synthesizer, such as an Advanced Chemtech Multiple Peptide Synthesizer (MPS396) or an Applied Biosystems Inc. peptide synthesizer (ABI 433a). If the MPS396 was used, up to 96 peptides were simultaneously synthesized. If the ABI 433a synthesizer was used, individual peptides were synthesized sequentially. In both cases the stepwise solid phase peptide synthesis was carried out utilizing the Fmoc/t-butyl protection strategy described herein.

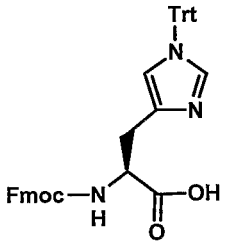
[0082] The non-natural non-commercial amino acids present at position-X_{aa10} and at position-X_{aa11} were incorporated into the peptide chain in one of two methods. In

the first approach a Boc- or Fmoc-protected non-natural amino acid was prepared in solution using appropriate organic synthetic procedures. The resulting derivative was then used in the step-wise synthesis of the peptide. Alternatively the required non-natural amino acid was built on the resin directly using synthetic organic chemistry procedures. When a non-natural non-commercial amino acid was needed for incorporation at position X_{aa6} or at any other Xaa position, the required Fmoc-protected non-natural amino acid was synthesized in solution. Such a derivative was then used in stepwise solid phase peptide synthesis.

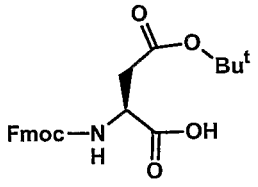
[0083] Useful Fmoc amino acids derivatives are shown below.

Examples of Orthogonally Protected Amino Acids used in Solid Phase Synthesis

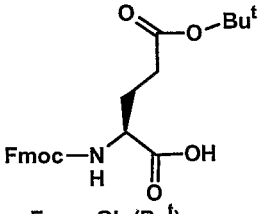




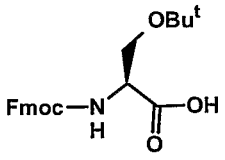
Fmoc-His (Trt)



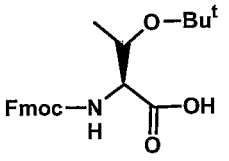
Fmoc-Asp(Bu^t)



Fmoc-Glu(Bu^t)

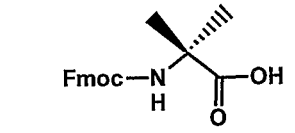


Fmoc-Ser(Bu^t)

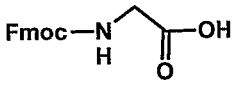


Fmoc-Thr-(Bu^t)

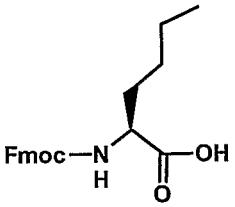
Protected Amino Acids used in Solid Phase Synthesis



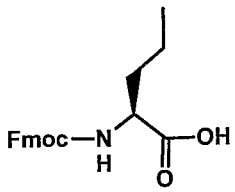
Fmoc-Aib
-a-aminoisobutyric acid-



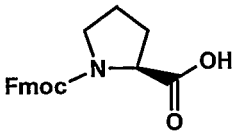
Fmoc-Gly



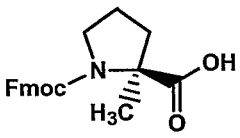
Fmoc-Nle
-Norleucine-



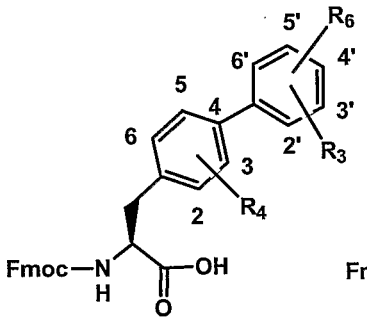
Fmoc-L-Nva
-L-Norvaline-



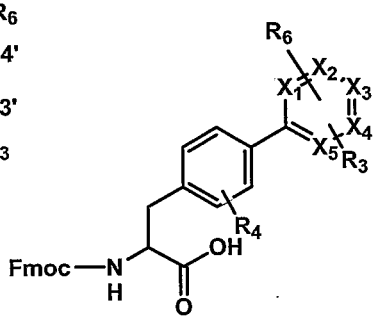
Fmoc-L-Pro



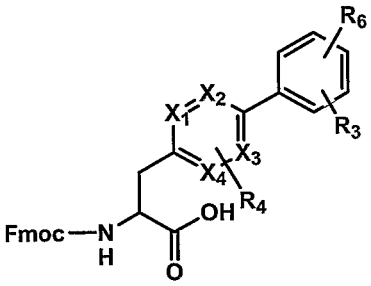
Fmoc-(S)-a-Methyl-Pro



Formula II



Formula III



Formula IV

[0084] The peptidyl-resin precursors for their respective peptides may be cleaved and deprotected using any standard procedure (see, for example, D. S. King et al. Int. J. Peptide Protein Res. 36, 1990, 255-266). A desired method is the use of TFA in the presence of water and TIS as scavengers. Typically, the peptidyl-resin is stirred in TFA/water/TIS (94:3:3, v:v:v; 1 mL/100 mg of peptidyl resin) for 2-6 hrs at room temperature. The spent resin is then filtered off and the TFA solution is concentrated or dried under reduced pressure. The resulting crude peptide is either precipitated and washed with Et2O or is redissolved directly into DMSO or 50% aqueous acetic acid for purification by preparative HPLC.

[0085] Peptides with the desired purity can be obtained by purification using preparative HPLC, for example, on a Waters Model 4000 or a Shimadzu Model LC-8A liquid chromatograph. The solution of crude peptide is injected into a YMC S5 ODS (20X 100 mm) column and eluted with a linear gradient of MeCN in water, both buffered with 0.1% TFA, using a flow rate of 14-20 mL/min with effluent monitoring by UV absorbance at 220 nm. The structures of the purified peptides can be confirmed by electro-spray MS analysis.

[0086] The following abbreviations are employed in the Examples and elsewhere herein:

Ph = phenyl

Bn = benzyl

i-Bu = iso-butyl

i-Pr = iso-propyl

Me = methyl

Et = ethyl

Pr = n-propyl

Bu = n-butyl

t-Bu = *tert*-butyl

Trt = trityl

TMS = trimethylsilyl

TIS =Triisopropylsilane

Et2O = diethyl ether

HOAc or AcOH = acetic acid

MeCN or AcCN = acetonitrile

DMF = N,N-dimethylformamide

EtOAc = ethyl acetate

THF = tetrahydrofuran

TFA = trifluoroacetic acid

TFE = α,α,α-trifluoroethanol

Et2NH = diethylamine

NMM = N-methylmorpholine

NMP = N-methylpyrrolidone

DCM = dichloromethane

n-BuLi = n-butyllithium

Pd/C = palladium on carbon

PtO2 = platinum oxide

TEA = triethylamine

min = minute(s)

h or hr = hour(s)

L = liter

mL or ml = milliliter

μL = microliter

g = gram(s)

mg = milligram(s)

mol = mole(s)

mmol = millimole(s)

meq = milliequivalent

rt or RT = room temperature

sat or sat'd = saturated

aq. = aqueous

mp = melting point

Bip = biphenylalanine LiBH4 = lithium borohydride

Mg = Magnesium

BOP reagent = benzotriazol-1-yloxy-tris-dimethylamino-phosphonium hexafluorophosphate (Castro's reagent)

PyBOP reagent = benzotriazol-1-yloxy-tripyrrolidino phosphonium hexafluorophosphate

HBTU = 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronim hexafluorophosphate

HATU = O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronim hexafluorophosphate

HCTU = 2-(6-Chloro-1-H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

DMAP = 4-(dimethylamino)pyridine

DIEA = Diisopropylethylamine

EDAC = 3-ethyl-3'-(dimethylamino)propyl-carbodiimide hydrochloride (or 1-[(3-(dimethyl)amino)propyl])-3-ethylcarbodiimide hydrochloride)

Fmoc or FMOC = fluorenylmethyloxycarbonyl

Boc or BOC = tert-butyloxycarbonyl

Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl

HOBT or HOBT•H2O = 1-hydroxybenzotriazole hydrate

Cl-HOBt = 6-Chloro-benzotriazole

HOAT = 1-hydroxy-7-azabenzotriazole

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

NMR = nuclear magnetic resonance

Sc or SC = sub-cutaneous

IP or ip = intra-peritoneal

GTT = glucose tolerance test

[0087] One of skill in the art of peptide chemistry is aware that amino acids occur as both D and L isomers, and that the subject matter disclosed and claimed herein includes the use of either or a mixture of isomers for amino acids incorporated in the synthesis of the peptides described herein.

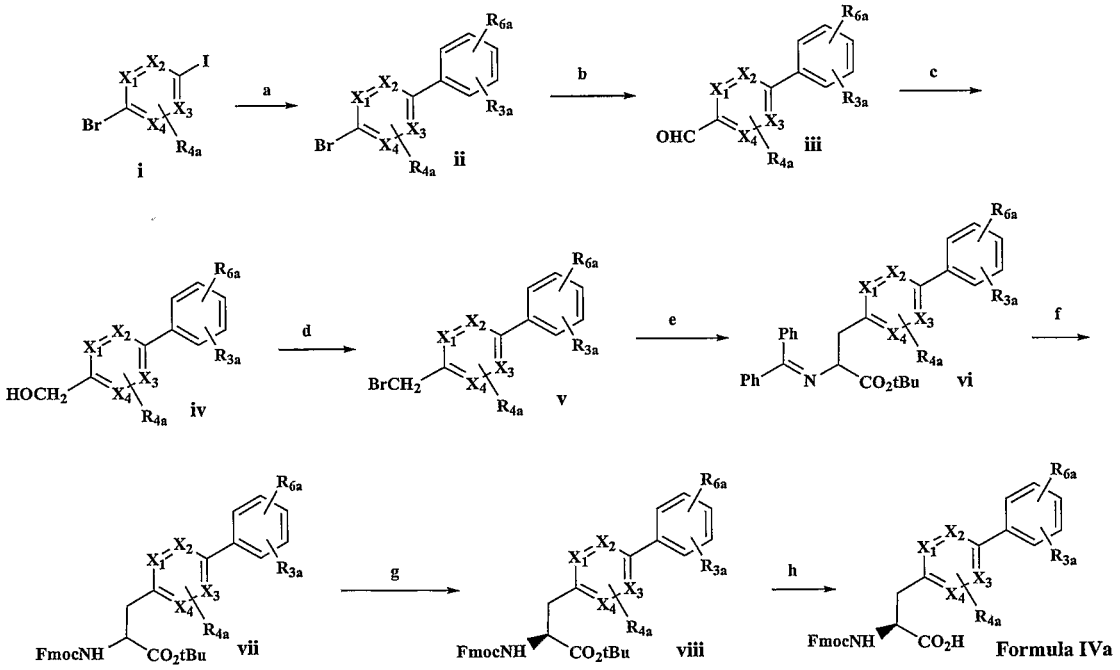
General procedures for the synthesis of amino acids of Formula IVa

[0088] Protected amino acids of Formula IVa can be prepared by several methods. For example (Scheme A), iodobromo-heterocycle **i** (where X_3 = N) can be coupled *via* palladium-mediated catalysis with a boronic acid by standard literature methods to provide aryl heterocyclic bromide **ii**, which by lithiation and reaction with a acylating such as dimethylformamide provides aldehyde **iii**. The aldehyde is reduced to alcohol **iv** by sodium borohydride or similar agent and the corresponding bromide **v** is prepared by extended refluxing of **iv** in 48% hydrobromic acid. Alkylation of tert-butyl 2-(diphenylmethyl-eneamino)acetate with **v** using a chiral catalyst after the

method of O'Donnell (*Tetrahedron Letters* **39** 8775 (1998)) leads to the chiral ester **vi**, which after deprotection with a strong non-aqueous acid and treatment with Fmoc-Cl provides Fmoc t-butyl ester **vii** of predominately one chiral form. Recrystallization of **vii** from common organic solvents provides **viii** with enantiomeric excess >95%. Removal of the ester using a strong non-aqueous acid provides compounds of Formula IVa.

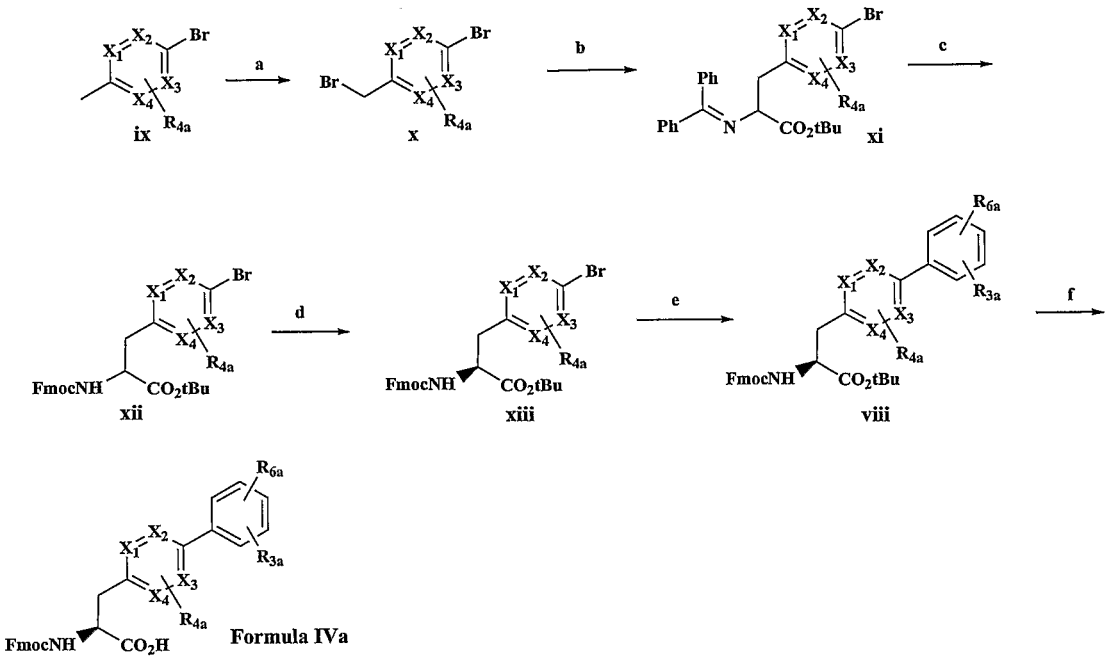
[0089] Alternatively, compounds of Formula IVa can be prepared by radical-induced bromination of methyl heterocycle **ix** (Scheme B) to give bromomethylheterocycle **x**. Alkylation of **x** by the method of O'Donnell as described above and similar recrystallization leads to chiral ester **xiii** in high enantiomeric excess. Boronic acid coupling as described in Scheme A leads to compounds of Formula IVa.

Scheme A



a) $R_3R_6C_6H_3B(OH)_2$, $Pd(Ph_3P)_4$, toluene/10% Na_2CO_3 b) s-BuLi, DMF/toluene c)$NaBH_4$/MeOH d) 48% HBr, reflux e) $PhC{=}NCH_2CO_2tBu$, chiral catalyst, 2-tert-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphos-phorine/THF f) i. 15% citric acid ii. FmocCl, Na_2CO_3/THF-H_2O g) recrystallization h) TFA

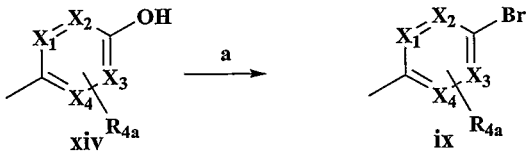
Scheme B



a) NBS, AIBN/CCl_4 b) $PhC{=}NCH_2CO_2tBu$, chiral catalyst, 2-tert-Butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphos-phorine/THF c) i. 15% citric acid ii. FmocCl, Na_2CO_3/THF-H_2O d) recrystallization e) $R_3R_6H_3B(OH)_2$, $Pd(Ph_3P)_4$/toluene-10% Na_2CO_3 f) TFA

[0090] Compound **ix** can be prepared from hydroxyheterocycle **xiv** by treatment with phosphorousoxybromide (Scheme C).

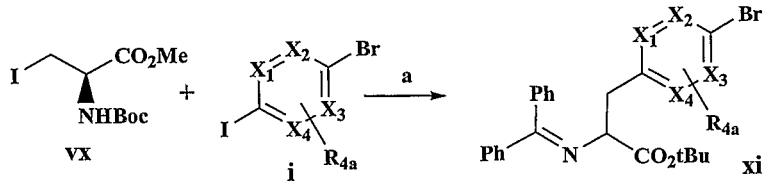
Scheme C



a) NBS, AIBN/CCl_4

[0091] An alternative synthesis of intermediate **ix** uses **xv**, methyl-3-iodo-alanate, and **i** by zinc-copper coupling (Scheme D).

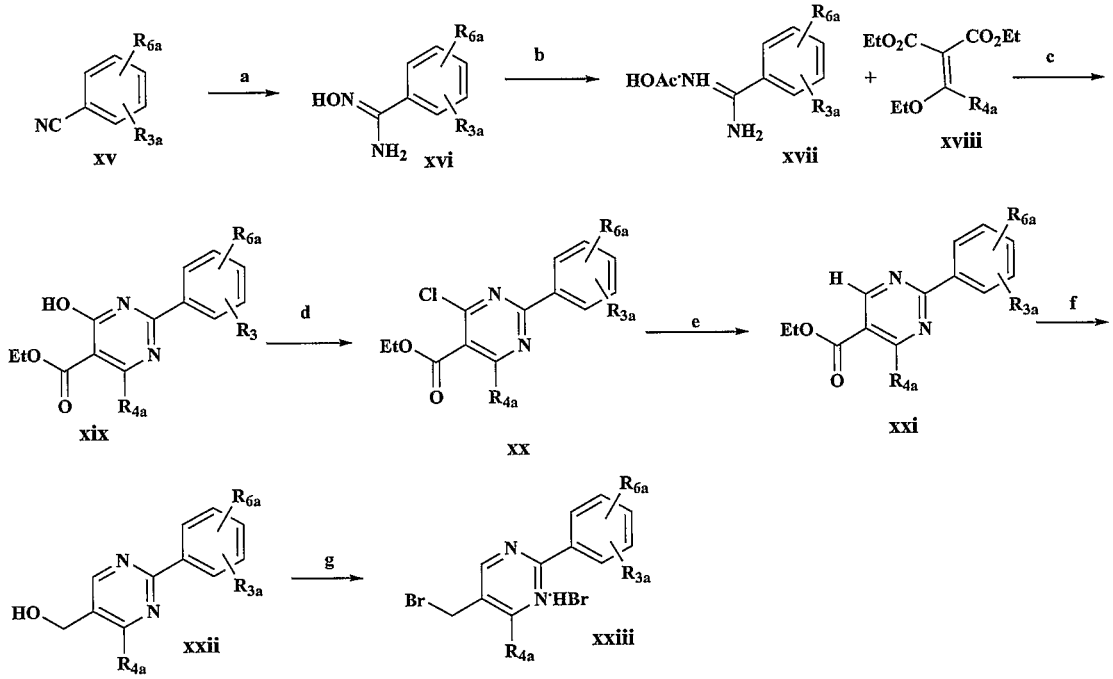
Scheme D



a) Zn-Cu $(Ph_3P)_2PdCl_2$, benezene, DMA

[0092] Arylpyrimidinylmethyl bromides **xxiii** (X_2, X_3 = N, X_1, X_4 = CR_{4a}) can be prepared from aryl nitriles **xv** (Scheme E).

Scheme E

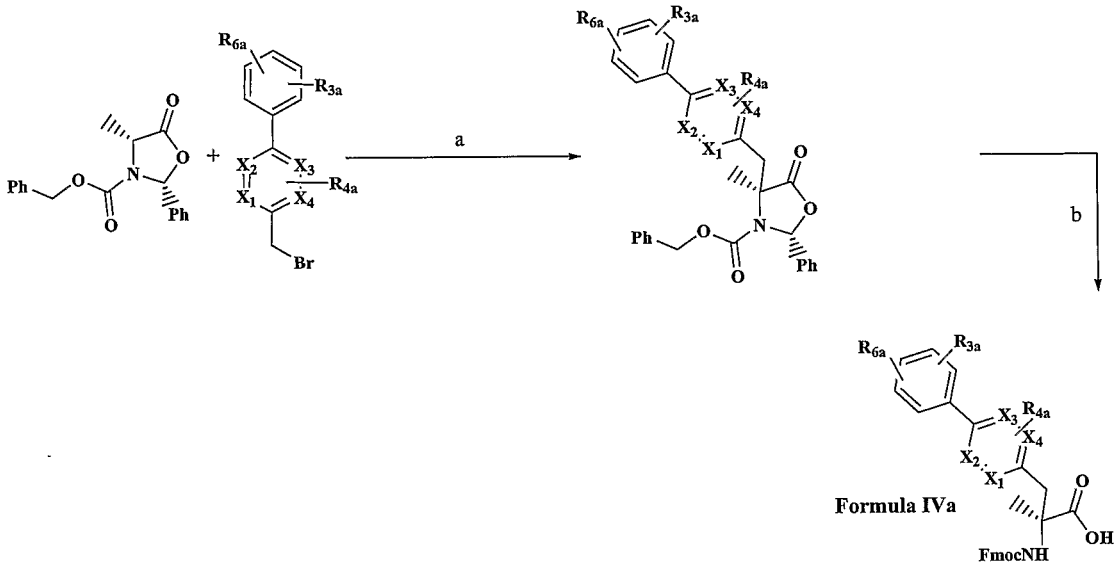


[0093] Hydroxypyrimidine **xvi** is prepared from **xv** by treatment of the nitrile with hydroxylamine hydrochloride. The pyrimidine **xvii** results from hydrogenation of **xvi**. Condensation of **xvii** with enolmethylene malonate **xviii** leads to pyrimidine **xix** which is chlorinated with phosphorous oxychloride to give **xx**. Dehalogenation *via* catalytic hydrogenation leads to **xxi** and reduction with DiBAl provides alcohol **xxii**. Treatment of the alcohol with phosphorous oxybromide leads to unstable bromide **xxiii**, which must be used immediately as in Scheme A to provide protected amino acid **vi**.

[0094] Compounds of Formula IVa (R_7 = Me) are prepared from oxazolidine **xxiv** by the method of Kapadia, *J. Org. Chem.* **66** 1903 (2001) (Scheme F). Thus

alkylation of **xxiv** with **v** using potassium hexamethyldisilazide or other strong base provides **xxv.** Strong acid hydrolysis of **xxv** followed by protection (with Fmoc-Cl or Fmoc-OSu or the like) of the amine gives compounds of the type of Formula IVa.

Scheme F



EXAMPLE 1

Simultaneous Solid Phase Peptide Synthesis of 11-mer Peptides

[0095] Dipeptidyl resin, containing, amino acid at positions Xaa_{10} and Xaa_{11}, was prepared using the following manual procedure in a batchwise mode before continuing peptide chain elongation utilizing the automated simultaneous synthesis protocol on an MPS-396 peptide synthesizer. The synthesis of the N-α-Fmoc-protected biphenylalanine or phenyl-heteroaryl-alanine derivatives used in the manual couplings is described in the general experimental above, and in Examples 10-19.

[0096] An amount of 9-Fmoc-aminoxanthen-3-yloxy-Merrifield resin (Sieber amide resin; loading: 0.5 to 0.7 mmol/g) sufficient to synthesize several 11-mer analogs, was swelled by washing with DMF (4x10 mL/g, 5 minutes). The Fmoc group was then removed using two treatments, 5 and 15 minutes each respectively, with 20% piperidine in DMF (10 mL/g). The resin was washed with DMF (4x10 mL/g) and NMP (4x10 mL/g). A 0.5 M solution of Fmoc-L-4-(2'-Methylphenyl)-3-pyridylalanine-OH (HCl salt)(1.1 eq.), (or of any other amino acid represented by

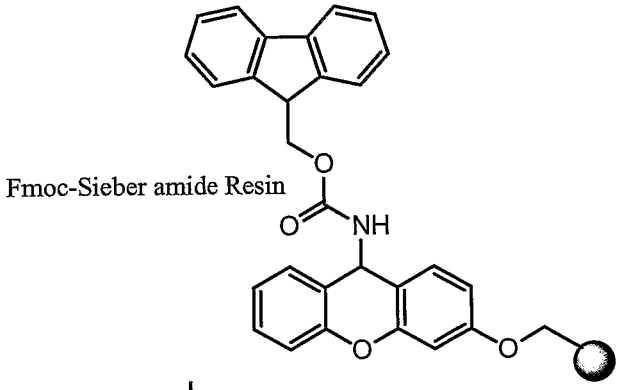
Formula IVa), PyBOP (1.1 eq.) and DIEA (3.3 eq.) in NMP was added to the resin. The resin was then shaken or vortexed for 16-24 hours. Coupling completion was monitored using a qualitative ninhydrin test. The resin was drained, washed with NMP (3x10 mL/g) and DMF (3x10 mL/g), and treated for 90 minutes with 10% acetic anhydride in DCM (10 mL/g). After DCM washes (4x10 mL/g), a second manual coupling cycle using a DIC/HOAt mediated was then performed, starting from the removal of the Fmoc group with 20% piperidine in DMF, and using a Fmoc-protected biphenylalanine analog, as represented by Formula II, in the coupling step. This synthesis scheme produced the desired Fmoc-protected dipeptidyl-Sieber amide resin.

[0097] Such dipeptidyl-resins required for the synthesis of a set of designed analogs were then used in the automated MPS synthesis of up to 96 peptides per run in the following manner. The dipeptidyl-resins were loaded as suspensions in dichloromethane/DMF (60:40) into the 96-well reactor of an Advanced ChemTech MPS 396 synthesizer in volumes corresponding to 0.01-0.025 mmol (20-50 mg) of resin per reactor well. The reactor was placed on the instrument and drained. The wells were then washed with DMF (0.5-1.0 mL, 3X2 min) and subjected to the number of automated coupling cycles required to assemble the respective peptide sequences as determined by the pre-programmed sequence synthesis table.

[0098] The detailed stepwise synthesis protocol used for a typical 0.025 mmol/well simultaneous synthesis of 96 compounds is described below. This protocol was adapted for the simultaneous synthesis of arrays of analogs ranging from 12 to 96 per individual run. The general synthesis protocol is depicted in Scheme 1.

Scheme 1

Automated synthesis of GLP-1 receptor modulator peptide analogs



1) Piperidine/DMF (Removal of Fmoc)
2) 1.1 eq. Fmoc-(S)-4-(2'-methylphenyl)-3-pyridylala/PyBOP/DIEA/NMP (16 h);
3) (a) repeat step 1; (b) 2-4 eq. Fmoc-(S)-Bip(2'-Et-4'-OMe)/DIC/HOAt/NMP (16 hr);
4) (a) repeat step 1; (b) 5 eq. Fmoc-Xaa_9/DIC/HOBt (2 hr);
5) repeat step 4 using Fmoc-Xaa_8;
6) repeat step 4 using Fmoc-Xaa_7;
7) (a) repeat step 1; (b)Xaa_6/HOAt/DIC (6 hr)
8) (a) repeat step 1; (b) 10 eq. Fmoc-Xaa_5/HOAt/DIC (4 hr);
(c) 10% Ac_2O/DCM (30 min) [unreacted amine capping step];
9) repeat step 1; (b) 10 eq. Fmoc-Xaa_4/HOAt/DIC (2 hr);
10) repeat step 9 using Fmoc-Xaa_3;
11) repeat step 1; (b) 5 eq. Fmoc-Xaa_2/HOAt/DIC (16 hr);
12) repeat step 11 using Fmoc-Xaa_1/HOAt/DIC;
13) (a) repeat step 1; (b) wash with NMP and DCM; (c) dry in vacuo;
14) TFA/Water/Triisopropylsilane (2 hr);
15) RP-HPLC purification

Xaa1-Xaa2-Xaa3-Xaa4-Xaa5-Xaa6-Xaa7-Xaa8-Xaa9-Xaa10-Xaa11

[0099] Prior to starting the synthesis, the following reagent solutions were prepared and placed on the instrument as required: 1.5 M (15%) piperidine in DMF; 0.5 M DIEA in NMP; 0.36 M DIC in NMP; 1 M (10%) acetic anhydride in DMF. The required Fmoc-protected amino acids were prepared as 0.36 M solutions in 0.36 M HOAt/NMP and placed into the appropriate positions in the 32-position amino acid rack.

[00100] The Fmoc-protected dipeptidyl-resin prepared above was deprotected by treating with 20% piperidine in DMF (1.0 mL; 1 x 5 minutes; 1 x 15 minutes). The resin was then washed with NMP (8 x 1.0 mL).

[00101] Coupling of the next amino acid, typically Fmoc-Asp(OtBu)-OH or another Fmoc-amino acid with appropriate orthogonal protection if required, was carried out by manual addition of a solution of the appropriate Fmoc-amino acid (0.075 mmol, 3.0 eq.), HCTU (0.075 mmol, 3.0 eq.) and DIEA (0.15 mmol, 6.0 eq.) in NMP (1 mL) to all wells. The coupling was allowed to proceed for 3 hrs. After reactor draining by nitrogen pressure (3-5 psi) and washing the wells with NMP (4 X 1.0 mL).

[00102] The next coupling cycle started with the removal of the Fmoc group as described above, and involved the coupling of either Fmoc-Ser(tBu)-OH or of a different Fmoc-amino acid as required by the sequence substitutions desired at this position. The coupling was carried out in a manner identical to that described for Fmoc-Asp(OtBu)-OH. The next coupling step was carried out in the same way to incorporate either Fmoc-Thr(tBu)-OH or any of the other selected Fmoc-amino acids into this sequence position as required.

[00103] The next Fmoc-amino acid (for example Fmoc-α-methyl-Phe-OH or an analog thereof) was coupled as follows: after Fmoc deprotection in the usual manner, the Fmoc-amino acid (1-5 eq.), HOAt (1-5 eq.) and DIC (1-5 eq.) were added manually as a solution in NMP (1.0 mL) and the coupling was allowed to proceed for 16-24 hrs. The coupling was not repeated in this case. After the usual post-coupling washes, the peptidyl-resins were capped with acetic anhydride as described herein.

[00104] The next coupling step involved either Fmoc-Thr(tBu)-OH or substitution analogs as required by sequence replacements at this position. The coupling was performed as described for the initial MPS coupling of Fmoc-Asp(OtBu)-OH and its analogs, except that 10 eq. of Fmoc-Thr(tBu)-OH or substitution analogs was used and the coupling was allowed to proceed for 16 hrs and the coupling reagents used were DIC/HOAt in NMP. After the usual post-coupling washes, the peptidyl-resins were capped with 10% acetic anhydride in DCM (1 x 1 mL x 60 mins.).

[00105] The identical coupling protocol described for the coupling of Fmoc-Asp(OtBu)-OH was used was repeated for the next three amino acid residues. Fmoc-

His(Trt)-OH was coupled as the Fmoc-Thr(tBu)-OH residue described in the paragraph above in order to complete the sequence assembly of the desired 11-mer peptide analogs. For the coupling of commercially and non-commercially available non-natural amino acids needed at a certain sequence position, a single coupling protocol similar to that described above for the novel amino acid at position 6 (X_{aa6}) was used.

[00106] Finally, the Fmoc group was removed with 20% piperidine in DMF as described above, and the peptidyl-resins were washed with DMF (4 x 1.0 mL) and DCM (4 x 1.0 mL). They were then dried on the reactor block by applying a constant pressure of nitrogen gas (5 psi) for 10-15 min.

Cleavage/Deprotection

[00107] The desired peptides were cleaved/deprotected from their respective peptidyl-resins by treatment with a TFA cleavage mixture as follows. A solution of TFA/DCM/tri-isopropylsilane (70:28:2) (1.0 mL) was added to each well in the reactor block, which was then vortexed for 10 mins. This was repeated twice more and the TFA solutions from the wells were collected by positive pressure into pre-tared vials located in a matching 96-vial block on the bottom of the reactor. The vials were capped and gently vortexed for an additional 90 minutes. The vials were uncapped and concentrated in a SpeedVac™ (Savant) to a volume of about 0.2 mL. The crude peptides were then precipitated by the addition of diisopropyl ether (3 mL) and being briefly vortexed. The precipitates were pelleted by centrifugation and the supernatants were decanted. The vials were dried in a SpeedVac™ (Savant) to yield the crude peptides, typically in >100% yields (20-40 mgs). The crude peptides dissolved directly in 2 mL of 0.6% ammonium hydroxide for purification by preparative HPLC as follows.

Preparative HPLC purification of the crude peptides

[00108] Preparative HPLC was carried out either on a Waters Model 4000 or a Shimadzu Model LC-8A liquid chromatograph. Each solution of crude peptide was injected into a YMC S5 ODS (20X100 mm) column and eluted using a linear gradient of MeCN in water, both buffered with 0.1% TFA. A typical gradient used was from

20% to 50% 0.1% TFA/MeCN in 0.1% TFA/water over 15 min. at a flow rate of 14 mL/min with effluent UV detection at 220 nm. The desired product eluted well separated from impurities, typically after 10-11 min., and was usually collected in a single 10-15 mL fraction on a fraction collector. The desired peptides were obtained as amorphous white powders by lyophilization of their HPLC fractions.

HPLC Analysis of the Purified Peptides

[00109] After purification by preparative HPLC as described above, each peptide was analyzed by analytical RP-HPLC on a Shimadzu LC-10AD or LC-10AT analytical HPLC system consisting of: a SCL-10A system controller, a SIL-10A auto-injector, a SPD10AV or SPD-M6A UV/VIS detector, or a SPD-M10A diode array detector. A YMC ODS S3 (4.6X50 mm) column was used and elution was performed using one of the following gradients: 10-70% B in A over 8 min, 2.5 mL/min. (method A); 5-80% B in A over 8 min, 2.5 mL/min. (method B); 5-70% B in A over 8 min., 2.5 mL/min. (method C); 25-75% B in A over 8 min, 2.5 mL/min (method D); 20-75% B in A over 8 min, 2.5 mL/min. (method E); 15-70% B in A over 8 min, 2.5 mL/min. (method F); 10-90% B in A over 8 min, 2.5 mL/min. (method G); 20-65% B in A over 8 min, 2.5 mL/min. (method H); 5-90% B in A over 8 min., 2.0 mL/min. (method I); 5-90% B in A over 8 min., 2.5 mL/min. (method J); 20-80% B in A over 8 min., 2.5 mL/min. (method K); 10-100% B in A over 8 min., 2.5 mL/min. (method L); 10-75% B in A over 8 min., 2.5 mL/min. (method M). Mobile phase A: 0.1% TFA/water; mobile phase B: 0.1% TFA/acetonitrile. The purity was typically >90%.

Characterization by Mass Spectrometry

[00110] Each peptide was characterized by electrospray mass spectrometry (ES-MS) either in flow injection or LC/MS mode. Finnigan SSQ7000 single quadrupole mass spectrometers (ThermoFinnigan, San Jose, CA) were used in all analyses in positive and negative ion electrospray mode. Full scan data was acquired over the mass range of 300 to 2200 amu for a scan time of 1.0 second. The quadrupole was operated at unit resolution. For flow injection analyses, the mass spectrometer was interfaced to a Waters 616 HPLC pump (Waters Corp., Milford, MA) and equipped with an HTS PAL autosampler (CTC Analytics, Zwingen, Switzerland). Samples

were injected into a mobile phase containing 50:50 water:acetonitrile with 0.1% ammonium hydroxide. The flow rate for the analyses was 0.42 mL/min. and the injection volume 6 µl. A ThermoSeparations Constametric 3500 liquid chromatograph (ThermoSeparation Products, San Jose, CA) and HTS PAL autosampler were used for LC/MS analyses. Chromatographic separations were achieved employing a Luna C_{18}, 5 micron column, 2 x 30 mm (Phenomenex, Torrance, CA). The flow rate for the analyses was 1.0 mL/min and column effluent was split, so that the flow into the electrospray interface was 400 µl/min. A linear gradient from 0% to 100% B in A over 4 minutes was run, where mobile phase A was 98:2 water:acetonitrile with 10 mM ammonium acetate and mobile phase B was 10:90 water:acetonitrile with 10 mM ammonium acetate. The UV response was monitored at 220 nm. The samples were dissolved in 200 µl 50:50 H_2O:MeCN (0.05% TFA). The injection volume was 5 µl.

[00111] In all cases, the experimentally measured molecular weight was within 0.5 Daltons of the calculated mono-isotopic molecular weight.

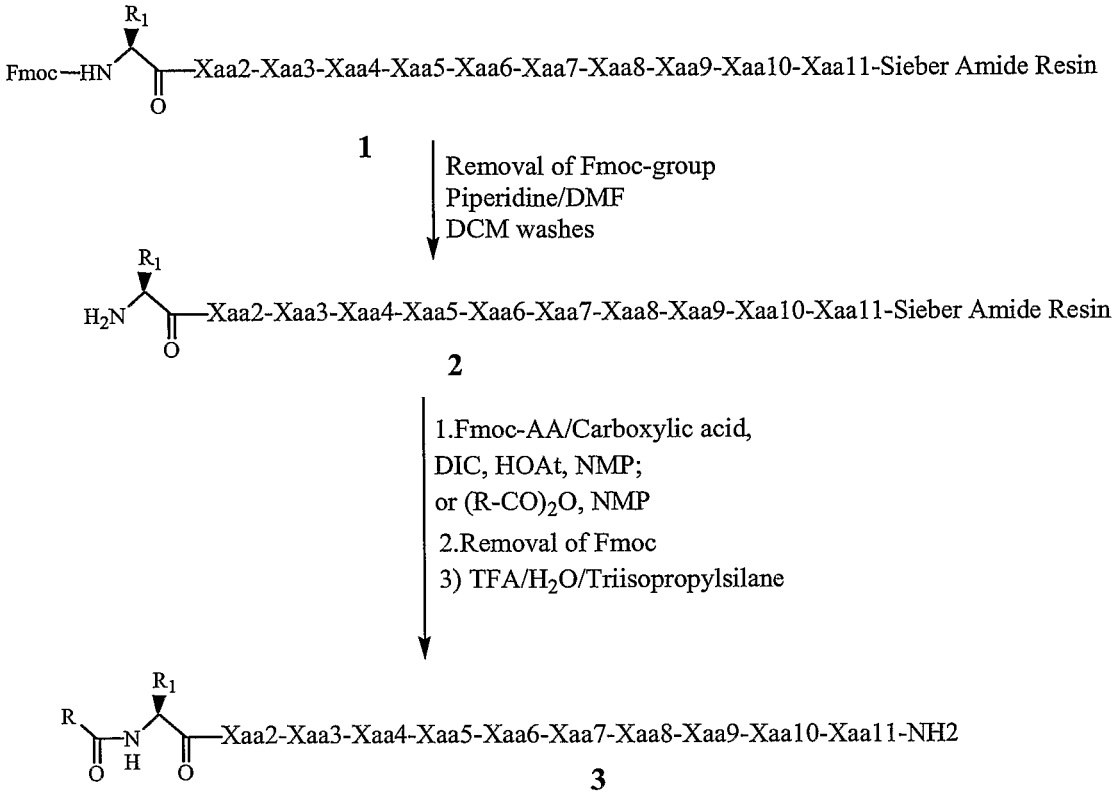
EXAMPLE 2

A. General procedure for the synthesis of N-acylated 11-mer peptide analogs (Scheme 2)

[00112] The synthesis of N-acylated 11-mer peptide analogs was started from the protected 11-mer peptidyl-resin intermediate (1) (0.015 mmol), prepared as described herein, as shown in Scheme 2. The Fmoc group was removed using the procedure described herein, and the resulting resin intermediate 2 was coupled with the relevant Fmoc-protected amino acid or carboxylic acid using the coupling protocol described in the general method described herein. In cases where the appropriate anhydride was available, the N-acylation was performed using 5 eq. of the anhydride in NMP. The resulting N-acylated 11-mer analogs (3) were cleaved/deprotected and purified by prep. HPLC by the general method described herein.

Scheme 2

Synthesis of Residue #1 substituted/derivatized 11-mer peptide analogs



B. General procedure for the synthesis of N-carbamate derivatives of 11-mer peptide analogs

[00113] The synthesis of N-carbamate derivatives of 11-mer peptide analogs may be started from the protected 11-mer peptidyl-resin intermediate (1) (0.015 mmol), prepared as described herein. The Fmoc group is removed using the procedure described herein, and the resulting resin intermediate 2 is allowed to react with the relevant alky/aryl chloroformate in the presence of an appropriate base such as a tertiary amine, or with a di-carbonate or an activated carbonate such as p-nitrophenyl or phenyl or hydroxy-succinimidyl carbonate.

C. General procedure for the synthesis of N-urea derivatives of 11-mer peptide analogs

[00114] The synthesis of N-urea derivatives of 11-mer peptide analogs may be started from the protected 11-mer peptidyl-resin intermediate (1) (0.025 mmol),

prepared as described herein. The Fmoc group is removed using the procedure described herein, and the resulting resin intermediate 2 is allowed to react with the relevant isocyanate prepared, for example, as in K. Burgess et al., J. Am. Chem. Soc. 1997, 119, 1556-1564; alternatively, the resin intermediate 2 may be allowed to react with the relevant carbamoyl chloride. Similarly, N-urea derivatives of 10-mer peptide analogs may be prepared starting from a protected 10-mer peptidyl-resin intermediate, Fmoc removal and reaction of the resulting peptidyl-resin intermediate with the relevant isocyanate or carbamyl chloride.

D. General procedure for the synthesis of N-sulfonamides of 11-mer peptide analogs

[00115] The synthesis of N-sulfonamides of 11-mer peptide analogs may be started from the protected 11-mer peptidyl-resin intermediate (1) (0.025 mmol), prepared as described herein. The Fmoc group is removed using the procedure described herein, and the resulting resin intermediate 2 is allowed to react with the relevant sulfonyl chloride. Similarly, N-sulfonamides of 10-mer peptide analogs may be prepared starting from a protected 10-mer peptidyl-resin intermediate, Fmoc removal and reaction of the resulting peptidyl-resin intermediate with the relevant sulfonyl chloride.

E. General procedure for the synthesis of N-sulfonylurea derivatives of 11-mer peptide analogs

[00116] The synthesis of N-sulfonylurea derivatives of 11-mer peptide analogs may be started from the protected 11-mer peptidyl-resin intermediate (1) (0.025 mmol), prepared as described herein. The Fmoc group is removed using the procedure described herein, and the resulting resin intermediate 2 is allowed to react with the relevant sulfamoyl chloride $R_4R_5N\text{-}SO_2\text{-}Cl$ to yield a sulfonyl urea intermediate (see, for example, P. Davern et al. J. Chem. Soc., Perkin Trans. 2, 1994 (2), 381-387). Similarly, N-sulfonyl urea derivatives of 10-mer peptide analogs may be prepared starting from a protected 10-mer peptidyl-resin intermediate, Fmoc removal and reaction of the resulting peptidyl-resin intermediate with the relevant sulfamoyl chloride $R_4R_5N\text{-}SO_2\text{-}Cl$.

EXAMPLE 3

Solid Phase Synthesis of 11-mer peptide analogs using an Applied Biosystems Model 433A Peptide Synthesizer

[00117] Following is the general description for the solid phase synthesis of typical 11-mer peptide analogs, using an upgraded Applied Biosystems Model 433A peptide synthesizer. The upgraded hardware and software of the synthesizer enabled conductivity monitoring of the Fmoc deprotection step with feedback control of coupling. The protocols allowed a range of synthesis scale from 0.05 to 1.0 mmol.

[00118] The incorporation of the two non-natural C-terminal amino acid was described above in connection with simultaneous synthesis of 11-mer analogs. Such a Fmoc-protected dipeptidyl resin was used in this ABI synthesis. The Fmoc-protected dipeptidyl-resin (0.1 mmol) was placed into a vessel of appropriate size on the instrument, washed 6 times with NMP and deprotected using two treatments with 22% piperidine/NMP (2 and 8 min. each). One or two additional monitored deprotection steps were performed until the conditions of the monitoring option were satisfied (<10% difference between the last two conductivity-based deprotection peaks). The total deprotection time was 10-12 min. The deprotected dipeptidyl-resin was washed 6 times with NMP and then coupled with the next amino acid. The procedure is illustrated by the example used in the next step.

[00119] Thus, Fmoc-Asp(OtBu)-OH was coupled next using the following method: Fmoc-Asp(OtBu)-OH (1 mmol, 10 eq.) was dissolved in 2 mL of NMP and activated by subsequent addition of 0.45 M HBTU/HOBt in DMF (2.2 mL) and 2 M DIEA/NMP (1 mL). The solution of the activated Fmoc-protected amino acid was then transferred to the reaction vessel and the coupling was allowed to proceed for 30 to 60 min., depending on the feedback from the deprotection steps. The resin was then washed 6 times with NMP, and subjected to 8 additional deprotection/coupling cycles as described above in order to complete the assembly of the desired sequence. The Fmoc-amino acids sequentially used were: Fmoc-Ser(tBu)-OH, Fmoc-Thr(tBu)-OH, Fmoc-α-methyl-Phe(2-Fluoro)-OH or analog thereof, Fmoc-Thr(tBu)-OH, Fmoc-Gly-OH, Fmoc-Glu(OtBu)-OH, Fmoc-Aib-OH and Fmoc-His(Trt)-OH. Finally, the

Fmoc group was removed with 22% piperidine in NMP as described above, and the peptidyl-resin was washed 6 times with NMP and DCM, and dried in vacuo.

[00120] Alternatively, a modified coupling protocol was used in which the Fmoc-protected amino acid (0.26 mmol) was activated by subsequent addition of 0.5 M HOAt in DMF (0.52 mL) and DIC (40 μL), transferred to the reaction vessel manually and allowed to couple for 14-18 hrs.

Cleavage/Deprotection

[00121] The desired peptide was cleaved/deprotected from its respective peptidyl-resin by treatment with a solution of TFA/water/tri-isopropylsilane (96:2:2) (3.0 mL) for 2 hrs. The resin was filtered off, rinsed with TFA (1.0 mL), and the combined TFA filtrates were added to 35 mL of Et2O. The resulting precipitate was collected by centrifugation and finally dried, to yield 232 mg of crude peptide product as a white solid. This was purified by preparative HPLC as described herein. The gradient used was from 15% to 45% 0.1% TFA/MeCN in 0.1% TFA/water over 40 min. The fractions containing pure product were pooled and lyophilized, to yield 28.4 mg (18% recovery) of pure product.

EXAMPLE 4

Synthesis of biphenylalanine analogs at position–X_{aa10} and position-X_{aa11} represented by Formulas II-IV and IIa-IVa

[00122] For those analogs wherein position–X_{aa10} and position-X_{aa11} residues were represented by substituted amino acid analogs represented by Formulas II-IV and IIa-IVa, *i.e.*, biphenylalanine analogs (Bip analogs) or hetero-biphenylalanine analogs, their incorporation into the peptide chain was carried out in one of the following two approaches.

Approach A: Solid phase Suzuki condensation

[00123] In approach A, solid phase Suzuki condensation was practiced to prepare the required modified biphenylalanine or hetero-biphenylalanine residue in a manner suitable for carrying out subsequent solid phase peptide synthesis to obtain the target peptides. When the amino acid at position-X_{aa11} in the target peptide was represented

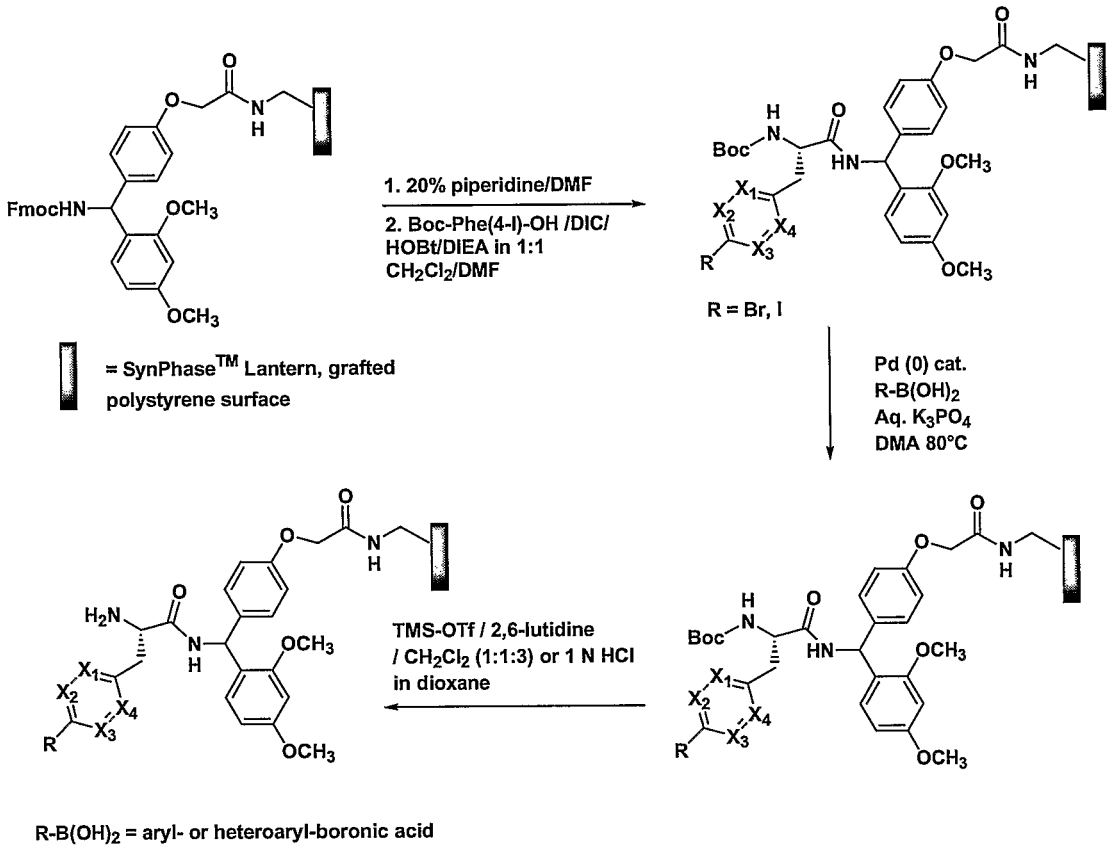
by a modified biphenylalanine or hetero-biphenylalanine residue, it was prepared as shown in Scheme 3. After removal of the Boc α-amine protecting group, chain elongation was continued using multiple peptide synthesis as described in the previous section to obtain the desired 11-mer peptides or its derivatives thereof.

When the modified biphenylalanine or hetero-biphenylalanine analog was in position X_{aa10} of the target peptides, the required amino acid was prepared using a suitable dipeptide on solid support as shown in Scheme 4.

[00124] The resulting dipeptidyl segment containing the required modified biphenylalanine or hetero-biphenylalanine derivative was then used to carry out the synthesis of the target 11-mer peptide or its derivatives thereof. When both position-X_{aa10} and position-X_{aa11} required novel biphenylalanine or hetero-biphenylalanine residues, two sequential solid phase Suzuki reactions were carried out as shown in Scheme 6 (below).

General Procedure for preparation of SynPhase™ Lanterns containing amino acids represented by Formulas II-IV and IIa-IVa at position-X_{aa11} (Suzuki couplings)

Scheme 3



General Procedure A

[00125] SynPhase™ Lanterns (A-series (0.075 mmole/lantern)) or D-series ((0.035 mmole/lantern), from Mimotopes) derivatized with an N-α-Boc-4-iodophenylalanine residue either attached directly via a Knorr linkage (Boc-amino acid-resin) or via an amino acid-Knorr linkage (Boc-dipeptide-resin) were placed into 13 X 100 mm glass culture tubes with screw caps. (The following procedure was used for D-series lanterns. Similar ratios of reactants were used for reactions involving A-series lanterns.) Aryl- or heteroaryl-boronic acids (0.140 mmole, 4 equivalents) were dissolved in 0.30 ml of N,N-dimethylacetamide.

[00126] Potassium phosphate (0.280 mmole, 8 equivalents, 0.14 ml of a 2 M aqueous solution) was added to the aryl- or heteroaryl-boronic acid solution, followed by 0.10 ml of an N,N-dimethylacetamide solution containing 4.0 mg of tetrakis (triphenylphosphine)palladium(0) catalyst (ca. 10 mole %, 0.0035 mmol). The resulting mixtures were blanketed with a stream of nitrogen and the reaction vessels

tightly capped and maintained at 80 °C for 17-20 hours while placed on an orbital shaker. The lanterns were washed with 3 X 1 ml of N,N-dimethylacetamide and 3 X 1 ml of dichloromethane (minimum of 3 minutes/wash cycle) prior to Boc group cleavage (see General Procedure below).

General Procedure B

[00127] The reactions were performed as in General Procedure A except a different catalyst was employed. For this procedure, the catalyst used was dichlorobis(triphenylphosphine)palladium(II). For the D-series lantern scale reactions, ca. 10 mol % (0.0035 mol) catalyst was used.

Procedures for Cleavage of the Boc Group

Method A

[00128] (The following procedure applies to D-series lanterns, 0.035 mmol/lantern. A similar, appropriately scaled procedure was used for A-series lanterns, 0.075 mmol/lantern.) The Boc-protected lanterns prepared as described in General Procedures A or B were treated with 0.5 ml of a reagent solution consisting of trimethylsilyl trifluoromethanesulfonate, 2,6-lutidine and dichloromethane (1:1:3 by volume). After 2 such reagent treatments for 1 hour each with mild agitation, the resins were washed with 4 X 1.0 ml of dichloromethane, 3 X 1.0 ml of N,N-dimethylformamide, and 3 X 1.0 ml dichloromethane. The lanterns were then subjected to the next acylation (coupling reaction) in the peptide synthesis sequence.

Method B

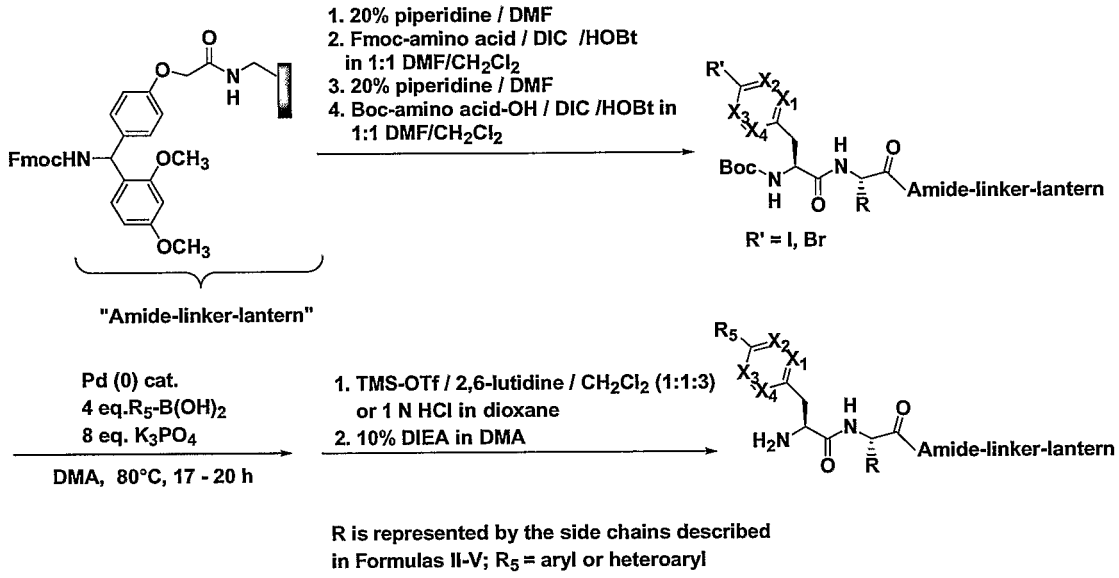
[00129] The Boc-protected lanterns prepared as described in General Procedures A or B were treated with 0.5 ml of 1 N HCl in anhydrous 1,4-dioxane for 1 hour at room temperature with mild agitation. The lanterns were washed with 2 X 1.0 ml of 1,4-dioxane, 2 X 1.0 ml of 10 % N,N-diisopropylethylamine in N,N-dimethylacetamide (vol:vol), 3 X 1.0 ml of N,N-dimethylacetamide, and 3 X 1.0 ml of dichloromethane to provide the free amino-lanterns ready for the next acylation (coupling reaction) step.

EXAMPLE 6

General Procedure for preparation of a lantern containing a modified biphenylalanine residue at position-X_{aa10}

[00130] The General Procedures described above (A or B) for Suzuki coupling were utilized to obtain the required dipeptidyl lantern containing modified Phe at position-X_{aa10} starting with the amino acid (at position-X_{aa11}) bound to SynPhase™ Lantern as shown in Scheme 4.

Scheme 4



EXAMPLE 7

General procedure for preparation of lantern containing amino acids represented by Formulas II-IV and IIa-IVa at both positions-X_{aa10} and -X_{aa11}

[00131] Utilizing the procedures described above for position-X_{aa11} modified analogs (Scheme 1) and carrying out the Suzuki coupling procedure two successive times produced dipeptidyl lanterns containing modified phenylalanine residues at both positions-X_{aa10} and -X_{aa11} as illustrated in Scheme 6, below.

EXAMPLE 8

General Procedures For Acylation/Elongation Of Peptides On Synphase™ Lanterns

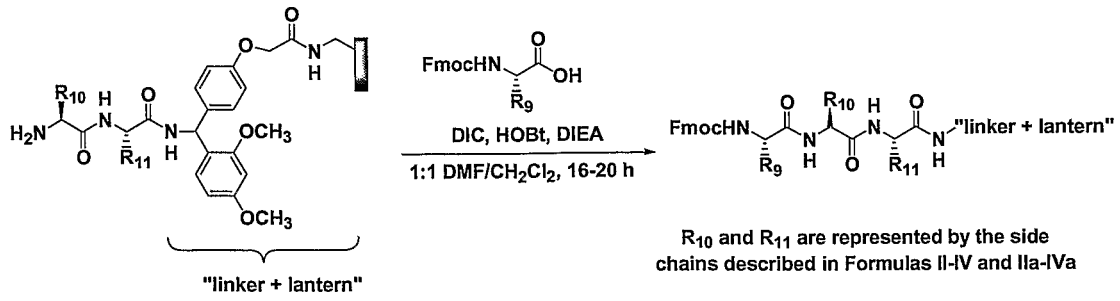
Procedure for Fmoc-deprotection

[00132] A D-series SynPhase™ Lantern (0.035 mmol/lantern loading) was added to 0.5 ml 8:2 N,N-dimethylformamide/piperidine (vol:vol). Mild agitation was applied. After 1 h, the lantern was washed with 3 X 1.0 ml N,N-dimethylformamide and 3 X 1.0 ml dichloromethane, allowing lantern to soak at least 3 min/wash.

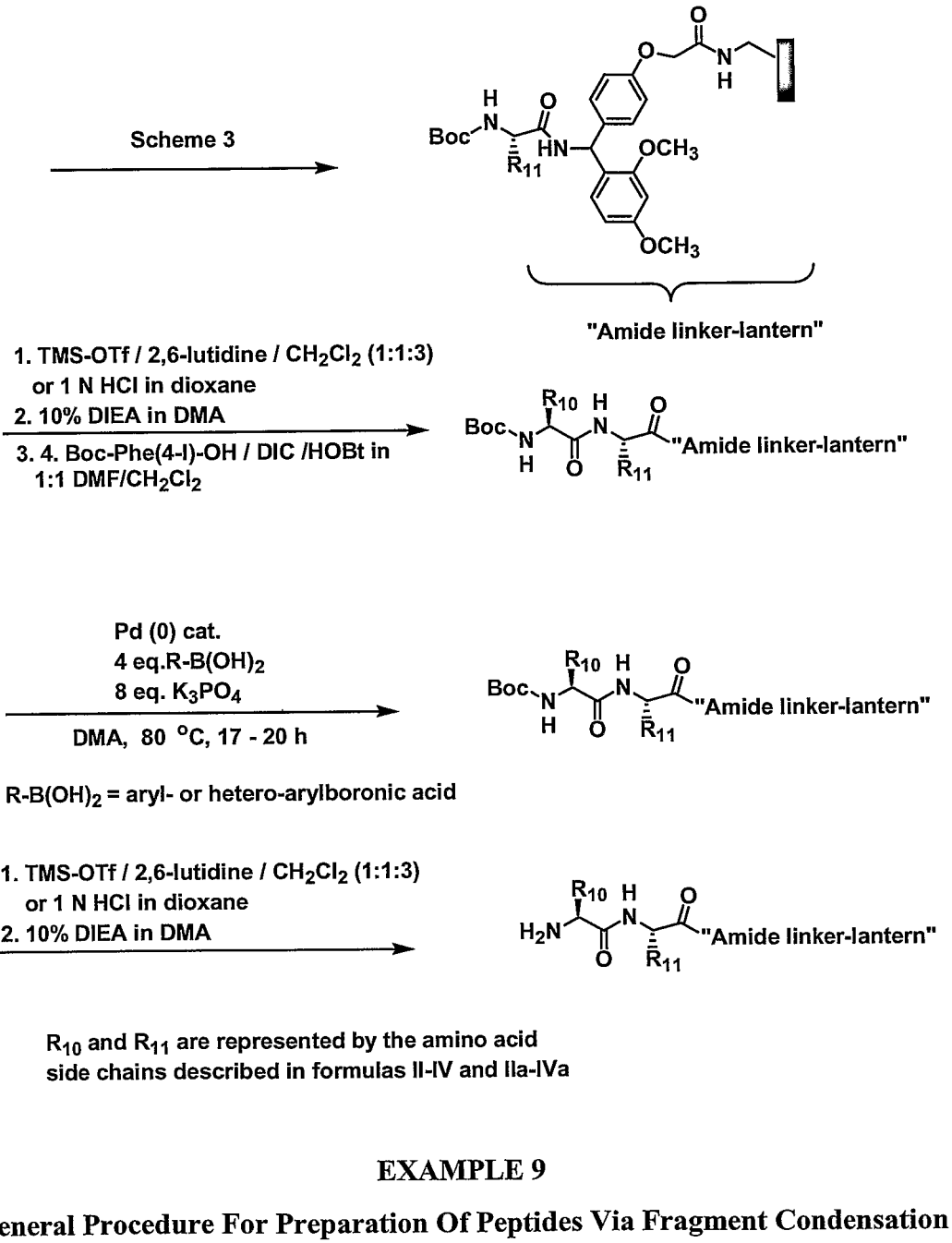
Procedure for acylation/amino acid coupling (Scheme 5)

[00133] A side chain and α-amine protected amino acid (0.105 mmol) was dissolved in 0.5 ml 1:1 N,N-dimethylformamide/ dichloromethane. To this solution was added N-hydroxybenzotriazole (0.105 mmol), N,N-diisopropylethylamine (0.315 mmol), and N,N'-diisopropylcarbodiimide (0.105 mmol). The amino acid solution was allowed to sit for 10 minutes, after which a D-series lantern containing α-amine deprotected peptide (0.035 mmol/lantern) was added to the solution. The vial was capped and gently agitated for 16-20 h. The lantern was then washed with 3 X 1.0 ml N,N-dimethylformamide and 3 X 1.0 ml dichloromethane, letting lantern soak for 3-5 min/wash cycle.

Scheme 5



Scheme 6



EXAMPLE 9

General Procedure For Preparation Of Peptides Via Fragment Condensation

[00134] In approach A, solid phase Suzuki condensation was practiced to prepare the required amino acids represented by Formulas II-IV and IIa-IVa at positions X_{aa10} and X_{aa11}, as described in Example 7. After removal of the Boc α-amine protecting group from the position-X_{aa10} amino acid, the dipeptide was cleaved from support. The dipeptide was then coupled to a fully side chain-protected 9 amino acid peptide (*see* infra). Subsequent deprotection of side chains and purification resulted in the desired 11-mer peptide products. In a variation of the above procedure, the dipeptide

incorporating the position-X_{aa10} and X_{aa11} amino acids may be coupled to the fully side chain-protected 9 amino acid peptide while on the solid support, as described in Scheme 10B.

Approach A: Solution phase fragment condensation

[00135] In Approach A, solid phase Suzuki condensations and acylations were performed (as described in Example 7) to prepare the desired dipeptides bound to SynPhase™ Lanterns, with the N-terminal α-amine either Boc-protected or Fmoc-protected. The dipeptides were cleaved from the Lantern support under acidic conditions. In the case of Boc-protected N-terminal α-amines, the acidic cleavage afforded simultaneous deprotection of the α-amine as shown in Scheme 7, and these were either purified or carried directly into the fragment coupling sequence.

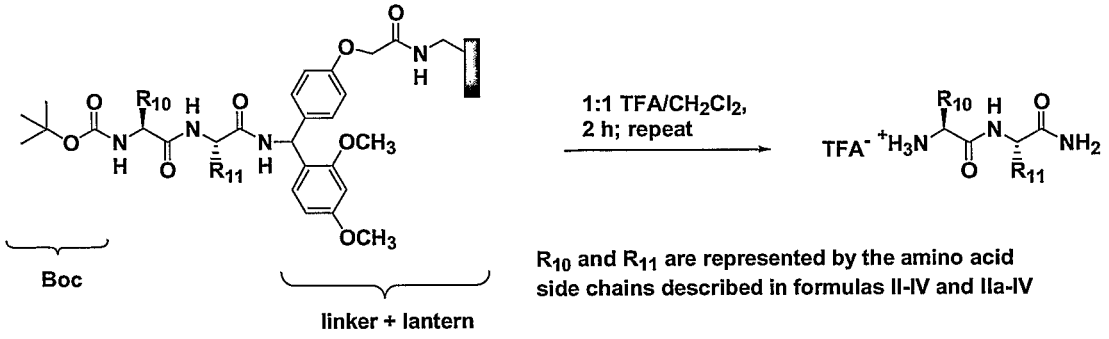
[00136] The dipeptides containing Fmoc-protected N-terminal α-amines were cleaved under acidic conditions and the N-terminal α-amine was deprotected in solution, as shown in Scheme 8. These dipeptides were purified, then carried into the fragment coupling sequence.

Procedures For Cleavage Of Dipeptides From Synphase™ Lanterns

Procedure A (Boc-protected dipeptides; see Scheme 7)

[00137] The D-series SynPhase™ Lantern was placed in a 1 dram glass vial. A solution of 1:1 trifluoroacetic acid/dichloromethane (0.5 ml) was added to the vial. The vial was capped, and mildly agitated on an orbital shaker (100 rpm) for 2 h. The cleavage solution was transferred to a fresh vial, and an additional 0.5 ml 1:1 trifluoroacetic acid/dichloromethane was added to the lantern. The vial was again capped, and mildly agitated on an orbital shaker (100 rpm) for 2 h. The second cleavage solution was added to the first, and the lantern was rinsed with dichloromethane. The rinse was added to the cleavage solutions, and solvent was evaporated to yield the dipeptide as the trifluoroacetic acid salt of the α-amine.

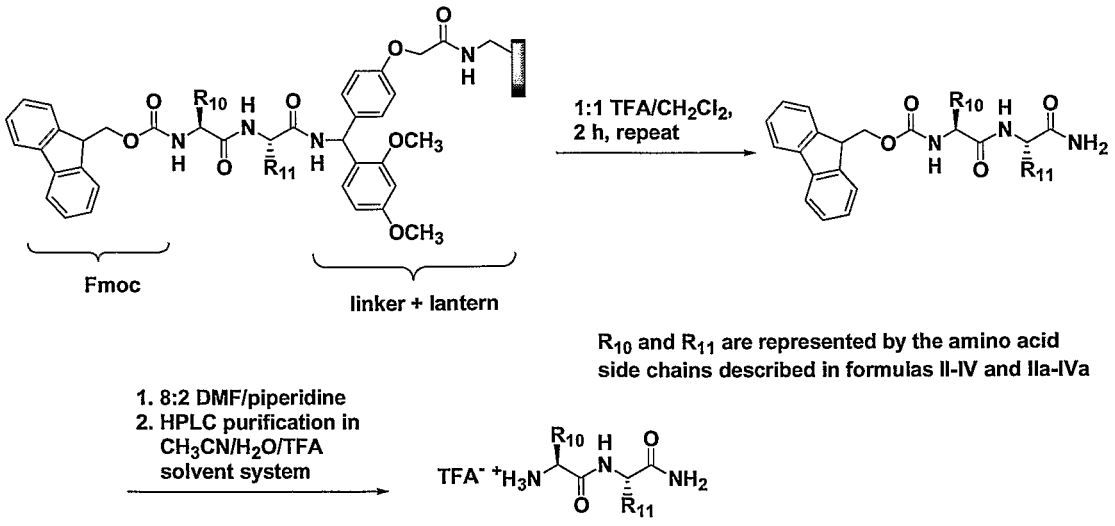
Scheme 7



Procedure B (Fmoc-protected dipeptides; see Scheme 8)

[00138] The Fmoc-protected dipeptides were cleaved from the SynPhase™ Lantern as described above in Procedure A. The lanterns were rinsed with dichloromethane, and solvent was evaporated from the combined rinse/cleavage solutions. To the resulting residue (in a 1 dram vial) was added 0.40 ml 8:2 dimethylformamide/ piperidine (vol:vol). The vial was capped and allowed to react for 45 min. The remaining solvent was evaporated off, and the resulting product was purified by HPLC, using a C-18 column and CH_3CN/H_2O/TFA solvent system to yield (after evaporation of solvent) the dipeptide as the trifluoroacetic acid salt of the α-amine.

Scheme 8

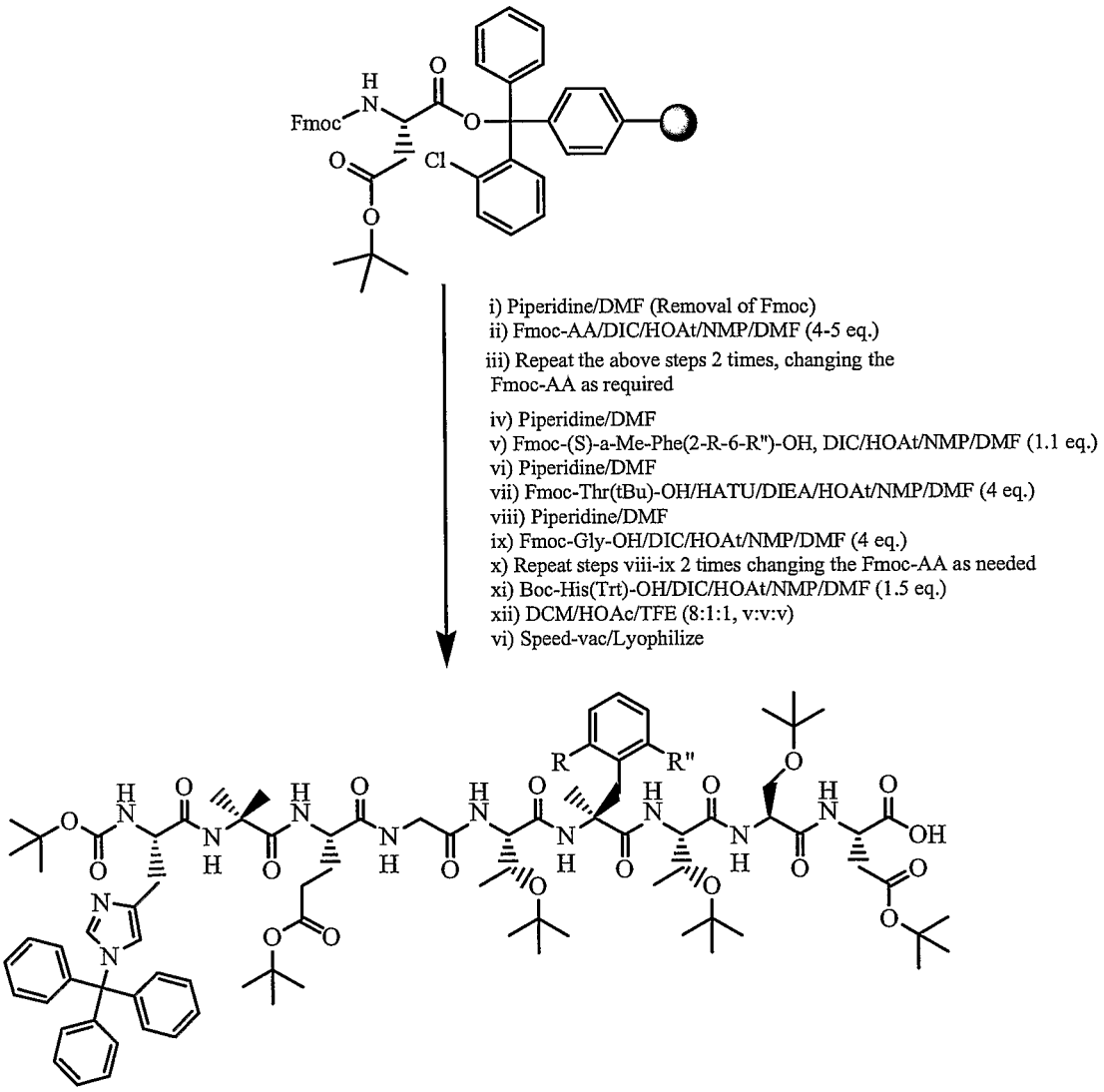


Procedure for solid phase synthesis of side chain protected 9-mer peptide C-terminal carboxylic acid (Scheme 9A)

[00139] A solution of Fmoc-(L)-Ser(tBu)-OH (5 eq.), 0.5 M HOAt/DMF (5 eq.) and DIC (5 eq.) in NMP (5 mL) was vortexed with(L)-Asp(OtBu)-2-chloro chlorotrityl resin (3.0 g, 2.16 mmol) for 18 hrs at RT. After several washes with NMP, the Fmoc group was removed by treatment with 1.5 M piperidine/DMF twice (5 min and 10 min). These coupling and deprotection steps were repeated seven times to assemble the desired sequence, except that 1.1 eq. and 1.5 eq. of Fmoc-α-Me-Phe(2-R-6-R")-OH and Boc-(L)-His(Trt)-OH were used, respectively, for their couplings, and that HATU/HOAt and DIEA (4 eq.) were used for coupling Fmoc-Thr(tBu)-OH onto (S)-α-Me-Phe(2-R-6-R")-peptidyl-resin.

[00140] Upon assembly completion, the peptidyl-resin was washed with DCM and then the protected 9-mer peptide C-terminal carboxylic acid was released from the resin by treatment with DCM/AcOH/TFE (8:1:1, v:v:v) for 1 hr at RT. The resin was filtered off and the filtrate was evaporated to dryness, redissolved in AcCN/water (2:1) and lyophilized twice, to yield 2.777 g of 81% pure product, which was used in the subsequent fragment coupling step with no further purification.

Scheme 9A

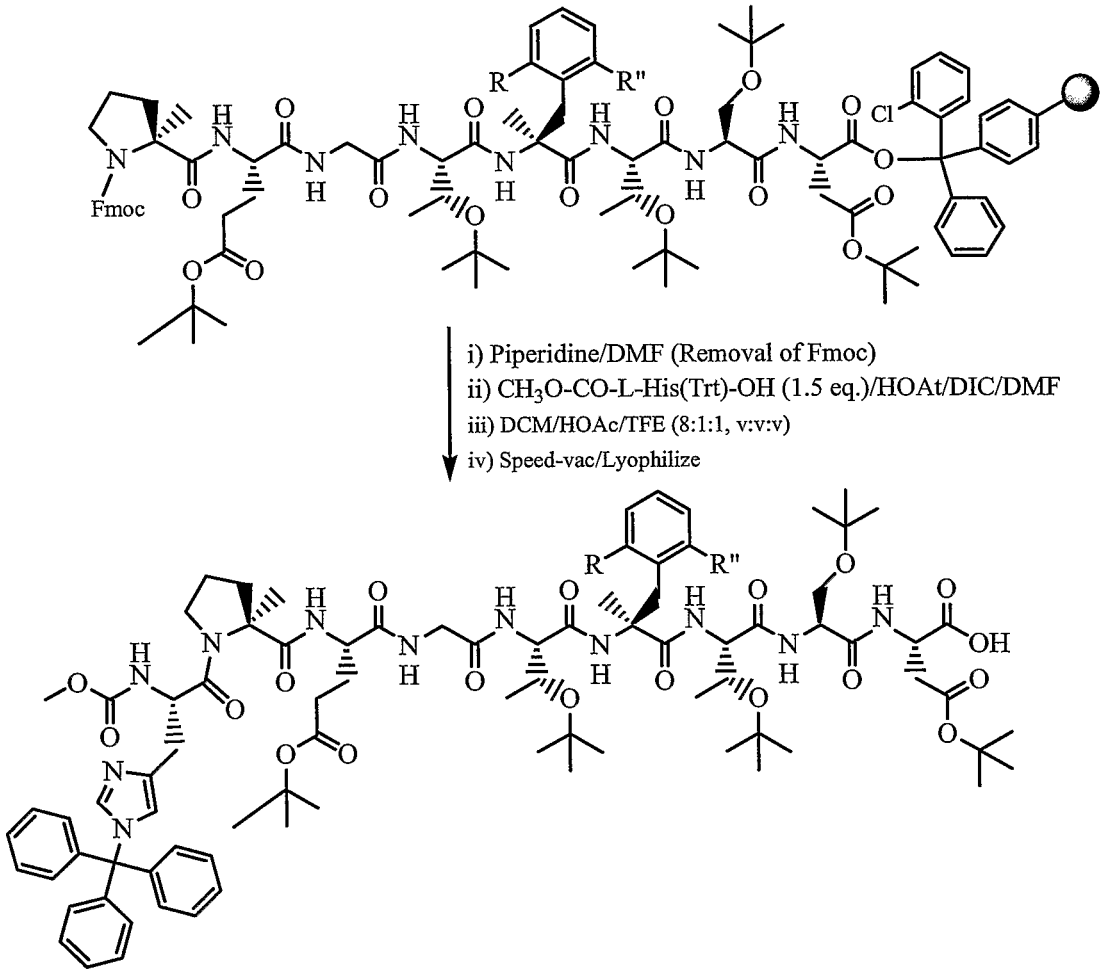


Procedure For Solid Phase Synthesis Of Side Chain Protected N-Methoxycarbonyl 9-Mer Peptide C-Terminal Carboxylic Acid (Scheme 9B)

[00141] The N-Fmoc side chain protected 8-mer peptidyl-(o-Cl)-Trityl resin (3.5 mmol) was prepared as described above (Scheme 9A). After Fmoc removal and DMF washes, the peptidyl-resin (3.5 mmol) was treated with N-α-Methyloxycarbonyl-N-*im*-Trityl-L-Histidine (2.4g, 5.33 mmol) in 0.546 M HOAt in DMF (9.8 mL, 5.33 mmol), followed by addition of DMF (10 mL) and DIC (0.633 mL, 5.33 mmol). After stirring for 72 hours, the N-derivatized 9-mer peptidyl-resin was washed with DMF (4X50 mL) and DCM (2X50 mL), and the protected 9-mer peptide C-terminal carboxylic acid was released from the resin by treatment with DCM/AcOH/TFE

(8:1:1, v:v:v) for 3 hours at RT. The resin was filtered off and the filtrate was evaporated to dryness, redissolved in AcCN/water (1:1.4) and lyophilized twice, to yield 4.05 g of 71% pure product, which was used in the subsequent fragment coupling steps with no further purification.

Scheme 9B



Procedure For Solution Phase Fragment Coupling Reaction

[00142] These reactions were performed both in a single-compound format in 1 dram vials, and in a parallel array of compounds in a 2 ml 96-well plate. The following description (shown in Scheme 10) applies to the single-compound case, but is entirely analogous to the reactions performed in the 96-well plate.

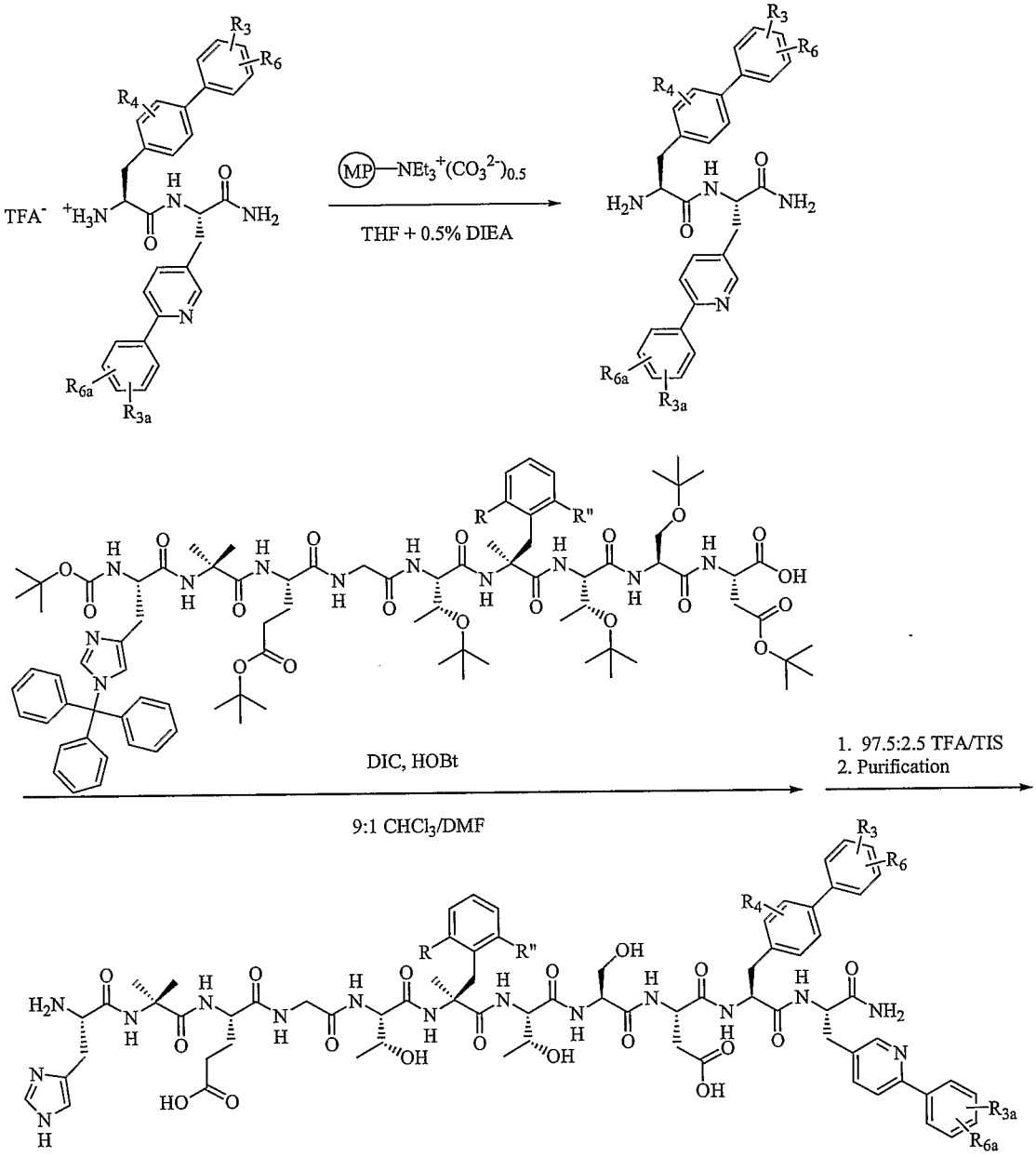
[00143] The TFA-salt of the dipeptide (0.01 mmol) was dissolved in 0.25 ml THF containing 0.5% N,N-diisopropylethylamine in a 1.5 ml glass vial. Macroporous

carbonate resin (MP-carbonate, 0.03 mmol, Argonaut Technologies) was added to the vial. The vial was capped and agitated for 2 h at room temperature. The solution was filtered, and excess solvent was removed by evaporation.

[00144] A solution of 0.15 ml of 9:1 chloroform/N,N-dimethylformamide containing the side chain protected 9-mer peptide C-terminal carboxylic acid (0.008 mmol) and N-hydroxybenzotriazole (HOBt, 0.008 mmol) was added to the vial containing the dipeptide amine. Diisopropylcarbodiimide (DIC, 0.08 mmol) was added in a solution of 0.05 ml 9:1 chloroform/N,N-dimethylformamide. The vial was capped, and the reaction was stirred on an orbital shaker at room temperature for 16 h. Remaining solvent was evaporated from the vial.

[00145] The 11-mer peptide side chains and N-terminal α-amine were deprotected with 0.40 ml 97.5:2.5 trifluoroacetic acid/ triisopropylsilane (TFA/TIS) for 1 h. The remaining solvent was evaporated away, and the 11-mer peptide products were then purified by HPLC, using a CH_3CN/H2O/TFA solvent system, and triggering effluent collection by the detection of desired product mass.

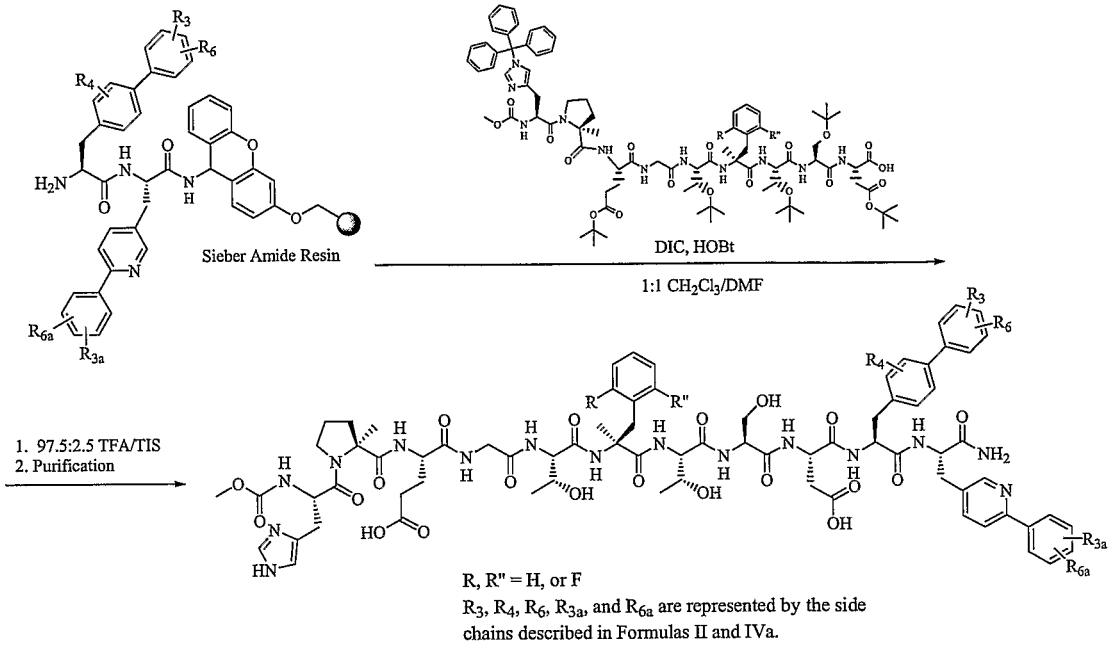
Scheme 10A



R, R" = H, or F

R_3, R_4, R_6, R_{3a}, and R_{6a} are represented by the side chains described in Formulas II and IVa.

Scheme 10B



Approach B: Synthesis of Fmoc-amino acids analogs represented by Formulas II-IV and IIa-IVa using Suzuki coupling in solution

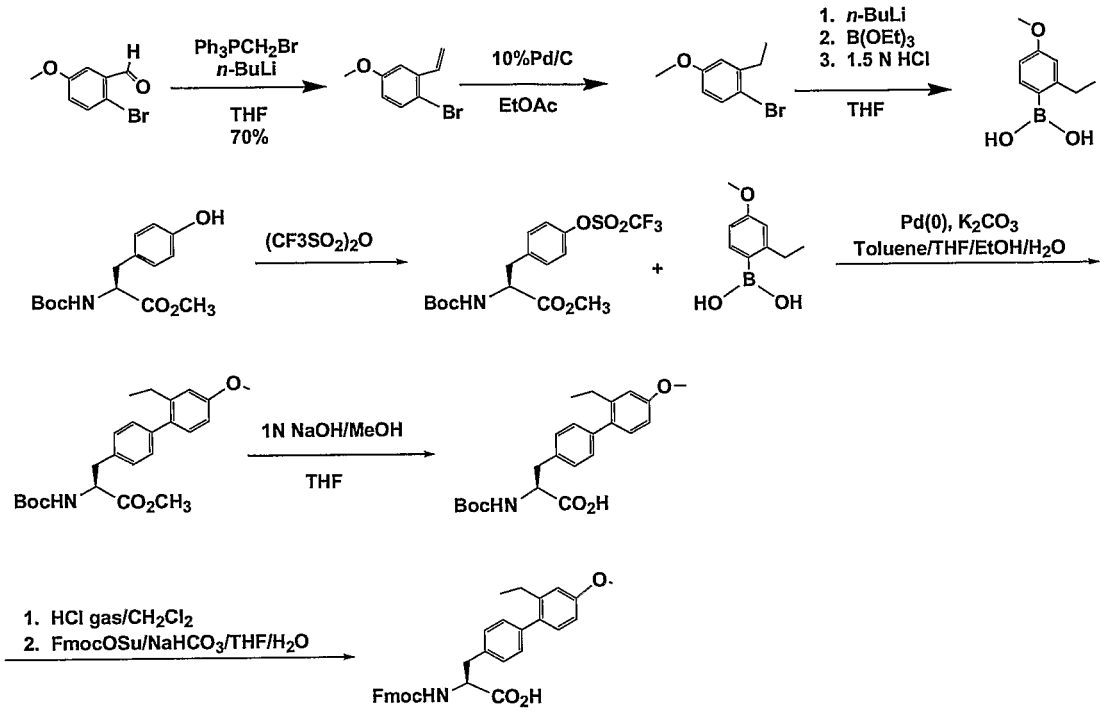
[00146] The examples below illustrate the synthesis of several Fmoc-amino acids analogs represented by Formulas II-IV and IIa-IVa, which were then utilized for the solid phase synthesis of 11-mers and other peptide analogs as described herein.

EXAMPLE 10

Synthesis of Fmoc-(S)-2'-ethyl-4'-methoxy-biphenylalanine [Fmoc-(S)-Bip(2'-Et-4'-OMe)]

[00147] Scheme 11 describes the synthesis of Fmoc-(S)-2'-ethyl-4'-methoxy-biphenylalanine.

Scheme 11



Boc-L-Tyrosine–O-triflate

[00148] To a solution of 25 g (85 mmol) of Boc-L-tyrosine methyl ester, and 36.25 g (339 mmol, 4 eq.) of 2,6-lutidine in 200 mL of dry DCM, kept at -40 °C under N2, was added slowly 47.74 mg (169.5 mmol, 2 eq.) of triflic anhydride in DCM(100 ml)over 30 minutes. The solution was stirred at –40 °C for an additional 2 hours. HPLC analysis indicated that the reaction was complete. The reaction was quenched by addition of 20 mL of water. The layers were separated, and the organic layer was washed with 3 x 200 ml of 1N HCl, 200 ml of saturated Na_2CO_3, 200 ml of water and 200 mL of brine. The organic layer was dried over magnesium sulfate, filtered and dried in vacuo to give the crude product as a red oil. It was subjected to silica gel flash chromatography (300 g silica gel, 0 to 50% EtOAc in hexanes gradient). The product-containing fractions were concentrated in vacuo to give the desired compound (27 g, 75% yield) as a white solid.

2-Ethyl-4-Methoxy-phenylboronic acid

Method A

[00149] A suspension of methyl triphenylphosphoniumbromide (199.5 g, 0.465 mol) in dry THF (800 ml) was purged for 10 min. and cooled to 10 °C. n-Butyl lithium (169 ml, 0.465 mol, 2.75 M solution) was added slowly over 30 min. and stirred for 1hr. 2-Bromo-5-methoxy benzaldehyde (100 g, 0.465 mol) in dry THF (300 ml) was added slowly over a period of 30 min. After the addition, the reaction mixture was stirred for 1 hr. Petroleum ether (2 L) was added and the reaction mixture was stirred for an additional 30 min. The reaction mixture was filtered over a silica gel pad. The pad was washed with diethyl ether. The combined organic washes were concentrated below 30 °C and the crude product was purified by 60-120 silica gel chromatography using 100 % pet ether as eluent. Yield: 92 g, 90 %, as pale yellow liquid.

[00150] 2,2'-Bipyridyl (24.3 g, 0.15 mol) and 2-bromo-5-methoxystyrene (65 g, 0.31 mol) in ethyl acetate (650 ml) were cooled to 0 °C. The solution was purged and 10 % palladium on carbon (16.25 g, 25 %) was added under a stream of nitrogen. The reaction mixture was stirred under 2 kg pressure in a Parr shaker for 3 days under hydrogen. The reaction progress was monitored by HPLC. The reaction mixture was filtered through Celite and the filtrate was washed with 5% solution of potassium bisulfate, dried over sodium sulfate and concentrated below 30 °C. Yield: 60 g, 91 %, as pale yellow liquid.

[00151] A solution of 4-bromo-3-ethyl anisole (94 g, 0.437 mol) in THF (900 ml) was cooled to –78 °C. n-Butyl lithium (249 ml, 0.55 mol) was added dropwise at the same temperature. Stirring was continued for 1 hr at –78 °C. Tri-n-butyl borate (177 ml, 0.655 mol) was added slowly at –78 °C. The cooling bath was removed, the reaction mixture was allowed to warm to 0 °C and was quenched with 1.5 N hydrochloric acid at 0 °C. The organic layer was separated. The aqueous layer was extracted with ethylacetate and the combined organic layers were washed with brine and concentrated. The residue obtained was stirred in petroleum ether for 30 min. The solid obtained was filtered and dried under vacuum. Yield: 65 g, 82 %, as a white solid.

Method B (see Scheme 12)

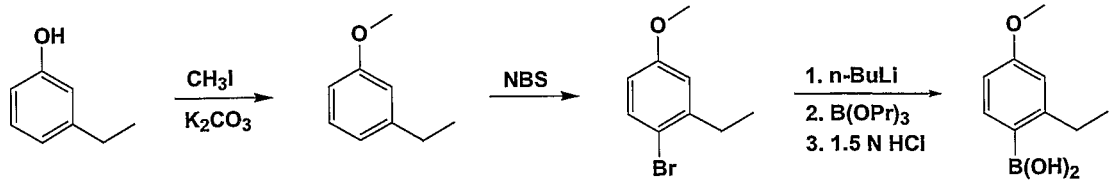
[00152] To a mixture of 3-Ethylphenol (50 g, 0.4 mol, 98 % pure, Fluka) and K_2CO_3 (283 g, 2.05 mol) in dry acetone (500 ml) was added methyliodide (290 g, 2.05 mol). The reaction mixture was transferred to an autoclave and refluxed at 70 °C overnight. The reaction mixture was filtered through a Celite pad. The pad was washed with acetone and the combined filtrate and washes were concentrated. The product was dissolved in DCM, filtered and evaporated to dryness. Yield: 50 g, 90 %, as a brown liquid.

[00153] 3-Ethylanisole (50 g, 0.3676 mol) and N-bromosuccinimide (72 g, 0.4 mol) in acetonitrile (1 L) were stirred for 8 hr under dark at RT. The reaction mixture was concentrated below 40 °C and the residue obtained was redissolved in CCl_4 and filtered. The filtrate was concentrated and the product was purified by fractional distillation. Yield: 35 g, 43 %, as pale yellow liquid.

[00154] The 4-bromo-3-ethyl anisole was converted to the corresponding boronic acid as described in Method A.

[00155] For the purpose of reaction scale up, the conversion of 4-bromo-3-ethyl anisole to 2-ethyl-4-methoxy-boronic acid may be accomplished using a Grignard method. Such method involves formation of the Grignard reagent by reaction of 4-bromo-3-ethyl anisole with Mg (1.1 eq.) in THF, followed by reaction of the resulting Grignard intermediate with tri-n-butyl- or trimethylborate as described in Method A.

Scheme 12



Fmoc-(S)-2'-ethyl-4'-methoxy-biphenylalanine

[00156] Boc-L-Tyrosine–O-triflate (81 g, 0.19 mol) in dry toluene (600 ml) was purged for 10 min with nitrogen. K2CO3 (36 g, 0.26 mol) in 200 ml of water was added followed by 2-Ethyl-4-Methoxy-phenylboronic acid (36 g, 0.2 mol) and the reaction mixture was purged for 10 min using nitrogen. Pd(PPh3)4 (16.18 g, 0.014

mol), ethanol (200 ml) and THF (400 ml) were added and the reaction mixture was heated to 100 °C with stirring for 4 hr. The reaction mixture was concentrated under vacuum and the residue was dissolved in DCM (1.0 L). The organic layer was washed with 10 % sodium hydroxide solution, 15 % of citric acid solution, dried over sodium sulfate and concentrated. The crude product was purified by 60-120-mesh silica gel column chromatography with 10 % of ethyl acetate in pet-ether. Yield: 50 g, 65 %, as a yellow liquid.

[00157] To a mixture of the methyl ester of Boc-(S)-2'-ethyl-4'-methoxy-biphenylalanine (60 g, 0.146 mol) in THF (450 ml) and methanol (85 ml) was added sodium hydroxide (24 g, 0.58 mol) in 85 ml of water. The reaction mixture was stirred at RT overnight, concentrated and the residue was dissolved in water (100 ml) and washed with diethyl ether. The aqueous layer was acidified to pH 1 using 20 % citric acid and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate and evaporated to dryness. Yield: 55 g, 94 %, as colorless liquid.

[00158] Boc-(S)-2'-ethyl-4'-methoxy-biphenylalanine (55 g, 0.138 mol) was dissolved in dry DCM (1 lit) and dry HCl gas was purged at RT for 6 hr. The solid product obtained was filtered and dried under vacuum. Yield: 46 g, 100 %.

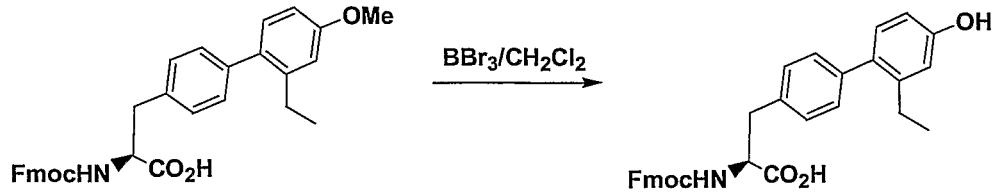
[00159] To the free amino acid hydrochloride salt (30 g, 0.089 mol) in THF (700 ml) was added $NaHCO_3$ (29 g, 0.358 mol) in water (240 ml). Fmoc-OSu (30 g, 0.089 mol) was added portionwise over a period of 30 min. The reaction mixture was stirred overnight at RT. The THF was removed under vacuum and water (2.0 L) was added. The clear solution was extracted with ether to remove any impurities. The aqueous solution was acidified to pH 1 and extracted with ethyl acetate. The organic layer was washed with water and brine, and was evaporated to dryness. Yield: 37 g, 80 %.

EXAMPLE 11

Synthesis of Fmoc-(S)-2'-ethyl-4'-hydroxy-biphenylalanine [Fmoc-(S)-Bip(2'-Et-4'-OH)]

[00160] The following Scheme 13 describes the synthesis of Fmoc-(S)-2'-ethyl-4'-hydroxy-biphenylalanine [Fmoc-(S)-Bip(2'-Et-4'-OH)]:

Scheme 13



[00161] To a stirred solution of 4.46 g (8.55 mmol) of (S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(2'-ethyl-4'-methoxybiphenyl-4-yl)propanoic acid [Fmoc-Bip(2'-Et-4'-OMe)-OH] in dichloromethane (34 mL)at -12 °C under argon was added a solution of 21.4 mL of 1 M borontribromide in dichloromethane (21.2 mmol) over the course of 20 min. The reaction mixture was stirred and allowed to warm to room temperature *in situ* as a gray slurry formed. After 3 h, the reaction mixture was added slowly to 300 mL of rapidly stirring water at room temperature. After 1 h, the reaction mixture was extracted twice with dichloromethane (100 mL portions). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to provide a tan foam, 4.65 g. The desired product was purified by reverse phase HPLC (Luna 5μ C18 30 x 100 mm column, 50% to 100% gradient (10 min) (900:100:1 to 100:900:1 water/acetonitrile/TFA) as elutant; Flow rate at 40 mL/min. UV detection at 220 nm.). Partial evaporation of the pooled fractions provided a gummy material which was decanted from the remaining solution, washed with water, redissolved in dichloromethane, dried ($MgSO_4$), filtered and evaporated to provide the product as a white amorphous solid, 3.50 g, 81% yield. HPLC/MS: retention time = 5.52 min [Zorbax SB C18 (4.6 x 75 mm) column; 0% to 100% gradient (8 min) (90:10:0.1 to 10:90:0.1 water/AcCN/TFA as elutant). Flow rate at 2.5 mL/min. UV detection at 220 nm.]; $[M+H]^+ = 508$. ^1H NMR (DMSO-d_6): δ 12.77 (br s, 1H), 9.29 (s, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.65 (t, J = 7.1 Hz, 2H), 7.38 (m, 2H), 7.28 (m, 4H), 7.11 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H), 6.57 (dd, J = 2.2, 8.3 Hz, 1H), 4.20 (m, 5H), 3.32 (br s, 1H), 3.10 (dd, J = 4.4, 13.8 Hz, 1H), 2.90 (dd, J = 10.5, 13.2 Hz, 1H), 2.37 (q, J = 7.7 Hz, 2H), 0.91 (t, J = 7.7 Hz, 3H).

[00162] 2.28 g of the above product was further purified by chiral HPLC (CHIRALPAK® AD, 10μm, 50 x 500 mm column, isocratic elution (n-heptane/acetonitrile/methanol/TFA, 839:80:80:1); flow rate at 60 mL/min. UV

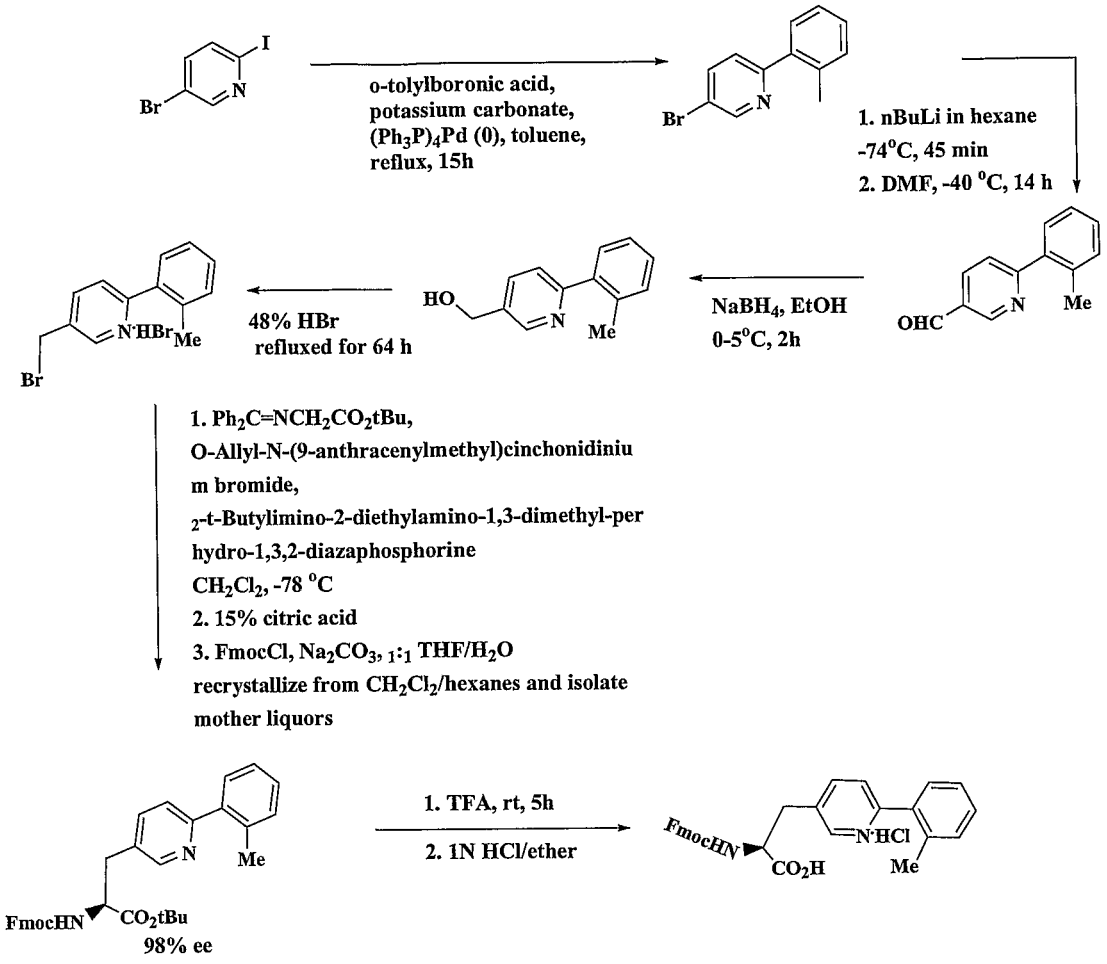
detection at 217 nm.). Evaporation of the pooled fractions, followed by re-evaporation with chloroform (3 x 20 mL) provided the product as an off-white amorphous solid, 2.17 g, 95% yield. Reverse phase HPLC: retention time = 21.42 mins. [YMC ODS-A C18 3μm(4.6 x 150 mm) column; 10% to 100% B gradient (30 min) (Buffer A: 0.1% trifluoroacetic acid in water, Buffer B: 0.1% trifluoroacetic acid in acetonitrile). Flow rate at 1 mL/min. UV detection at 217 nm.]. MS analysis: $[M+NH_3]^+$ = 525.3 and $[M-H]^-$ = 506.2. Chiral HPLC analysis: >99% ee, retention time = 12.17 mins [CHIRALPAK® AD, 10μm, 4.6 x 250 mm column, isocratic elution (n-heptane/acetonitrile/methanol/TFA, 799:100:100:1); flow rate at 1 mL/min. UV detection at 217 nm.]. $[\alpha]^{25}_D$ = -12.6 (c = 1.0 in DMF).

EXAMPLE 12

Synthesis of (2S)-2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-(6-o-tolylpyridin-3-yl)propanoic acid hydrochloride [Fmoc-(S)-4-(2'-methylphenyl)-3-pyridylalanine hydrochloride]

[00163] The following Scheme 14 describes the synthesis of (2S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-o-tolylpyridin-3-yl)propanoic acid hydrochloride:

Scheme 14



5-Bromo-2-o-tolylpyridine

[00164] To an argon-purged and evacuated slurry of 910 mg (3.21 mmol) of 5-bromo-2-iodopyridine and 436 mg (3.21 mmol, 1.0 eq.) of 2-o-tolylboronic acid in 8 mL of toluene and 3.2 mL of 2 M aqueous sodium carbonate, was added 36 mg (0.032 mmol, 0.01 eq) of tetrakis(tri-phenylphosphine) palladium. The reaction mixture was purged and evacuated with argon twice more and then set to reflux under argon for 15 h. The reaction was cooled and partitioned between water and EtOAc. The layers were separated, and the aqueous layer extracted once more with EtOAc. The organic extracts were combined, dried over magnesium sulfate, filtered, concentrated and dried in vacuo to give the crude product as an orange oil. Purification by silica gel chromatography (7:3 CH_2Cl_2/ hexanes) provided the title compound as a yellow oil, 666 mg, 84% yield.

6-o-Tolylnicotinaldehyde

[00165] To a stirred solution of 125 mg of the above compound (0.50 mmol)in THF (2.0 mL) under argon at -74°C was added 220 µL of nBuLi solution in hexane (2.5 M, 0.55 mmol, 1.1 eq) over 5 min, the temperature not allowed to rise above -71 °C. A light green solution formed, which became dark green after 30 min. After 45 min, 49.4 µL (0.61 mmol, 1.2 eq) of DMF was added and the reaction allowed to warm to -40 °C. After 14h, a bright orange solution had formed. The reaction was quenched with 10% citric acid and the mixture stirred rapidly for 20 min at room temperature. The resulting bright yellow solution was extracted twice with EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated to give a yellow oil. The crude mixture thus obtained was purified by silica gel chromatography using ethyl acetate/ dichloromethane (1:24) as eluant, (2.5 x 10 cm column), to give white solid, mp 82-84 °C, 90.3 mg, 91% yield.

(6-o-Tolylpyridin-3-yl) methanol

[00166] To a solution of 1.070 g (5.43 mmol) of 6-o-tolylnicotinaldehyde in 19 mL of ethanol at 0-5 °C, was added 287 mg(7.5 mmol, 1.4 eq.) of sodium borohydride. After 2 h, the reaction mixture was quenched with saturated sodium bicarbonate solution and, after 30 min, partitioned between dichloromethane and brine. The organic extract was dried over magnesium sulfate and concentrated to give the indicated product as a colorless oil, 1.08 g, 100% yield.

5-(Bromomethyl)-2-o-tolylpyridine hydrobromide

[00167] A solution of 4.49 g (22.5 mmol) of (6-o-tolylpyridin-3-yl)methanol in 75 mL of 48% hydrobromic acid was heated to reflux for 64 h. The reaction mixture was partially cooled and excess hydrobromic acid was removed by vacuum distillation (110 °C @ 2 Torr) until a tan solid residue remained in the flask. Distillation was carried out using a large KOH pellet trap placed between the distillation apparatus and the vacuum pump. The solid residue was slurried in diethyl ether, filtered and dried under a nitrogen stream to give 7.38 g of product, 95% yield.

(2S)-tert-butyl 2-(diphenylmethyleneamino)-3-(6-o-tolylpyridin-3-yl)propanoate

[00168] To a stirred mixture of 800 mg (2.33 mmol) of 5-(bromomethyl)-2-o-tolylpyridine hydrobromide, 689 mg (2.33 mmol, 1.0 equivalent) of tert-butyl 2-(diphenylmethyleneamino)acetate and 141 mg (0.233 mmol, 0.1 equivalent) of O-allyl-N-(9-anthracenylmethyl) cinchonidinium bromide in 14 mL of dichloromethane at -78 °C under argon was added 1.687 mL (5.83 mmol, 2.5 eq) of 2-t-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine over 5 min. The reaction mixture was stirred at -78 °C for 10 h and then allowed to warm to room temperature in situ. The mixture was directly purified by silica gel chromatography using ethyl acetate/dichloro-methane (1:4) as eluant (5 x 10 cm column), to give tan oil, 1.10 g, 100% yield.

(2S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-o-tolylpyridin-3-yl)propanoate

[00169] To a stirred solution of 1.10 g (2.33 mmol)of (2S)-tert-butyl 2-(diphenylmethyleneamino)-3-(6-o-tolylpyridin-3-yl)propanoate in 9 mL of THF at room temperature under argon was added 2.795 g (14.54 mmol, 6.5 equivalents) of citric acid in 9 mL of water. After 20 h, the reaction mixture was diluted with water (5 mL) and washed twice with ether (10 mL). The aqueous phase was then brought to pH 9 with solid sodium carbonate and extracted twice with dichloromethane.

[00170] The dichloromethane extracts were combined, dried with sodium sulfate and concentrated. The resulting oil was dissolved in 10 mL of THF and treated with 7.2 mL of 10% sodium carbonate solution and then 703 mg (2.56 mmol, 1.1 equivalents) of 9-fluorenylmethyloxycarbonylchloride at room temperature. After 14 h, the reaction mixture was extracted twice with dichloromethane, dried with sodium sulfate, filtered, concentrated and purified by chromatography on silica gel using ethyl acetate/dichloromethane (1:19) as eluant (2.5 x 10 cm column), to give colorless oil, 1.082 g, 91% yield. Recrystallization from 20 mL of 7:1 hexanes: dichloromethane provided a white solid, 287 mg. The mother liquors were concentrated to provide an amorphous white solid, the title compound, 779 mg, 63% yield. Chiral HPLC analysis (4.6 x 250 mm AD column, 38:1:1 heptane:methanol:ethanol as eluant 1 mL/min flow rate) indicated 98% ee.

(2S)-2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-(6-o-tolylpyridin-3-yl) propanoic acid hydrochloride

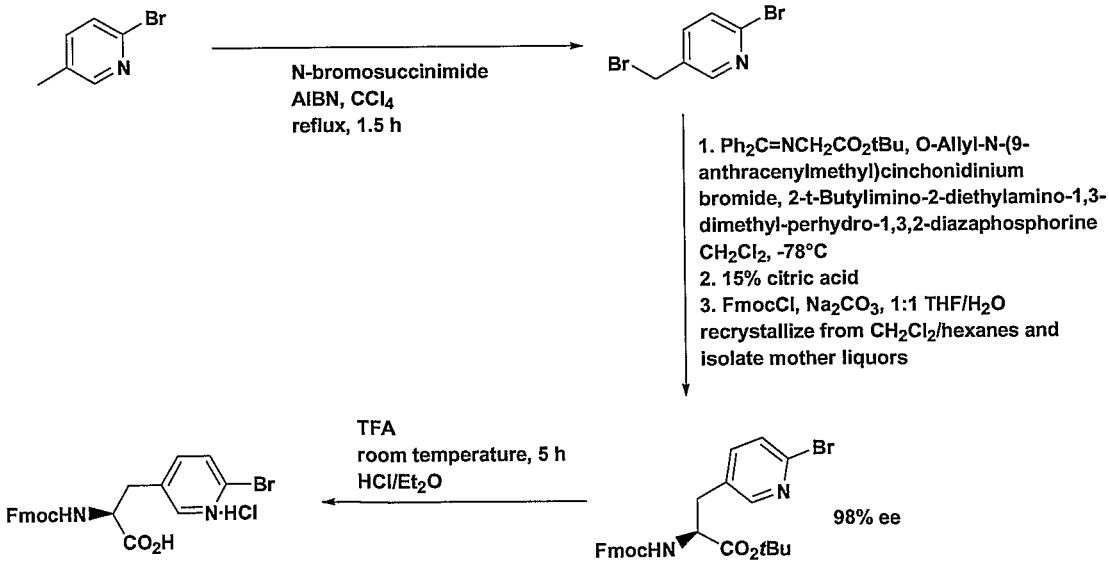
[00171] A solution of 1.75 g (3.19 mmol) of (2S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-o-tolylpyridin-3-yl)propanoate in TFA (5.0 mL), protected from the atmosphere by a calcium chloride-filled drying tube was stirred at room temperature for two hours. The reaction mixture was concentrated in vacuo at less than 40 °C and the resulting orange oil was dissolved in 10 mL of ether to which a solution of 5 mL of 1 M HCl/ether was added. The resulting white solid was filtered and washed with ether to give the desired compound as a white powder, 1.65 g, 100% yield.

EXAMPLE 13

Synthesis of (2S)-2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-4-(6-bromopyridin-3-yl)propanoic acid hydrochloride

[00172] The following Scheme 15 describes the synthesis of 3-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromopyridin-3-yl)propanoic acid hydrochloride:

Scheme 15



2-Bromo-5-(bromomethyl)pyridine

[00173] To a stirred slurry of 10.320 g (60.0 mmol) of 5-methyl-2-bromopyridine and 5.339 g (30.0 mmol, 0.5 eq) of recrystallized N-bromosuccinimide in 150 mL of carbon tetrachloride was added 200 mg of AIBN. The reaction mixture was purged twice with argon and evacuated and set to reflux under argon. After 90 min, the reaction mixture was cooled to room temperature, filtered and the filtrate concentrated to give a yellow oil. Proton NMR indicated that the mixture contains 53% (mol) unreacted 5-methyl-2-bromopyridine, 43% of the title product and 4% of 2-bromo-5-(dibromomethyl)pyridine. The mixture was used immediately without further purification for the following procedure.

(S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromopyridin-3-yl) propanoate

[00174] To a stirred mixture of 2-bromo-5-(bromomethyl)pyridine (nominally 26.4 mmol), 7.798 g (26.4 mmol, 1.0 equivalents) of tert-butyl 2-(diphenyl methyleneamino)acetate and 1.60 g (2.64 mmol, 0.1 equivalent) of O-allyl-N-(9-anthracenylmethyl) cinchonidinium bromide in 100 mL of dichloromethane at -78 °C under argon was added 11.46 mL (39.6 mmol, 1.5 eq) of 2-t-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine over 5 min. The reaction mixture was stirred at -78 °C for 7 h and then allowed to warm to room temperature in situ. The reaction mixture was then concentrated, redissolved in 75 mL of THF and treated with citric acid (22 g) in 75 mL of water. After stirring vigorously for 7 h, the mixture was extracted twice with ether (75 mL). The organic extracts were combined and washed once with water (25 mL). The aqueous extracts were combined and brought to pH 8 with solid sodium carbonate. The aqueous solution was used without further treatment for the next reaction.

(S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromopyridin-3-yl)propanoate

[00175] The aqueous solution from above was added to a solution of 7.545 g (27.5 mmol, 1.04 equivalents) of 9-fluorenylmethyloxycarbonylchloride in 75 mL of THF at room temperature. After 14 h, the reaction mixture was extracted twice with ethyl

acetate, dried with magnesium sulfate, filtered, concentrated and purified by chromatography on silica gel using ethyl acetate/dichloro-methane (1:24) as eluant (12 x 25 cm column), to give colorless oil, 7.25 g, 91% yield. Recrystallization from 120 mL of 5:1 hexanes/dichloromethane gave a small amount of a white solid, which was filtered off. The mother liquors were concentrated to provide an amorphous white solid, the title compound, 4.96 g, 62% yield. Chiral HPLC analysis (4.6 x 250 mm AD column, 38:1:1 heptane: methanol: ethanol as eluant 1 mL/min flow rate) indicated 97.2% ee.

2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromopyridin-3-yl)propanoic acid hydrochloride

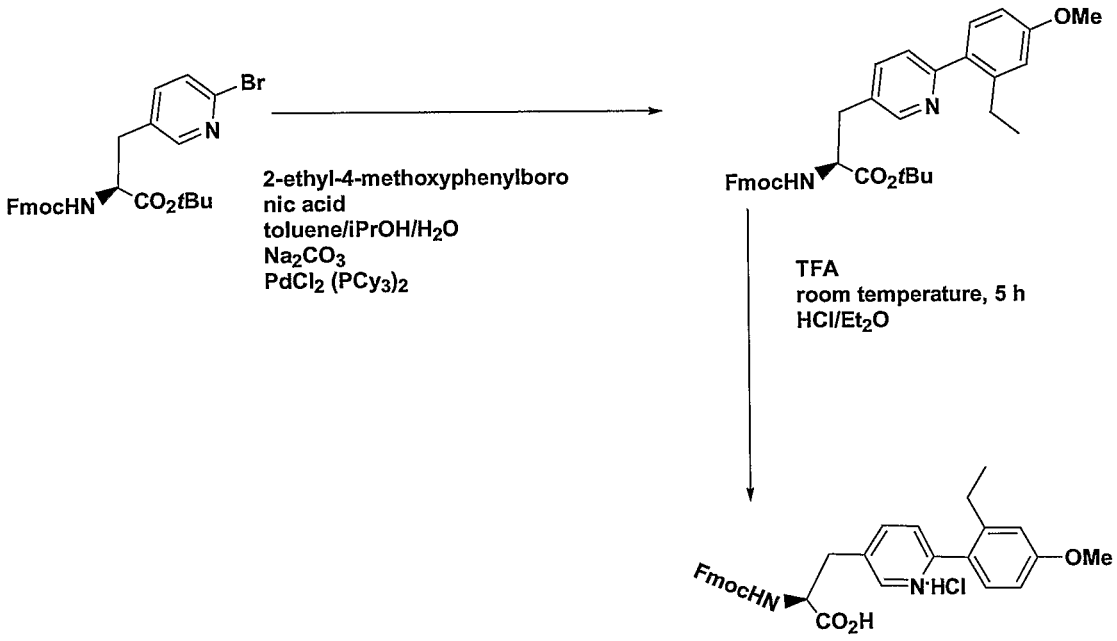
[00176] A solution of 1.02 g (1.95 mmol) of (2S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromopyridin-3-yl)propanoate in TFA (3.0 mL), protected from the atmosphere by a calcium chloride-filled drying tube was stirred at room temperature for two hours. The reaction mixture was concentrated in vacuo at less than 35 °C and the resulting orange oil was dissolved in 3 mL of dichloromethane to which a solution of 6 mL of 1 M HCl/ether was added. The resulting white solid was filtered and washed with ether to give the title compound as a white powder, 845 mg, 86% yield.

EXAMPLE 14

Synthesis of (2S) 2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethylphenyl)pyridin-3-yl)propanoic acid hydrochloride [Fmoc-(S)-4- (2'-ethylphenyl)-3-pyridylalanine]

[00177] The following Scheme 16 describes the synthesis of (2S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethylphenyl)pyridine-3-yl)propanoic acid hydrochloride:

Scheme 16



((S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethylphenyl)pyridine-3-yl)propanoate

[00178] To a stirred slurry of 1.75 g (3.35 mmol) of (S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromo-pyridin-3-yl) propanoate and 1.005 g (6.70 mmol, 2 eq.) of 2-ethylphenylboronic acid in 50 mL of 1:1 isopropanol/toluene was added 25.0 mL of 2 M aqueous sodium carbonate solution. The reaction mixture was purged twice with argon and evacuated and then 124 mg (0.167 mmol, 0.05 equivalents) of bis(tricyclohexylphosphine) palladium (II) chloride was added and the mixture was again purged with argon and evacuated. The rapidly stirred mixture was heated at 80 °C under argon. After 20 h, the reaction mixture was cooled to room temperature and partially concentrated to remove isopropanol. The residue was partitioned between ethyl acetate and water and the aqueous phase was extracted once more with ethyl acetate. The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated to give a brown oil. Purification by chromatography on silica gel using ethyl acetate/ dichloromethane (1:9) as eluant (5 x 15 cm column), gave the desired compound as a colorless oil, 1.25 g, 77% yield.

(2S) 2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethylphenyl)pyridine-3-yl)propanoic acid hydrochloride

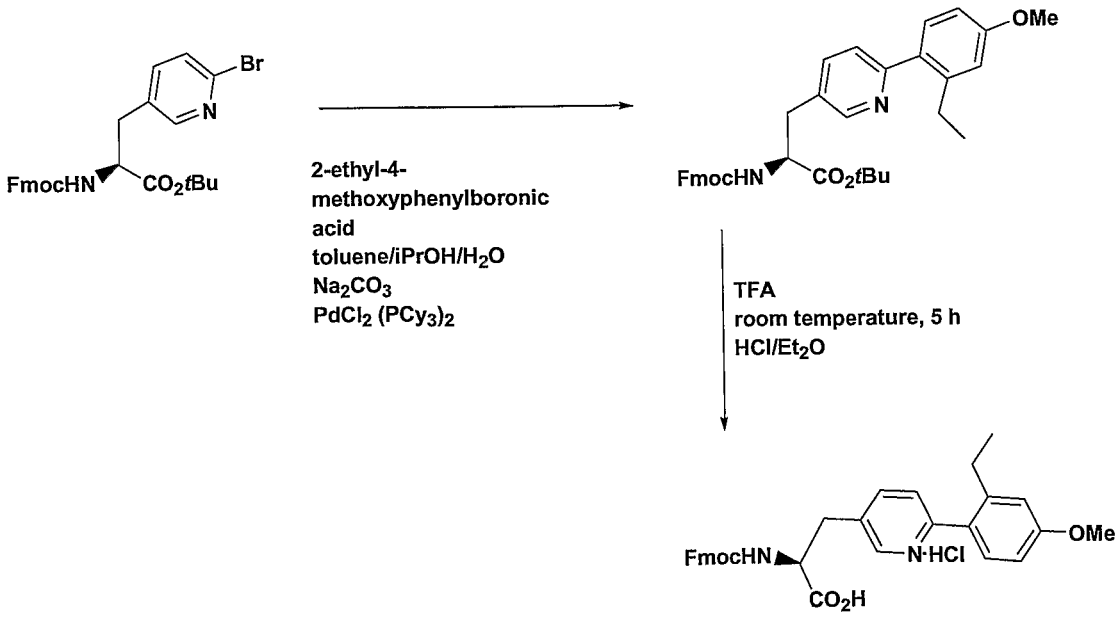
[00179] A solution of 1.53 g (2.79 mmol) of (2S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-4-(6-(2-ethylphenyl)pyridine-3-yl)propanoate in TFA (5.0 mL), protected from the atmosphere by a calcium chloride-filled drying tube was stirred at room temperature for two hours. The reaction mixture was concentrated in vacuo at less than 35 °C and the resulting orange oil was dissolved in ether to which a solution of 6 mL of 1 M HCl/ether was added. The resulting white solid was filtered and washed with ether to give the desired product as a white powder, 1.38 g, 93% yield.

EXAMPLE 15

Synthesis of (2S) 2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethyl-4-methoxy)phenyl)pyridin-3-yl)propanoic acid hydrochloride [Fmoc-(S)-4-[(2'-ethyl-4'-methoxy)phenyl]-3-pyridylalanine]

[00180] The following Scheme 17 describes the synthesis of (2S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethyl-4-methoxy)phenyl)pyridine-3-yl)propanoic acid hydrochloride:

Scheme 17



(S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethyl-4-methoxyphenyl)pyridine-3-yl)propanoate

[00181] To a stirred slurry of 613 mg (1.17 mmol) of (S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromo-pyridin-3-yl)propanoate and 422 mg (2.34 mmol, 2 eq.)of 2-ethylphenylboronic acid in 20 mL of 1:1 isopropanol/toluene was added 10.0 mL of 2 M aqueous sodium carbonate solution. The reaction mixture was purged twice with argon and evacuated and then 43.2 mg (0.059 mmol, 0.05 equivalents) of bis(tricyclohexylphosphine) palladium (II) chloride was added and the mixture was again purged with argon and evacuated. The rapidly stirred mixture was heated at 80 °C under argon. After 9 h, the reaction mixture was cooled to room temperature and partially concentrated to remove isopropanol. The residue was partitioned between ethyl acetate and water and the aqueous phase was extracted once more with ethyl acetate. The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated to give a brown oil. Purification by chromatography on silica gel using ethyl acetate/ dichloromethane (3:17) as eluant (5 x 15 cm column), gave the expected compound as a colorless oil, 401 mg, 59% yield.

(2S)2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethyl-4-methoxyphenyl)pyridine-3-yl)propanoic acid hydrochloride

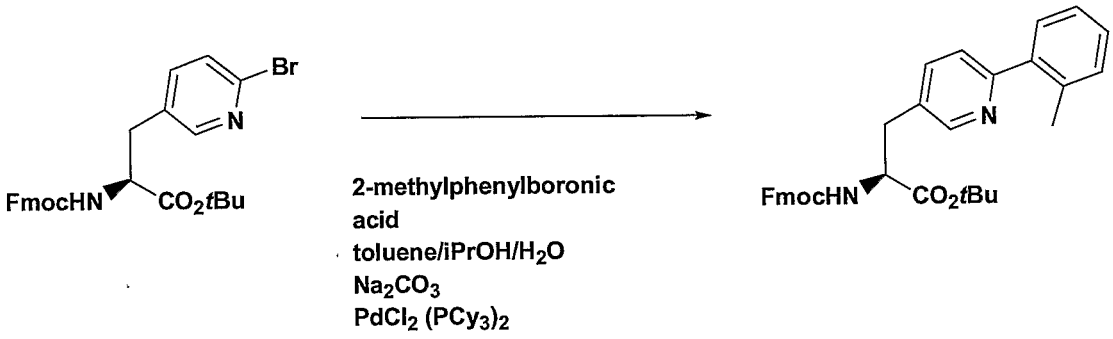
[00182] A solution of 401 mg (0.69 mmol) of (2S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethyl-4-methoxyphenyl)pyridine-3-yl)propanoate in TFA (2.0 mL), protected from the atmosphere by a calcium chloride-filled drying tube was stirred at room temperature for two hours. The reaction mixture was concentrated in vacuo at less than 30 °C and the resulting orange oil was dissolved in ether to which a solution of 2 mL of 1 M HCl/ether was added. The resulting white solid was filtered and washed with ether to give the desired product as a white powder, 336 mg, 84% yield.

EXAMPLE 16

Alternative synthesis of (S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-methylphenyl)pyridin-3-yl)propanoate

[00183] The following Scheme 18 describes the alternate synthesis of (S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-methylphenyl)pyridin-3-yl)propanoate:

Scheme 18



(S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-methylphenyl)pyridin-3-yl)propanoate

[00184] To a stirred slurry of 1.75 g (3.35 mmol) of (S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromo-pyridin-3-yl)propanoate and 913 mg (6.70 mmol, 2 eq.)of 2-methylphenylboronic acid in 50 mL of 1:1 isopropanol/ toluene was added 25.0 mL of 2 M aqueous sodium carbonate solution. The reaction mixture was purged twice with argon and evacuated and then 124 mg (0.167 mmol, 0.05 equivalents) of bis(tricyclohexylphosphine) palladium (II) chloride was added and the mixture again purged with argon and evacuated.

[00185] The rapidly stirred mixture was set to heating at 80 °C under argon. After 20 h, the reaction mixture was cooled to room temperature and partially concentrated to remove isopropanol. The residue was partitioned between ethyl acetate and water and the aqueous phase was extracted once more with ethyl acetate. The organic extracts were combined, dried over magnesium sulfate, filtered and concentrated to give a brown oil. Purification by chromatography on silica gel using ethyl acetate/

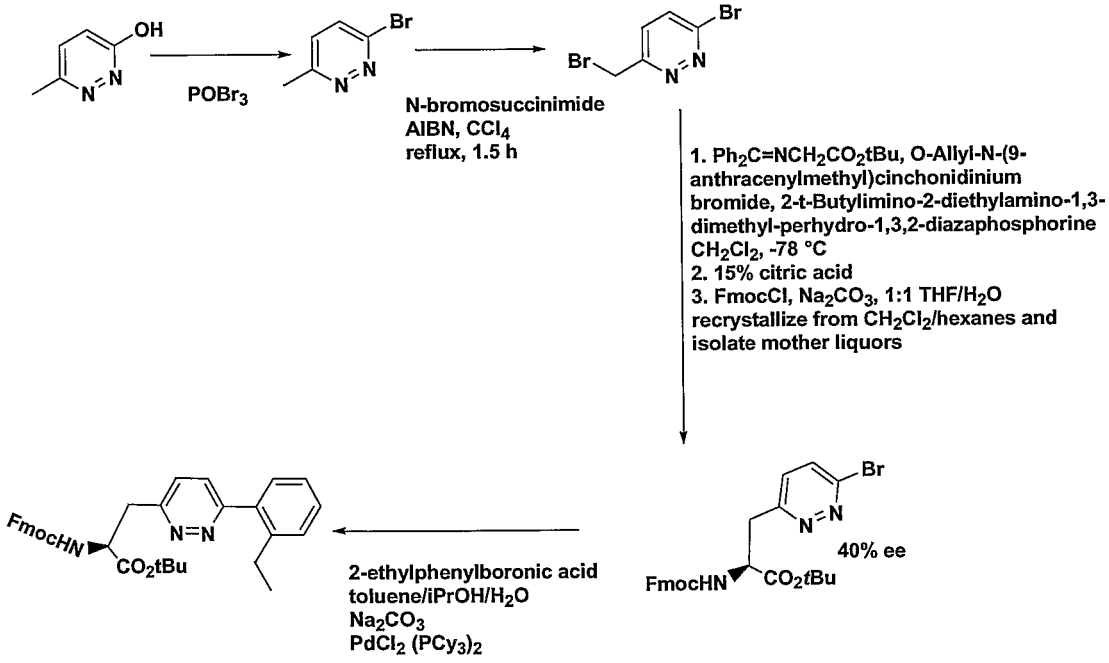
dichloromethane (1:9) as eluant (5 x 15 cm column), gave the desired compound as a colorless oil, 1.81 g, 90% yield.

EXAMPLE 17

Synthesis of (2S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethylphenyl)pyridazin-3-yl)propanoate [Fmoc-(S)-4-(2'-ethylphenyl)-2,3-pyridazylalanine]

[00186] The following Scheme 19 describes the synthesis of (2S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethylphenyl)pyridazin-3-yl)propnoate:

Scheme 19



3-Bromo-6-methylpyridazine

[00187] A mixture of 2.20 g of 3-methyl-6-pyrazinol (20.0 mmol) and 13.06 g of phosphorous oxybromide (45.6 mmol, 2.3 equivalents) was stirred and heated to 130 deg C (pre-heated oil bath) for 50 min. The solid reaction mixture was cooled in an ice bath and ~20 g of chipped ice was added. The resulting solution was chilled in an ice bath and 50% KOH was added to neutralize. The resulting solid was collected, washed with water and air-dried for 15 h. Purification by silica gel chromatography

using ether/dichloromethane (3:17) as eluant (5 x 15 cm column), provided the title compound as a light yellow solid, 1.37 g, 39% yield.

3-Bromo-6-(bromomethyl)pyridazine

[00188] A solution of 1.00 g (5.78 mmol) of 3-bromo-6-methylpyridazine and 1.03 g (5.79 mmol, 1.0 eq)of recrystallized N-bromosuccinimide in 20 mL of carbon tetrachloride was added 95 mg of AIBN. The reaction mixture was purged twice with argon and evacuated and set to reflux under argon. After 3 h, the reaction mixture was cooled to room temperature, filtered and the filtrate was concentrated to give a yellow oil. The mixture was directly purified by silica gel chromatography using hexanes/dichloromethane (1:9) as eluant (5 x 12 cm column), to give a colorless oil, 444 mg, 30% yield.

(S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromopyridazin-3-yl)propanoate

[00189] To a stirred mixture of 374 mg (1.48 mmol) of 3-bromo-6-(bromomethyl)pyridazine, 439 mg (1.48 mmol, 1.0 equivalent) of tert-butyl 2-(diphenylmethyleneamino)acetate and 112 mg (0.186 mmol, 0.12 equivalent) of O-allyl-N-(9-anthracenylmethyl) cinchonidinium bromide in 4 mL of dichloromethane at -78 °C under argon was added 0.645 mL (2.23 mmol, 1.5 eq) of 2-t-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine over 5 min. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to -40 °C in situ. After 16 h, the mixture was directly purified by silica gel chromatography using ethyl acetate/dichloro-methane (1:9) as eluant (5 x 10 cm column), to give a yellow oil, 540 mg, 78% yield.

[00190] To a stirred solution of the above product in 10 mL of THF at room temperature under argon was added 10 mL of 15% aqueous citric acid. After 16 h, the reaction mixture was diluted with water (5 mL) and washed twice with ether (10 mL).

[00191] The aqueous phase was then brought to pH 9 with solid sodium carbonate and extracted twice with dichloromethane. The dichloromethane extracts were combined, dried with sodium sulfate and concentrated. The resulting oil was dissolved in 5 mL of THF and treated with 5 mL of 10% sodium carbonate solution

and then 480 mg (1.86 mmol, 1.3 eq.) of 9-fluorenylmethyloxycarbonylchloride at room temperature. After 6 h, the reaction mixture was extracted twice with dichloromethane, dried with sodium sulfate, filtered, concentrated and purified by chromatography on silica gel using ethyl acetate/dichloromethane (1:5) as eluant (5 x 15 cm column), to give a colorless oil, 507 mg, 65% yield. Chiral HPLC analysis (4.6 x 250 mm AD column, 38:1:1 heptane:methanol:ethanol as eluant, 1 mL/min flow rate) indicated 40% ee.

(2S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-(2-ethylphenyl)pyridazin-3-yl)propanoate

[00192] To a stirred slurry of 507 mg (0.967 mmol) of (S)-tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-bromopyridazin-3-yl)propanoate and 290 mg (1.93 mmol, 2 eq.)of 2-ethylphenylboronic acid in 16 mL of 1:1 isopropanol/toluene was added 8.0 mL of 2 M aqueous sodium carbonate solution. The reaction mixture was purged twice with argon and evacuated and then 35.7 mg (0.048 mmol, 0.05 equivalents) of bis(tricyclohexylphosphine) palladium (II) chloride was added and the mixture was again purged with argon and evacuated. The rapidly stirred mixture was heated at 90 °C under argon.

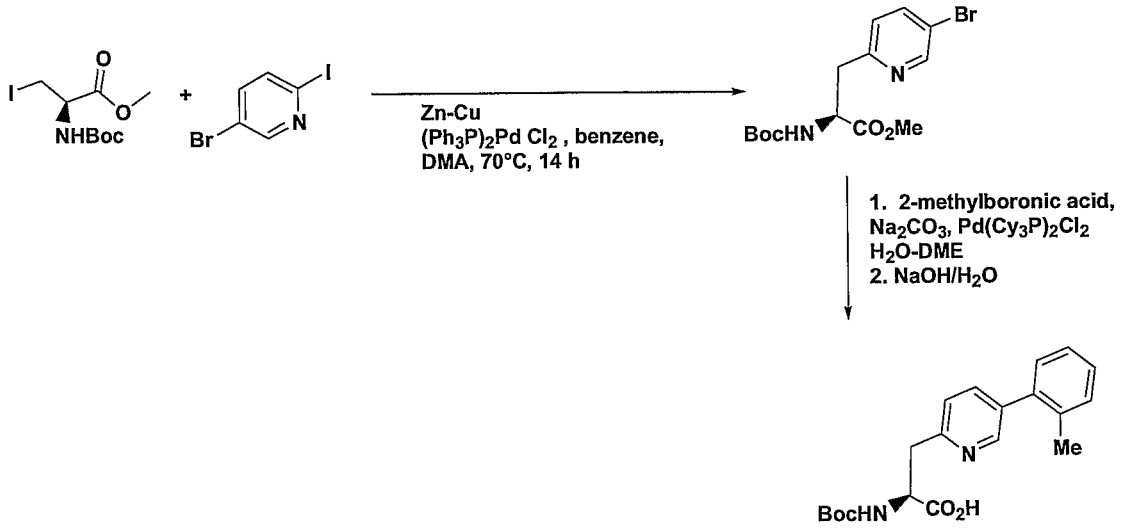
[00193] After 8 h, the reaction mixture was cooled to room temperature and partially concentrated to remove isopropanol. The residue was partitioned between ethyl acetate and water and the aqueous phase was extracted once more with ethyl acetate. The organic extracts were combined, concentrated and the residue was redissolved in 2 mL of THF. To this solution was added 300 mg (1.17 mmol) of 9-fluorenylmethylchloroformate and 100 µL of triethylamine. After 21 h, the reaction mixture was diluted with ethyl acetate and washed once with brine. The organic phase was dried over magnesium sulfate, filtered and concentrated. Purification by chromatography on silica gel using ethyl acetate/dichloromethane (1:2) as eluant (2.5 x 15 cm column), gave the desired compound as a colorless oil, 428 mg, 81% yield.

EXAMPLE 18

Synthesis of (2S)-2-(tert-Butoxycarbonylamino)-3-(5-o-tolylpyridin-2-yl)propanoic acid [Boc-(S)-4-(2'-methylphenyl)-2-pyridylalanine)]

[00194] The following Scheme 20 describes the synthesis of (2S)-2-(tert-butoxycarbonylamino)-3-(5-o-tolylpyridin-2-yl)propanoic acid:

Scheme 20



(S)-Methyl 2-(tert-butoxycarbonylamino)-3-(5-bromopyridin-2-yl)propanoate.

[00195] An argon-purged and evacuated slurry of 210 mg of zinc-copper couple (prepared as in Organic Synthesis Collective Volume 5, page 855) and 580 mg (1.76 mmol) of 3-iodoalanine were dissolved in 7 mL of benzene to which was added 0.5 mL of N,N-dimethylacetamide. The slurry was sonicated in a sealed flask for 40 min, and then 500 mg (1.76 mmol, 1.0 eq.) of 5-bromo-2-iodopyridine and 82 mg (0.11 mmol, 0.06 eq.) of bis(tri-phenylphosphine) palladium dichloride were added.

[00196] The reaction mixture was purged and evacuated with argon twice more and then heated at 70 °C under argon for 15 h. The reaction was cooled and partitioned between water and EtOAc. The layers were separated, and the aqueous layer was extracted once more with EtOAc. The organic extracts were combined, dried over magnesium sulfate, filtered, concentrated and dried in vacuo to give the crude product as a yellow oil. Purification by silica gel chromatography CH2Cl2/hexanes (3:1)as

eluant (2.5 x 15 cm column), provided the expected compound as a yellow oil, 288 mg, 46% yield.

(2S)-2-(tert-Butoxycarbonylamino)-3-(5-o-tolylpyridin-2-yl)propanoic acid

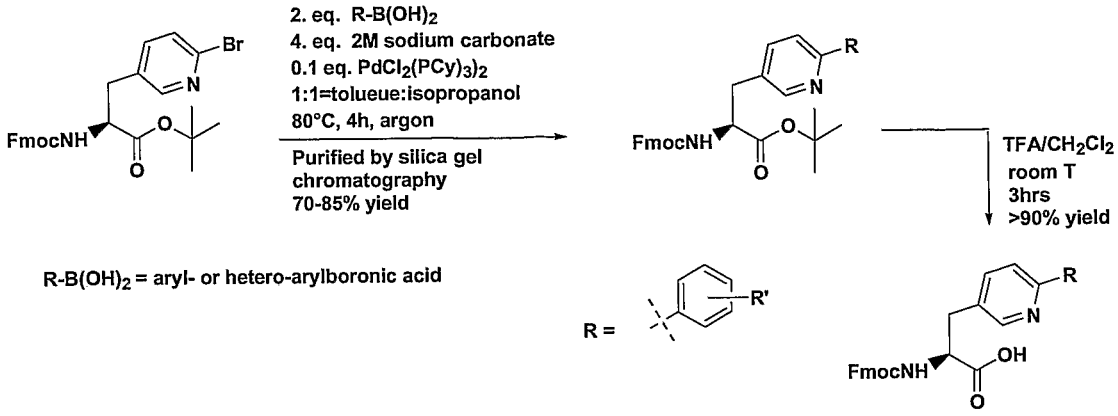
[00197] To a stirred slurry of 285 mg (0.79 mmol) of (S)-methyl 2-(tert-butoxycarbonylamino)-3-(5-bromopyridin-2-yl)propanoate and 162 mg (1.19mmol, 1.5 eq.)of 2-methylphenylboronic acid in 7 mL of 1,2-dimethoxyethane was added 168 mg (1.59 mmol, 2.0 eq.) of sodium carbonate and 0.5 mL of water. The reaction mixture was purged twice with argon and evacuated and then 29 mg (0.040 mmol, 0.05 eq.) of bis(tricyclohexylphosphine) palladium (II) chloride was added and the mixture again purged with argon and evacuated. The rapidly stirred mixture was heated at 80 °C under argon.

[00198] After 14 h, the reaction mixture was cooled to room temperature and 4 mL of 1 N sodium hydroxide solution was added. The reaction mixture was heated to 70 deg C for 1 h. After cooling to room temperature the mixture was extracted once with ether. The aqueous phase was acidified to pH 3 with 10% sodium bisulfate solution and then extracted twice with DCM. The DCM extracts were combined, dried over magnesium sulfate, filtered and concentrated to give a yellow semi-solid. Purification by preparative reverse-phase HPLC (YMC ODS S5 30 x 100 mm column, 10% to 90% acetonitrile/water gradient [10 min], 0.1% TFA) gave (after concentration) the desired product as a white amorphous solid, 46.5 mg, 17% yield.

EXAMPLE 19

[00199] The following Scheme 21 describes the general synthesis of analogs of (2S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-phenyl)pyridin-3-yl)propanoate.

Scheme 21



(2S)-tert-Butyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-[(3-chloro-4-fluoro)phenyl)pyridin-3-yl)propanoate

[00200] To a round bottom flask was added 300 mg Fmoc-L-bromo-3-pyridylalanine (0.573 mmol), 200 mg 3-chloro-4-fluorophenylboronic acid (1.145 mmol, 2 eq.), 1.145 mL 2M sodium carbonate solution (2.29 mmol, 4 eq.), 5 mL toluene, 5mL isopropylnol and 42 mg PdCl2(PCy)3)2 (0.0573 mmol, 0.1 eq.). The reaction solution was purged with argon before it was brought to 80°C for 5 hrs. The reaction was cooled to room temperature and diluted with 50 mL EtOAc. The solution was washed with water (30 mL)and brine (20 mL), dried over magnesium sulfate, filtered and concentrated. The crude oil was subjected to silica gel chromatography (12 gm silica gel, 0-40% EtOAc/Hexanes gradient) to give 245 mg of the desired compound (75% yield)as an oil.

(2S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(6-[(3-chloro-4-fluoro)phenyl)pyridin-3-yl)propanoic acid

[00201] To a solution of (2S)-tert-butyl 2-(((9H-fluoren-9-yl) methoxy) carbonylamino)-3-(6-[(3-chloro-4-fluoro)phenyl)pyridin-3-yl)propanoate (240 mg, 0.429 mmol) and 3 mL dichloromethane was added TFA (3 mL). The reaction was stirred at room temperature for 5 hrs. The solvent was evaporated to dryness and the residue was subjected to prep-HPLC (methanol-water gradient, 0.1% TFA). Concentration of the fractions containing the product yielded 200 mg (93% yield) of the desired compound as the TFA salt.

EXAMPLE 20

General Synthesis of 11-mer peptides starting from Dipeptidyl resin containing non-natural non-commercial amino acid at positions 10 and 11

[00202] Dipeptidyl resin, containing non-natural non-commercial amino acid at positions 10 and 11, was prepared using the following procedure on a Advanced Chemtech ACT 90 synthesizer in a batch-wise mode before continuing peptide chain elongation utilizing the automated simultaneous synthesis protocol on a MPS-396 peptide synthesizer.

[00203] An amount of 9-Fmoc-aminoxanthen-3-yloxy-Merrifield resin(Sieber Amide resin; loading: 0.5 mmol/g; Novabiochem) sufficient to synthesize several 11-mer analogs, was swelled by washing with DMF ($2X_10$ mL/g, 1 minutes). The Fmoc group was then removed using two treatments, 5 and 15 minutes each respectively, with 20% piperidine in DMF (10 mL/g). The resin was washed with DMF (2X 10 mL/g) and NMP (4X10 mL/g). A solution of Fmoc-(S)-4-(2'-Methylphenyl)-3-pyridylalanine-OH (HCl salt)(1.2 eq.), or analog thereof, PyBOP (1.07 eq.), HOBt (1.07 eq.), and DIEA (3.6 eq.) in NMP were added to the resin. The resin was then shaken or vortexed for 18 hours. Coupling completion was monitored using a qualitative ninhydrin test. The resin was drained, washed with NMP (3X10 mL/g) and DCM (3X10 mL/g), and any unreacted amines were capped with 2.6% acetic anhydride, 2.4% DIEA in DCM (v/v)for 30 minutes. After DMF washes (3X10 mL/g), the capping protocol was repeated with 10% acetic anhydride, 2% DIEA in DCM (v/v)for 30 minutes. A quantitative Fmoc determination assay indicated a 0.39 mmol/gram substitution.

[00204] A second manual coupling cycle was then performed as described above, starting from the removal of the Fmoc group with 20% piperidine in DMF, and, after several DMF washes, by adding to the deprotected resin a solution of Fmoc-L- (2'-Ethyl-4'-Methoxy)biphenylalanine-OH (1.27 eq.), or analog thereof, and HOBt (1.29 eq.) in NMP (4 mL), which was vortexed for 5 minutes. DIC (1.27 eq.) was then added to the resin slurry and the resin was shaken or vortexed for 15 hours. The resin was drained, washed with NMP (3X10 mL/g) and DCM (3X10 mL/g), and then capped with 5.0% acetic anhydride, 1.0% DIEA in DCM (10 mL) for 30 minutes.

The resin was finally washed with DCM (3X10 mL/g). This synthesis scheme produced the desired Fmoc-protected dipeptidyl-Sieber Amide resin.

[00205] The Fmoc group was removed as described previously. A solution of Fmoc-L-Asp(OtBu)-OH (3 eq.) and HOBt (3 eq.) in NMP (2 mL) was vortexed for 5 minutes, and DIC (3 eq.) was then added. The resulting solution was added to the resin. The resin was then shaken or vortexed for 2 hours. The resin was drained, and washed with NMP (3X10 mL/g) and DCM (3X10 mL/g). Coupling completion was monitored using a qualitative ninhydrin test.

[00206] This resin was subjected to 2 additional deprotection/coupling cycles as described above in order to assemble the desired sequence from X_{aa7} to X_{aa11} onto the resin. The Fmoc-amino acids sequentially used were: Fmoc-L-Ser(tBu)-OH and Fmoc-L-Thr(tBu)-OH. Fmoc-[(S)-2-fluoro-α-Me-Phe]-OH was coupled using the following protocol. A solution of Fmoc-[(S)-2-fluoro-α-Me-Phe]-OH (1.5 eq.),PyBOP (1.5 eq.), HOBt (1.5 eq.), and DIEA (3.0 eq.) in NMP (2 mL) were added to the resin. The resin was then shaken or vortexed for 2 hours. The resin was drained, and washed with NMP (3X10 mL/g) and DCM (3X10 mL/g).

[00207] In order to couple residue X_{aa5}, the Fmoc group was removed as described previously. A solution of Fmoc-The(tBu)-OH (5 eq.) and 2-Cl-HOBt (5 eq.) and DIC (5 eq.) in NMP (4 mL) was vortexed briefly, then added to the resin. The resin was then shaken or vortexed for 18 hours. The resin was drained, and washed with NMP (3X10 mL/g) and DCM (3X10 mL/g). The resin was capped with 10.0% acetic anhydride in DCM (10 mL/g) for 30 minutes. After DCM washes (3X10 mL/g), the Fmoc group was removed as described previously and Fmoc-Gly-OH, residue X_{aa4}, was coupled/deprotection as described for Fmoc-L-Asp(OtBu)-OH. The resulting X_{aa4}-X_{aa11} peptidyl-resin used was used to synthesize different 11-mer peptide analogs as follows.

Synthesis of the Compound of SEQ ID NO: 118

[00208] A sample of the X_{aa4}-X_{aa11} peptidyl-resin (0.067 mmole) described above was vortexed with a solution of Fmoc-L-Glu(OtBu)-OH (5 eq.), residue X_{aa3}, and 0.5M HOAt (5 eq.) in DMF, pre-vortexed for 5 minutes, and DIC (5 eq.) for 18 hours. The resin was drained, washed with DMF (4X3 mL).The resin bound peptide (0.034

mmole) was deprotected and coupled with Fmoc-[(S)-α-Me-Pro]-OH (5 eq.) as described previously for residue X_{aa3} to afford the resin bound Fmoc-[X_{aa2}-X_{aa11}]-peptide.

[00209] The resin (0.017 mmole)was deprotected and coupled with Boc-L-His(Trt)-OH (5 eq.) as described for residue X_{aa2}. The desired peptide was cleaved/deprotected from its respective peptidyl-resin by treatment with a solution of TFA/water/tri-isopropylsilane (94:3:3) (5.0 mL) for 3 hrs. The resin was filtered off, rinsed with TFA (1.0 mL), and the combined TFA filtrates were evaporated to yield 39 mg of crude peptide product as a oily solid. This was purified by preparative HPLC using a gradient of 0.1% TFA/AcCN in 0.1% TFA/water, from 5% to 65% over 20 min. The fractions containing pure product were pooled and lyophilized, to yield 5.4 mg (18.9% recovery) of the compound of SEQ ID NO: 118.

Synthesis of The Compound of SEQ ID NO: 119

[00210] A sample of the Fmoc-[X_{aa3}-X_{aa11}]-peptidyl-Sieber resin (0.015 mmole), described in the previous synthesis, was vortexed with a solution of Fmoc-[N-methyl-(D)-Ala]-OH (5 eq.) and 0.5M HOAt (5 eq.) in DMF, pre-vortexed for 5 minutes, and DIC (5 eq.) for 4 hours. The resin was drained and washed with DMF (4X3 mL). The Fmoc group was removed by treating with 20% piperidine in DMF (3 mL) for 5 and 15 minutes. The resin was washed with DMF (8X3 mL) and then coupled with Boc-L-His(Trt)-OH (5 eq.) as described in the previous synthesis. The desired peptide was cleaved/deprotected from its respective peptidyl-resin by treatment with a solution of TFA/water/tri-isopropylsilane (94:3:3) (5.0 mL) for 3 hrs. The resin was filtered off, rinsed with TFA (1.0 mL), and the combined TFA filtrates were evaporated. The resulting oily solid was dissolved in (1:1) acetonitrile / water (2mL) and purified by preparative HPLC using a gradient used of 0.1% TFA/MeCN in 0.1% TFA/water, from 5% to 65% over 20 min. The fractions containing pure product were pooled and lyophilized, to yield 5.2 mg (18.5% recovery) of the compound of SEQ ID NO: 119.

Synthesis of the Compound of SEQ ID NO: 133

[00211] A sample of the Fmoc-deprotected [X_{aa2}-X_{aa11}]-peptidyl-Sieber resin (0.017 mmole), described in the previous synthesis, was vortexed with a solution of

des-amino-His(Trt)-OH (5 eq) and HATU (5 eq.) in 0.5 HOAt in DMF (5 eq.), and a solution of 2M DIEA in NMP (5 eq.) for 18 hours. The resin was drained and washed with DMF ($6X_2$ mL) and DCM (3X2 mL). The desired peptide was cleaved/deprotected from its respective peptidyl-resin by treatment with a solution of TFA/water/tri-isopropylsilane (94:3:3) (5.0 mL) for 3 hrs. The resin was filtered off, rinsed with TFA (1.0 mL), and the combined TFA filtrates were evaporated. The resulting oily solid (32 mg) was dissolved in (1:1) acetonitrile / water (2 mL) and purified by preparative HPLC using a gradient of 0.1% TFA/MeCN in 0.1% TFA/water, from 5% to 65% over 20 min. The fractions containing pure product were pooled and lyophilized, to yield 7.4 mg (24.6% recovery) of the compound of SEQ ID NO: 133.

Synthesis of the Compound of SEQ ID NO: 120

[00212] A sample of Fmoc-deprotected [X_{aa10}-X_{aa11}]-dipeptidyl-Sieber resin (0.05 mmol), prepared as described previously, was subjected to 9 additional coupling cycles using the FastMoc™ protocol of an Applied Biosystems 433a Peptide Synthesizer as described in Example 3.

[00213] The Fmoc-protected dipeptidyl-resin (0.05 mmol) was placed into a vessel of appropriate size on the instrument, washed 6 times with NMP and deprotected using two treatments with 20% piperidine/NMP (2 and 8 min. each). One additional monitored deprotection step was performed until the conditions of the monitoring option were satisfied. The total deprotection time was 10-12 min. The deprotected dipeptidyl-resin was washed 6 times with NMP and then coupled with the next amino acid. The procedure is illustrated by the example used in the next step.

[00214] Fmoc-L-Asp(OtBu)-OH was coupled next using the following method: Fmoc-L-Asp(OtBu)-OH (1 mmol, 20 eq.) was dissolved in 2 mL of NMP and activated by subsequent addition of 0.45 M HBTU/HOBt in DMF (2.2 mL) and 2 M DIEA/NMP (1 mL). The solution of the activated Fmoc-protected amino acid was then transferred to the reaction vessel and the coupling was allowed to proceed for 30 to 60 min., depending on the feedback from the deprotection steps. The resin was then washed 6 times with NMP and the coupling protocol was repeated. This was subjected to 5 additional deprotection/coupling cycles as described above in order to

complete the assembly of the desired X_{aa4}-X_{aa11} sequence. The Fmoc-amino acids sequentially coupled were: Fmoc-(L)-His(Trt)-OH, Fmoc-(L)-Thr(tBu)-OH, Fmoc-(S)-2-fluoro-α-Me-Phe-OH, Fmoc-(L)-Thr(tBu)-OH and Fmoc-Gly-OH. Finally, the peptidyl-resin was washed 6 times with NMP and DCM. The Fmoc-protected dipeptidyl-resin (0.025 mmole) was added to a ACT 396 multiple peptide synthesizer in a slurry of N,N-dimethylformamide/dichloromethane (55:45). The resin was washed 2 times with DMF and deprotected using two treatments with 1.5 M piperidine/DMF as described in Example 1. Fmoc-L-Glu(OtBu)-OH (4.0 eq.) was activated by subsequent addition of 0.5 M HOAt in DMF (4.0 eq.) and DIC (4.0 eq.), transferred to the reaction vessel manually and allowed to couple for 2 hrs. The resin was rinsed with NMP (4 x 0.5 mL) with vortexing for 1 min. After deprotection of the Fmoc group as described for the previous coupling, Fmoc-[(S)-α-Me-Pro]-OH was coupled as follows: Fmoc-[(S)-α-Me-Pro]-OH (2.4 eq.) was activated by subsequent addition of 0.5 M HOAt in DMF (2.4 eq.), diluted with NMP (0.12 mL), and of DIC (2.4 eq.). The solution was transferred to the reaction vessel manually and allowed to couple for 18 hrs. The resin was rinsed with NMP. After deprotection of the Fmoc group, Fmoc-(L)-His(Trt)-OH was coupled by adding manually a solution of the amino acid (4 eq.) in 0.5 M HOAt in DMF (4 eq.), diluted with NMP (0.2 mL), and DIC (4 eq.) to the reaction vessel. The coupling reaction was allowed to couple for 18 hrs. The resin was rinsed with NMP. The Fmoc group was removed as described for the previous coupling. The TFA cleavage /deprotection of the peptide was performed as described in Example 1. This was purified by preparative HPLC using a gradient of 0.1% TFA/MeCN in 0.1% TFA/water, from 10% to 60% over 20 min. The fractions containing a pure product were pooled and lyophilized, to yield 21.7 mg (42% recovery) of the compound of SEQ ID NO: 120.

EXAMPLE 21

Synthesis of the Compound of SEQ ID NO: 151

[00215] The synthesis was initiated on an Advanced ChemTech Model 90 Synthesizer in a 50 ml reactor starting with 2.67 g (0.56 mmole/g, 1.5 mmole) of Sieber Amide resin. The general deprotection/coupling repetitive cycle used for the stepwise assembly was as follows:

1. DMF wash 1 x 20 ml x 1 min.
2. 20% piperidine in DMF 1 x 20 ml x 5 min.
3. 20% piperidine in DMF 1 x 20 ml x 15 min.
4. DMF washes 3 x 20 ml x 1 min.
5. NMP washes 4 x 20 ml x 1 min.
6. Coupling step (see below).
7. DMF washes 4 x 15 ml x 1 min.
8. Kaiser Ninhydrin test or cleavage/deprotection with HPLC and mass spectral analyses.

[00216] The Fmoc group was removed from the Sieber Amide resin using steps 1 to 5 above. N-α-Fmoc-4-(2'-Methylphenyl)-3-pyridylalanine (0.73 g, 1.50 mmole), PyBOP (0.78 g, 1.50 mmole) and HOBt (0.39 g, 1.50 mmole) were dissolved in NMP (5 ml) and the solution was then added to the resin followed by the addition of DIEA (0.39 g, 3.05 mmole). The coupling mixture was vortexed for 16 hours. The resin was treated with 10% acetic anhydride in DCM (1 x 50 mL x 60 mins.), washed with DCM (4 x 50 ml x 1 min.) and dried *in vacuo* for overnight. An Fmoc determination test gave a substitution of 0.456 mmole/gram. The synthesis was continued with 3.11 g (1.42 mmole) of resin. Following resin deprotection, a solution of N-α-Fmoc-(L)-Bip(2'-Et-4'-OMe)-OH (0.98 g, 1.9 mmole), HCTU (0.78 g, 1.9 mmole) in NMP (5 ml) was added to the resin, followed by the addition of DIEA (0.48 g, 3.80 mmole), and the mixture was vortexed for 16 hrs. After washing with NMP, a Kaiser ninhydrin test was negative. Following deprotection of the resin, N-α-Fmoc-L-Aspartic acid β-t-butyl ester (0.6487 g, 1.24 mmole) was coupled for 48 hrs using HCTU (1.03 g, 2.49 mmole) and DIEA (0.65 g, 5.03 mmole) in NMP (10 ml). Following deprotection of the resin, N-α-Fmoc-N-*im*-trityl-L-Histidine (3.85 g, 6.25 mmole) was coupled for 16 hours using 0.546 M HOAt in DMF (11.5 mL, 6.3 mmole) and DIC (0.96 mL, 6.3 mmole). The protocol was repeated to couple N-α-Fmoc-O-t-butyl-L-Threonine (2.5 g, 6.30 mmole) to the resin. After resin deprotection, N-α-Fmoc-α-methyl-2-fluoro-L-Phenylalanine (0.78 g, 1.86 mmole) in 0.546M HOAt in DMF (3.4 mL, 1.87 mmole) was added to the resin followed by DIC (0.24 g, 1.87 mmole) in DMF (3.5 ml), and coupling was allowed to proceed for 4

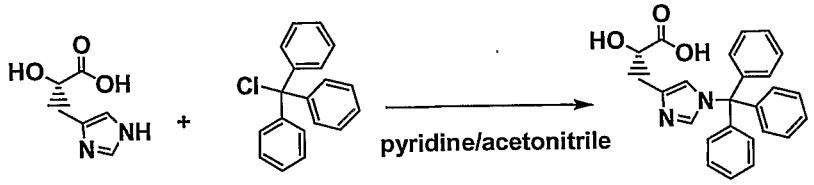
hours. After resin deprotection, N-α-Fmoc-O-t-butyl-L-Threonine (4.97 g, 12.50 mmole) was coupled for 16 hours using a solution of 0.546 M HOAt in DMF (25 mL, 12.50 mmole) and DIC (1.58 g, 12.52 mmole) . The resin was capped with 10% acetic anhydride in DMF (20 mL) for 1 hour and washed with DMF (4 x 20mL). The Fmoc group was removed, and N-Fmoc-Glycine (1.11 g, 3.75 mmole) was coupled for 90 min. as described for the previous N-α-Fmoc-L-Aspartic acid β-t-butyl ester coupling step, followed by N-α-Fmoc-L-glutamic acid γ-t-butyl ester (1.60 g, 3.75 mmole) in the same manner. A portion of the peptidyl-resin (0.030 mmole) was deprotected and N-α-Fmoc-α-methyl-L-proline (21.2 mg, 0.06 mmole) was coupled for 16 hours using 0.546 M HOAt in DMF (0.110 ml, 0.83 mmole) and DIC (7.6 mg, 0.06 mmole) in DMF (0.1 ml). Finally, L-β-(N-1-Trityl)imidazolelactic acid (39.8 mg, 0.10 mmole) and HATU (38 mg, 0.10 mmole) in NMP (0.9 mL) was added to a portion of peptidyl-resin (0.01 mmole) followed by addition of DIEA (17.4 mL, 0.10 mmole). After vortexing for one hour and washing with NMP, the coupling was repeated as described above and allowed to proceed for 48 hours. The resin-bound peptide was treated with TFA/TIS/water (94:3:3) (2 mL) for 2.5 hours, followed by two rinses of TFA/TIS/water (94:3:3) (2x 1 mL each). The combined filtrates were concentration *in vacuo* to yield 18.1 mg (92%) of crude peptide. This was dissolved in 2 mL of (1:1) acetonitrile / water and the solution was loaded onto a Luna [C18(2), 5 μm] Phenomenex column, 250 x 21.2 mm I.D. The column was eluted with a gradient of 15 % to 55 % solvent B in solvent A over 50 minutes at a flow rate of 15 ml/min. Solvent A: 0.1% TFA in water. Solvent B: 0.1% TFA in AcCN. The fractions containing a pure product were pooled and lyophilized to give 4.2 mg of Compound of SEQ ID NO:151.

EXAMPLE 22

Synthesis of (S)-3-(N-1-Trityl-imidazol-4-yl)-2-hydroxypropanoic acid (L-β-(N-1-Trityl)imidazolelactic acid)

[00217] The following Scheme 22 describes the synthesis of (S)-3-(N-1-Trityl-imidazol-4-yl)-2-hydroxypropanoic acid:

Scheme 22



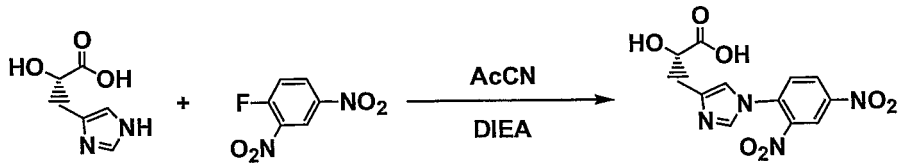
[00218] (S)-3-(1H-imidazol-4-yl)-2-hydroxypropanoic acid (0.5265 g, 3.0 mmole) and trityl chloride (1.2991 g, 4.7 mmole) were charged to a 100 mL flask. Pyridine/acetonitrile 1:1 (20 mL) was added under stirring. The flask was heated in an oil bath at 50° to 55° C for 4 hours. The solvents were removed to near dryness on a rotovap. To the residue was added equal volumes of water and ethyl acetate (30 mL each). The mixture was stirred for about 20 minutes. The resultant solid was collected by filtration, washed with water (2 x 10 mL), then with ethyl acetate (2 x 10 mL) and dried *in vacuo*. Yield: 0.6953 g (58 %).

EXAMPLE 23

Synthesis of (S)-3-(N-1-(2,4-dinitrophenyl)imidazol-4-yl)-2-hydroxypropanoic acid (L-β-(N-1-(2,4-dinitrophenyl)imidazolelactic acid)

[00219] The following Scheme 23 describes the synthesis of (S)-3-(N-1-(2,4-dinitrophenyl)imidazol-4-yl)-2-hydroxypropanoic acid:

Scheme 23



[00220] (S)-3-(1H-imidazol-4-yl)-2-hydroxypropanoic acid monohydrate (0.8971 g, 5.2 mmole), acetonitrile (60 mL), DIEA (1.3438g, 10.4 mmole) and 1-fluoro-2,4-dinitrobenzene (0.9564 g, 5.1 mmole) were charged to a round bottom flask, covered with aluminum foil and stirred overnight. The reaction mixture was filtered and the solvent was removed under reduced pressure. The oily residue was triturated with diisopropyl ether (2 x 20 mL) and was then dissolved in chloroform (20 mL) and re-evaporated from chloroform and AcCN. Addition of DCM (60 mL) produced a precipitate, which was stirred at RT after adding more DCM (30 mL). The solid

product was collected, washed with DCM (2 x 10 mL) and dried *in vacuo* overnight. Yield: 1.37 g (83%).

EXAMPLE 24

Synthesis of The Compound of SEQ ID NO: 158

Method A. Fragment coupling (Schemes 10A and 10B)

[00221] The synthesis was performed manually in an 8 ml reactor starting with 0.1896 g (0.56 mmole/g, 0.11 mmole) of Sieber Amide resin. The following cycles were used to remove the Fmoc group from the resin:

1. DMF wash 1 x 2 ml x 5 mins.
2. 20% piperidine in DMF 1 x 2 ml x 5 mins.
3. 20% piperidine in DMF 1 x 2 ml x 15 mins.
4. DMF washes 8 x 2 ml x 1 min.

[00222] N-α-Fmoc-4-(2'-Methylphenyl)-3-pyridylalanine HCl salt (0.0549 g, 0.11 mmole) and PyBOP (0.0667 g, 0.13 mmole) were dissolved in DMF (1 ml). This solution was added to the deprotected resin, followed by DIEA (0.0423 g, 0.33 mmole) in DMF (1 mL). The resin was vortexed for 3.5 hours, washed with DMF and DCM (4 x 2 mL x 1 min). The resin was treated with 10% acetic anhydride in DCM (2 mL) overnight, washed with DCM (6 x 2 ml x 1 min.) and dried in vacuo for 1 hour. Yield: 0.2508 g. An Fmoc determination test gave a substitution of 0.35 mmole/gram. 0.083 g (0.029 mmol) of the resin was used in the next step.

[00223] Following deprotection of the resin using the above cycles 1 to 4, a solution of N-α-Fmoc-(L)-Bip(2'-Et-4'-OH)-OH (0.0251 g, 0.049 mmole), HOBt (0.0084 g, 0.055 mmole) and DIC (0.0067 g, 0.053 mmole) in DMF (1 ml) was added to the resin. After vortexing for 16 hours, the peptidyl-resin was washed with DMF then DCM (4 x 1 mL x 1 min.). The Fmoc group was removed as using steps 1 to 3 above followed by DMF then DCM washes (4 x 1 mL x 1 min.).

[00224] The peptide-resin was treated with trifluoroacetic acid/triisopropylsilane/water 96:2:2 (2 x 1 mL x 10 mins.). The filtrates were collected and concentrated in vacuo to a residue which was triturated with diisopropyl ether and centrifuged to yield a solid product. This was washed with diisopropyl ether

and dried in vacuo to give 0.0244 g of dipeptide. The dipeptide was dissolved in 0.2% DIEA in THF (1 mL) and treated for 2 hours with macroporous triethylammonium methylpolystyrene carbonate resin (0.0682 g, 0.211 mmole, Argonaut Technologies). The resin beads were removed and washed with 0.2% DIEA in THF (2 x 1 mL). The combined filtrate and wash solution was dried in vacuo. To the resulting residue was added a solution of the side-chain protected N-methyloxycarbonyl Xaa1-Xaa9 9-mer peptide (55.8 mg, 0.035 mmole), HOBt (5.47 mg, 0.036 mmole) and DIC (6 μL, 0.035 mmole) in CHCl3/DMF 9:1 (1 mL). The resultant solution was vortexed overnight. Afetr solvent removal in vacuo, the resulting residue was treated with 2% triisopropylsilane in trifluoroacetic acid (1 mL) for 90 minutes after which diisopropyl ether (20 mL) was added. The precipitated solid was dried and dissolved in 2 mL of 1.5% ammonium hydroxide. The pH was adjusted to ~9.5 with acetic acid. This solution was loaded onto a Luna [C18(2), 5 μm] Phenomenex column, 250 x 21.2 mm I.D. The column was eluted with a gradient of 20 % to 50 % solvent B over 60 minutes at a flow rate of 15 ml/min. Solvent A: 0.1% TFA in water. Solvent B: 0.1% TFA in AcCN. The fractions containing a pure product were pooled and lyophilized to give 5.5 mg of the Compound of SEQ ID NO:158.

[00225] A different fragment coupling procedure for the synthesis of the Compound of SEQ ID NO:158 followed the method described in Scheme 10B. The synthesis was performed manually in an 8 ml reactor starting with 0.1182 g (0.47 mmole/g, 0.056 mmole) of N-α-Fmoc-4-(2'-Methylphenyl)-3-pyridylalanyl-Sieber Amide resin prepared as described earlier in this Example. The cycles used to remove the Fmoc group from the resin were the same as those described above. N-α-Fmoc-(L)-Bip(2'-Et-4'-OH)-OH (0.0419 g, 0.083 mmole) was coupled to the resin as described above. Following resin treatment with 10% acetic anhydride in DCM (2 mL) for 30 minutes, DCM washes (6 x 2 ml x 1 min.) and removal of the Fmoc group, a solution of the side-chain protected N-methyloxycarbonyl Xaa1-Xaa9 9-mer peptide (0.1347 g, 0.084 mmole), HOBt (0.0130 g, 0.085 mmole) and DIC (0.0118 g, 0.94 mmole) in DCM (0.1 mL) and DMF (0.45 mL) was added to the deprotected dipeptidyl-resin and the mixture was vortexed for 4.5 hours. The resin was washed

with DMF and DCM (4 x 2 mL x 1 min.), and then treated with 2% triisopropylsilane, 2% water in trifluoroacetic acid (5 x 1 mL x 3 mins.); the filtrates were collected and allowed to stand for 75 minutes. The solvents were removed in vacuo and the resultant residue triturated with diisopropyl ether (20 mL) to yield the crude peptide as a solid (0.0818 g). This was purified as described above, except that the gradient used was 25 % to 35 % solvent B in solvent A over 120 minutes at a flow rate of 15 ml/min. Solvent A: 0.1% TFA in water; solvent B: 0.1% TFA in AcCN. The fractions containing a pure product were pooled and lyophilized to give 19 mg of the Compound of SEQ ID NO:158.

Method B. Stepwise elongation (Scheme 1)

[00226] The synthesis was performed on an Advanced ChemTech Model 90 Synthesizer in a 50 ml reactor starting with 1.46 g (0.72 mmole/g, 1.05 mmole) of Sieber Amide resin. The general deprotection/coupling repetitive cycle used for the stepwise assembly was as follows:

1. DMF wash 1 x 15 ml x 1 min.
2. 20% piperidine in DMF 1 x 15 ml x 5 min.
3. 20% piperidine in DMF 1 x 15 ml x 15 min.
4. DMF washes 4 x 15 ml x 1 min.
5. NMP washes 4 x 15 ml x 1 min.
6. Coupling step (see below).
7. DMF washes 4 x 15 ml x 1 min.
8. DCM washes 4 x 15 ml x 1 min.
9. Kaiser Ninhydrin test or cleavage/deprotection with HPLC and mass spectral analyses.

[00227] The Fmoc group was removed from the Sieber Amide resin using steps 1 to 5 above. N-α-Fmoc-4-(2-Methylphenyl)-3-pyridylalanine HCl salt (1.0977 g, 2.13 mmole), PyBOP (1.0972 g, 2.11 mmole) and HOBt monohydrate (0.3228 g, 2.11 mmole) were dissolved in DMF (8 ml). DIEA (0.8052 g, 6.23 mmole) was added to the solution, which was then added to the resin. The coupling mixture was vortexed for 16 hours. The resin was treated with 10% acetic anhydride in DCM (1 x 15 mL x 60 mins.), washed with DCM (6 x 15 ml x 1 min.) and dried in vacuo for 6 hours.

Yield: 1.6816 g. An Fmoc determination test gave a substitution of 0.48 mmole/gram. The synthesis was continued with 0.8602 g (0.41 mmole) of resin. Following resin deprotection, a solution of N-α-Fmoc-(L)-Bip(2'-Et-4'-OH)-OH (0.2660 g, 0.524 mmole), HOBt (0.0796 g, 0.520 mmole) and DIC (0.0647 g, 0.513 mmole) in DMF (8 ml) was added to the resin and the mixture was vortexed for 16 hrs. After washing with DMF and DCM, a Kaiser ninhydrin test was negative. Following deprotection of the resin, N-α-Fmoc-L-Aspartic acid β-t-butyl ester (0.6487 g, 1.24 mmole) was coupled for 45 min. using HOBt (0.1893 g, 1.24 mmole) and DIC (0.1566 g, 1.24 mmole) in DMF/DCM (1:1) (6 ml). The same coupling cycle was repeated with N-α-Fmoc-O-t-butyl-L-Serine (0.4750 g, 1.24 mmole) and N-α-Fmoc-O-t-butyl-L-Threonine (0.4924 g, 1.24 mmole). After resin deprotection, N-α-Fmoc-α-methyl-2-fluoro-L-Phenylalanine (0.3497 g, 0.834 mmole) was coupled for 1 hour using HOBt (0.1271 g, 0.830 mmole) and DIC (0.1044 g, 0.827 mmole) in DMF/DCM (1:1) (6 ml). After resin deprotection, N-α-Fmoc-O-t-butyl-L-Threonine (1.6413 g, 4.14 mmole) was coupled for 16 hours using a solution of 0.5 M HOAt in DMF (8.3 mL, 4.15 mmole) and DIC (0.5240 g, 4.15 mmole). After DMF and DCM washes, 3 mg of wet resin was treated with 1 ml of TFA/TIS/water (96:2:2) for 1.5 hours. The resin was filtered off and the solvents were removed in a speed-vac. The residue was dissolved in 2 ml of water/acetonitrile (1:1). HPLC and MS analyses showed no uncoupled peptide. The Fmoc group was removed, and N-Fmoc-Glycine (0.3691 g, 1.24 mmole) was coupled for 1 hr as described for the previous N-α-Fmoc-L-Aspartic acid β-t-butyl ester coupling step, followed by N-α-Fmoc-L-glutamic acid γ-t-butyl ester (0.5297 g, 1.24 mmole) in the same manner. N-α-Fmoc-α-methyl-L-proline (0.2902 g, 0.83 mmole) was then coupled for 3.5 hours using HOBt (0.1271 g, 0.83 mmole) and DIC (0.1042 g, 0.83 mmole) in DMF/DCM 1:1 (6 ml). Finally, N-α-Fmoc-N-im-trityl-L-Histidine (2.5564 g, 4.13 mmole) was coupled for 12 hours as described for the N-α-Fmoc-O-t-butyl-L-Threonine coupling to the N-α-Fmoc-α-methyl-2-fluoro-L-Phenylalanine. A deprotected peptide sample released from the peptidyl-resin as described above showed some uncoupled peptide by MS. The Fmoc group was manually removed and, after DMF and DCM washes, a solution of N-(methyloxycarbonyloxy)succinimide (0.2163 g, 1.25 mmole) in DCM (6 mL) was

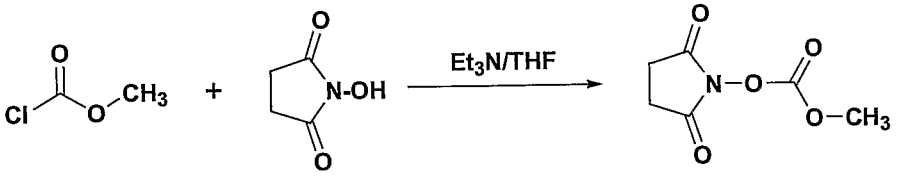
added and the mixture was vortexed for 16 hours. The peptide-resin was washed with DCM (4 x 10 ml x 1 min.). A Kaiser ninhyrin test was negative. The N-methyloxycarbonyl-derivatized peptidyl-resin was treated with TFA/TIS/water (96:2:2) (10 mL) for 10 minutes, followed by two additional treatments with 5 mL each. The combined filtrates were left to stand for an additional 2 hours at RT. Following concentration in vacuo to about 4 mL, the solution was added dropwise to diethyl ether (50 ml) with stirring. The resulting solid was collected by filtration, washed with diethyl ether (2 x 5 ml) and dried in vacuo to yield 0.691 g (92%) of crude peptide. This was purified by preparative HPLC using the procedures described in Method A of this Example.

EXAMPLE 25

Synthesis of N-(methyloxycarbonyloxy)succinimide [2,5-(dioxopyrrolidin-1-yl) methyl carbonate]

[00228] The following Scheme 24 describes the synthesis of N-(methyloxycarbonyloxy) succinimide [2,5-(dioxopyrrolidin-1-yl) methyl carbonate]:

Scheme 24



[00229] To a stirred solution of 64.61 g (0.561 mol) of N-hydroxysuccinimide and 58.95 g (0.624 mol) of methyl chloroformate in THF (900 mL) at -5 °C under argon was added 82.6 mL (0.593 mol) of triethylamine at a rate such that the temperature remained below +3 °C. The reaction mixture was stirred and allowed to warm to RT. After 15 h, the resulting slurry was filtered and the solids were washed with THF (100 mL). The filtrate was evaporated under reduced pressure to give a white solid. Recrystallization from EtOAc/hexanes (2:1, 150 mL) provided the desired product as white crystals, mp 84-86 °C, 79.4 g, 82% yield.

EXAMPLE 26

Synthesis of (R,S)-3-(1-(2,4-dinitrophenyl)-imidazol-4-yl)-2-methylpropionic acid [α-Methyl-β-[1-(2,4-dinitrophenyl)-imidazol-4-yl]propionic acid, Imp]

1-Tosyl-4(5)-hydroxymethylimidazole

[00230] The following procedure was adapted from Agr. Biol. Chem., 38 (5), 1097-1099, 1974. To a solution of Na2CO3 (8.4 g., 0.08 mole) in water (40 mL) was added 4-(hydroxymethyl)imidazole hydrochloride (2.7 g, 0.02 mole,). Upon complete dissolution, a solution of p-toluenesulfonyl chloride (4.58 g, 0.024 mole) in ethyl acetate (30 mL) was added dropwise over a 5 minute period. The reaction mixture was allowed to stir for 5 hours. The layers were separated and more ethyl acetate was added (20 mLs). The organic phase was washed with 0.1 M Na2CO3 (2 x 20 mL), water (1 x 20 mL) and then saturated NaCl (1 x 20 mL). The ethyl acetate was treated with 2 g of MgSO4 and 1 g of activated charcoal for 10 minutes. The solids were removed by filtration through a celite pad and the solvent removed on a rotavap. The residue began to crystallize. Fresh ethyl acetate was added (10 mL) and the solution was warmed with a heat gun to redissolve the solids. The product crystallized overnight at room temperature. The crystalline material was collected, washed with ethyl acetate (5 mL) and then ethyl ether (10 mL), and dried in vacuo to a constant weight of 3.59 g.

1-Tosyl-4(5)-acetoxymethylimidazole

[00231] 1-Tosyl-4(5)-hydroxymethylimidazole (2.52 g, 10 mmole) was dissolved in chloroform (10 ml). To this was added triethylamine (2.02 g, 20 mmole) dropwise at room temperature, followed by dropwise addition of acetic anhydride (1.33 g, 13 mmole) over 15 minutes. The mixture was stirred at room temperature and monitored by LC/MS for four days. The chloroform was removed by reduced pressure and the residue was dissolved in ethyl acetate (60 ml). The organic layer was washed successively with 0.1 M sodium bicarbonate, water and then saturated sodium chloride, all 1 x 40 ml each. The organic layer was treated with activated charcoal and magnesium sulfate simultaneously and then filtered through a celite pad. The solvent was removed by reduced pressure and the resultant residue was dissolved in

warm ethyl acetate (10 ml). To this solution was slowly added 20 ml of diethyl ether. The solution was left to crystallize overnight at room temperature. The crystals were collected, washed with diethyl ether (2 x 10 ml) and dried in vacuo overnight to yield 1.55 g.

Methyl-α-carbomethoxy-α-methyl-β-4-(1-tosylimidazole)-propionate

[00232] The following procedure was adapted from Synthetic Communications, 19(7&8), 1157-1165, 1989. A solution of 1-Tosyl-4(5)-acetoxymethylimidazole (0.3516 g, 1.2 mmole) and dimethyl methylmalonate (0.1485 g, 1.0 mmole) in acetonitrile (2 ml) was added to a stirred suspension of powdered KOH (0.1694 g, 3.0 mmole) and tetrabutylammonium bromide (0.0496 g, 0.15 mmole) in acetonitrile (1 ml). The reaction was complete after 40 mins, as determined by HPLC analysis. The reaction mixture was poured into ethyl ether (100 ml), filtered through a celite pad and the solvents were removed by evaporation under reduced pressure. The residual oil was dissolved in 30 ml of ethyl acetate and washed with 0.1 M NaHCO3 (1 x 15 ml), saturated NaCl (1 x 15 ml) and dried over MgSO4. The solvent was removed under reduced pressure and the resultant oil was left in a desiccator in vacuum for 3 days to yield 0.207 g.

α-Methyl-β-4-imidazole propionic acid

[00233] Methyl-α-carbomethoxy-α-methyl-β-4-(1-tosylimidazole)-propionate (0.186 g, 0.5 mmole) was dissolved in 2 ml of methanol. To this was added 1.5 ml of 1.0 N NaOH and the reaction was allowed to stir overnight. After purification by preparative HPLC, the product obtained by lyophilization (0.1366 g) was dissolved with 5 ml of 1.0 N NaOH and heated at 100 °C for 2 hours in a 16 x 100 mm screw-cap tube sealed with a PTFE lined cap, followed by addition of 2 ml of concentrated HCl and heating at 145° C for 6 hours. The desired decarboxylated product was formed. The entire solution was filtered and loaded onto a YMC G-340-10P ODS 50 x 20 mm preparative HPLC column. The product was eluted with a gradient of 0% to 60% 0.1% TFA/MeCN in 0.1% TFA/water over 60 minutes. The fractions

corresponding to 11 to 13 minutes in the gradient were pooled, frozen and lyophilized to give 32 mg of product.

α-Methyl-β-[1-(2,4-dinitrophenyl)-imidazol-4-yl]propionic acid

[00234] To a solution of α-Methyl-β-4-imidazole propionic acid (0.0305 g, 0.114 mmoles) and sodium bicarbonate (0.0617 g, 0.734 mmole) in water (1 mL) (pH 8.04) was added a solution of 2,4-dinitrofluorobenzene (0.0323 g, 0.174 mmole) in MeCN (1.0 mL). The reaction mixture was vortexed overnight. The MeCN was removed under reduced pressure and the residue was re-dissolved in 2 mL of water, filtered and loaded onto a Phenomenex Luna C18(2) 5μm 100 x 21.2 mm preparative HPLC column in two aliquots of 1.5 and 0.5 mL each. The product was eluted with a gradient of 0% to 80% 0.1% TFA/MeCN in 0.1% TFA/water over 40 minutes. The fractions corresponding to 12.5 to 14.5 minutes in the gradient were pooled and dried in a Savant SpeedVac™ overnight. Additional product was recovered by dissolving the water-insoluble crude product in DMSO, followed by preparative HPLC as described above. The combined fractions produced 31 mg of pure product after lyophilization.

EXAMPLE 27

Synthesis of the Compounds SEQ ID NOs: 137 and 138

[00235] (R,S)-3-(1-(2,4-dinitrophenyl)-imidazol-4-yl)-2-methylpropionic acid was coupled to the relevant X_{aa2}-X_{aa11}-peptidyl-Sieber resin as described below.

[00236] To a solution of (R,S)-3-(1-(2,4-dinitrophenyl)-imidazol-4-yl)-2-methylpropionic acid (0.0267 g, 0.083 mmoles), 6-Cl-HOBt (0.0151 g, 0.089 mmoles) and HCTU (0.0360 g, 0.087 mmoles) in 1 mL of NMP/DCM (3:1) was added DIEA (0.0315 g, 0.244 mmole); the solution was briefly vortexed and then added to the relevant Fmoc deprotected X_{aa2}-X_{aa11}-peptidyl-Sieber resin prepared as described in Example 19. The coupling was allowed to proceed for 16 hours. The peptidyl-resin was washed with NMP then DCM (3 x 1.5 mL x 1 min) and then treated with 10% acetic anhydride in DCM, 1 x 2 mL x 90 minutes, followed by DCM then DMF washes (3 x 1.5 mL x 1 min). The peptidyl-resin was treated with 10%

thiophenol in DMF (1.5 mL) for 1 hr and washed with DMF and DCM (4 x 1.5 mL x 1 min). The peptidyl-resin was then treated with TFA/DCM/TIS (3:1.9:0.1) (1 mL) for 10 min and filtered. The filtrates were collected and gently vortexed for another hr. The TFA mixture was concentrated in a speed-vac to about 0.5 mL and added to 4 mL of MTBE. After 1 hr the precipitated product was collected by centrifugation, washed and then dried to give 0.0841 g of crude product. This was purified by preparative HPLC as follows: the crude peptide was dissolved and injected into a Phenomenex Luna C18(2) (5 μm, 250 x 30 mm) column and eluted using a linear gradient from 20% to 50% 0.1% TFA/MeCN in 0.1% TFA/water over 40 min at a flow rate of 15 mL/min with effluent UV detection at 217 nm. The fractions containing the desired product pooled and lyophilized to give 26.7 mg of 97.5% pure peptide.

Preparative chiral HPLC purification of the peptide

[00237] The diastereomeric peptide mixture (10 mg) was dissolved in MeCN/MeOH. The solution was loaded onto a Chirobiotic V 2.2 x 50 cm, 5 μm column and eluted with MeCN/MeOH/N(CH2CH3)3/CH3COOH: 65/35/0.5/0.5 at 20 mL/min. Isomer A was collected between 29 and 35 minutes. Isomer B was collected between 36 and 44 min. A second run was made as described above. The fractions containing Isomer A were combined, concentrated to about 5 mL, diluted with water/MeCN (4:1) and the solution was lyophilized. Isomer B was processed in the same manner. The resultant residues were converted to TFA salts by preparative HPLC. Each peptide was injected into a Phenomenex Luna C18(2) 5 μm 100 x 21.2 mm column and eluted using a linear gradient from 20% to 50% 0.1%TFA/MeCN in 0.1%TFA/water over 40 min. at a flow rate of 10 mL/min with effluent UV detection at 217 nm. The fractions containing the desired product were pooled, frozen and lyophilized to give 6.0 mg of purified peptide Isomer A and 4.9 mg of purified peptide Isomer B.

EXAMPLE 28

[00238] Exemplary 11-mer peptides are set forth in Table 3.

Table 3

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
1.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me)	4-(2'-pyridyl)Phenylalanine-NH_2
2.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(3',5'-di-Me)	4-(2'-pyridyl)Phenylalanine-NH_2
3.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-OBu)	4-(2'-pyridyl)Phenylalanine-NH_2
4.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me)	4-(4'-pyridyl)Phenylalanine-NH_2
5.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Cl)	4-(4'-pyridyl)Phenylalanine-NH_2
6.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-methoxy-5'-iso-propyl)	4-(4'-pyridyl)Phenylalanine-NH_2
7.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(2'-Ethylphenyl)-3-pyridylalanine	Bip(2'-Me)-NH_2
8.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[(2'-Ethyl-4'-methoxy)phenyl]-3-pyridylalanine	Bip(2'-Me)-NH_2
9.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
10.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
11.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
12.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
13.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
14.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
15.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Methyl)pyridyl)]phenylalanine-NH_2
16.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Methyl)pyridyl)]phenylalanine-NH_2
17.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-Pyridazyl)phenylalanine-NH_2
18.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-Pyridazyl)phenylalanine-NH_2
19.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Me,6-OMe)pyridyl)] phenylalanine-NH_2
20.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3-(4'-Methyl)pyridyl)] phenylalanine	Bip(2'-Me)-NH_2
21.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me)-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
22.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me)-NH_2
23.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[2(1H)Pyridonyl]phenylalanine-NH_2
24.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(8-Quinoline)-NH_2
25.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(3-Quinoline)-NH_2
26.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(6-Quinoline)-NH_2
27.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(5-Quinoline)-NH_2
28.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-(6-OMe)pyridyl)phenylalanine-NH_2
29.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-(2-Methoxy)pyridyl)phenylalanine-NH_2
30.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-pyridyl)phenylalanine-NH_2
31.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
32.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(5-Quinoline)phenylalanine	Bip(2'-Me)-NH_2
33.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[3-(2'-OMe)pyridyl]phenylalanine	Bip(2'-Me)-NH_2
34.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(6-Quinoline)phenylalanine	Bip(2'-Me)-NH_2
35.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(4'-pyridyl)phenylalanine	Bip(2'-Me)-NH_2
36.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[4'-(3',5'-dimethylisoxazole)]phenylalanine	Bip(2'-Me)-NH_2
37.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2-trifluoromethylphenyl)-3-pyridylalanine-NH_2
38.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2-methyl-5-fluorophenyl)-3-pyridylalanine-NH_2
39.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4-methanesulfonylphenyl)-3-pyridylalanine-NH_2
40.	H	Aib	E	G	T	L-α-Me-Phe	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
41.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
42.	H	Aib	E	G	Nle	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
43.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-Cl, 4'-CF3)-3'-pyridyl]phenylalanine-NH_2
44.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3'-(2'-CN-6'-Me)pyridyl]phenylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
45.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Cl)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
46.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2',4'-di-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
47.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(3'-pyridyl)phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
48.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(4'-pyridyl)phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
49.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Me-3'-F)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
50.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-F)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
51.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(2'-Cl-6'-CF3)pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
52.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(2'-Cl)-NH_2
53.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(3'-Cl-4'-F)-NH_2
54.	H	Aib	E	G	Nva	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
55.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(3',5'-di-Me)-NH_2
56.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2',3'-pyridazyl)phenylalanine-NH_2
57.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-ethylphenyl)-3-pyridylalanine-NH_2
58.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-[3'-(2'-Cl-6'-CF3)pyridyl]phenylalanine-NH_2
59.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-[3'-(2'-CN-6'-Me)pyridyl]phenylalanine-NH_2
60.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Cl)-NH_2
61.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(3'-Cl-4'-F)-NH_2
62.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(3',5'-di-Me)-NH_2
63.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Me-4'-OMe)-NH_2
64.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Me-3'-F)-NH_2
65.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-F)-NH_2
66.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Cl)-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
67.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(3',4'-di-OMe)-NH_2
68.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	4-(2'-pyridyl)phenylalanine-NH_2
69.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me-4'-OMe)-NH_2
70.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
71.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-ethylphenyl)-3-pyridylalanine-NH_2
72.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Methyl)pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
73.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-pyridyl)-phenylalanine-NH_2
74.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-quinoline)phenylalanine-NH_2
75.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-(2'-Methoxy)pyridyl)phenylalanine-NH_2
76.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-phenyl-3-pyridylalanine-NH_2
77.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-dimethylphenyl)-3-pyridylalanine-NH_2
78.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3'-chloro-4'-fluoro)phenyl]-3-pyridylalanine-NH_2
79.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3',4'-dimethoxy)phenyl]-3-pyridylalanine-NH_2
80.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-ethyl-4'-methoxy)phenyl)]-3-pyridylalanine-NH_2
81.	L-β-Imidazole-lactyl	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
82.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-(5-o-Tolyl)thienylalanine-NH_2
83.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3'-Methoxy)phenyl]thienylalanine-NH_2
84.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3',5'-di-Methyl)phenyl]thienylalanine-NH_2
85.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3'-Cl,5'-F)phenyl]thienylalanine-NH_2
86.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Isopropoxyphenyl)-3-pyridylalanine-NH_2
87.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 5'-Fluoro)phenyl)-3-pyridylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
88.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Isopropoxyphenyl)-3-pyridylalanine-NH_2
89.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	3-(4-Br)pyridylalanine-NH_2
90.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Methoxyphenyl)-3-pyridylalanine-NH_2
91.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 4'-Fluoro)phenyl)-3-pyridylalanine-NH_2
92.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
93.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Trifluoromethoxyphenyl)-3-pyridylalanine-NH_2
94.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Trifluoromethoxyphenyl)-3-pyridylalanine-NH_2
95.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	3-pyridylalanine-NH_2
96.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 4'-Chloro)phenyl)-3-pyridylalanine-NH_2
97.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
98.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
99.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Fluorophenyl)-3-pyridylalanine-NH_2
100.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
101.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Chlorophenyl)-3-pyridylalanine-NH_2
102.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Chlorophenyl)-3-pyridylalanine-NH_2
103.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Isopropylphenyl)-3-pyridylalanine-NH_2
104.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-dimethylisoxazol-4'-yl)-3-pyridylalanine-NH_2
105.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-Methyl-4'-methoxy)phenyl)-3-pyridylalanine-NH_2
106.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
107.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Chlorophenyl)-3-pyridylalanine-NH_2

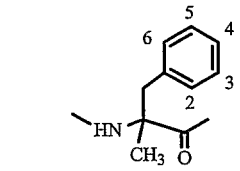
SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
108.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Pyridyl)-3-pyridylalanine-NH_2
109.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
110.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(6'-Methoxypyridin-3'-yl)-3-pyridylalanine-NH_2
111.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Isopropylphenyl)-3-pyridylalanine-NH_2
112.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methoxyphenyl)-3-pyridylalanine-NH_2
113.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3',5'-di-Fluoro-2'-methoxy)phenyl]-3-pyridylalanine-NH_2
114.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-methylphenyl)-3-pyridylalanine-NH_2
115.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-fluorophenyl)-3-pyridylalanine-NH_2
116.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-fluorophenyl)-3-pyridylalanine-NH_2
117.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
118.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
119.	H	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
120.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
121.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	(S)-4-(2'-Methylphenyl)-α-Me-3-pyridylalanine-NH_2
122.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	(S)-4-(2'-Methylphenyl)-α-Me-3-pyridylalanine-NH_2
123.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
124.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
125.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
126.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
127.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2
128.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
129.	H	N-Me-(L)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
130.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3,5-pyrimidylalanine-NH_2
131.	H	(S)-α-Me-Pro	D	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
132.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Ethylphenyl)-3-pyridylalanine-NH_2
133.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
134.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
135.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2
136.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
137.	(R)-Imp	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
138.	(S)-Imp	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
139.	CH3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
140.	CH3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
141.	CH3O-CO-His	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
142.	CH3O-CO-His	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
143.	CH3 SO2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
144.	CH3 SO2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
145.	L-Lactyl-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
146.	L-Lactyl-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
147.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-di-Me)phenyl-3-pyridylalanine-NH_2
148.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
149.	H	D-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2

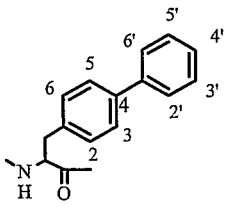
SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
150.	H	Aib	H	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
151.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
152.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
153.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
154.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
155.	L-β-Imidazole-lactyl	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
156.	L-β-Imidazole-lactyl	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
157.	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
158.	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
159.	CH_3O-CO-His	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
160.	CH_3O-CO-His	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
161.	CH_3O-CO-His	Aib	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
162.	CH_3O-CO-His	Aib	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2

Amino Acid Abbreviations and Structures

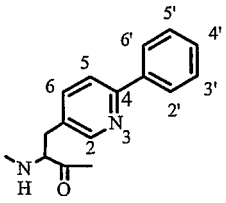
A = L-Ala; ala = D-Ala
Aib = a-aminoisobutyric acid
Bip = L-4,4'-biphenylalanine;
D = L-Asp
E = L-Glu
G = Gly
H = L-His
Nle = L-norleucine
Nva = L-norvaline
F = L-Phe
S = L-Ser;
T = L-Thr.



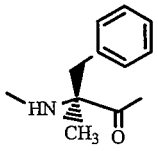
Numbering of the a-methyl-phenylalanine (a-Me-Phe) ring carbons



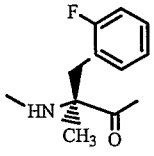
Numbering of the biphenylalanine ring carbons



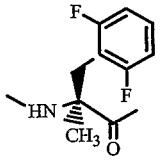
Numbering of the hetero-biphenylalanine ring carbons



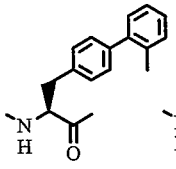
(L)-a-Me-Phe



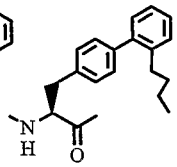
(L)-a-Me-Phe(2-Fluoro)



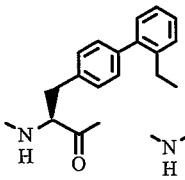
(L)-a-Me-Phe(2,6-di-Fluoro)



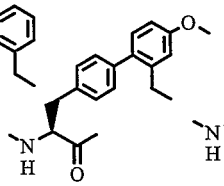
Bip(2'-Me)



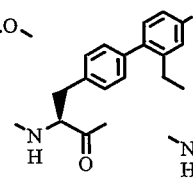
Bip(2'-OBu)



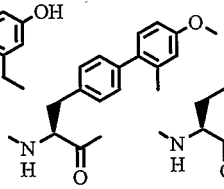
Bip(2'-Et)



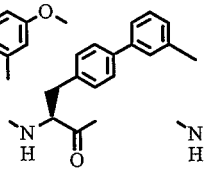
Bip(2'-Et-4'-OMe)



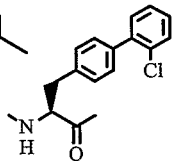
Bip(2'-Et-4'-OH)



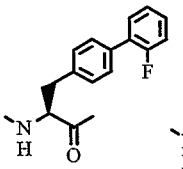
Bip(2'-Me-4'-OMe)



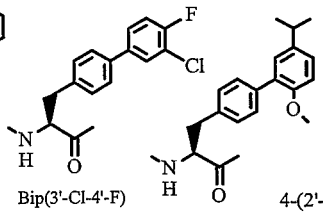
Bip(3',5'-di-Me)



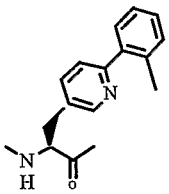
Bip(2'-Cl)



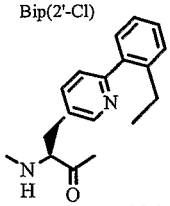
Bip(2'-F)



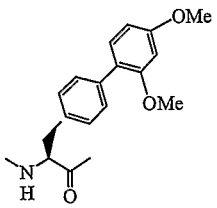
Bip(3'-Cl-4'-F)



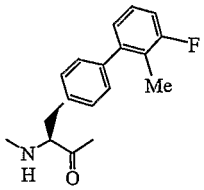
4-(2'-Methylphenyl)-3-pyridylalanine



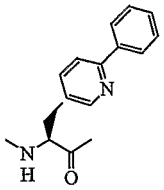
4-(2'-Ethylphenyl)-3-pyridylalanine



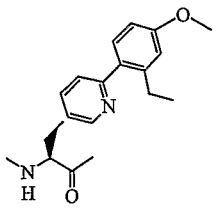
Bip(2',4'-di-OMe)



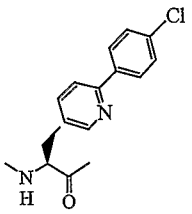
Bip(2'-Me-3'-F)



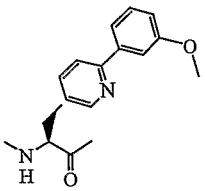
4-phenyl-3-pyridylalanine



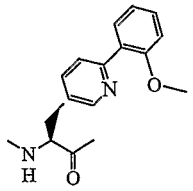
4-[(2'-Ethyl-4'-Methoxy)phenyl]-3-pyridylalanine



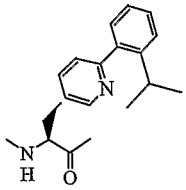
4-(4'-Chlorophenyl)-3-pyridylalanine



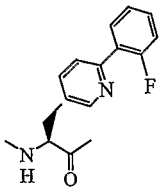
4-(3'-Methoxyphenyl)-3-pyridylalanine



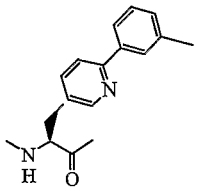
4-(2'-Methoxyphenyl)-3-pyridylalanine



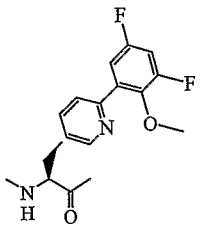
4-(2'-Isopropylphenyl)-3-pyridylalanine



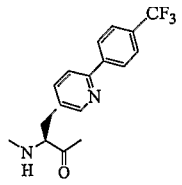
4-(2'-fluorophenyl)-3-pyridylalanine

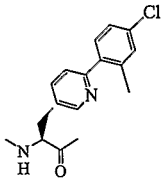


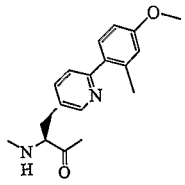
4-(3'-methylphenyl)-3-pyridylalanine

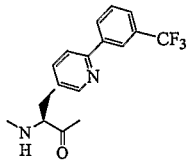


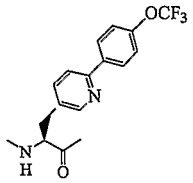
4-[(3',5'-di-Fluoro-2'-methoxy)phenyl]-3-pyridylalanine

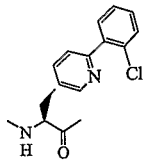

4-(4'-Trifluoromethylphenyl)-3-pyridylalanine

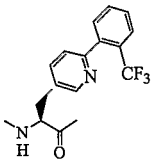

4-(2'-Methyl, 4'-Chloro)phenyl)-3-pyridylalanine

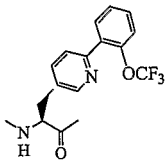

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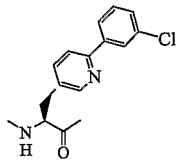

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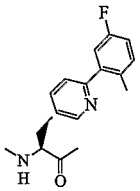

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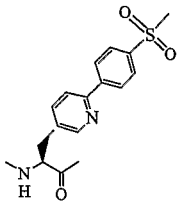

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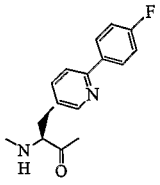

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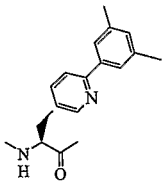

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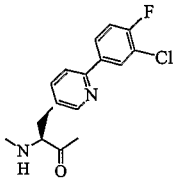

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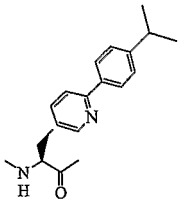

4-[(2'-Methyl-5'-fluoro)phenyl)]-3-pyridylalanine

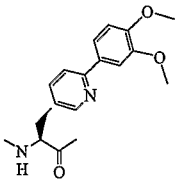

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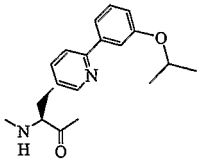

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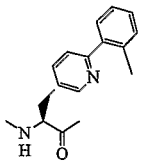

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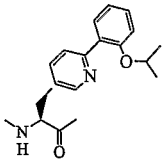

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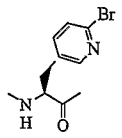

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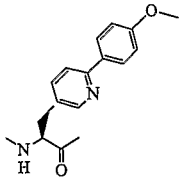

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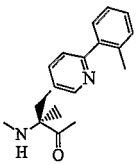

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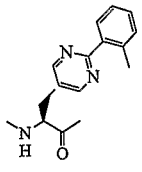

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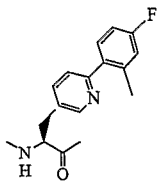

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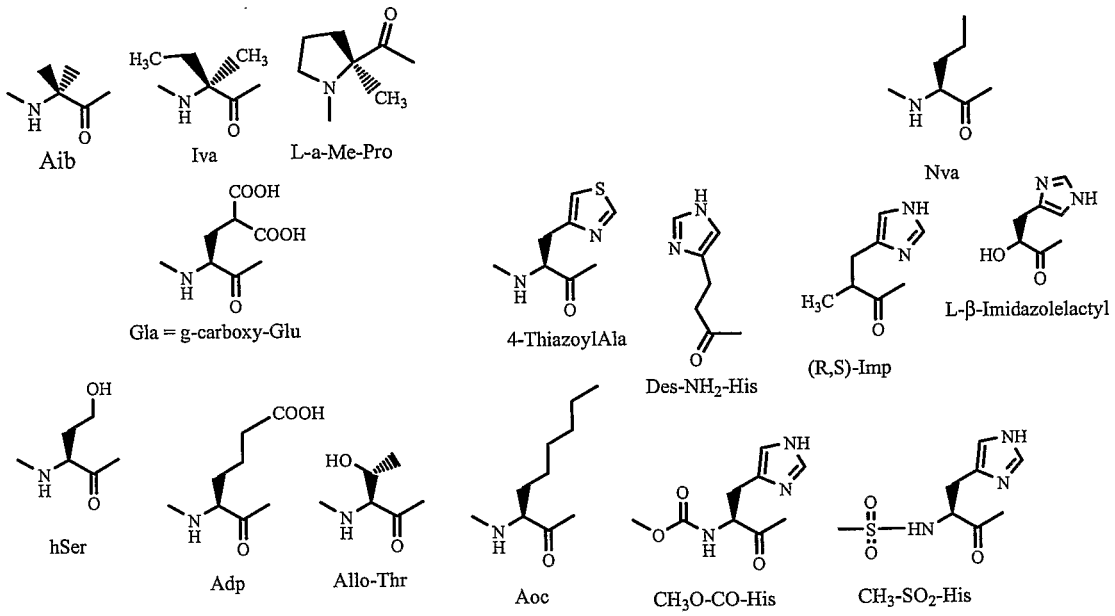

3-(4-Br)pyridylalanine


4-(4'-Methoxyphenyl)-3-pyridylalanine


(S)-4-(2'-Methylphenyl)-a-Me-3-pyridylalanine


4-(2'-Methylphenyl)-3,5-pyrimidylalanine


4-(2'-Methyl-4'-Fluoro)phenyl)-3-pyridylalanine



[00239] Those skilled in the art of amino acid and peptide chemistry are aware that a phenylalanine amino acid bearing a phenyl substituent at the 4 or para position may otherwise be defined as a 4-(phenyl)phenylalanine or 4,4'-biphenylalanine and thus may be abbreviated as "Bip". For the purpose of the abbreviations shown in the "Amino Acid Abbreviations and Structures" section and in the Tables herein, a biphenylalanine amino acid may be abbreviated, for example, as "Bip(2'-Me)", which is intended to represent a phenylalanine substituted at its 4 position with a 2'-methylphenyl group in which the 2'-methyl group is ortho relative to the attachment point of the phenyl ring.

EXAMPLE 29

Cyclic AMP determination

[00240] The GLP-1 receptor is a G-protein coupled receptor. GLP-1 (7-36)-amide, the biologically active form, binds to the GLP-1 receptor and through signal transduction causes activation of adenylyl cyclase and increases intracellular cAMP concentrations. To monitor agonism of peptides in stimulating the GLP-1 receptor, adenylyl cyclase activity was monitored by assaying for intracellular cAMP content. Full-length human glucagon-like peptide 1 receptor was stably expressed in CHO-K1 cells and clonal lines were established. The clones were screened for the greatest

increase in cAMP content in response to a saturating dose of GLP-1 and clone CHO-GLP1R-19 was selected.

[00241] Cells were cultured in Ham's F12 nutritional media (Gibco # 11765-054), 10% FBS, 1x L-Glutamine, 1x Pen/Strep, and 0.4 mg/ml G418. CHO-GLP-1R-19 cells (20,000 in 100 µl of media) were plated into each well of a 96-well tissue culture microtiter plate and incubated overnight in a 5% CO2 atmosphere at 37° C. On the day of the assay, cells were washed once with 100 µl of phosphate-buffered saline (PBS). A Biomek 2000 was used to serially dilute all peptides prior to beginning the assay. Serial dilutions were carried out in 100% DMSO. Peptide plates were created prior to the initiation of the assay using a Platemate Plus; 1.5 uL of Compound was transferred to a V bottom plate and 150 uL of assay buffer supplemented with 100 µM 3-isobutyl-1-methylxanthine (a nonselective phosphodiesterase inhibitor) was added to the plate to give a 1:100 dilution and a 1% final concentration of DMSO.

[00242] In order to create a cAMP standard curve, a serial dilution of cAMP in the range 0.2-25.6 pmol/well was made up in lysis reagent 1 (Amersham cAMP SPA kit). 50µl of each cAMP standard was added by hand and 70 µl of mix reagent (Amersham cAMP SPA kit) was added using the multidrop. The plates were then sealed and counted on a Trilux counter after 15 hours. This standard curve was used to convert CPM to pmol of cAMP.

cAMP assay protocol on the Platemate Plus

[00243] Cell plates and peptide plates were loaded onto the Platemate. The media was aspirated from the wells and discarded. 100 uL per well of the peptide/buffer mixture were then added from the peptide plates to initiate the assay. After 30 minutes of incubation the peptide/buffer was removed and 50 uL of the lysis reagent 1 solution was added per well. The plate was kept for one hour at RT or overnight if refrigerated and sealed. 70 uL of the cAMP detection reagent (premixed ^{125}I-cAMP analog, anti-cAMP antibody and anti-rabbit antibody conjugated to SPA beads - all from the Amersham cAMP SPA kit) was added using the multidrop and the plates were sealed. After 15 hours the plates were counted on the Trilux counter.

[00244] Dose dependence for Compounds was determined at half-log concentrations in duplicate. In each 96-well plate, GLP-1 (control), and five Compounds (in duplicate) were run at seven half-log doses. Ten nM GLP-1 was plated into ten additional wells to serve as a reference standard for determination of maximal activity. A standard curve was determined using known amounts of cyclic AMP. The amounts of cAMP synthesized by the treated cells were determined from the cyclic AMP standard curve, and the percent of the maximal GLP-1 stimulated activity was calculated and plotted against log compound concentration. The data were analyzed by nonlinear regression curve fitting (4 parameter sigmoidal dose-response curve) to determine the EC50 of the compounds. By way of example, the peptides described herein have EC50 values in the range of 0.0005nM to 10 nM, more preferably in the range of 0.0005 nM to 0.200 nM.

[00245] Alternatively, CHO cells expressing the GLP-1 receptor were plated at 10,000 cells per well in a 384 well plate and cultured overnight at 37 °C in 5% CO2 as described above. Following treatment with peptidyl GLP-1 receptor agonists, the intracellular level of cAMP was measured with the Hithunter™ XS cAMP kit (DiscoveRx®) by following the manufacturer's protocol.

EXAMPLE 30

In vivo studies

[00246] Peptides were dissolved in an appropriate vehicle at a concentration in nmol/ml equivalent to the dose that was to be administered in nmol/kg so that each mouse would receive the same volume/weight of dosing solution. Male C57BL/6J-ob/ob mice (10 weeks old) were randomized into groups of 6 mice per group based on fed plasma glucose and body weight. After an overnight fast, mice were weighed and placed in the experimental lab. After 30 min in the environment, the mice were bled via tail tip at -30 min and immediately injected subcutaneously (sc) with vehicle or the peptide dissolved in vehicle (0.1 ml solution/100 g body weight). At time 0 the mice were bled and then injected intraperitoneally with 50% glucose (2 g/kg) to initiate the intraperitoneal glucose tolerance test (ipGTT). The mice were bled 30, 60, 120 and 180 min after the glucose injection. Blood samples were drawn into potassium EDTA, placed on ice during the study and subsequently centrifuged for 10

min at 3000 rpm at 4°C. Plasma samples were diluted 11-fold for glucose analysis in the Cobas System. Another 5 µl plasma sample was diluted 5-fold with 20 µl of Sample Diluent (Insulin ELISA assay kit, Crystal Chem Inc.) and stored at -20°C for subsequent analysis using the Ultra Sensitive Mouse Insulin ELISA kit (Crystal Chem Inc.).

[00247] The *in vivo* glucose lowering properties for Compound I, and for the compounds of SEQ ID NOs: 9, 118, 151 and 158 in ob/ob mice (a mouse model of insulin resistance) are described below. Subcutaneous administration of Compound I attenuated the postprandial glucose excursion curve in an intraperitoneal glucose tolerance test (ipGTT), with the plasma glucose area under the curve (AUC) decreasing in a dose-dependent manner between 0 and 180 minutes (Figure 1). The ED50 of Compound I was determined to be 50 nmoles/kg. There was a concomitant and statistically significant dose-dependent increase in postprandial plasma insulin levels in these animals (Figure 2). The correlation between changes in plasma glucose and insulin in animals treated with Compound I (Figure 1 and Figure 2) suggests that the glucose lowering effect is mediated by stimulation of insulin release by said compound.

[00248] More significantly and unexpectedly, the compounds of SEQ ID NOs: 9, 118, 151 and 158 produced a time-dependent (between 0 and 180 or 210 minutes) statistically significant decrease in postprandial plasma glucose following subcutaneous administration in ob/ob mice (Figures 3, 5, 6 and 7). The effect of the compound of SEQ ID NO: 9 on postprandial glucose was dose-dependent between 1-100 nmol/kg and plasma glucose AUC decreased 85.8% at 100 nmol/kg dose (Figure 3). The ED50 for the compound of SEQ ID NO: 9 was determined to be 5 nmoles/kg. The effect of the compound of SEQ ID NO: 9 on plasma glucose is also accompanied by a significant increase in postprandial insulin in these animals (Figure 4). The effect on insulin appears to be dose-dependent with a maximum increase of 187.7% in AUC at 30 nmol/kg dose (Figure 4).

[00249] The effect of the compound of SEQ ID NO: 118 on postprandial glucose was dose-dependent between 1-30 nmol/kg and plasma glucose AUC decreased 81%

at 30 nmol/kg dose (Figure 5). The ED50 for the compound of SEQ ID NO: 118 was determined to be 2.5 nmoles/kg.

[00250] The effect of the compound of SEQ ID NO: 151 on postprandial glucose was dose-dependent between 0.03 and 3 nmol/kg and plasma glucose AUC decreased 67% at 3 nmol/kg dose (Figure 6). The ED50 for the compound of SEQ ID NO: 151 was determined to be 1 nmoles/kg.

[00251] The effect of the compound of SEQ ID NO: 158 on postprandial glucose was dose-dependent between 0.1 and 10 nmol/kg and plasma glucose AUC decreased 66% at 10 nmol/kg dose (Figure 7). The ED50 for the compound of SEQ ID NO: 151 was determined to be 2 nmoles/kg.

EXAMPLE 31

Dog Pharmacokinetic Study

[00252] The pharmacokinetic parameters of the Compounds of SEQ ID NO: 9, 118, 151 and 158 were determined in male beagle dogs (n=4, 14 ± 1kg). Following an overnight fast, each animal received the Compounds of SEQ ID NO: 9, 118, 151 and 158 either as an intravenous bolus via femoral vein (67 μg/kg) or by subcutaneous injection given at near the shoulder blades (67 μg/kg). Each animal received both intravenous and subcutaneous doses with a one-week washout between doses following a crossover design. The dosing vehicle for both routes of administration was propylene glycol:pH 7.4 phosphate buffer (50:50) or 0.2 M Tris (pH 8.0). Serial blood samples were collected in EDTA-containing microcentrifuge tubes at predose, 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 24, and 30 hours post-dose after intravenous administration; at predose, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 24, and 30 hours post-dose after subcutaneous administration. Approximately 0.3 mL of blood was collected at each time point. Blood samples were immediately centrifuged at 4°C. The obtained plasma was frozen with dry ice and stored at -20°C. Plasma drug levels were determined using the LC-MS/MS assay described below.

Quantitation of the Compound of SEQ ID NO: 9 by LC-MS/MS

[00253] Plasma samples from *in vivo* dog study were prepared for analysis by precipitating plasma proteins with two volumes of acetonitrile containing an internal standard. The samples were vortex mixed and removed the precipitated proteins by centrifugation. The resulting supernatants were transferred to a 96-well plate and 10 µL were injected for analysis. Samples were prepared with the Packard Multiprobe II and Quadra 96 Liquid Handling System.

[00254] The HPLC system consisted of two Shimadzu LC10AD pumps (Columbia, MD), a CTC PAL autosampler (Leap Technologies, Switzerland). The column used was a YMC Hydrosphere C18 (2.0 x 50 mm, 3 µm) (YMC, Inc., Milford, MA). The column temperature was maintained at 50°C and the flow rate was 0.3 mL/minute. The mobile phase A consisted of 10 mM ammonium formate and 0.1% formic acid in water and mobile phase B consisted of 0.1% formic acid in acetonitrile. The initial mobile phase composition was 5% B, and remained at 5% B for one minute to equilibrate the column. The composition was ramped to 95% B over two minutes and held there for one additional minute. The mobile phase was then returned to initial conditions in one minute. Total analysis time was five minutes. A switching valve was used. The eluents between 0 – 1 minute were diverted to the waste.

[00255] The HPLC was interfaced to a Sciex API 4000 mass spectrometer, (Applied Biosystems, Foster City, CA) and was equipped with a TurboIonspray ionization source. Ultra high purity nitrogen was used as the nebulizing and turbo gas. The temperature of turbo gas was set at 300°C and the interface heater was set at 60°C. Data acquisition utilized selected reaction monitoring (SRM). Ions representing the (M+2H)2+ species for the compound of SEQ ID NO: 9, and (M+2H)2+ for BMS-501143 (IS) were selected in Q1 and were collisionally dissociated with high purity nitrogen at a pressure of 3.5 x 10-3 torr to form specific product ions which were subsequently monitored by Q3. The transitions and voltages are summarized in Table 2.

Table 4

Parameters for MS/MS Analysis of the Compound of SEQ ID NO: 9 and internal standard

	Compound of SEQ ID NO: 9	Internal Standard
SRM transition (mz)	765.1->195.2	740.7-> 210.0
Declustering Potential (V)	60	60
Collision Energy (V)	45	30

[00256] The standard curve concentrations, ranging from 1 to 1000 nM and from 4 to 5000 nM, were used for the *in vivo* samples obtained from low and high doses, respectively. The curves were fitted with a quadratic regression weighted by reciprocal concentration ($1/X_2$). Standards were analyzed in duplicate. Quality control (QC) samples, prepared in blank matrix at the same concentrations as the standard were also analyzed in each analytical set. For the compound of SEQ ID NO: 9, the calculated concentrations of more than 80% of the QCs were within 20% of nominal concentration, indicating acceptable assay performance.

Data Analysis

[00257] The compound of SEQ ID NO: 9 plasma concentration vs. time data were analyzed by noncompartmental methods using the KINETICATM software program. The Cmax and Tmax values were recorded directly from experimental observations. The AUC0-n and AUCtot values were calculated using a combination of linear and log trapezoidal summations. The total plasma clearance (CLP), terminal half life (t1/2), mean residence time (MRT), and the steady state volume of distribution (Vss) were calculated after intraarterial or intravenous administration. The total blood clearance (CLB) was calculated using the total plasma clearance and the blood to plasma concentration ratio. CLB and Vss values were compared to standard liver blood flow and total body water values, respectively, reported in the literature. The absolute subcutaneous bioavailability (expressed as %) was estimated by taking the ratio of dose-normalized AUC values after a subcutaneous dose of the compound of SEQ ID NO: 9 to that after an intravenous dose.

Dog Pharmacokinetics Results

[00258] The pharmacokinetic parameters of the compounds of SEQ ID NO: 9, 151 and 158 in male beagle dogs, following intravenous (IV) and subcutaneous (SC) administration are summarized in Tables 5A, 5B, and 5C, respectively.

[00259] The compound of SEQ ID NO: 9 exhibited low systemic clearance (1.4 ± 0.4 mL/min/kg). The steady-state volume of distribution (Vss) was 0.21 ± 0.07 L/kg, indicating limited extravascular distribution. The estimated elimination half-life was 7.1 ± 2.1 h and the mean residence time was 2.4 ± 0.5 h. The time to reach peak concentrations (Tmax) after a subcutaneous dose of 67 μg/kg occurred at 1.1 ± 0.6 h. The maximum plasma concentration (Cmax) after subcutaneous administration was 116 ± 34 nM. The subcutaneous bioavailability of Compound of SEQ ID NO: 9 in dogs was 93 ± 22 %.

Table 5A

Pharmacokinetic Parameters of the Compound of SEQ ID NO: 9 in the Dog (dosing vehicle: 0.2 M Tris, pH 8.0)

Parameter	Intravenous (n=3)	Subcutaneous (n=3, Mean ± SD)
Dose (μg/kg)	67	67
Cmax (nM)	-	116 ± 34
Tmax (h)	-	1.1 ± 0.6
AUCtot (nM×h)	529 ± 125	452 ± 153
CLp (mL/min/kg)	1.4 ± 0.4	-
Vss (L/kg)	0.21 ± 0.07	-
t1/2 (h)	7.1 ± 2.1	2.6 ± 1.2
MRT (h)	2.4 ± 0.5	3.6 ± 1.0
Bioavailability (%)	-	93 ± 22

Table 5B

Pharmacokinetic Parameters of the Compound of SEQ ID NO: 151 in the Dog

Parameter	Intravenous (n=3, Mean ± SD)	Subcutaneous (n=3, Mean ± SD)
Dose (μg/kg)	67	67
Cmax (nM)	-	252 ± 15
Tmax (h)	-	1.8 ± 0.5
AUCtot (nM×h)	1519 ± 424	1566 ± 235
CLp (mL/min/kg)	0.49 ± 0.16	-

Parameter	Intravenous (n=3, Mean ± SD)	Subcutaneous (n=3, Mean ± SD)
Vss (L/kg)	0.13 ± 0.05	-
t1/2 (h)	4.0 ± 0.2	4.4 ± 1.4
MRT (h)	4.4 ± 0.1	5.8 ± 1.0
Bioavailability (%)	-	110 ± 41

Table 5C

Pharmacokinetic Parameters of the Compound of SEQ ID NO: 158 in the Dog

Parameter	Intravenous (n=3, Mean ± SD)	Subcutaneous (n=3, Mean ± SD)
Dose (μg/kg)	67	67
Cmax (nM)	-	279 ± 82
Tmax (h)	-	1.4 ± 0.7
AUCtot (nM×h)	1385± 227	1467 ± 563
CLp (mL/min/kg)	0.51 ± 0.08	-
Vss (L/kg)	0.15 ± 0.018	-
t1/2 (h)	4.4 ± 0.4	3.9 ± 1.3
MRT (h)	4.9 ± 0.7	5.2 ± 1.5
Bioavailability (%)	-	110 ± 49

EXAMPLE 32

Parenteral routes of administration

[00260] A liquid formulation for pulmonary/inhalation or nasal delivery, having the following composition is prepared as described below.

Ingredient	Amount
11-mer peptide drug	10 mg
HCl or NaOH	To adjust pH between 5-8
SBE-cyclodextrin (Captisol)	50 mg
Purified water	q.s. to 1 ml

[00261] Weighed amounts of 11-mer peptide are dissolved in a portion of water at an optimum pH. Captisol is added to the drug solution and stirred for about 5 min. NaOH and HCl are added to adjust pH to desired value (between 5-8). Purified water is added to bring final volume to 1 ml. Other inactive ingredients such as preservatives, antioxidants, buffer salts, and cosolvents may be added as needed, prior to pH adjustment. Water is added to the desired target volume.

[00262] The above solution formulation can be administered to the lung as a fine spray with a syringe microsprayer, or an air-jet or ultrasound nebulizer. The above solution can be delivered to the nasal cavity with a metered nasal spray pump or syringe microsprayer.

[00263] A dry powder formulation for pulmonary/inhalation or nasal delivery, having the following composition is prepared as described below.

Ingredient	Amount
11-mer peptide drug	10 mg
Lactose	90 mg

[00264] Weighed amounts of 11-mer peptides, preferably with a mass median aerodynamic diameter (MMAD) of less than 5 micron, are blended with inhalation grade lactose 30-100 μm (Respitose, DMV International) in a Turbula® mixer for 5 min. The above dry powder blend can be delivered to the lung by a powder insufflator, or dry powder inhaler.

[00265] A suspension formulation for pulmonary/inhalation or nasal delivery, having the following composition is prepared as described below.

Ingredient	Amount
11-mer peptide drug	10 mg
Lecithin	0.1%
Propellant gas	1 ml

[00266] Micronized 11-mer peptides are homogeneously suspended in a mixture of lecithin and propellant gas such as hydrofluorocarbons (HFA's). The suspension is transferred to a pressurized metered dose inhaler.

11-mer peptide absorption from a solution formulation in rats

Pharmacokinetic Parameters	Intra-trachea	Intra-nasal
Dose (mg/kg)	1	0.6
AUC (nM·h)	918.9 ± 103	177 ± 77
Cmax (nM)	359 ± 50.9	236 ± 125
Tmax (h)	0.03	0.17

[00267] An 11-mer peptide was administered as a solution (described above) to male Sprague-Dawley rats anesthetized with intraperitoneal injection of pentobarbital. Drug was introduced into the trachea with a syringe microsprayer to assess pulmonary delivery or instilled with a pipettor into each nostril for intra-nasal delivery. Blood samples were collected from the cannulated carotid artery into heparinized vaccutainers over a 4 hr period. The blood samples were centrifuged, the isolated plasma stored at -80°C till analysis by LC/MS. From the plasma-time concentration curves the pharmacokinetic parameters were calculated and reported in the table. Three rats were used for each route of administration. Data is provided as a mean ± standard deviation. Tmax is reported as a median value.

UTILITIES AND COMBINATIONS

A. Utilities

[00268] The subject matter described herein provides novel 11-mer peptides which have superior properties and act as GLP-1 receptor modulators, for example such that the 11-mer peptides have agonist activity for the GLP-1 receptor. Further, the 11-mer peptides described herein exhibit increased stability to proteolytic cleavage as compared to GLP-1 native sequences.

[00269] Accordingly, compounds described herein can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating or delaying the progression or onset of diabetes (preferably Type II, impaired glucose tolerance, insulin resistance, and diabetic complications, such as nephropathy, retinopathy, neuropathy and cataracts), hyperglycemia, hyperinsulinemia, hypercholesterolemia, elevated blood levels of free fatty acids or glycerol, hyperlipidemia, hypertriglyceridemia, obesity, wound healing, tissue ischemia, atherosclerosis, hypertension, AIDS, intestinal diseases (such as necrotizing enteritis, microvillus inclusion disease or celiac disease), inflammatory bowel syndrome, chemotherapy-induced intestinal mucosal atrophy or injury, anorexia nervosa, osteoporosis, dysmetabolic syndrome, as well as inflammatory bowel disease(such as Crohn's disease and ulcerative colitis). The compounds described herein may also be utilized to increase the blood levels of high density lipoprotein (HDL).

[00270] In addition, the conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome as detailed in Johannsson J. Clin. Endocrinol. Metab., 82, 727-34 (1997), may be treated employing the compounds described herein.

B. Combinations

[00271] The subject matter described and claimed herein includes pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of Formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, the compounds described herein can be used alone, in combination with other compounds described herein, or in combination with one or more other therapeutic agent(s), *e.g.*, an antidiabetic agent or other pharmaceutically active material.

[00272] The compounds described herein may be employed in combination with other GLP-1 receptor modulators (*e.g.*, agonists or partial agonists, such as a peptide agonist) or other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents; anti-hyperglycemic agents; hypolipidemic/lipid lowering agents; anti-obesity agents (including appetite suppressants/modulators) and anti-hypertensive agents. In addition, the compounds described herein may be combined with one or more of the following therapeutic agents; infertility agents, agents for treating polycystic ovary syndrome, agents for treating growth disorders, agents for treating frailty, agents for treating arthritis, agents for preventing allograft rejection in transplantation, agents for treating autoimmune diseases, anti-AIDS agents, anti-osteoporosis agents, agents for treating immunomodulatory diseases, antithrombotic agents, agents for the treatment of cardiovascular disease, antibiotic agents, anti-psychotic agents, agents for treating chronic inflammatory bowel disease or syndrome and/or agents for treating anorexia nervosa.

[00273] Examples of suitable anti-diabetic agents for use in combination with the compounds described herein include biguanides (*e.g.*, metformin or phenformin), glucosidase inhibitors (e.g,. acarbose or miglitol), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (*e.g.*, repaglinide), sulfonylureas

(*e.g.*, glimepiride, glyburide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide combinations (*e.g.*, Glucovance®), thiazolidinediones (*e.g.*, troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2), DPP-IV inhibitors, and SGLT2 inhibitors.

[00274] Other suitable thiazolidinediones include Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi).

[00275] Suitable PPAR alpha/gamma dual agonists include muraglitazar (Bristol-Myers Squibb), AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation – Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), and in U.S. application Serial No. 09/644,598, filed September 18, 2000, the disclosure of which is incorporated herein by reference, employing dosages as set out therein, which compounds designated as preferred are preferred for use herein.

[00276] Suitable aP2 inhibitors include those disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. application Serial No. 09/519,079, filed March 6, 2000, employing dosages as set out herein.

[00277] Suitable DPP4 inhibitors that may be used in combination with the compounds described herein include those disclosed in WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) as disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999, LAF237, saxagliptin, MK0431, TSL-225 (tryptophyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cyanopyrrolidides and 4- cyanopyrrolidides, as disclosed by Ashworth et al, Bioorg. &

Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) employing dosages as set out in the above references.

[00278] Suitable meglitinides include nateglinide (Novartis) or KAD1229 (PF/Kissei).

[00279] Examples of other suitable glucagon-like peptide-1 (GLP-1,) compounds that may be used in combination with the GLP-1 receptor modulators (*e.g.*, agonists or partial agonists) described herein include GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener), as well as AC2993 (Amylin), LY-315902 (Lilly) and NN2211 (Novo Nordisk).

[00280] Examples of suitable hypolipidemic/lipid lowering agents for use in combination with the compounds described herein include one or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na+/bile acid cotransporter inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, cholesterol ester transfer protein inhibitors (*e.g.*, CP-529414 (Pfizer)) and/or nicotinic acid and derivatives thereof.

[00281] MTP inhibitors which may be employed as described above include those disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Patent No. 5,962,440, all of which are incorporated by reference herein.

[00282] The HMG CoA reductase inhibitors which may be employed in combination with one or more compounds of Formula I include mevastatin and related compounds, as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds, as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds, such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds, as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin, as disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin, as disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, atavastatin (Nissan/Sankyo's nisvastatin (NK-104)), as disclosed in U.S. Patent No. 5,011,930,

visastatin (Shionogi-Astra/Zeneca (ZD-4522)), as disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives, as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof, as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives, as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes, such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin), as disclosed in European Patent Application No.0142146 A2, and quinoline and pyridine derivatives, as disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

[00283] Desired hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin and ZD-4522.

[00284] In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase, such as those disclosed in GB 2205837, are suitable for use in combination with the compounds described herein.

[00285] The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinyl-methyl)phosphonates, as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

[00286] In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al,

J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

[00287] The fibric acid derivatives which may be employed in combination with one or more compounds of Formula I include fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds, as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants, such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives, such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes, such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

[00288] The ACAT inhibitor which may be employed in combination with one or more compounds of Formula I include those disclosed in Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem.

(1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd).

[00289] The hypolipidemic agent may be an upregulator of LD2 receptor activity, such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

[00290] Examples of suitable cholesterol absorption inhibitor for use in combination with the compounds described herein include SCH48461 (Schering-Plough), as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

[00291] Examples of suitable ileal Na+/bile acid cotransporter inhibitors for use in combination with the compounds described herein include compounds as disclosed in Drugs of the Future, 24, 425-430 (1999).

[00292] The lipoxygenase inhibitors which may be employed in combination with one or more compounds of Formula I include 15-lipoxygenase (15-LO) inhibitors, such as benzimidazole derivatives, as disclosed in WO 97/12615, 15-LO inhibitors, as disclosed in WO 97/12613, isothiazolones, as disclosed in WO 96/38144, and 15-LO inhibitors, as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

[00293] Examples of suitable anti-hypertensive agents for use in combination with the compounds described herein include beta adrenergic blockers, calcium channel blockers (L-type and T-type; *e.g.* diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (*e.g.*, chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors,

ACE inhibitors (*e.g.*, captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (*e.g.*, losartan, irbesartan, valsartan), ET receptor antagonists (*e.g.*, sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (*e.g.*, compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (*e.g.*, omapatrilat and gemopatrilat), and nitrates.

[00294] Examples of suitable anti-obesity agents for use in combination with the compounds described herein include a NPY receptor antagonist, a NPY-Y2 or NPY-Y4 receptor agonist, Oxyntomodulin, a MCH antagonist, a GHSR antagonist, a CRH antagonist, a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta drug, a CB-1 antagonist and/or an anorectic agent.

[00295] The beta 3 adrenergic agonists which may be optionally employed in combination with compounds described herein include AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer,) or other known beta 3 agonists, as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

[00296] Examples of lipase inhibitors which may be optionally employed in combination with compounds described herein include orlistat or ATL-962 (Alizyme), with orlistat being preferred.

[00297] The serotonin (and dopamine) reuptake inhibitor which may be optionally employed in combination with a compound of Formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

[00298] Examples of thyroid receptor beta compounds which may be optionally employed in combination with compounds described herein include thyroid receptor ligands, such as those disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio) and WO 00/039077 (KaroBio), with compounds of the KaroBio applications being preferred.

[00299] Examples of CB-1 antagonists which may be optionally employed in combination with compounds described herein include CB-1 antagonists and rimonabant (SR141716A).

[00300] Examples of NPY-Y2 and NPY-Y4 receptor agonists include PYY(3-36) and Pancreatic Polypeptide (PP), respectively.

[00301] The anorectic agent which may be optionally employed in combination with compounds described herein include dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

[00302] Examples of suitable anti-psychotic agents include clozapine, haloperidol, olanzapine (Zyprexa®), Prozac® and aripiprazole (Abilify®).

[00303] The aforementioned patents and patent applications are incorporated herein by reference.

[00304] The above other therapeutic agents, when employed in combination with the compounds described herein may be used, for example, in those amounts indicated in the Physician's Desk Reference, as in the patents set out above or as otherwise determined by one of ordinary skill in the art.

DOSAGE AND FORMULATION

[00305] A suitable 11-mer peptide of Formula I can be administered to patients to treat diabetes and other related diseases as the compound alone and or mixed with an acceptable carrier in the form of pharmaceutical formulations. Those skilled in the art of treating diabetes can easily determine the dosage and route of administration of the compound to mammals, including humans, in need of such treatment. The route of administration may include but is not limited to oral, intraoral, rectal, transdermal, buccal, intranasal, pulmonary, subcutaneous, intramuscular, intradermal, sublingual, intracolonic, intraoccular, intravenous, or intestinal administration. The compound is formulated according to the route of administration based on acceptable pharmacy practice (Fingl et al., in "The Pharmacological Basis of Therapeutics", Ch. 1, p.1, 1975; "Remington's Pharmaceutical Sciences", 18th ed., Mack Publishing Co, Easton, PA, 1990).

[00306] The pharmaceutically acceptable 11-mer peptide compositions described herein can be administered in multiple dosage forms such as tablets, capsules (each of

which includes sustained release or timed release formulations), pills, powders, granules, elixirs, in situ gels, microspheres, crystalline complexes, liposomes, micro-emulsions, tinctures, suspensions, syrups, aerosol sprays and emulsions. The compositions described herein can also be administered in oral, intravenous (bolus or infusion), intraperitoneal, subcutaneous, transdermally or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. The compositions may be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[00307] The dosage regimen for the compositions described herein will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the disease state.

[00308] By way of general guidance, the daily oral dosage of the active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 0.6 to 20 mg/kg/day. Intravenously, the daily dosage of the active ingredient when used for the indicated effects will range between 0.001ng to 100.0 ng per min/per Kg of body weight during a constant rate infusion. Such constant intravenous infusion can be preferably administered at a rate of 0.01 ng to 50 ng per min per Kg body weight and most preferably at 0.01 ng to 10.0 mg per min per Kg body weight. The compositions described herein may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily. The compositions described herein may also be administered by a depot formulation that will allow sustained release of the drug over a period of days/weeks/months as desired.

[00309] The compositions described herein can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using

transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

[00310] The compositions are typically administered in a mixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, aerosol sprays generated with or without propellant and syrups, and consistent with conventional pharmaceutical practices.

[00311] For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as but not limited to, lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, and sorbitol; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as, but not limited to, ethanol, glycerol, and water. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include, but not limited to, starch, gelatin, natural sugars such as, but not limited to, glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, and waxes. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, and sodium chloride. Disintegrants include, but are not limited to, starch, methyl cellulose, agar, bentonite, and xanthan gum.

[00312] The compositions described herein may also be administered in the form of mixed micellar or liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. Permeation enhancers may be added to enhance drug absorption.

[00313] Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*i.e.*, solubility, bioavailability, manufacturing, etc.) the compounds described herein may be delivered in prodrug form. Thus, the subject matter

described herein is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same, and compositions containing the same.

[00314] The compositions described herein may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinyl-pyrrolidone, pyran copolymer, polyhydroxypropyl- methacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compositions described herein may be combined with a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

[00315] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 0.01 milligram to about 500 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

[00316] Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivative, magnesium stearate, and stearic acid. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[00317] Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

[00318] In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solution for parenteral administration preferably contains a water-soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable

stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

[00319] Suitable pharmaceutical carriers are described in Remington: "The Science and Practice of Pharmacy", Nineteenth Edition, Mack Publishing Company, 1995, a standard reference text in this field

[00320] Representative useful pharmaceutical dosage forms for administration of the compounds described herein can be illustrated as follows:

Capsules

[00321] A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

[00322] A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

[00323] Tablets may be prepared by conventional procedures so that the dosage unit, for example is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

[00324] An injectable formulation of an 11-mer peptide composition described herein may or may not require the use of excipients such as those that have been approved by regulatory bodies. These excipients include, but are not limited to,

solvents and co-solvents, solubilizing, emulsifying or thickening agents, chelating agents, anti-oxidants and reducing agents, antimicrobial preservatives, buffers and pH adjusting agents, bulking agents, protectants and tonicity adjustors and special additives. An injectable formulation has to be sterile, pyrogen free and, in the case of solutions, free of particulate matter.

[00325] A parenteral composition suitable for administration by injection may be prepared by stirring for example, 1.5% by weight of active ingredient in a pharmaceutically acceptable buffer that may or may not contain a co-solvent or other excipient. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

[00326] An aqueous suspension can be prepared for oral and/or parenteral administration so that, for example, each 5 mL contains 100 mg of finely divided active ingredient, 20 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin or other palatable flavoring.

Biodegradable Microparticles

[00327] A sustained-release parenteral composition suitable for administration by injection may be prepared, for example, by dissolving a suitable biodegradable polymer in a solvent, adding to the polymer solution the active agent to be incorporated, and removing the solvent from the matrix thereby forming the matrix of the polymer with the active agent distributed throughout the matrix.

[00328] Numerous modifications and variations of the subject matter described and claimed herein are possible in light of the above teachings. It is therefore understood that within the scope of the appended claims, the subject matter recited in the claims may be practiced otherwise than as specifically described herein.

[00329] The subject matter recited in the claims is not to be limited in scope by the specific embodiments described that are intended as single embodiments of the claimed subject matter. Functionally equivalent methods and components in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are

intended to fall within the scope of the appended claims. All references cited herein are hereby incorporated by reference in their entirety.

WHAT IS CLAIMED IS:

1. An isolated polypeptide comprising a sequence of Formula I:

X_{aa1}-X_{aa2}-X_{aa3}-X_{aa4}-X_{aa5}-X_{aa6}-X_{aa7}-X_{aa8}-X_{aa9}-X_{aa10}-X_{aa11}

Formula I

wherein,

X_{aa1} is a naturally or nonnaturally occurring amino acid comprising an imidazole or thiazole ring, such as histidine or thiazolylalanine; wherein any of the carbon atoms of said amino acid are optionally substituted with hydrogen with one or more alkyl groups, or with one or more halo groups; wherein the free amino group of said amino acid may be replaced with a hydroxyl group or is optionally substituted with hydrogen, alkyl, acyl, benzoyl, alkyloxycarbonyl, methyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heterocyclyloxycarbonyl, heteroarylalkyloxycarbonyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, heterocyclylsulfonyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, heteroarylalkylsulfonyl or heteroarylsulfonyl;

and wherein the amino group of X_{aa1} is optionally absent, such that X_{aa1} is des-amino acid of histidine or thiazolylalanine in which any of the carbon atoms are optionally substituted with alkyl, halo, or hydroxyl groups;

X_{aa2} is naturally or nonnaturally occurring amino acid selected from the group consisting of α-amino-isobutyric acid (Aib); (L)-alanine, D-Alanine, N-methyl-L-Alanine, N-methyl-D-Alanine, (L)-proline, (S)-α-methyl-proline [α-Me-Pro], (L)-azetidine (Azt), (S)-α-methyl-azetidine (α-Me-Azt), (L)-valine, and (R)- or (S)-isovaline, and wherein the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

X_{aa3} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which contains a carboxylic acid, for example aspartic acid or glutamic acid; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

X_{aa4} is glycine;

X_{aa5} is a naturally or nonnaturally occurring amino acid selected from the group consisting of (L)-threonine, (L)-allo-threonine, (L)-serine, (L)-norvaline, (L)-norleucine; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups or halo groups;

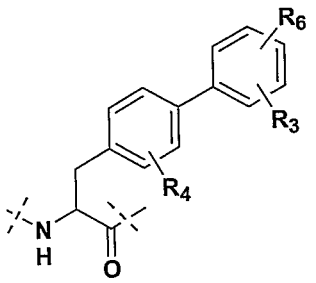
X_{aa6} is a naturally or nonnaturally occurring amino acid comprising an alpha carbon which is disubstituted; wherein one of the side chains of said amino acid contains an aromatic or heteroaromatic ring, for example alpha-methyl-phenylalanine, alpha-methyl-2-fluorophenylalanine, and alpha-methyl-2,6-difluorophenylalanine, wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl groups; and wherein any of the carbon atoms of said amino acid are optionally substituted with one or more halo groups;

X_{aa7} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which is substituted with a hydroxyl group, for example L-threonine or L-allo-threonine; wherein any of the carbon atoms of said amino acid are optionally substituted with one or more alkyl or halo groups;

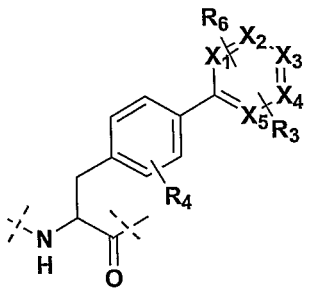
X_{aa8} is a naturally or nonnaturally occurring amino acid selected from the group consisting of L-serine, L-histidine and L-asparagine; wherein one or more of the carbon atoms of said amino acid is optionally substituted with one or more alkyl groups or halo groups;

X_{aa9} is a naturally or nonnaturally occurring amino acid comprising an amino acid side chain which contains a carboxylic acid, for example L-aspartic acid or L-glutamic acid; wherein one or more of the carbon atoms of said amino acid is optionally substituted with one or more alkyl or halo groups;

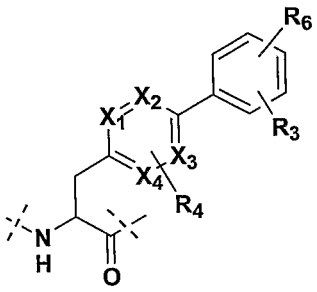
X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II, III, or IV;



Formula II



Formula III



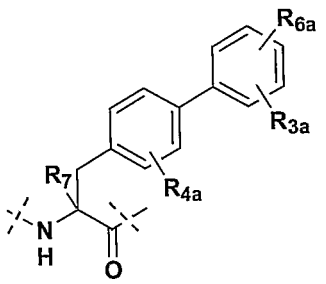
Formula IV

wherein R_3, R_4 and R_6 are each selected from the group consisting of hydrogen, alkyl, methyl, ethyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxyalkyl, cyano, amino, aminoalkyl, carboxyl, carboxyalkyl, alkoxy, methoxy, aryloxy, carboxamides, substituted carboxamides, alkyl esters, aryl esters, alkyl sulfonyl, and aryl sulfonyl;

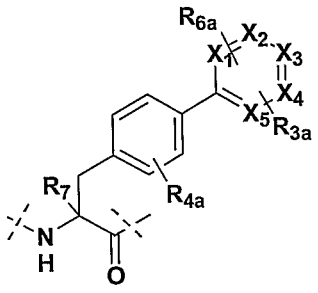
and

wherein X_1, X_2, X_3, X_4, and X_5 are each C or N, with the proviso that at least one of X_1, X_2, X_3, X_4, and X_5 is N;

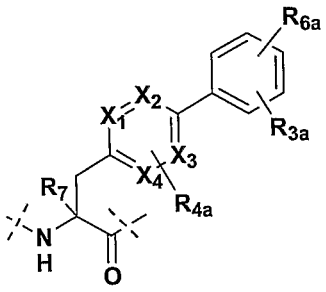
X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IIa, IIIa, or IVa;



Formula IIa



Formula IIIa



Formula IVa

wherein the C-terminal carbonyl carbon of said amino acid is attached to a nitrogen to form a carboxamide (NH_2), an alkyl carboxamide (NHR_1), or a dialkylcarboxamide (NR_1R_2);

wherein each of R_1 and R_2 is an alkyl or arylalkyl group;

wherein R_{3a}, R_{4a} and R_{6a} are each selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, halogen, hydroxyl, hydroxyalkyl, cyano, amino, aminoalkyl, carboxyl, carboxyalkyl, alkoxy, methoxy, aryloxy, carboxamides, substituted carboxamides, alkyl esters, aryl esters, alkyl sulfonyl, and aryl sulfonyl;

wherein R_7 is selected from the group consisting of hydrogen, methyl, and ethyl;

wherein X_1, X_2, X_3, X_4, and X_5 are each C or N, with the proviso that at least one of X_1, X_2, X_3, X_4, and X_5 is N; and

wherein X_{aa11} is not an amino acid of Formula IIa when X_{aa10} is an amino acid of Formula II.

2. The isolated polypeptide of Claim 1, wherein X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II.

3. The isolated polypeptide of Claim 1, wherein X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula III.

4. The isolated polypeptide of Claim 1, wherein X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IVa.

5. The isolated polypeptide of Claim 1, wherein said X_{aa1} is selected from the group consisting of L-His, D-His, L-N-Methyl-His, D-N-Methyl-His, L-4-ThiazolylAla, D-4-ThiazolylAla, des-amino-His, des-amino-thiazolylAla, 3-(1H-imidazol-4-yl)-2-methylpropanoyl, (S)-3-(1H-imidazol-4-yl)-2-hydroxypropanoyl (L-β-imidazolelactyl); and

wherein if a terminal amino group is present, said terminal amino group is optionally substituted with hydrogen, alkyl, dialkyl, acyl, benzoyl, alkyloxycarbonyl methyloxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, heterocyclyloxycarbonyl, heteroarylalkyloxycarbonyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, heterocyclylsulfonyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, heteroarylalkylsulfonyl or heteroarylsulfonyl.

6. The isolated polypeptide of Claim 1, wherein said X_{aa2} is selected from the group consisting of L-Ala, D-Ala, N-methyl-L-Ala, N-methyl-D-Ala, L-Pro, (S)-α-methyl-L-Pro (α-Me-Pro), (L)-azetidine (Azt), (S)-α-methyl-azetidine (α-Me-Azt) and α-aminoisobutyric (Aib).

7. The isolated polypeptide of Claim 1, wherein said X_{aa3} is selected from the group consisting of L-Glu, L-Asp, and L-Gla.

8. The isolated polypeptide of Claim 1, wherein said X_{aa4} is Gly.

9. The isolated polypeptide of Claim 1, wherein said X_{aa5} is selected from the group consisting of L-Thr, L-Nle, L-Nva, L-Aoc and L-allo-Thr.

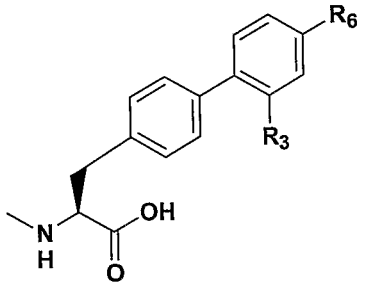
10. The isolated polypeptide of Claim 1, wherein said X_{aa6} is selected from the group consisting of L-α-Me-Phe, L-α-Et-Phe, L-α-Me-2-fluoro-Phe, L-α-Me-3-fluoro-Phe, L-α-Me-2,3-di-fluoro-Phe, L-α-Me-2,6-di-fluoro-Phe, and L-α-Me-Phe(penta-Fluoro).

11. The isolated polypeptide of Claim 1, wherein said X_{aa7} is L-Thr or L-allo-threonine.

12. The isolated polypeptide of Claim 1, wherein said X_{aa8} is selected from the group consisting of L-Ser, L-His, and L-Asn.

13. The isolated polypeptide of Claim 1, wherein said X_{aa9} is L-Asp.

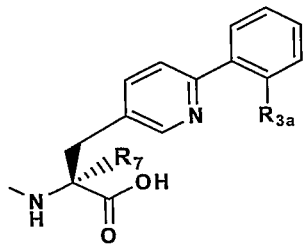
14. The isolated polypeptide of Claim 1, wherein X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II, further defined by Formula VI:



wherein, R_3 is selected from the group consisting of alkyl and halogen; and R_6 is selected from the group consisting of hydroxyl and methoxy.

15. The isolated polypeptide of Claim 2, wherein said naturally or nonnaturally occurring amino acid of Formula II is selected from the group consisting of 4-[(4'-methoxy-2'-ethyl)-phenyl]phenylalanine; 4-[(4'-ethoxy-2'-ethyl)phenyl]phenylalanine; 4-[(4'-methoxy-2'-methyl) phenyl] phenylalanine; 4-[(4'-ethoxy-2'-methyl)phenyl]phenylalanine; 4-(2'-ethylphenyl)phenylalanine; 4-(2'-methylphenyl)phenylalanine; 4-[(3',5'-dimethyl)phenyl]phenylalanine, 4-[(3',4'-dimethoxy)phenyl]phenylalanine; and 4-[(2'-ethyl-4'-hydroxy)-phenyl]phenylalanine.

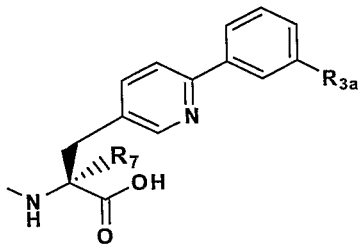
16. The isolated polypeptide of Claim 1, wherein X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IVa, further defined by Formula VIa:



Formula VIa

wherein, R_{3a} is selected from the group consisting of methyl, ethyl and fluoro; and wherein R_7 is selected from the group consisting of hydrogen and methyl.

17. The isolated polypeptide of Claim 1, wherein X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IVa, further defined by Formula VIIa:



Formula VIIa

wherein R_{3a} is methoxy; and

R_7 is selected from the group consisting of hydrogen and methyl.

18. The isolated polypeptide of Claim 3, wherein said naturally or nonnaturally occurring amino acid of Formula III is selected from the group consisting of 4-[2'-(4'-methoxy-6'-ethyl)pyridyl]phenylalanine; 4-[2'-(4'-methoxy-6'-methyl)pyridyl]-4-phenylalanine; 4-[2'-(6'-ethyl)pyridyl]phenylalanine; 4-[2'-(6'-methyl)pyridyl]phenylalanine; 4-[2'-(3',5'-dimethyl)pyridyl]phenylalanine; 4-[2'-(4'-methoxy-6'-ethyl)pyridyl]phenylalanine; 4-[3'-(4'-methoxy-6'-methyl)pyridyl]phenylalanine; 4-[3'-(2'-ethyl)pyridyl]phenylalanine; and 4-[3'(6'-methyl)pyridyl)phenylalanine.

19. The isolated polypeptide of Claim 1, wherein said X_{aa10} is a naturally or nonnaturally occurring amino acid of said Formula IV.

20. The isolated polypeptide of Claim 19, wherein said naturally or nonnaturally occurring amino acid of Formula IV is selected from the group consisting of 4-[(4'-methoxy-2'-ethyl)phenyl]-3-pyridylalanine; 4-[(4'-methoxy-2'-methyl)phenyl]-3-pyridylalanine; 4-(2'-ethylphenyl)-3-pyridylalanine; 4-(2'-methylphenyl)-3-pyridylalanine; 4-[(3',5'-dimethyl)phenyl]-3-pyridylalanine and 4-[(2'-ethyl-4'-hydroxy)phenyl]-3-pyridylalanine.

21. The isolated polypeptide of Claim 1, wherein said X_{aa11} is a naturally or nonnaturally occurring amino acid of said Formula IIa.

22. The isolated polypeptide of Claim 21, wherein said naturally or nonnaturally occurring amino acid of Formula IIa is selected from the group consisting of 4-(2'-methylphenyl)phenylalanine; 4-(2'-fluorophenyl)phenylalanine; 4-(2'-chlorophenyl)phenylalanine; 4-[(3',4'-dimethoxy)phenyl]phenylalanine; and 4-[(3',5'-dimethyl)phenyl]phenylalanine;

wherein the C-terminal carbonyl carbon of said amino acid is attached to a nitrogen to form a carboxamide (NH_2), an alkyl carboxamide (NHR_1) or a dialkylcarboxamide (NR_1R_2), where each of R_1 and R_2 is an alkyl or arylalkyl group;

wherein R_7 is chosen from the group consisting of hydrogen and methyl.

23. The isolated polypeptide of Claim 1, wherein said X_{aa11} is a naturally or nonnaturally occurring amino acid of said Formula IIIa.

24. The isolated polypeptide of Claim 23, wherein said naturally or nonnaturally occurring amino acid of Formula IIIa is selected from the group consisting of 4-[(6'-methyl)-2'-pyridyl]phenylalanine; 4-[(6'-methyl)-3'-pyridyl]phenylalanine; 4-[(6'-ethyl)-2'-pyridyl)]phenylalanine; and 4-[(6'-ethyl)-3'-pyridyl)]phenylalanine;

wherein the C-terminal carbonyl carbon of said amino acid is attached to a nitrogen to form a carboxamide (NH_2), an alkyl carboxamide (NHR_1) or a dialkylcarboxamide (NR_1R_2), where each of R_1 and R_2 is an alkyl or arylalkyl group;

wherein R_7 is chosen from the group consisting of hydrogen and methyl.

25. The isolated polypeptide of Claim 4, wherein said naturally or nonnaturally occurring amino acid of Formula IVa is selected from the group consisting of 4-(2'-methylphenyl)-3-pyridylalanine; 4-(2'-fluorophenyl)-3-pyridylalanine; 4-[(3',5'-dimethyl)phenyl]-3-pyridylalanine; 4-(4'-trifluoromethylphenyl)-3-pyridylalanine; and 4-(2'-ethylphenyl)-3-pyridylalanine.

26. The isolated polypeptide of Claim 1, wherein:

X_{aa1} is an amino acid selected from the group consisting of L-His, D-His, L-N-Methyl-His, D-N-Methyl-His, L-α-methyl-His, D-α-methyl-His, L-4-Thiazolylalanine, D-4-Thiazolylalanine, des-amino-His, des-amino-thiazolylalanine, 3-(1H-imidazol-4-yl)-2-methylpropanoyl, (S)-3-(1H-imidazol-4-yl)-2-hydroxypropanoyl (L-β-imidazolelactyl);

wherein if a terminal amino group is present, said terminal amino group is optionally substituted with hydrogen, alkyl, acyl, benzoyl, alkyloxycarbonyl (e.g., methyloxycarbonyl), aryloxycarbonyl, aralkyloxycarbonyl, heterocyclyloxycarbonyl, heteroarylalkyloxycarbonyl, alkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, heterocyclylsulfonyl, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, heteroarylalkylsulfonyl or heteroarylsulfonyl;

X_{aa2} is an amino acid selected from the group consisting of L-Ala, D-Ala, N-methyl-L-Ala, N-methyl-D-Ala, L-Pro, (S)-α-methyl-proline [α-Me-Pro], (L)-azetidine (Azt), (S)-α-methyl-azetidine (α-Me-Azt),, and aminoisobutyric (Aib);

X_{aa3} is an amino acid selected from the group consisting of L-Glu, L-Asp, and L-Gla;

X_{aa4} is an amino acid selected from the group consisting of Gly;

X_{aa5} is an amino acid selected from the group consisting of L-Thr, L-Nle, L-Nva, L-Aoc and L-allo-Thr;

X_{aa6} is an amino acid selected from the group consisting of L-α-Me-Phe, L-α-Et-Phe, L-α-Me-2-fluoro-Phe, L-α-Me-3-fluoro-Phe, L-α-Me-2,3-di-fluoro-Phe, L-α-Me-2,6-di-fluoro-Phe, and L-α-Me-Phe(penta-Fluoro)

X_{aa7} is an amino acid selected from the group consisting of L-Thr and L-allo-threonine;

X_{aa8} is an amino acid selected from the group consisting of L-Ser, L-His, and L-Asn;

X_{aa9} is L-Asp;

X_{aa10} is a naturally or nonnaturally occurring amino acid selected from the group consisting of amino acids of Formulas II, III, and IV

wherein Formula II is an amino acid selected from the group consisting of 4-[(4'-methoxy-2'-ethyl)phenyl]phenylalanine; 4-[(2'-ethyl-4'-hydroxy)phenyl]phenylalanine;4-[(4'-ethoxy-2'-ethyl)phenyl]phenylalanine; 4-[(4'-methoxy-2'-methyl)phenyl]phenylalanine; 4-[(4'-ethoxy-2'-methyl)phenyl]phenylalanine; 4-(2'-ethylphenyl)phenylalanine; 4-(2'-methylphenyl)phenylalanine; 4-[(3',5'-dimethyl)phenyl]phenylalanine and 4-[(3',4'-dimethoxy)phenyl]phenylalanine;

wherein Formula III is an amino acid selected from the group consisting of 4-[2'-(4'-methoxy-6'-ethyl)pyridyl]phenylalanine; 4-[2'-(4'-methoxy-6'-methyl)pyridyl]-4-phenylalanine; 4-[2'-(6'-ethyl)pyridyl]phenylalanine; 4-[2'-(6'-methyl)pyridyl]phenylalanine; 4-[2'-(3',5'-dimethyl)pyridyl]phenylalanine; 4-[2'-(4'-methoxy-6'-ethyl)pyridyl]phenylalanine; 4-[3'-(4'-methoxy-6'-methyl)pyridyl]phenylalanine; 4-[3'-(2'-ethyl)pyridyl]phenylalanine; and 4-[3'-(6'-methyl)pyridyl)phenylalanine;

wherein Formula IV is an amino acid selected from the group consisting of 4-[(4'-methoxy-2'-ethyl)phenyl]-3-pyridylalanine; 4-[(4'-methoxy-2'-methyl)phenyl]-3-pyridylalanine; 4-(2'-ethylphenyl)-3-pyridylalanine; 4-(2'-methylphenyl)-3-pyridylalanine; and 4-[(3',5'-dimethyl)phenyl]-3-pyridylalanine;

and

X_{aa11} is a naturally or nonnaturally occurring amino acid selected from the group consisting of amino acids of Formulas IIa, IIIa, and IVa;

wherein Formula IIa is an amino acid selected from the group consisting of 4'-(2-methylphenyl)phenylalanine; 4'-(2'-fluorophenyl)phenylalanine; and 4-[(3',5'-dimethyl)phenyl]phenylalanine;

wherein Formula IIIa is an amino acid selected from the group consisting of 4-(6'-methyl-2'-pyridyl)phenylalanine; 4-(6'-methyl-2'-pyridyl)phenylalanine; 4-(6'-ethyl-2'-pyridyl)phenylalanine; and 4-(6'-ethyl-3'-pyridyl)phenylalanine;

wherein Formula IVa is an amino acid selected from the group consisting of 4-(2'-methylphenyl)-3-pyridylalanine; 4-(2'-fluorophenyl-3-pyridylalanine; 4-[(3',5'-dimethyl)phenyl]-3-pyridylalanine; 4-(4'-trifluoromethylphenyl)-3-pyridylalanine; and 4-(2'-ethylphenyl)-3-pyridylalanine;

wherein the C-terminal carbonyl carbon is attached to a nitrogen to form a carboxamide (NH_2), an alkyl carboxamide (NHR_1), or a dialkylcarboxamide (NR_1R_2), where each of R_1 and R_2 is an alkyl or arylalkyl group;

wherein R_7 is chosen from the group consisting of hydrogen and methyl, and

wherein X_{aa11} is not an amino acid of formula IIa when X_{aa10} is an amino acid of Formula II.

27. An isolated polypeptide of Claim 1, selected from the group consisting of

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
1.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me)	4-(2'-pyridyl) Phenylalanine-NH_2
2.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(3',5'-di-Me)	4-(2'-pyridyl)Phenylalanine-NH_2
3.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-OBu)	4-(2'-pyridyl)Phenylalanine-NH_2
4.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me)	4-(4'-pyridyl)Phenylalanine-NH_2
5.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Cl)	4-(4'-pyridyl)Phenylalanine-NH_2
6.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-methoxy-5'-iso-propyl)	4-(4'-pyridyl)Phenylalanine-NH_2
7.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(2'-Ethylphenyl)-3-pyridylalanine	Bip(2'-Me)-NH_2
8.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[(2'-Ethyl-4'-methoxy)phenyl]-3-pyridylalanine	Bip(2'-Me)-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
9.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
10.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
11.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
12.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
13.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
14.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
15.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Methyl)pyridyl)]phenylalanine-NH_2
16.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Methyl)pyridyl)]phenylalanine-NH_2
17.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-Pyridazyl)phenylalanine-NH_2
18.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-Pyridazyl)phenylalanine-NH_2
19.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3-(4-Me,6-OMe)pyridyl)] phenylalanine-NH_2
20.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3-(4'-Methyl)pyridyl)] phenylalanine	Bip(2'-Me)-NH_2
21.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me)-NH_2
22.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me)-NH_2
23.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[2(1H)Pyridonyl]phenylalanine-NH_2
24.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(8-Quinoline)-NH_2
25.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(3-Quinoline)-NH_2
26.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(6-Quinoline)-NH_2
27.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	Bip(5-Quinoline)-NH_2
28.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-(6-OMe)pyridyl)phenylalanine-NH_2
29.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3-(2-Methoxy)pyridyl)phenylalanine-NH_2
30.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-pyridyl)phenylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
31.	Des-NH_2-His	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
32.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(5-Quinoline)phenylalanine	Bip(2'-Me)-NH_2
33.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[3-(2'-OMe)pyridyl]phenylalanine	Bip(2'-Me)-NH_2
34.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(6-Quinoline)phenylalanine	Bip(2'-Me)-NH_2
35.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-(4'-pyridyl)phenylalanine	Bip(2'-Me)-NH_2
36.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	4-[4'-(3',5'-dimethylisoxazole)]phenylalanine	Bip(2'-Me)-NH_2
37.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2-trifluoromethylphenyl)-3-pyridylalanine-NH_2
38.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2-methyl-5-fluorophenyl)-3-pyridylalanine-NH_2
39.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4-methanesulfonylphenyl)-3-pyridylalanine-NH_2
40.	H	Aib	E	G	T	L-α-Me-Phe	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
41.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
42.	H	Aib	E	G	Nle	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
43.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-Cl, 4'-CF3)-3'-pyridyl]phenylalanine-NH_2
44.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[3'-(2'-CN-6'-Me)pyridyl]phenylalanine-NH_2
45.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Cl)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
46.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2',4'-di-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
47.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(3'-pyridyl)phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
48.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(4'-pyridyl)phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
49.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Me-3'-F)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
50.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-F)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
51.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(2'-Cl-6'-CF3)pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
52.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(2'-Cl)-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
53.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(3'-Cl-4'-F)-NH_2
54.	H	Aib	E	G	Nva	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
55.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	Bip(3',5'-di-Me)-NH_2
56.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-(2',3'-pyridazyl)phenylalanine-NH_2
57.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-ethylphenyl)-3-pyridylalanine-NH_2
58.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-[3'-(2'-Cl-6'-CF3)pyridyl]phenylalanine-NH_2
59.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-(2'-ethylphenyl)-3-pyridylalanine	4-[3'-(2'-CN-6'-Me)pyridyl]phenylalanine-NH_2
60.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Cl)-NH_2
61.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(3'-Cl-4'-F)-NH_2
62.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(3',5'-di-Me)-NH_2
63.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Me-4'-OMe)-NH_2
64.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-Me-3'-F)-NH_2
65.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Me)pyridyl]phenylalanine	Bip(2'-F)-NH_2
66.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Cl)-NH_2
67.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(3',4'-di-OMe)-NH_2
68.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	4-(2'-pyridyl)phenylalanine-NH_2
69.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	Bip(2'-Me-4'-OMe)-NH_2
70.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[(4'-Me-6'-OMe)-3-pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
71.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-ethylphenyl)-3-pyridylalanine-NH_2
72.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	4-[3'-(4'-Methyl)pyridyl]phenylalanine	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
73.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-pyridyl)-phenylalanine-NH_2
74.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-quinoline)phenylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
75.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-(2'-Methoxy)pyridyl)phenylalanine-NH_2
76.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-phenyl-3-pyridylalanine-NH_2
77.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-dimethylphenyl)-3-pyridylalanine-NH_2
78.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3'-chloro-4'-fluoro)phenyl]-3-pyridylalanine-NH_2
79.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3',4'-dimethoxy)phenyl]-3-pyridylalanine-NH_2
80.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-ethyl-4'-methoxy)phenyl)]-3-pyridylalanine-NH_2
81.	L-β-Imidazole-lactyl	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
82.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-(5-o-Tolyl)thienylalanine-NH_2
83.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3'-Methoxy)phenyl]thienylalanine-NH_2
84.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3',5'-di-Methyl)phenyl]thienylalanine-NH_2
85.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	2-[(5-(3'-Cl,5'-F)phenyl]thienylalanine-NH_2
86.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Isopropoxyphenyl)-3-pyridylalanine-NH_2
87.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 5'-Fluoro)phenyl)-3-pyridylalanine-NH_2
88.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Isopropoxyphenyl)-3-pyridylalanine-NH_2
89.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	3-(4-Br)pyridylalanine-NH_2
90.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Methoxyphenyl)-3-pyridylalanine-NH_2
91.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 4'-Fluoro)phenyl)-3-pyridylalanine-NH_2
92.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
93.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Trifluoromethoxyphenyl)-3-pyridylalanine-NH_2
94.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Trifluoromethoxyphenyl)-3-pyridylalanine-NH_2
95.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	3-pyridylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
96.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl, 4'-Chloro)phenyl)-3-pyridylalanine-NH_2
97.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Me-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
98.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
99.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Fluorophenyl)-3-pyridylalanine-NH_2
100.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
101.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Chlorophenyl)-3-pyridylalanine-NH_2
102.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Chlorophenyl)-3-pyridylalanine-NH_2
103.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Isopropylphenyl)-3-pyridylalanine-NH_2
104.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-dimethylisoxazol-4'-yl)-3-pyridylalanine-NH_2
105.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(2'-Methyl-4'-methoxy)phenyl)-3-pyridylalanine-NH_2
106.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Trifluoromethylphenyl)-3-pyridylalanine-NH_2
107.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Chlorophenyl)-3-pyridylalanine-NH_2
108.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(4'-Pyridyl)-3-pyridylalanine-NH_2
109.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
110.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(6'-Methoxypyridin-3'-yl)-3-pyridylalanine-NH_2
111.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Isopropylphenyl)-3-pyridylalanine-NH_2
112.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methoxyphenyl)-3-pyridylalanine-NH_2
113.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-[(3',5'-di-Fluoro-2'-methoxy)phenyl]-3-pyridylalanine-NH_2
114.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-methylphenyl)-3-pyridylalanine-NH_2
115.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-fluorophenyl)-3-pyridylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
116.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-fluorophenyl)-3-pyridylalanine-NH_2
117.	H	Aib	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
118.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
119.	H	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
120.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
121.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	(S)-4-(2'-Methylphenyl)-α-Me-3-pyridylalanine-NH_2
122.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	(S)-4-(2'-Methylphenyl)-α-Me-3-pyridylalanine-NH_2
123.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
124.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
125.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
126.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
127.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2
128.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2
129.	H	N-Me-(L)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
130.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3,5-pyrimidylalanine-NH_2
131.	H	(S)-α-Me-Pro	D	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
132.	H	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et)	4-(2'-Ethylphenyl)-3-pyridylalanine-NH_2
133.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
134.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
135.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Fluorophenyl)-3-pyridylalanine-NH_2
136.	Des-NH_2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3'-Methoxyphenyl)-3-pyridylalanine-NH_2
137.	(R)-Imp	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
138.	(S)-Imp	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
139.	CH3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
140.	CH3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
141.	CH3O-CO-His	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
142.	CH3O-CO-His	N-Me-(D)-Ala	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
143.	CH3 SO2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
144.	CH3 SO2-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
145.	L-Lactyl-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
146.	L-Lactyl-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe(2,6-di-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
147.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(3',5'-di-Me)phenyl-3-pyridylalanine-NH_2
148.	H	Aib	E	G	T	L-α-Me-Phe(2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
149.	H	D-Ala	E	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
150.	H	Aib	H	G	T	L-α-Me-Phe(2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methylphenyl)-3-pyridylalanine-NH_2
151.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
152.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
153.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
154.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
155.	L-β-Imidazole-lactyl	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
156.	L-β-Imidazole-lactyl	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
157.	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
158.	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
159.	CH_3O-CO-His	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
160.	CH_3O-CO-His	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
161.	CH_3O-CO-His	Aib	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2; and
162.	CH_3O-CO-His	Aib	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2.

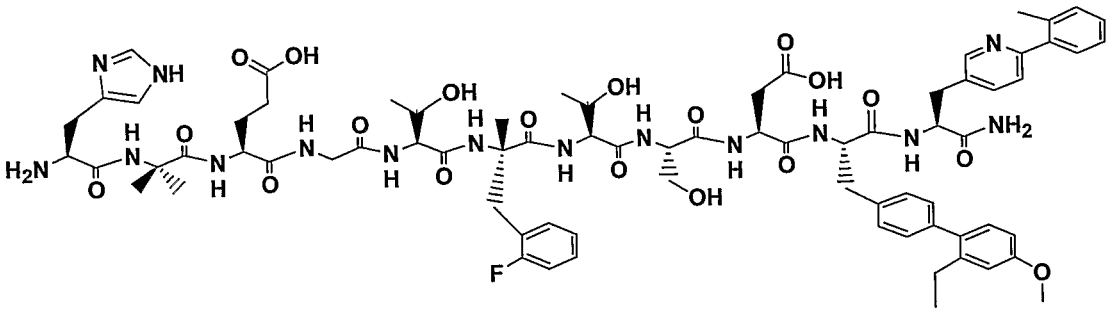
28. An isolated polypeptide selected from the group consisting of:

SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
151.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
152.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
153.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
154.	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
155.	L-β-Imidazole-lactyl	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
156.	L-β-Imidazole-lactyl	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
157.	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
158.	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
159.	CH_3O-CO-His	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
160.	CH_3O-CO-His	N-Me-D-Ala	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2
161.	CH_3O-CO-His	Aib	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2; and
162.	CH_3O-CO-His	Aib	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2.

29. An isolated polypeptide of Claim 1, selected from the group consisting of:

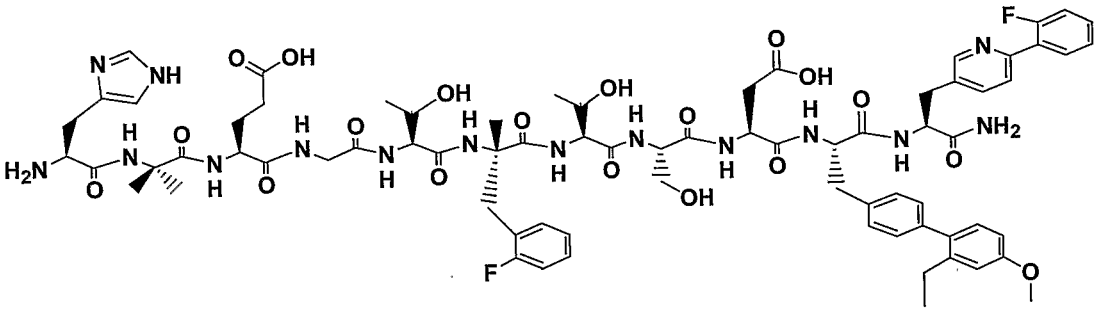
SEQ ID No.	X_{aa1}	X_{aa2}	X_{aa3}	X_{aa4}	X_{aa5}	X_{aa6}	X_{aa7}	X_{aa8}	X_{aa9}	X_{aa10}	X_{aa11}-NH_2
151	L-β-Imidazole-lactyl	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	H	D	Bip(2'-Et-4'-OMe)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2; and
158	CH_3O-CO-His	(S)-α-Me-Pro	E	G	T	L-α-Me-Phe (2-Fluoro)	T	S	D	Bip(2'-Et-4'-OH)	4-(2'-Methyl phenyl)-3-pyridyl alanine-NH_2.

30. An isolated polypeptide of Claim 1, wherein said isolated polypeptide is



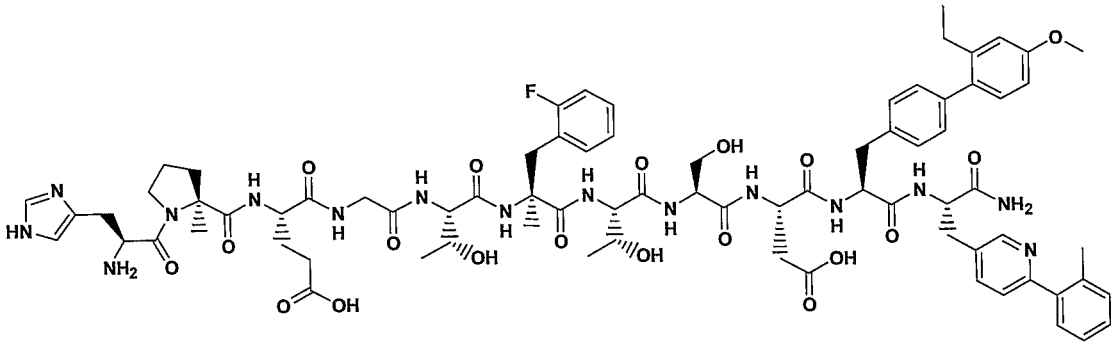
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or



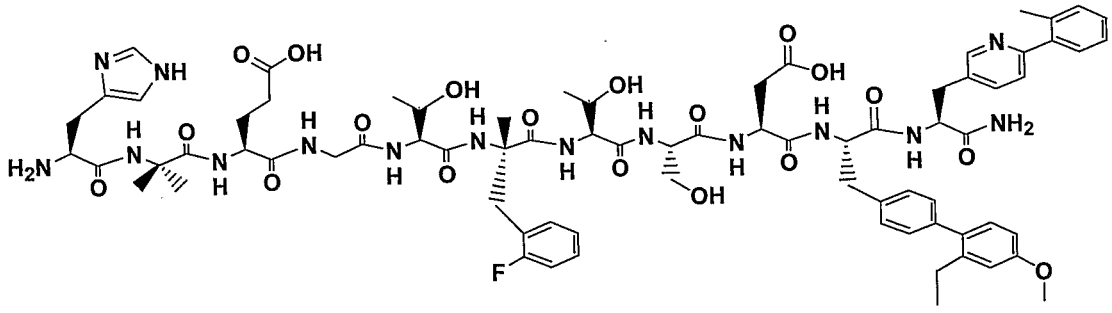
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31. An isolated polypeptide, wherein said isolated polypeptide is



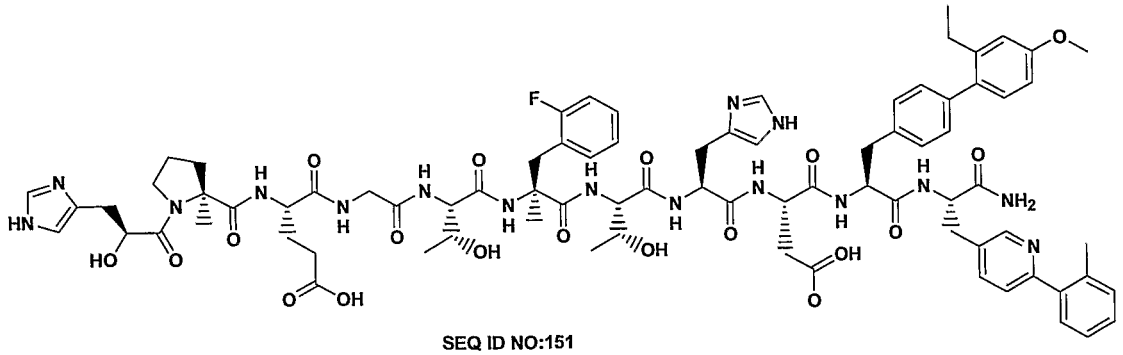
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or



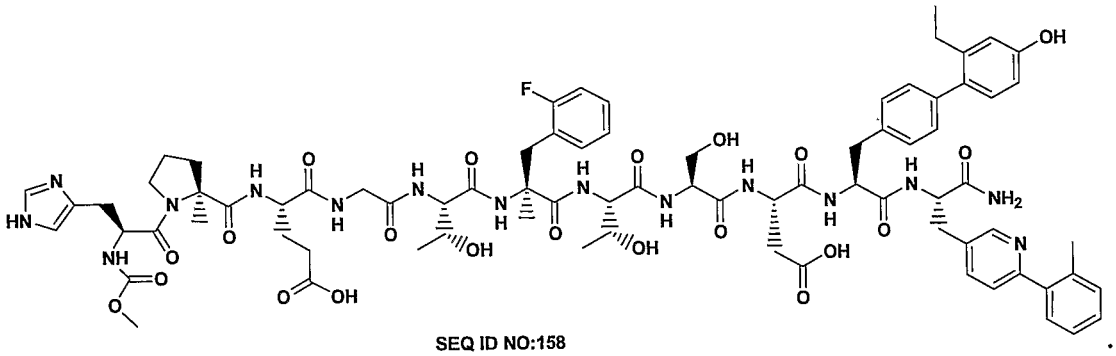
SEQ ID NO:9

or



SEQ ID NO:151

or



SEQ ID NO:158

32. A pharmaceutical composition, comprising an isolated polypeptide of Formula I and a pharmaceutically acceptable carrier thereof.

33. A pharmaceutical combination comprising an isolated polypeptide of Formula I and at least one therapeutic agent selected from the group consisting of an antidiabetic agent, an anti-obesity agent, an anti-hypertensive agent, an anti-atherosclerotic agent and a lipid-lowering agent.

34. The combination of claim 33 wherein the antidiabetic agent is at least one agent selected from the group consisting of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ agonist, a PPAR α/γ dual agonist, an aP2 inhibitor, a DPP4 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and a meglitinide.

35. The combination of claim 34 wherein the antidiabetic agent is at least one agent selected from the group consisting of metformin, glyburide, glimepiride,

glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, farglitizar, isaglitazone, reglitizar, balaglitazone, CAS RN:335149-08-1, (Z)-1,4-bis{4-[(3,5-Dioxo-1,2,4-oxadiazolidin-2-yl) methyl]phenoxy}but-2-ene, rivoglitazone, rafaegron, repaglinide, nateglinide, (S)-2-benzyl-4-oxo-4-(cis-perhydroisoindol-2-yl)butyric acid calcium salt, tesaglitizar, L-phenylalanine,N-[(1Z)-1-methyl-3-oxo-3-phenyl-1-propenyl]-4-[3-(5-methyl-2-phenyl-4-oxazolyl)propyl], benzamide, 5-[(2,4-dioxo-5-thiazolidinyl) methyl]-2-methoxy-N-[[4-(trifluoromethyl) phenyl]methyl], exenatide, 8-37-glucagon-like peptide I (human), N-[3-(1H-imidazol-4-yl)-1-oxopropyl]- 26-L-arginine-34-[N6-(1-oxooctyl)-L-lysine], 8-36-glucagon-related peptide 1 (octodon degus), N-[3-(1H-imidazol-4-yl)-1- oxopropyl]-26-L-arginine-34-[N6-(1-oxooctyl)-L-lysine]-36a, and vildagliptin.

36. The combination of claim 33 wherein the anti-obesity agent is at least one agent selected from the group consisting of a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin reuptake inhibitor, a dopamine reuptake inhibitor, a serotonin and dopamine reuptake inhibitor, a thyroid receptor beta compound, and an anorectic agent.

37. The combination of claim 36 wherein the anti-obesity agent is at least one agent selected from the group consisting of orlistat, cetilistat, rafabregon, benzenesulfonamide, N-[4-[2-[[(2S)-3-[(6-amino-3-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]phenyl]-4-(1-methylethyl), benzenesulfonamide, N-[4-[2-[[3-[(6-amino-3-pyridinyl)oxy]-2-hydroxypropyl] amino]ethyl]phenyl]-4-(1-methylethyl)-(S) CAS RN:335149-25-2, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine and mazindol.

38. The combination of claim 33 wherein the lipid lowering agent is at least one agent selected from the group consisting of an MTP inhibitor, cholesterol ester transfer protein, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor.

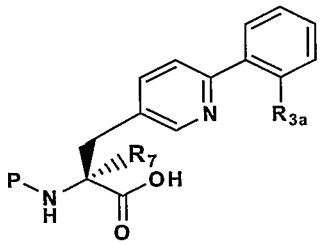
39. The combination of claim 38 wherein the lipid lowering agent is at least one agent selected from the group consisting of pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, acetamide, N-[2,6-bis(1-methylethyl)phenyl]-2-(tetradecylthio)-, 1(3H)-isobenzofuranone, 3-(13-hydroxy-10-oxotetradecyl)-5,7-dimethoxy, torcetrapib, and/or (3 alpha, 4 alpha, 5 alpha)-4-(2-propenylcholestan-3-ol).

40. A method for treating or delaying the progression or onset of diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, Syndrome X, diabetic complications, elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, atherosclerosis or hypertension, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of an isolated polypeptide of Formula I.

41. A method of treating or delaying of Claim 40, further comprising administering, concurrently or sequentially, a therapeutically effective amount of one or more therapeutic agents selected from the group consisting of an antidiabetic agent, an anti-obesity agent, a anti-hypertensive agent, and an anti-atherosclerotic agent and a lipid-lowering agent.

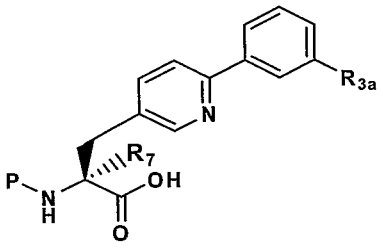
42. A method for treating or delaying the progression or onset of diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, Syndrome X, diabetic complications, elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, atherosclerosis or hypertension, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a pharmaceutical combination of Claims 34-40.

43. A compound comprising the following structure:



wherein, P is hydrogen or fluorenylmethyloxycarbonyl (Fmoc) or t-butyloxycarbonyl (t-Boc); and wherein R_{3a} is selected from the group consisting of methyl, ethyl and fluoro; and wherein R_7 is selected from the group consisting of hydrogen and methyl.

44. A compound comprising the following structure:

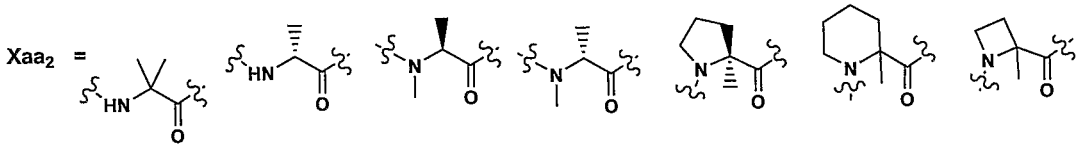


wherein P is hydrogen or fluorenylmethoxycarbonyl (Fmoc) or t-butyloxycarbonyl (t-Boc); and wherein R_{3a} is methoxy; and wherein R_7 is selected from the group consisting of hydrogen and methyl.

45. An isolated polypeptide of Claim 1, wherein

X_{aa1} is L-Histidine and wherein the amino group of X_{aa1} is unsubstituted;

X_{aa2} is selected from the following group consisting of:

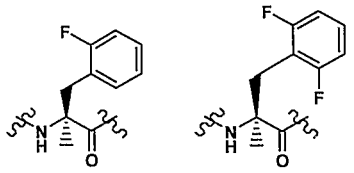


X_{aa3} is L-Glutamic acid or L-Histidine;

X_{aa4} is Glycine;

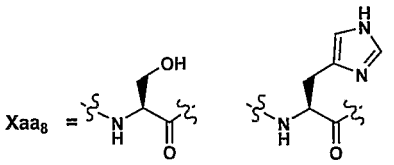
X_{aa5} is L-Threonine;

X_{aa6} is selected from the following group consisting of:



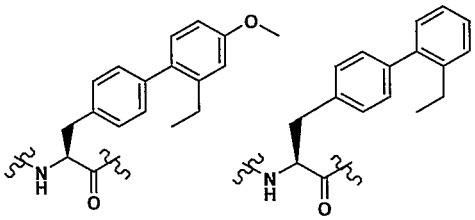
X_{aa7} is L-Threonine;

X_{aa8} is selected from the following group consisting of:

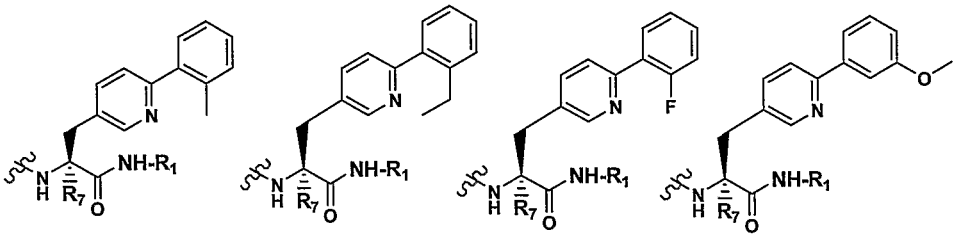


X_{aa9} is L-Aspartic acid;

X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II, wherein said naturally or nonnaturally occurring amino acid of Formula II is selected from the following group consisting of:



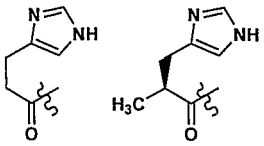
wherein X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IVa, wherein said naturally or nonnaturally occurring amino acid of Formula IVa is selected from the following group consisting of:



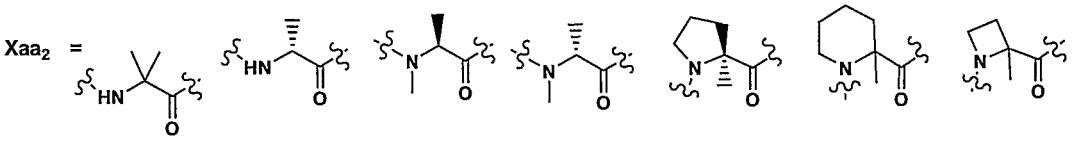
and;

R_1 and R_7 are selected from the group consisting of hydrogen and methyl.

46. An isolated polypeptide of Claim 1, wherein X_{aa1} is selected from the following group:

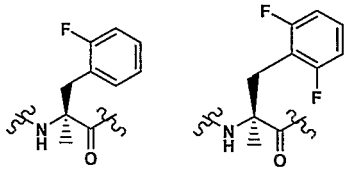


X_{aa2} is selected from the following group:

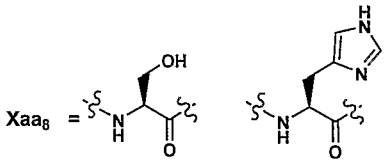


X_{aa3} is L-Glutamic acid or L-Histidine; X_{aa4} is Glycine; X_{aa5} is L-Threonine;

X_{aa6} is selected from the following group:

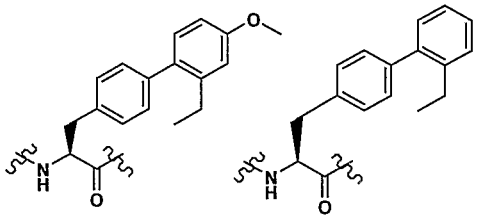


X_{aa7} is L-Threonine; X_{aa8} is selected from the following group:

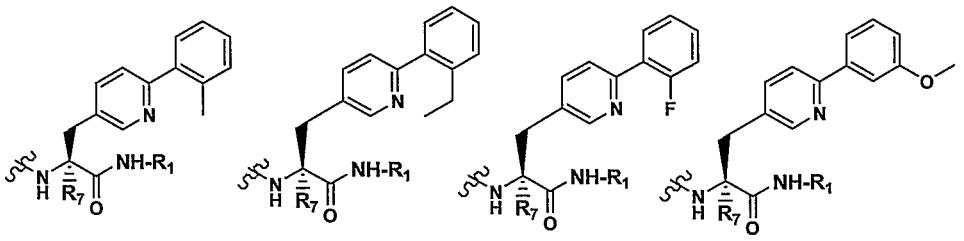


X_{aa9} is L-Aspartic acid;

X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II, wherein said naturally or nonnaturally occurring amino acid of Formula II is selected from the following group:

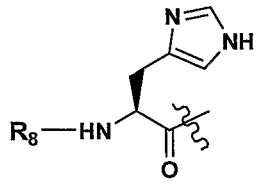


and wherein X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IVa, wherein said naturally or nonnaturally occurring amino acid of Formula IVa is selected from the following group:



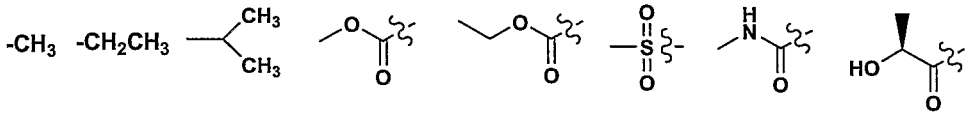
and wherein R_1 and R_7 are selected from the group consisting of hydrogen and methyl.

47. An isolated polypeptide of Claim 1, wherein X_{aa1} is:

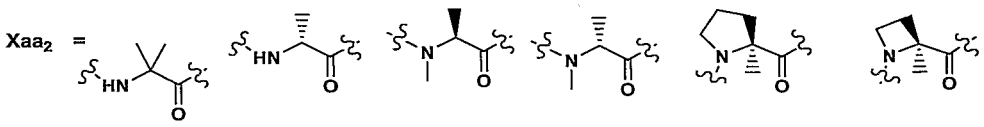


and;

R_8 is selected from the group consisting of:



X_{aa2} is selected from the group consisting of:

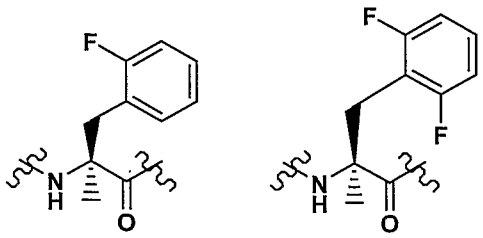


X_{aa3} is L-Glutamic acid or L-Histidine;

X_{aa4} is Glycine;

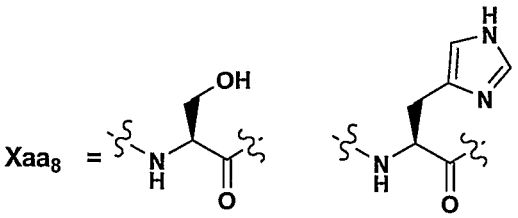
X_{aa5} is L-Threonine;

X_{aa6} is selected from the group consisting of:



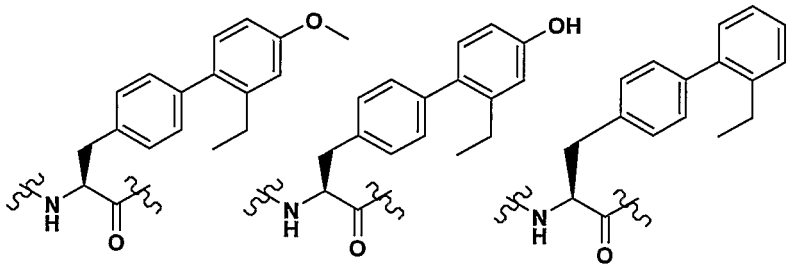
X_{aa7} is L-Threonine;

X_{aa8} is selected from the group consisting of:

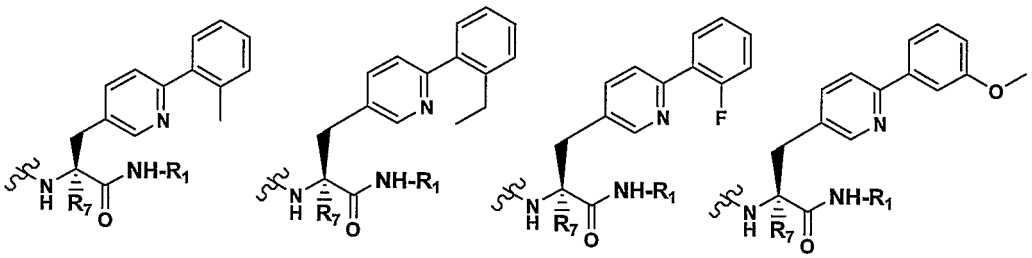


X_{aa9} is L-Aspartic acid;

X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II, wherein said naturally or nonnaturally occurring amino acid of Formula II is selected from the group consisting of:

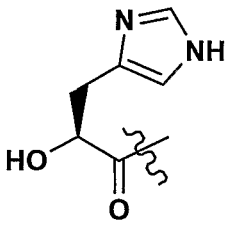


X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IVa, wherein said naturally or nonnaturally occurring amino acid of Formula IVa is selected from the group consisting of:



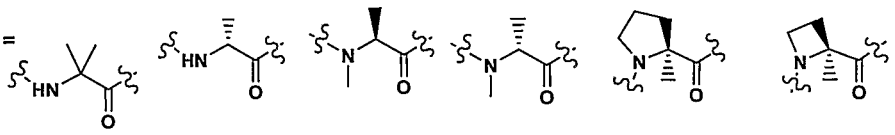
and wherein R_1 and R_7 are selected from the group consisting of hydrogen and methyl.

48. An isolated polypeptide of Claim 1, wherein X_{aa1} is the following an α-hydroxy acid:



X_{aa2} is selected from the group consisting of:

Xaa_2 =

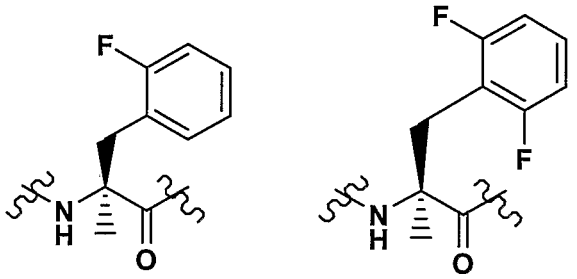


X_{aa3} is L-Glutamic acid or L-Histidine;

X_{aa4} is Glycine;

X_{aa5} is L-Threonine;

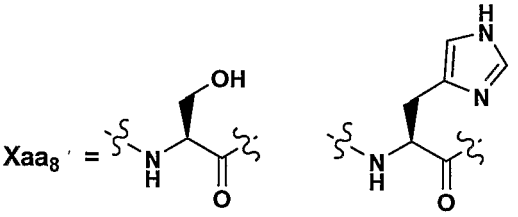
X_{aa6} is selected from the group consisting of:



X_{aa7} is L-Threonine;

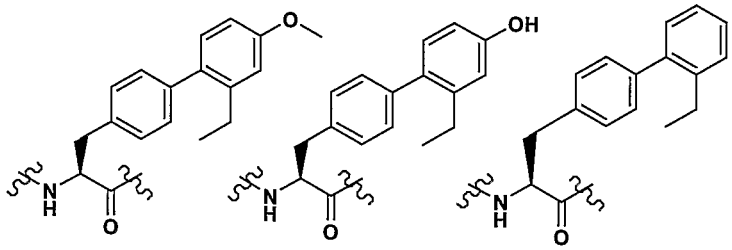
X_{aa8} is selected from the group consisting of:

Xaa_8 =

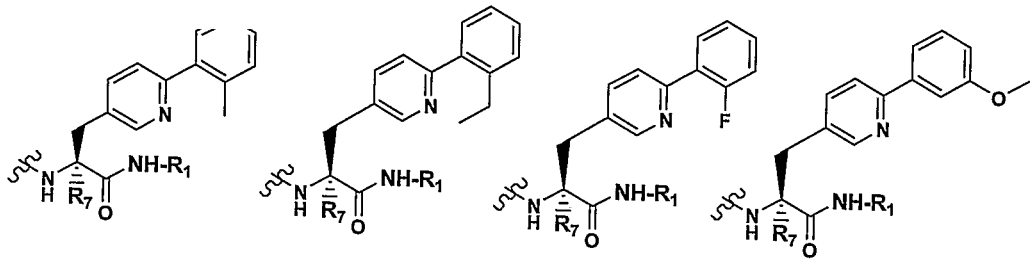


X_{aa9} is L-Aspartic acid;

X_{aa10} is a naturally or nonnaturally occurring amino acid of Formula II, wherein said naturally or nonnaturally occurring amino acid of Formula II is selected from the following group:



X_{aa11} is a naturally or nonnaturally occurring amino acid of Formula IVa, wherein said naturally or nonnaturally occurring amino acid of Formula IVa is selected from the following group:



and wherein R_1 and R_7 are selected from the group consisting of hydrogen and methyl.