

Industria y Comercio

SUPERINTENDENCIA

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Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

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PATENTE DE INVENCION

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

07-121830

21. EXPEDIENTE No.

54. TÍTULO

COMPUESTOS NOVEDOSOS COMO AGONISTAS GLP-1

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE

CADILA HEALTHCARE LIMITED

DOMICILIO

GUJARAT, INDIA

74. APODERADO

DILIA MARIA RIDRIGUEZ D ALEMAN

22. BOGOTÁ, D. C.,

NOV. 19, 2007



FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT

ENTRADA EN FASE NACIONAL

dic 5 2007

1) SOLICITUD DE:



Patente de invención



Patente de Modelo de Utilidad



Capítulo I.



Capítulo II.

2) SOLICITANTE
(71)

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Lugar de constitución: India

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Nacionalidad o Domicilio: Todos los anteriores, Hindúes

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10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☒ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☒ Otros:
 1. Reporte internacional de búsqueda
 2. Opinión escrita
 3. IB301, IB304, IB308, IB311
 4. Demand

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA:

C.C. 41.654.882 de Bogota TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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***** CONCEPTO *****

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL COMPOUNDS AS GLP-I AGONISTS

A-X₁-S₁-Y-S₂-X₂-B

(I)

(57) Abstract: The present invention describes a group of novel peptidomimetics useful for the treatment of diabetes. These compounds are defined by the general formula (I) as given below. A-X₁-S₁-Y-S₂-X₂-B (I)

WO 2007/017892 A2

NOVEL COMPOUNDS AS GLP-1 AGONISTS**Field of Invention**

The present invention relates to novel compounds of general formula (I), their tautomeric forms, novel intermediates involved in their synthesis, their
5 pharmaceutically acceptable salts and pharmaceutical compositions containing them.



In particular, the present invention relates to novel Glucagon-Like Peptide-1
10 (GLP-1) peptide mimics (peptidomimetic), which act as GLP-1 receptor agonists and exhibit most of the biological activity of the native GLP-1. Furthermore, these GLP-1 peptidomimetics exhibit increased stability to proteolytic cleavage, especially against DPP-IV (Dipeptidyl peptidase-IV) enzyme and can be delivered by both invasive and various non-invasive routes of administrations such as oral, nasal, buccal, pulmonary
15 and transdermal route of administration, for the treatment or prevention of diabetes and related conditions.

The present invention also relates to a process of preparing compounds of general formula (I), their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, and novel intermediates involved in
20 their synthesis.

Background to the invention

The GLP-1 (7-36) amide is a product of the preproglucagon gene, which is secreted from intestinal L-cells, in response to the ingestion of food. The physiological action of GLP-1 has gained considerable interest. GLP-1 exerts multiple action by
25 stimulating insulin secretion from pancreatic β -cells, in a glucose dependent manner (insulinotropic action). GLP-1 also lowers circulating plasma glucagon concentration, by inhibiting its secretion from α -cells (Drucker D. J., Endocrinology, 142, 521-527, 2001). More recently, it has become clear that GLP-1 also exhibits properties like stimulation of β -cell growth, appetite suppression, delayed gastric emptying and
30 stimulation of insulin sensitivity (Nauck, Horm. Metab. Res., 47, 1253-1258, 1997).

The venom of the Gila Monster *Heloderma Suspectum* contains a 39 amino acid peptide called Exendin-4 (EX-4) that shares around 50 % sequence identity to GLP-1 itself, exhibits a very potent GLP-1R (Glucagon like peptide-1 receptor) agonist activity (Thorens B., Diabetes, 42, 1678 – 1682, 1993). Indeed, it was found that EX-4
35 is much more potent than native GLP-1 peptide, because of its relatively longer half-

5

life (25 min., iv route of administration), compared to GLP-1 (2-5 min., iv route of administration). Exendin-4 binds with greater affinity to the GLP-1R, due to presence of the nine extra C-terminal sequence (Doyle M.E., *Regulatory Peptides*, 114, 153-158, 2003). Thus, the above stated pharmacological properties of GLP-1R agonists make it a highly desirable therapeutic agent for the treatment of diabetes.

Native or synthetic GLP-1 peptide is rapidly metabolized by the proteolytic enzymes, such as dipeptidyl peptidase-IV (DPP-IV) into an inactive metabolite, thereby limiting the use of GLP-1 as a drug. Currently, various analogs of GLP-1 and EX-4, such as Liraglutide / NN2211 (Novo Nordisk; Phase-III; WO 1998 008871), BIM 51077 (Ipsen; Phase-II; WO 2000 034331), CJC-1131 (ConjuChem; Phase-II; WO 2000 069911), ZP-10 (Zealand & Aventis; Phase-II; WO 2001 004156) are in different stages of clinical development (Nauck M.A., *Regulatory Peptides*, 115, 13-19, 2004). However, all these peptides require delivery via parenteral route of administration, including BYETTA® (Exendin-4, AC 2933; WO 2001 051078), which is recently launched in the market (Amylin & Lilly). Thus, there exists a critical need to develop a biologically active GLP-1 mimic that possesses extended pharmacodynamic profiles.

The GLP-1 R is a seven-transmembrane domain G-protein-coupled receptor (GPCR) and it is located on the cell membrane of pancreatic β -cells. The effector system of GLP-1 R is the Adenylyl Cyclase (AC) enzyme. Interaction of GLP-1 agonist with GLP-1R causes activation of AC, which converts ATP to cAMP. Increase in the intracellular cAMP level raises the ratio of ADP/ATP, thereby initiating the cell depolarization (due to closure of K_{ATP} channel). Increase in the intracellular cAMP level also activates Protein Kinase (PK-A & PK-C), which raises the cytosolic Ca^{2+} concentration, by opening of L-type of Ca^{2+} channel. An increase in the intracellular Ca^{2+} leads to exocytosis of insulin, in pancreatic β -cells (Fehmann, H.C., *Endocr. Rev.*, 16, 390 – 410, 1995).

A general mechanism of peptide ligand interaction with class-B GPCRs has emerged recently, termed the 'two-domain' model (Hoare S.R.J., *Drug Discovery Today*, Vol. 10 (6), 417-427, 2005). In this two-domain model, the C-terminal portion of the peptide binds to the N-domain of the receptor and the N-terminal ligand region binds to the J-domain (transmembrane) region of GPCR. This interaction activates the receptor and thereby stimulates intracellular signaling. The receptor binding and activation occurs in two separate domains of Exendin, but they are closely coupled in GLP-1 (Eng J., *J.B.C.*, 272 (34), 21291-21296, 1997).

Prior art

Earlier, Bristol-Myers Squibb (BMS), Princeton, NJ (US), reported human GLP-1 mimics, with general formula Xaa1-Xaa11, wherein Xaa1-Xaa9 represent the first 1-9 residues of GLP-1 peptide with some analogs wherein Xaa2 represents either
5 Ala or is optionally replaced with Aib, and Xaa6 represents Phe or is optionally replaced with α -Me-Phe(2-F)-OH and Xaa10 & Xaa11 represents combination of substituted or unsubstituted biphenyl alanine (Bip) derivatives (WO 03/ 033671A2; US 2004/ 0127423 A1; WO 2004/ 094461 A2; US 2006 / 0004222 A1 and WO 2006/ 014287 A1).

10 The present invention provides novel GLP-1 peptide mimics of formula (I) (hereinafter referred to as peptidomimetics), which act as a GLP-1R agonist and exhibit most of the biological activity of the native GLP-1 peptide. Furthermore, these GLP-1 peptidomimetics exhibit increased stability to proteolytic cleavage, especially against DPP-IV enzyme and therefore, surprisingly found to have an increased half-life making
15 them suitable for the treatment / mitigation / prophylaxis of both type 1 & type 2 diabetes, metabolic disorders, obesity and related disorders.

Summary of the invention

The present invention describes a group of novel peptidomimetics useful for the treatment of diabetes. These compounds are defined by the general formula (I) as given
20 below. The compounds of the present invention are useful in the treatment of the human or animal body, by regulation of insulin secretion. The compounds of this invention are therefore suitable for the treatment/mitigation/regulation or prophylaxis of both type 1 & type 2 diabetes and obesity.

25 Preferred embodiments

The main object of the present invention is to provide novel compounds of general formula (I), their tautomeric forms, novel intermediates involved in their synthesis, their pharmaceutically acceptable salts, their pharmaceutically acceptable
30 solvates and pharmaceutical compositions containing them or their mixtures, suitable for the treatment treatment/mitigation/regulation of diabetes.

In an embodiment is provided a process for the preparation of novel compounds of general formula (I), their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

In another embodiment, is provided pharmaceutical compositions containing compounds of general formula (I), their tautomeric forms, their pharmaceutically acceptable salts, solvates and their mixtures having pharmaceutically acceptable carriers, solvents, diluents, excipients and other media normally employed in their
5 manufacture.

In a further another embodiment is provided the use of the novel compounds of the present invention as antidiabetic agents, by administering a therapeutically effective & non-toxic amount of the compound of formula (I), or their pharmaceutically acceptable compositions to the mammals those are need of such treatment.

10 Abbreviations used

The following abbreviations are employed in the examples and elsewhere herein:

Aib = α -Aminoisobutyric acid,

ACN or MeCN = Acetonitrile,

15 Bip = Biphenylalanine residue,

Bip(4-fluro)= 4-fluoro-biphenylalanine residue,

Bip(2-Me)= 2-methyl biphenyl residue,

Bip(2-Et)= 2-ethyl biphenyl residue,

Bip(2-CN)= 2-nitrile biphenyl residue,

20 Bip(2-Ipr)= 2-Isopropyl biphenyl residue,

Bip(2'-Et-4'-OMe)= 2-ethyl-4-methoxy-biphenyl residue,

Bip(2-F)= 2-fluro-biphenyl residue,

Bn = Benzyl,

Boc = tert-Butoxycarbonyl,

25 But= O-tert-butyl group,

cAMP= Adenosine 3',5'-cyclic monophosphate,

DCM = Dichloromethane,

DMF = N,N-Dimethylformamide,

DIPCDI= Di-isopropylcarbodiimide,

30 DIPEA= Diisopropylethylamine,

4-DBF=4-dibenzofuran-Phe-OH residue,

4-DBT=4-dibenzothiophene-Phe-OH residue,

Dihydro-Phen=2-(9,10-Dihydro-phenanthrenyl]-Ala-OH residue,

Et = Ethyl,

- Et₂O = Diethyl ether,
Fmoc = Fluorenylmethoxycarbonyl,
2-Flu=2-Fluorenyl-Ala-OH residue,
g = Gram (s),
- 5 GTT = Glucose Tolerance Test,
GLP-1R = Glucagon Like Peptide-1 Receptor,
h = Hour (s),
HOBt = Hydroxybenzotriazole,
HOAT= 7-Aza-hydroxybenzotriazole,
- 10 HBTU = 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl aminium hexafluorophosphate,
HPLC = High Performance Liquid Chromatography,
L = Liter,
LC /MS = Liquid Chromatography / Mass Spectrometry,
4-(2'-Me-Ph)-3-Pyr-Ala= 4-(2'-methylphenyl)-3-pyridylalanine residue,
- 15 Me = Methyl,
Min = minute (s),
ml = milliliter,
μl = microliter,
mg = milligram (s),
- 20 mmol = millimole (s),
fmol = femtomolar
MS= Mass Spectrometry,
1-Nap=4-(1-Naphthyl)-Phe residue,
2-Nap=4-(2-Naphthyl)-Phe residue,
- 25 Phen=2-(Phenanthrenyl)-Ala-OH residue,
Pbf= Pentamethylbenzofuran-5-sulfonyl,
PyBOP = Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate,
SPPS = Solid Phase Peptide Synthesis,
Sc = sub-cutaneous,
- 30 TrPh=4-phenyl-biphenylalanine residue,
TMS = Trimethylsilyl,
TIPS = Triisopropylsilane,
TFA = Trifluoroacetic acid,
TBTU= 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate,

Trt= Trityl group,

(α -Me)Phe(2-F)= α -methyl-2-fluoro-phenylalanine residue,

-(N(Me))- = N-methylated amide bond,

D-Alanine represented by 'a' and D-Bip represent 'D'-Biphenyl alanine residue,

5 ip = intra-peritoneal,

Sequence of GLP-1 peptide =

NH₂-HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-CONH₂ (30 amino acids). The

30 amino acids of said GLP-1 peptide are shown in **Seq ID 1**.

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR ---**Seq ID 1**

10 Sequence of Exendin-4 =

NH₂-HGEFTFTSDLSKQMEEEEAVRLFIEWLKNGGPSSGAPPPS-CONH₂ (39

amino acids). The 39 amino acids of Exendin -4 are shown in **Seq ID 2**.

HGEFTFTSDLSKQMEEEEAVRLFIEWLKNGGPSSGAPPPS ---**Seq ID 2**

15 Detailed description

In accordance with the present invention, synthetic GLP-1 analog peptides /
peptidomimetics are provided, which have the structural formula (I),



wherein,

- 20 A represents -NH-R₁, wherein R₁ represents hydrogen, groups selected from linear or branched (C₁-C₁₅) alkyl chain, such as methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, t-butyl, pentyl, isopentyl, hexyl, heptyl, octyl, decyl groups and the like, an amino acid or peptide containing one, two or three natural amino acid residues, R₃-CO-group, such as (2-Hydroxy-phenyl)-acetyl group and the like, R₃O-C(O)- group, such
- 25 as Fmoc group and the like, a sulfonyl group of formula R₃-SO₂-, each of these groups may be substituted, wherein R₃ is selected from linear or branched (C₁-C₁₀) alkyl, such as methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, t-butyl, pentyl, isopentyl, hexyl, heptyl, octyl, decyl groups and the like, (C₃-C₆) cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl groups and the like, aryl groups selected from
- 30 phenyl, naphthyl, indanyl, fluorenyl, biphenyl and the like, heteroaryl groups selected from pyridyl, thienyl, furyl, imidazolyl, benzofuranyl and the like, arylalkyl groups selected from benzyl, naphthylmethyl and the like, each of these groups may be substituted;

B represents $-\text{COOR}_2$, $-\text{CONHR}_2$ or CH_2OR_2 , R_2 represents H, groups selected from linear or branched (C_1 - C_{10}) alkyl group, such as methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, t-butyl, pentyl, isopentyl, hexyl, heptyl, octyl, decyl groups and the like, aryl groups selected from phenyl, naphthyl, indanyl, fluorenyl, biphenyl and the like, aralkyl groups, each of these groups may be substituted,
 5 each of S_1 and S_2 may independently be a bond or independently represents a group ' $-\text{NH}-(\text{CH}_2)_n-\text{COO}-$ ', where, $n=1-9$; such as derivatives of amino acetic acid, amino propionic acid, amino butanoic acid, amino pentanoic acid, amino hexanoic acid, amino heptanoic acid, amino octanoic acid, amino-nonanoic acid, amino-decanoic acid and
 10 the like;

Y represents a bond or $-\text{CO}-$, $-(\text{CH}_2)_m-$ ($m = 1-3$), 'O', 'S', $-\text{CO}-\text{NH}-$, $-\text{CO}-\text{NR}_4-$, or represents a short peptide containing one or two or three amino acids selected from natural or non-natural amino acids; where R_4 represents H, optionally substituted groups selected from linear or branched (C_1 - C_{10}) alkyl group such as methyl, ethyl,
 15 propyl, isopropyl, n-butyl, iso-butyl, t-butyl, pentyl, isopentyl, hexyl, heptyl, octyl, decyl groups and the like, aryl groups selected from phenyl, naphthyl, indanyl, fluorenyl, biphenyl and the like; with the proviso that

i) when S_1 -Y- S_2 represents a bond,

X_1 is selected from the following amino acid sequences

20 HAEGTFTSD (Seq ID 3), HAEGTFTSDV (Seq ID 4), HAEGTFTSDVS (Seq ID 5),
 HAEGTFTSDVSS (Seq ID 6), HAEGTFTSDVSSY (Seq ID 7),
 HAEGTFTSDVSSYL (Seq ID 8), HAEGTFTSDVSSYLE (Seq ID 9),
 HAEGTFTSDVSSYLEG (Seq ID 10), HAEGTFTSDVSSYLEGQ (Seq ID 11),
 HAEGTFTSDVSSYLEGQA (Seq ID 12), HAEGTFTSDVSSYLEGQAA (Seq ID 13),
 25 HAEGTFTSDVSSYLEGQAQ (Seq ID 14), HAEGTFTSDVSSYLEGQAQKE (Seq
 ID 15), HAEGTFTSDVSSYLEGQAQKEF (Seq ID 16),
 HAEGTFTSDVSSYLEGQAQKEFI (Seq ID 17), with the further option that one or
 more of these amino acids may be replaced by unnatural amino acids, and X_2 is
 selected from the following amino acid sequences

30 GPSSGAPPPS (Seq ID 18) or

KELEKLL (Seq ID 19) or

GPPS or (Seq ID 20)

VKGR (Seq ID 21);

ii) and when S_1 -Y- S_2 does not represent a bond

X₁ is selected from the following amino acid sequences

HA (Seq ID 22), HAE (Seq ID 23), HAEG (Seq ID 24), HAEGT (Seq ID 25), HAEGTF (Seq ID 26), HAEGTFT (Seq ID 27), HAEGTFTS (Seq ID 28), HAEGTFTSD (Seq ID 29) with the further option that one or more of these amino

5 acids may be replaced by unnatural amino acids;

X₂ is selected from

GPSSGAPPPS (Seq ID 18) or

KELEKLL (Seq ID 19) or

GPPS (Seq ID 20) or

10 VKGR (Seq ID 21) or

a dipeptide, selected from combination of two amino acids, consisting of natural or unnatural amino acids, having a side chain containing an arylalkyl or heteroarylalkyl

moieties selected from benzyl, naphthylmethyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, isooxazolylmethyl, quinolylmethyl,

15 benzofuranylmethyl, benzothienylmethyl, indolylmethyl, indolylmethyl,

dibenzofuranylmethyl, dibenzothienylmethyl, benzodihydrofuranylmethyl,

benzodihydrothienylmethyl, thienopyrimidylmethyl, benzimidazolylmethyl,

phenanthrenylmethyl, dihydrophenanthrenylmethyl, fluorenylmethyl,

dibenzofuranylmethyl, dibenzothiophenyl methyl groups and the like, where each of

20 these groups may be optionally substituted with (C₁-C₆)alkyl group such as methyl,

ethyl, propyl, isopropyl, n-butyl, iso-butyl, t-butyl, pentyl, isopentyl, hexyl groups and

the like, (C₁-C₆)alkoxy group such as methoxy, ethoxy, propoxy, butoxy, pentoxy,

hexanoxo groups, cyano, halo group such as chloro, bromo, iodo, fluoro groups,

hydroxy or optionally substituted aryl or heteroaryl groups selected from phenyl,

25 naphthyl, pyridyl, thienyl, furyl, imidazolyl, isooxazolyl, quinolyl, benzofuranyl,

benzothienyl, indolyl, indolyl, dibenzofuranyl, dibenzothienyl, benzodihydrofuranyl,

benzodihydrothienyl, thienopyrimidyl, benzimidazolyl, phenanthrenyl,

dihydrophenanthrenyl, fluorenyl, dibenzofuranyl, dibenzothiophenyl and the like, with

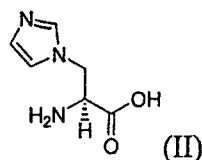
the further provision that such aryl or heteroaryl substituents may further be optionally

30 substituted with (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, halo, hydroxy or aryl or heteroaryl groups.

In a preferred embodiment, the dipeptide sequence may comprise of one or more amino acids selected from Bip, Bip(2-Me), Bip(2-Et), Bip(2-Ipr), Bip(2-CN), Bip(2'-Et-4'-OMe), Bip(4'-fluoro), Bip(4'-Phenyl), 2-(9,10-Dihydro-phenanthrenyl]-

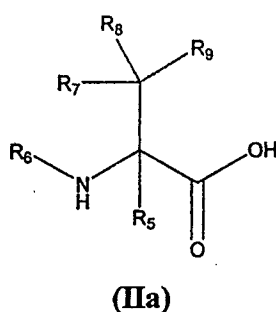
Ala, 2-(Phenanthrenyl)-Ala, 4-(2-Naphthyl)-Phe, 4-(1-Naphthyl)-Phe, 2-Fluorenyl-Ala, 4-dibenzofuran-Phe, 4-dibenzothiophene-Phe, 4-(2'-methylphenyl)-3-pyridylalanine;
The term 'natural amino acids' indicates all those twenty amino acids, which are present in nature.

- 5 The term 'unnatural amino acids' or 'non-natural amino acids' represents either replacement of L-amino acids with corresponding D-amino acids such as replacement of L-Ala with D-Ala or L-Pro with D-Pro and the like or suitable modifications of the L or D amino acids, amino alkyl acids, either by
- α -alkylation such as substitution of Ala with α -methyl Ala (Aib), replacement of
 - 10 Phe with α -methyl Phe, replacement of substituted Bip with with α -methyl Bip;
 - N-alkylation with groups selected from (C₁-C₆)alkyl or (C₃-C₆)cycloalkyl groups;
 - modification of side chain such as replacement of His with histidine analogs such as 1-imidazolyl-alanine (II) or des-amino-His,



- 15 or replacement of phenyl ring of Phe with pyridyl, naphthyl, biphenyl groups;
- substitution on the side chain of amino acid such as substitution of aromatic amino acid side chain with halogen, (C₁-C₃)alkyl, aryl groups, more specifically the replacement of Phe with 2 & 4-halo Phe;

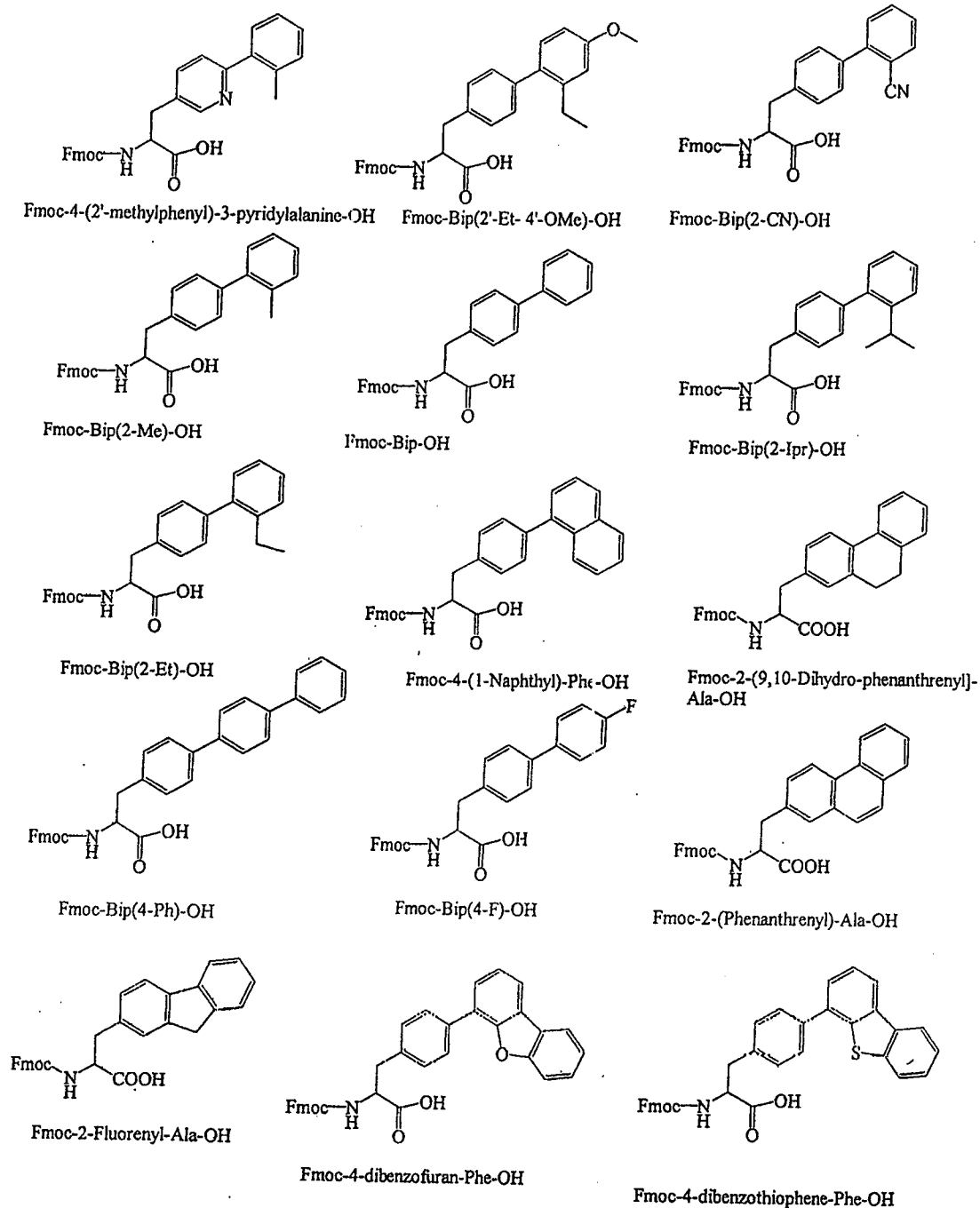
Such 'unnatural amino acids' or 'non-natural amino acids' may be represented
20 generally by the following structure:



wherein R₅ is selected from H, F, (C₁-C₅) alkyl, the stereochemical configuration at the carbon bearing R₅ may be (R) or (S); R₆ is selected from H or (C₁-C₃) alkyl; each of R₇ and R₈ is independently selected from H, (C₁-C₃) alkyl, such as methyl and ethyl or
25 halogen atom, preferably fluorine atom; R₉ represents groups, selected from (C₁-C₅) alkyl, aryl or heteroryl moieties selected from phenyl, naphthyl, pyridyl, thienyl, furyl,

imidazolyl, isooxazolyl, quinolyl, benzofuranyl, benzothienyl, indolinyl, indolyl, dibenzofuranyl, dibenzothienyl, benzodihydrofuranyl, benzodihydrothienyl, thienopyrimidyl, benzimidazolyl, phenanthrenyl, dihydrophenanthrenyl, fluorenyl, dibenzofuranyl, dibenzothiophenyl groups, where each of these groups may be
5 optionally substituted with (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, halo, hydroxy or optionally substituted aryl or heteroaryl groups, with the further provision that such aryl or heteroaryl substituents may further be optionally substituted with (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, halo, hydroxy or aryl or heteroaryl groups.

List of Fmoc protected Bip analogs used for the synthesis of GLP-1 peptidomimetics



5

The suitable substituents include, but are not limited to the following radicals,
 alone or in combination with other radicals – hydroxy, oxo, halo, thio, nitro, amino,
 cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy,

heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, carboxylic acid and its derivatives such as esters and amides;

The various groups, radicals and substituents used anywhere in the specification are described in the following paragraphs.

5 The term "alkyl" used herein, either alone or in combination with other radicals, denotes a linear or branched radical containing one to ten carbons, such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, *iso*-hexyl, heptyl, octyl, decyl and the like.

10 The term "cycloalkyl" used herein, either alone or in combination with other radicals, denotes a radical containing three to seven carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

15 The term "aryl" or "aromatic" used herein, either alone or in combination with other radicals, denotes an aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused, such as phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and the like.

 The term "arylalkyl" denotes an alkyl group, as defined above, attached to an aryl, such as benzyl, phenylethyl, naphthylmethyl, and the like. The term "aryloxy" denotes an aryl radical, as defined above, attached to an alkoxy group, such as phenoxy, naphthyloxy and the like, which may be substituted.

20 The term "aralkoxy" denotes an arylalkyl moiety, as defined above, such as benzyloxy, phenethyloxy, naphthylmethyloxy, phenylpropyloxy, and the like, which may be substituted.

 The term "heteroaryl" or "heteroaromatic" used herein, either alone or in combination with other radicals, denotes an aromatic system containing one, two or
25 three rings wherein such rings may be attached together in a pendant manner or may be fused containing one or more hetero atoms selected from O, N or S, such as pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzothienyl, indolyl, azaindolyl, azaindolyl, benzodihydrofuranyl, benzodihydrothienyl, pyrazolopyrimidinyl, pyrazolopyrimidonyl,
30 azaquinazolinyl, azaquinazolinoyl, pyridofuranyl, pyridothienyl, thienopyrimidyl, thienopyrimidonyl, quinolyl, pyrimidinyl, pyrazolyl, quinazolinyl, quinazolonyl, pyrimidonyl, pyridazinyl, triazinyl, benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl,

phthalazynyl, naphthylidiny, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl, and the like.

The term "heteroaralkyl" used herein, either alone or in combination with other radicals, denotes a heteroaryl group, as defined above, attached to a straight or
5 branched saturated carbon chain containing 1 to 6 carbons, such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like. The terms "heteroaryloxy", "heteroaralkoxy", "heterocycloxy" denotes heteroaryl, heteroarylalkyl, groups respectively, as defined above, attached to an oxygen atom.

10 The term "acyl" used herein, either alone or in combination with other radicals, denotes a radical containing one to eight carbons such as formyl, acetyl, propanoyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like, which may be substituted.

The term "carboxylic acid" used herein, alone or in combination with other
15 radicals, denotes a -COOH group, and includes derivatives of carboxylic acid such as esters and amides. The term "ester" used herein, alone or in combination with other radicals, denotes -COO- group, and includes carboxylic acid derivatives, where the ester moieties are alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, and the like, which may be substituted.

20 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.

The absolute 'S' configuration at the ' α ' carbon is commonly referred to as the 'L' or natural configuration. The 'R' configuration at the ' α ' carbon is commonly
25 referred to as the 'D' amino acid. In the case where both the ' α -substituents' is equal, such as hydrogen or methyl, the amino acids are Gly or Aib and are not chiral.

The term 'receptor modulator' refers to a compound that acts at the GLP-1 receptor to alter its ability to regulate downstream signaling events. Example of
30 receptor modulators includes agonist, partial agonist, inverse agonist, allosteric potentiators.

Preferably, the isolated peptidomimetics are a 3-30 mer and such peptide bind to and activates the GLP-1 receptor.

In accordance with the present invention, the synthetic isolated peptidomimetics described herein possess the ability to mimic the biological activity of GLP-1 peptide,

with preference for agonist activity at GLP-1R. These synthetic peptidomimetics GLP-1 mimetic exhibit desirable in-vivo properties, thus making them ideal therapeutic candidates for oral or parenteral administration.

The present invention provides for compounds of formula (I) pharmaceutical compositions employing such compounds either alone or in combination and for methods of using such compounds. In particular, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I), alone or in combination(s), with a pharmaceutically acceptable carrier.

Further provided is a method for treating or delaying the progression or onset of diabetes, especially type II diabetes, including complications of diabetes, including retinopathy, neuropathy, nephropathy and delayed wound healing and related diseases such as insulin resistance (impaired glucose homeostasis), hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, obesity, hyperlipidemia including hypertriglyceridemia, syndrome X, atherosclerosis and hypertension, wherein a therapeutically effective amount of a compound of formula (I) or their combination(s) are administered to a mammal, example, human, a patient in need of treatment.

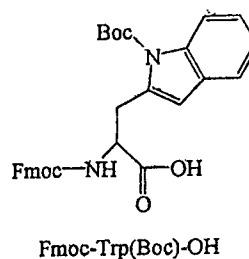
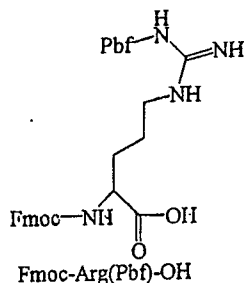
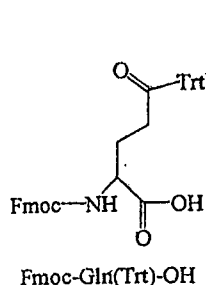
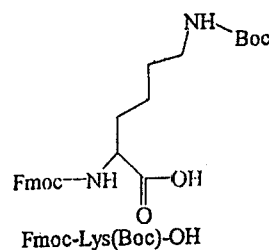
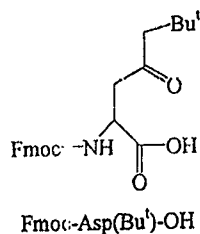
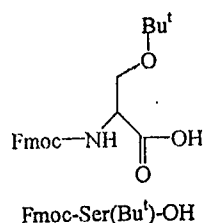
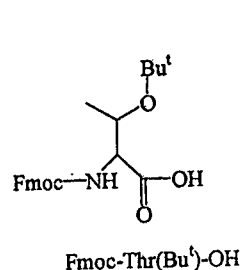
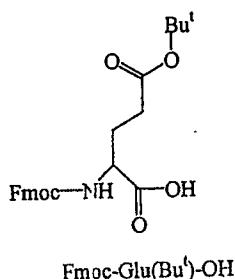
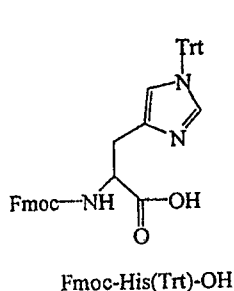
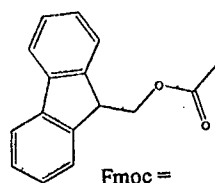
Several synthetic routes can be employed to prepare the compounds of the present invention well known to one skilled in the art of peptide synthesis. The compounds of formula (I), where all symbols are as defined earlier can be synthesized using the methods described below, together with conventional techniques known to those skilled in the art of peptide synthesis, or variations thereon as appreciated by those skilled in the art. Referred methods include, but not limited to those described below.

The peptidomimetics thereof described herein may be produced by chemical synthesis using suitable variations of various solid-phase techniques generally known such as those described in G. Barany & R. B. Merrifield, "The peptides: Analysis, synthesis, Biology"; Volume 2- "Special methods in peptide synthesis, Part A", pp. 3-284, E. Gross & 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 preferred strategy for preparing the peptidomimetics of this invention is based on the use of Fmoc-based SPPS approach, wherein Fmoc (9-Fluorenyl-methyl-methyloxycarbonyl) group is used for temporary protection of the α -amino group, in

combination with the acid labile protecting groups, such as t-butyloxy carbonyl (Boc), tert-butyl (Bu^t), Trityl (Trt) group for temporary protection of the amino acid side chains (see for example E. Atherton & R.C. Sheppard, "The Fluorenylmethoxycarbonyl amino protecting group", in "The peptides: Analysis, synthesis, Biology"; Volume 9 -
 5 "Special methods in peptide synthesis, Part C", pp. 1-38, S. Undenfriend & J. Meienhofer, Eds., Academic Press, San Diego, 1987).

Examples of orthogonally protected amino acids used in Fmoc-solid phase peptide synthesis for the synthesis of peptidomimetics



10

The peptidomimetics can be synthesized in a stepwise manner on an insoluble polymer support (resin), starting from the C-terminus of the peptide. In an embodiment, the synthesis is initiated by appending the C-terminal amino acid of the peptide to the
 15 resin through formation of an amide, ester or ether linkage. This allows the eventual

release of the resulting peptide as a C-terminal amide, carboxylic acid or alcohol, respectively.

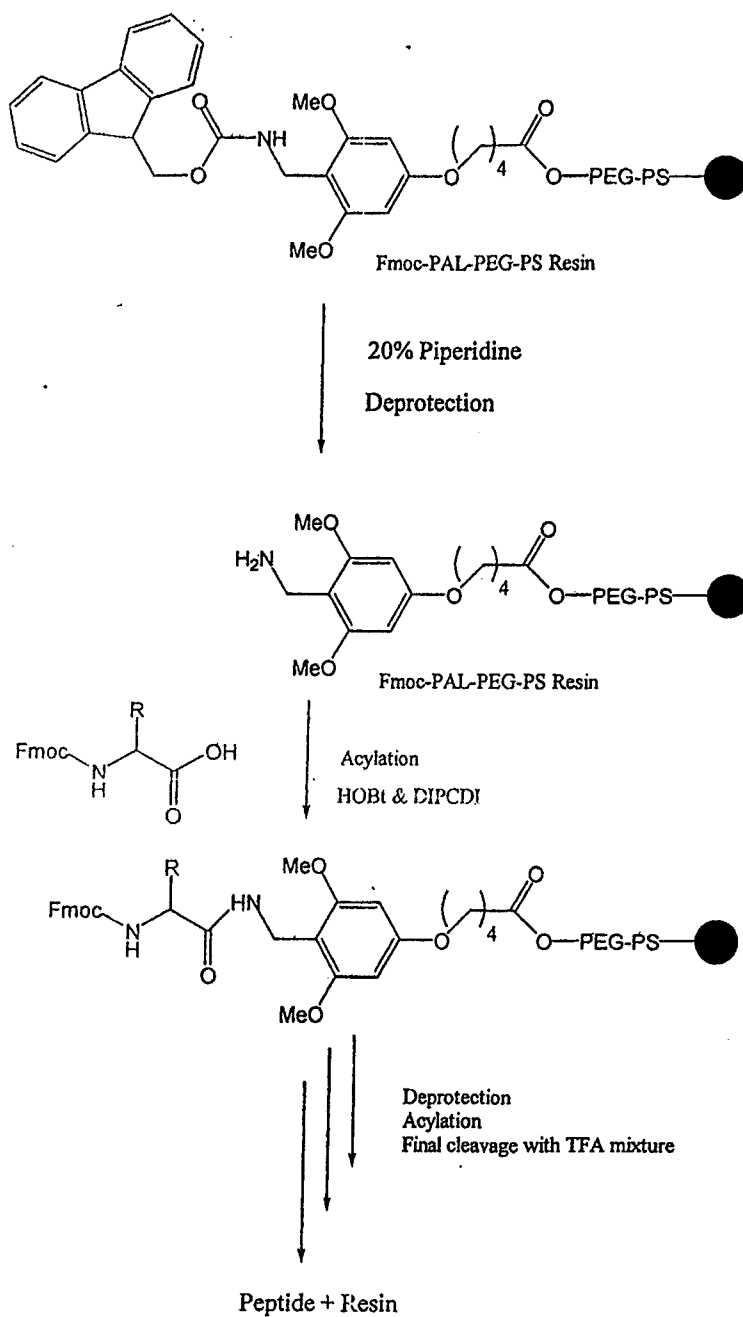
In the Fmoc-based SPPS, the C-terminal amino acid and all other amino acids used in the synthesis are required to have their α -amino groups and side chain functionalities (if present) differentially protected (orthogonal protection), such that the α -amino protecting group may be selectively removed during the synthesis, using suitable base such as 20% piperidine solution, without any premature cleavage of peptide from resin or deprotection of side chain protecting groups, usually protected with the acid labile protecting groups.

The coupling of an amino acid is performed by activation of its carboxyl group as an active ester and reaction thereof with unblocked α -amino group of the N-terminal amino acid appended to the resin. After every coupling and deprotection, peptidyl-resin was washed with the excess of solvents, such as DMF, DCM and diethyl ether. The sequence of α -amino group deprotection and coupling is repeated until the desired peptide sequence is assembled. The peptide is then cleaved from the resin with concomitant deprotection of the side chain functionalities, using an appropriate cleavage mixture, usually in the presence of appropriate scavengers to limit side reactions. The resulting peptide is finally purified by reverse phase HPLC.

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). Preferred for use in this invention are Fmoc-PAL-PEG-PS resin, 4-(2', 4'-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxyacetyl-*p*-methyl benzhydrylamine resin (Fmoc-Rink amide MBHA resin), 2-chloro-Trityl-chloride resin or *p*-benzyloxybenzyl alcohol resin (HMP resin) to which the C-terminal amino acid may or may not be already attached. If the C-terminal amino acid is not attached, its attachment may be achieved by HOBt active ester of the Fmoc-protected amino acid formed by its reaction with DIPCDI. In case of 2-Chloro-trityl resin, coupling of first Fmoc-protected amino acid was achieved, using DIPEA. For the assembly of next amino acid, N-terminal protection of peptidyl resin was selectively deprotected using a solution of 10-20 % piperidine solution. After every coupling and deprotection, excess of amino acids and coupling reagents was removed by washed with a DMF, DCM and ether. Coupling of the subsequent amino acids can be accomplished using HOBt or HOAT active esters produced from DIPCDI/ HOBt or DIPCDI/HOAT, respectively. In case of some difficult coupling, especially coupling of those amino acids, which are hydrophobic or

amino acids with bulky side chain protections, complete coupling can be achieved using a combination of highly efficient coupling agents such as HBTU, PyBOP or TBTU, with additives such as DIPEA.

5 General Scheme for Fmoc-Based SPPS:



The synthesis of the peptide analogs described herein can be carried out by using batchwise or continuous flow peptide synthesis apparatus. The non-natural non-commercial amino acids present at different position were incorporated into the peptide chain, using one or more methods known in the art. In one approach, a Fmoc-protected
5 non-natural amino acid was prepared in solution, using appropriate literature procedures. For example, the Fmoc-protected Bip analogs, described above, were prepared using modified Suzuki cross coupling method, as known in literature (for e.g. Tetrahedron Letter 58, 9633-9695, 2002). The Fmoc-protected α -methylated amino acids were prepared using asymmetric Strecker synthesis, as described for e.g. in Org.
10 Letters 3(8), 1121-1124, 2001. The Fmoc-protected N-methylated amino acids were prepared using a literature method as described in for e.g. JOC, 2005, 70, 6918-6920. 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 and a linear peptide chain were build.

15 The peptide-resin precursors for their respective peptidomimetics may be cleaved and deprotected using suitable variations of any of the standard cleavage procedures described in the literature (see, for example, D. S. King et al. Int. J. peptide Protein res. 36, 1990, 255 - 266). A preferred method for use in this invention is the use of TFA cleavage mixture, in the presence of water and TIPS as scavengers. Typically,
20 the peptidyl-resin was incubated in TFA / Water /TIPS (94:3:3; V: V: V; 10 ml / 100 mg of peptidyl resin) for 1.5-2 hrs at room temperature. The cleaved resin is then filtered off, the TFA solution is concentrated or dried under reduced pressure. The resulting crude peptide is either precipitated or washed with Et₂O or is re-dissolved directly into DMF or 50 % aqueous acetic acid for purification by preparative HPLC.

25 Peptidomimetics with the desired purity can be obtained by purification using preparative HPLC. The solution of crude peptide is injected into a semi-Prep column (Luna 10 μ ; C₁₈; 100 Å), dimension 250 X 50 mm and eluted with a linear gradient of ACN in water, both buffered with 0.1 % TFA, using a flow rate of 15 -50 ml /min with effluent monitoring by PDA detector at 220 nm. The structures of the purified
30 peptidomimetics can be confirmed by Electrospray Mass Spectroscopy (ES-MS) analysis.

All the peptide prepared were isolated as trifluoro-acetate salt, with TFA as a counter ion, after the Prep-HPLC purification. However, some peptides were subjected for desalting, by passing through a suitable ion exchange resin bed, preferably through anion-exchange resin

Dowex SBR P(Cl) or an equivalent basic anion-exchange resin. In some cases, TFA counter ions were replaced with acetate ions, by passing through suitable ion-exchange resin, eluted with dilute acetic acid solution. For the preparation of the hydrochloride salt of peptides, in the last stage of the manufacturing, selected peptides, with the acetate salt was treated with 4 M HCl. The resulting solution was filtered through a membrane filter (0.2 μ m) and subsequently lyophilized to yield the white to off-white HCl salt. Following similar techniques and/or such suitable modifications, which are well within the scope of persons skilled in the art, other suitable pharmaceutically acceptable salts of the peptidomimetics of the present invention were prepared.

10 In a preferred embodiment, the present invention provides a method of making a peptidomimetics that mimics the activity of an endogenous polypeptide GLP-1R agonist. In another preferred embodiment, the polypeptide receptor agonist is GLP-1.

The novel compounds of the present invention can be formulated into suitable pharmaceutically acceptable compositions by combining with suitable excipients as are well known.

The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula (I) either alone or combination, according to this invention.

20 The quantity of active component, that is, the compounds of formula (I) according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. By way of 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.

General method of preparation of peptidomimetics, using SPPS approach:

Assembly of peptidomimetics on resin:

30 Sufficient quantity (50–100 mg) of Fmoc-PAL-PEG-PS resin or Fmoc-Rink amide MBHA resin, loading: 0.5–0.6 mmol / g was swelled in DMF (1–10 ml / 100 mg of resin) for 2–10 minutes. The Fmoc-group on resin was then removed by incubation of resin with 10–30 % piperidine in DMF (10–30 ml / 100 mg of resin), for 10–30 minutes. Deprotected resin was filtered and washed excess of DMF, DCM and ether (50 ml X 4). Washed resin was incubated in freshly distilled DMF (1 ml / 100 mg of

resin), under nitrogen atmosphere for 5 minutes. A 0.5 M solution of first Fmoc-protected amino acid (1-3 eq.), pre-activated with HOBt (1-3 eq.) and DIPCDI (1-2 eq.) in DMF was added to the resin, and the resin was then shaken for 1-3 hrs, under nitrogen atmosphere. Coupling completion was monitored using a qualitative ninhydrin test. After the coupling of first amino acid, the resin was washed with DMF, DCM and Diethyl ether (50 ml X 4). For the coupling of next amino acid, firstly, the Fmoc-protection on first amino acid, coupled with resin was deprotected, using a 10-20% piperidine solution, followed by the coupling the Fmoc-protected second amino acid, using a suitable coupling agents, and as described above. The repeated cycles of deprotection, washing, coupling and washing were performed until the desired peptide chain was assembled on resin, as per general scheme above.

Finally, the Fmoc-protected peptidyl-resin prepared above was deprotected by 20% piperidine treatment as described above and the peptidyl-resins were washed with DMF, DCM and Diethyl ether (50 ml X 4). Resin containing desired peptide was dried under nitrogen pressure for 10-15 minutes and subjected for cleavage/ deprotection.

Cleavage and deprotection:

The desired peptidomimetics were cleaved and deprotected from their respective peptidyl-resins by treatment with TFA cleavage mixture as follows. A solution of TFA / Water / Triisopropylsilane (95: 2.5: 2.5) (10 ml / 100 mg of peptidyl-resin) was added to peptidyl-resins and the mixture was kept at room temperature with occasional stirring. The resin was filtered, washed with a cleavage mixture and the combined filtrate was evaporated to dryness. Residue obtained was dissolved in 10 ml of water and the aqueous layer was extracted 3 times with ether (20 ml each) and finally the aqueous layer was freeze-dried. Crude peptide obtained after freeze-drying was purified by preparative HPLC as follows:

Preparative HPLC purification of the crude peptidomimetics:

Preparative HPLC was carried out on a Shimadzu LC-8A liquid chromatograph. A solution of crude peptide dissolved in DMF or water was injected into a semi-Prep column (Luna 10 μ ; C₁₈; 100 Å⁰), dimension 250 X 50 mm and eluted with a linear gradient of ACN in water, both buffered with 0.1 % TFA, using a flow rate of 15 -50 ml / min, with effluent monitoring by PDA detector at 220 nm. A typical gradient of 20 % to 70 % of water-ACN mixture, buffered with 0.1 % TFA was used, over a period of 50 minutes, with 1% gradient change per minute. The desired product eluted were

collected in a single 10-20 ml fraction and pure peptidomimetics were obtained as amorphous white powders by lyophilisation of respective HPLC fractions.

HPLC analysis of the purified peptidomimetics

After purification by preparative HPLC as described above, each peptide was
 5 analyzed by analytical RP-HPLC on a Shimadzu LC-10AD analytical HPLC system. For analytic HPLC analysis of peptidomimetics, Luna 5 μ ; C₁₈; 100 Å, dimension 250 X 4.6 mm column was used, with a linear gradient of 0.1% TFA and ACN buffer and the acquisition of chromatogram was carried out at 220 nm, using a PDA detector.

Characterization by Mass Spectrometry

10 Each peptide was characterized by electrospray ionisation mass spectrometry (ESI-MS), either in flow injection or LC/MS mode. Triple quadrupole mass spectrometers (API-3000 (MDS-SCIEX, Canada) was used in all analyses in positive and negative ion electrospray mode. Full scan data was acquired over the mass range of quadrupole, operated at unit resolution. In all cases, the experimentally measured
 15 molecular weight was within 0.5 Daltons of the calculated monoisotopic molecular weight. Quantification of the mass chromatogram was done using Analyst 1.4.1 software.

Utilizing the synthetic methods described herein along with other commonly known techniques and suitable variations thereof, the following GLP-1
 20 peptidomimetics were prepared. This list is indicative of the various groups of peptidomimetics, which can be prepared according to the present invention, and are expected to at least include obvious variations of these compounds. However, such disclosure should not be construed as limiting the scope of the invention in any way.

Table 1:

S. No.	Sequence
1	HGEGTFTSD-(CH ₂) ₃ -GPSSGAPPPS
2	HGEGTFTSD-(CH ₂) ₄ -GPSSGAPPPS
3	HGEGTFTSD-(CH ₂) ₅ -GPSSGAPPPS
4	HGEGTFTSD-(CH ₂) ₆ -GPSSGAPPPS
5	HGEGTFTSD-(CH ₂) ₇ -GPSSGAPPPS
6	HGEGTFTSD-(CH ₂) ₁₀ -GPSSGAPPPS
7	HGEGTFTSD-(CH ₂) ₁₁ -GPSSGAPPPS

8	HGEGTFTSDLSKQM-(CH ₂) ₃ -GPSS
9	HGEGTFTSDLSKQM-(CH ₂) ₄ -GPSS
10	HGEGTFTSDLSKQM-(CH ₂) ₅ -GPSS
11	HGEGTFTSDLSKQM-(CH ₂) ₆ -GPSS
12	HGEGTFTSDLSKQM-(CH ₂) ₇ -GPSS
13	HGEGTFTSDLSKQM-(CH ₂) ₁₀ -GPSS
14	HGEGTFTSDLSKQM-(CH ₂) ₁₁ -GPSS
15	HGEGTFTSDLSKQME-G-GPSSGAPPPS
16	HGEGTFTSDLSKQME-(CH ₂) ₂ -GPSSGAPPPS
17	HGEGTFTSDLSKQME-(CH ₂) ₃ -GPSSGAPPPS
18	HGEGTFTSDLSKQME-(CH ₂) ₄ -GPSSGAPPPS
19	HGEGTFTSDLSKQME-(CH ₂) ₅ -GPSSGAPPPS
20	HGEGTFTSDLSKQME-(CH ₂) ₆ -GPSSGAPPPS
21	HGEGTFTSDLSKQME-(CH ₂) ₇ -GPSSGAPPPS
22	HGEGTFTSDLSKQME-(CH ₂) ₁₀ -GPSSGAPPPS
23	HGEGTFTSDLSKQME-(CH ₂) ₁₁ -GPSSGAPPPS

Table 2:

S. No.	Sequence
1	HAEGTFTSD-(CH ₂) ₂ -VKGR
2	HAEGTFTSD-(CH ₂) ₃ -VKGR
3	HAEGTFTSD-(CH ₂) ₄ -VKGR
4	HAEGTFTSD-(CH ₂) ₅ -VKGR
5	HAEGTFTSD-(CH ₂) ₆ -VKGR
6	HAEGTFTSD-(CH ₂) ₁₀ -VKGR
7	HAibEGTFTSD-(CH ₂) ₂ -VKGR
8	HAibEGTFTSD-(CH ₂) ₃ -VKGR
9	HAibEGTFTSD-(CH ₂) ₄ -VKGR
10	HAibEGTFTSD-(CH ₂) ₅ -VKGR
11	HAibEGTFTSD-(CH ₂) ₆ -VKGR

12	HAibEGTFTSD-(CH ₂) ₁₀ -VKGR
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Table 3:

S. No.	Sequence
1	HGEGTFTSDLSKQMKELEKLL
2	HAEGTFTSDKELEKLL
3	HGEGTFTSDKELEKLL
4	HAibEGTFTSDGKELEKLL
5	HGEGTFTSDGKELEKLL
6	HGEGTFTSDVSKELEKLL
7	HAEGTFTSDVSKELEKLL
8	HAEGTFTSDVSEKELEKLL
9	HAEGTFTSDVSGKELEKLL
10	HAEGTFTSDVSSYLEKELEKLL
11	HAEGTFTSDVSSYLEGKELEKLL
12	HGEGTFTSDVSSYLEGKELEKLL
13	HAEGTFTSDVSSYLEGKELEKLL
14	HAibEGTFTSDVSSYLEGKELEKLL
15	HAEGTFTSDVSSYLEGKELEKLLVKG
16	HAEGTFTSDVSSYLEPKELEKLL
17	HAEGTFTSDVSSYLEGQAAKELEKLL
18	HAEGTFTSDVSSYLEGQAAKEFIKELEKLL
19	HAibEGTFTSDVSSYLEGQAAKEFIKELEKLL
20	HAibEGT-(α -Me)Phe(2-F)- TSDVSSYLEGQAAKEFIKELEKLL
21	Des-amino-HAibEGT-(α -Me)Phe(2-F)- TSDVSSYLEGQAAKEFIKELEKLL
22	HAEGTFTSD-(CH ₂) ₃ -KELEKLL
23	HAEGTFTSD-(CH ₂) ₄ -KELEKLL
24	HAEGTFTSD-(CH ₂) ₅ -KELEKLL
25	HAEGTFTSD-(CH ₂) ₆ -KELEKLL
26	HA-(CH ₂) ₃ -DVSSYLEGQAAKEFIKELEKLL

27	HAib-(CH ₂) ₃ -DVSSYLEGQAAKEFIKELEKLL
28	HAibEGTFTSDVSSYLEGQ-(CH ₂) ₂ -KELEKLL
29	HAibEGTFTSDVSSYLEGQ-(CH ₂) ₃ -KELEKLL
30	HAibEGTFTSDVSSYLE-(CH ₂) ₂ -FIKELEKLL

Table 4:

S. No.	Sequence
1	HGEGTFTSD-(CH ₂) ₃ -Bip-Bip
2	HAibEGTFTSD-(CH ₂) ₃ -Bip-Bip
3	HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₃ -Bip-Bip
4	HAEGTFTSD-G-Bip(2-Me)-Bip(2-Me)
5	HAibEGTFTSD-G-Bip(2-Me)-Bip(2-Me)
6	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Me)
7	HAEGTFTS-G-Bip(2-Me)-Bip(2-Me)
8	HAibEGTFTS-G-Bip(2-Me)-Bip(2-Me)
9	HAibEGT-(α -Me)-Phe(2-F)-TS-G-Bip(2-Me)-Bip(2-Me)
10	HAEGTFTS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
11	HAibEGTFTS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
12	HAibEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
13	HAEGTFT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
14	HAibEGTFT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
15	HAibEGT-(α -Me)-Phe(2-F)-T-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
16	HAEGTF-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
17	HAibEGTF-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
18	HAibEGT-(α -Me)-Phe(2-F)-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
19	HAEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
20	HAibEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
21	HAEG-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
22	HAibEG-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
23	HAEGTFTSD-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
24	HAibEGTFTSD-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)

25	HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
26	HAEGTFTSD-G-Bip-Bip(2-Me)
27	HAibEGTFTSD-G-Bip-Bip(2-Me)
28	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip(2-Me)
29	HAEGTFTSD-G-Bip(2-Me)-Bip
30	HAibEGTFTSD-G-Bip(2-Me)-Bip
31	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip
32	HAEGTFTSD-G-Bip-Bip
33	HAibEGTFTSD-G-Bip-Bip
34	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip
35	HAEGTFTSD-G-Bip-Bip(2-Et)
36	HAibEGTFTSD-G-Bip-Bip(2-Et)
37	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip(2-Et)
38	HAEGTFTSD-G-Bip(2-Et)-Bip(2-Et)
39	HAibEGTFTSD-G-Bip(2-Et)-Bip(2-Et)
40	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Et)
41	HAEGTFTSD-G-Bip(2-Et)-Bip
42	HAibEGTFTSD-G-Bip(2-Et)-Bip
43	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip
44	HAEGTFTSD-G-Bip(2-Et)-Bip(2-Me)
45	HAibEGTFTSD-G-Bip(2-Et)-Bip(2-Me)
46	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Me)
47	HAEGTFTSD-G-Bip(2-Me)-Bip(2-Et)
48	HAibEGTFTSD-G-Bip(2-Me)-Bip(2-Et)
49	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Et)
50	HGEGTFTSD-G-Bip(2-Me)-Bip(2-Me)
51	HGEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Me)
52	HGEGTFTSD-G-Bip(2-Et)-Bip(2-Et)
53	HGEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Et)
54	HGEGTFTSD-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
55	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
56	HGEGTFTSD-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)

57	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
58	HGEGTFTSD-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
59	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
60	HGEGTFTSD-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
61	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
62	HGEGTFTSD-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
63	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
64	HGEGTFTSD-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)
65	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)
66	HGEGTFTSD-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
67	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
68	HGEGTFTSD-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
69	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
70	HGEGTFTSD-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
71	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Et)
72	HGEGTFTSD-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)
73	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)
74	HGEGTFTSD-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)
75	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)
76	HGEGTFTS-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
77	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
78	HGEGTFTS-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
79	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
80	HGEGTFTS-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
81	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
82	HGEGTFTS-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
83	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
84	HGEGTFTS-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
85	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
86	HGEGTFTS-(CH ₂) ₁₁ -Bip(2-Me)-Bip(2-Me)
87	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₁₁ -Bip(2-Me)-Bip(2-Me)
88	HGEGTFTS-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)

89	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)
90	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
91	HGEGTFTS-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
92	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
93	HGEGTFTS-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
94	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
95	HGEGTFTS-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Et)
96	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Et)
97	HGEGTFTS-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)
98	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)
99	HGEGTFTS-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)
100	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)
101	HGEGTFTS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
102	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
103	HGEGTFTS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
104	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
105	HAEGTFTS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
106	HAibEGTFTS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
107	HAibEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
108	HGEGTFTSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
109	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
110	HAEGTFTSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
111	HAibEGTFTSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
112	HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
113	HAEGTF-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Et)
114	HAibEGTF-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Et)
115	HAibEGT-(α -Me)-Phe(2-F)-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Et)
116	HAEGTFTSD-G-TrPh-TrPh
117	HAibEGTFTSD-G-TrPh-TrPh
118	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-TrPh-TrPh
119	HAibEGT-(α -Me)-Phe(2-F)-(CH ₂) ₂ -TrPh-TrPh
120	HAibEG-(CH ₂) ₂ -TrPh-TrPh

121	HAibE-(CH ₂) ₂ -TrPh-TrPh
122	HAib-(CH ₂) ₃ -TrPh-TrPh
123	HAEGTFTSD-G-Nap-Nap
124	HAibEGTFTSD-G-Nap-Nap
125	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Nap-Nap
126	HAEGTFTSD-G-Bip(2-F)-Bip(2-F)
127	HAibEGTFTSD-G-Bip(2-F)-Bip(2-F)
128	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-F)-Bip(2-F)
129	HAEGTFTSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
130	HAibEGTFTSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
131	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
132	HAEGTFTSD-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
133	HAibEGTFTSD-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
134	HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
135	HAEGTFTS-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
136	HAibEGTFTS-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
137	HAibEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
138	HAEGTFT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
139	HAibEGTFT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
140	HAibEGT-(α -Me)-Phe(2-F)-T-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
141	HAEGTF-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
142	HAibEGTF-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
143	HAibEGT-(α -Me)-Phe(2-F)-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
144	HAEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
145	HAibEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
146	HAEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala

147	HAibEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
148	HAEG-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
149	HAibEG-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala

Table 5:

S. No.	Sequence
1	HAEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
2	HGEGT-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
3	HGEGT-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
4	HGEGT-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
5	HGEGT-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
6	HAEGT-(CH ₂) ₂ -Bip(2-Me)-DBip(2-Me)
7	HAEGT-(CH ₂) ₂ -DBip(2-Me)-Bip(2-Me)
8	HaEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
9	HGEG-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
10	HAEG-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
11	HGEG-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
12	HGEG-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
13	HGEG-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
14	HAEG-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
15	HAEG-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
16	HAEG-(CH ₂) ₄ -Bip(2-Me)-DBip(2-Me)
17	HAEG-(CH ₂) ₅ -Bip(2-Me)-DBip(2-Me)
18	HGEG-(CH ₂) ₅ -DBip(2-Me)-Bip(2-Me)
19	HAE-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
20	HAE-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
21	HAE-(CH ₂) ₂ -D-Bip(2-Me)-Bip(2-Me)
22	HAE-(CH ₂) ₃ -D-Bip(2-Me)-Bip(2-Me)
23	HAE-(CH ₂) ₄ -D-Bip(2-Me)-Bip(2-Me)
24	HAE-(CH ₂) ₄ -Bip(2-Me)-DBip(2-Me)
25	HAE-(CH ₂) ₅ -D-Bip(2-Me)-Bip(2-Me)
26	HAE-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)

27	HAE-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
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Table 6:

S. No.	Sequence
1	H-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
2	H-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
3	H-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
4	H-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
5	H-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Me)
6	H-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Me)
7	H-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Me)
8	H-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Me)
9	H-(CH ₂) ₅ -Bip(2-Me)-DBip(2-Me)
10	H-(CH ₂) ₅ -DBip(2-Me)-Bip(2-Me)
11	H-(CH ₂) ₅ -DBip(2-Me)-DBip(2-Me)
12	HG-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
13	HG-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
14	HG-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
15	HG-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Me)
16	HG-(CH ₂) ₃ -Bip(2-Et)-DBip(2-Me)
17	HG-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
18	FA-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Et)
19	FA-(CH ₂) ₃ -DBip-DBip
20	Ha-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
21	Ha-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
22	Ha-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
23	Ha-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
24	Ha-(CH ₂) ₃ -Bip(2-Et)-DBip(2-Me)
25	Ha-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
26	Ha-(CH ₂) ₃ -Bip(2-Et)-DBip(2-Et)
27	Ha-(CH ₂) ₃ -Bip(2-Me)-Bip
28	Ha-(CH ₂) ₃ -(N(Me))-DBip(2-Me)-Bip(2-Et)

29	Ha-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)
30	Ha-(CH ₂) ₃ -(N(Me))-DBip-Bip(2-Et)
31	Ha-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Et)
32	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
33	HA-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
34	HA-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
35	HA-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
36	HA-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
37	HA-(CH ₂) ₁₁ -Bip(2-Me)-Bip(2-Me)
38	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
39	HA-(CH ₂) ₃ -Bip(2-Et)-DBip(2-Et)
40	HA-(CH ₂) ₃ -DBip(2-Me)-DBip(2-Me)
41	HA-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Me)
42	HA-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
43	HA-(CH ₂) ₃ -Bip(2- <i>l</i> pr)-Bip(2- <i>l</i> pr)
44	HA-(CH ₂) ₃ -Bip(2- <i>l</i> pr)-Bip(2-Me)
45	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2- <i>l</i> pr)
46	HA-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Me)
47	HA-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Et)
48	HA-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Me)
49	HA-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Me)
50	HA-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Me)
51	HA-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
52	HA-(CH ₂) ₃ -DBip(2-Et)-DBip(2-Me)
53	HA-(CH ₂) ₃ -DBip(2-Et)-Bip(2-Me)
54	HA-(CH ₂) ₂ -Bip(2-Me)-DBip(2-Me)
55	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)
56	HA-(CH ₂) ₃ -DBip(2-Et)-DBip(2-Et)
57	HA-(CH ₂) ₃ -DBip(2-Et)-Bip(2-Et)
58	HA-(CH ₂) ₃ -DBip(2-Me)-DBip(2-Et)
59	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Et)
60	HA-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Et)
61	HA-(CH ₂) ₃ -Bip-Bip

62	HA-(CH ₂) ₃ -Bip-DBip
63	HA-(CH ₂) ₃ -DBip-DBip
64	HA-(CH ₂) ₃ -DBip-Bip
65	HA-(CH ₂) ₃ -Bip-Bip(2-Me)
66	HA-(CH ₂) ₃ -Bip(2-Me)-Bip
67	HA-(CH ₂) ₃ -Bip(2-Et)-Bip
68	HA-(CH ₂) ₃ -Bip-Bip(2-Et)
69	HA-(CH ₂) ₃ -Bip(2-Ipr)-DBip(2-Ipr)
70	HA-(CH ₂) ₃ -DBip(2-Ipr)-Bip(2-Ipr)
71	HA-(CH ₂) ₃ -DBip(2-Ipr)-DBip(2-Ipr)
72	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-CN)
73	HA-(CH ₂) ₃ -Bip-Bip(2-CN)
74	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-CN)
75	HA-(CH ₂) ₃ -Bip(2-Ipr)-Bip(2-CN)
76	HA-(CH ₂) ₃ -Bip(2-CN)-Bip(2-Me)
77	HA-(CH ₂) ₃ -Bip(2-CN)-Bip
78	HA-(CH ₂) ₃ -Bip(2-CN)-Bip(2-Et)
79	HA-(CH ₂) ₃ -Bip(2-CN)-Bip(2-Ipr)
80	HA-(CH ₂) ₃ -Bip(2-CN)-Bip(2-CN)
81	HA-(CH ₂) ₂ -F-(CH ₂) ₂ -Bip(2-Et)-DBip(2-Et)
82	HA-(CH ₂) ₂ -F-(CH ₂) ₂ -Bip(2-Et)-DBip(2-Me)
83	HA-(CH ₂) ₅ -Bip(2-Me)-DBip
84	HA-(CH ₂) ₃ -Bip(2-Me)-DBip-R
85	IIA-(CH ₂) ₃ -DBip(2-Me)-DBip
86	HA-(CH ₂) ₅ -Bip(2-Me)-DBip(2-Me)
87	HA-(CH ₂) ₅ -DBip(2-Me)-Bip(2-Me)
88	HA-(CH ₂) ₄ -D(Bip)-Bip(2-Et)
89	HA-(CH ₂) ₅ -D(Bip)-Bip(2-Et)
90	HA-(CH ₂) ₄ -Bip(2-Me)-DBip(2-Me)
91	HA-(CH ₂) ₅ -Bip(2-Me)-DBip(2-Me)
92	HA-(CH ₂) ₃ -(N(Me))-DBip-Bip(2-Et)
93	HA-(CH ₂) ₄ -DBip(2-Me)-Bip(2-Et)
94	HA-(CH ₂) ₅ -DBip(2-Me)-Bip(2-Et)

95	HA-(CH ₂) ₃ -(N(Me))-DBip(2-Me)-Bip(2-Et)
96	HA-(CH ₂) ₄ -Bip(2-Me)-DBip
97	HA-(CH ₂) ₅ -Bip(2-Me)-DBip
98	HA-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)
99	HA-(N(Me))-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Et)
100	HA-(N(Me))-(CH ₂) ₃ -Bip-Bip(2-Et)
101	HA-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
102	HA-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-DBip
103	HAE-(CH ₂) ₂ -F-(CH ₂) ₂ -Bip(2-Et)-DBip(2-Et)
104	HAE-(CH ₂) ₂ -F-(CH ₂) ₂ -Bip(2-Et)-DBip(2-Me)
105	HAib-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)

The following compounds can be prepared according to the general processes described above and are included within the scope of the present invention (Tables 7-9)

Table 7:

S. No.	Sequence
1	HA-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
2	H-Aib-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
3	Ha-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
4	H-(N(Me))A-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
5	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
6	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
7	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
8	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
9	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
10	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂

11	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
12	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
13	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
14	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
15	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
16	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
17	CH ₃ -(CH ₂) ₆ -NH-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
18	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
19	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
20	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
21	HA-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
22	H-Aib-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
23	Ha-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
24	H-(N(Me))A-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
25	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
26	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
27	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
28	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
29	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-

	Me-Ph)-3-Pyr-Ala-NH ₂
30	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
31	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
32	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
33	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
34	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
35	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
36	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
37	CH ₃ -(CH ₂) ₆ -NH-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
38	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
39	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
40	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
41	HA-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
42	H-Aib-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
43	H-a-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
44	H-(N(Me))A-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
45	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
46	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
47	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂

48	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
49	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
50	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
51	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
52	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
53	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
54	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
55	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
56	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
57	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
58	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
59	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
60	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
61	HAE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
62	H-Aib-E-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
63	HaE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
64	H-(N(Me))AE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
65	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
66	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-

	Ala-NH ₂
67	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
68	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
69	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
70	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
71	Des-amino-H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
72	Des-amino-H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
73	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
74	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
75	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
76	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
77	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
78	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
79	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
80	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
81	HAEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
82	H-Aib-EG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
83	HaEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
84	H-(N(Me))AEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂

85	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
86	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
87	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
88	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
89	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
90	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
91	Des-amino-H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
92	Des-amino-H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
93	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
94	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
95	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
96	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
97	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
98	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
99	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
100	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
101	HAEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂

102	H-Aib-EGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
103	HaEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
104	H-(N(Me))AEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
105	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
106	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
107	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
108	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
109	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
110	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
111	Des-amino-H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
112	Des-amino-H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
113	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
114	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
115	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
116	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
117	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
118	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
119	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃

120	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
121	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
122	H-Aib-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
123	Ha-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
124	H-(N(Me))A-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
125	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
126	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
127	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-Bip(2-Me)-NH ₂
128	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-Bip(2-Me)-NH ₂
129	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH ₂
130	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH ₂
131	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH ₂
132	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH ₂
133	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
134	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
135	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₁₀ -CH ₃
136	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₁₀ -CH ₃
137	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
138	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
139	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
140	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃

141	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
142	H-Aib-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
143	Ha-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
144	H-(N(Me))A-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
145	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
146	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
147	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)-NH ₂
148	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)-NH ₂
149	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH ₂
150	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH ₂
151	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH ₂
152	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH ₂
153	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
154	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
155	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₁₀ -CH ₃
156	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₁₀ -CH ₃
157	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
158	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
159	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
160	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃

Table 8:

S. No.	Sequence
1	HA-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
2	H-Aib-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
3	Ha-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
4	H-(N(Me))A-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
5	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
6	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
7	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
8	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
9	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
10	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
11	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
12	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
13	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
14	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
15	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
16	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
17	CH ₃ -(CH ₂) ₆ -NH-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
18	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃

19	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
20	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
21	HA-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
22	H-Aib-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
23	Ha-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
24	H-(N(Me))A-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
25	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
26	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
27	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
28	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
29	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
30	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
31	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
32	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
33	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
34	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
35	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
36	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
37	CH ₃ -(CH ₂) ₆ -NH-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃

38	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
39	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
40	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
41	HA-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
42	H-Aib-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
43	Ha-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
44	H-(N(Me))A-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
45	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
46	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
47	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
48	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
49	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
50	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
51	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
52	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
53	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
54	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
55	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
56	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃

57	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
58	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
59	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
60	CH ₃ -(CH ₂) ₁₀ -NH-H-N(Me)Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
61	HAE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
62	H-Aib-E-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
63	HaE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
64	H-(N(Me))AE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
65	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
66	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
67	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
68	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
69	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
70	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
71	Des-amino-H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
72	Des-amino-H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
73	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
74	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
75	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-

	Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
76	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
77	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
78	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
79	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
80	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
81	HAEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
82	H-Aib-EG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
83	HaEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
84	H-(N(Me))AEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
85	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
86	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
87	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
88	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
89	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
90	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
91	Des-amino-H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
92	Des-amino-H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
93	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃

94	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
95	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
96	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
97	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
98	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
99	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
100	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
101	HAEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
102	H-Aib-EGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
103	HaEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
104	H-(N(Me))AEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
105	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
106	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
107	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
108	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
109	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
110	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
111	Des-amino-H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
112	Des-amino-H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-

	(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
113	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
114	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
115	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
116	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
117	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
118	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
119	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
120	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
121	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
122	H-Aib-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
123	Ha-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
124	H-(N(Me))A-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
125	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
126	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
127	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-Bip(2-Me)-OH
128	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-Bip(2-Me)-OH
129	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
130	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
131	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
132	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
133	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃

134	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
135	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₁₀ -CH ₃
136	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₁₀ -CH ₃
137	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
138	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
139	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
140	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
141	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
142	H-Aib-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
143	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
144	H-(N(Me))A-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
145	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
146	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
147	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)-OH
148	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)-OH
149	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
150	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
151	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
152	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
153	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
154	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
155	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-

	(CH ₂) ₁₀ -CH ₃
156	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₁₀ -CH ₃
157	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
158	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
159	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
160	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃

Table 9:

S. No.	Sequence
1	HA-(CH ₂) ₃ -DVSSYLEGQAAKEFIKELEKLL
2	HAib-(CH ₂) ₃ -DVSSYLEGQAAKEFIKELEKLL
3	HAibEGTFTSDVSSYLEGQ-(CH ₂) ₂ -KELEKLL
4	HAibEGTFTSDVSSYLEGQ-(CH ₂) ₃ -KELEKLL
5	HAibEGTFTSDVSSYLE-(CH ₂) ₂ -FIKELEKLL
6	HAibEGT-(α -Me)Phe(2-F)-TSDVSSYLE-(CH ₂) ₂ -FIKELEKLL
7	HAib-(CH ₂) ₃ -VSSYLE-(CH ₂) ₂ -FIKELEKLL
8	HAib-(CH ₂) ₃ -VSSYLE-(CH ₂) ₃ -FIKELEKLL
9	HAib-(CH ₂) ₃ -YLE-(CH ₂) ₃ -FIKELEKLL
10	HAib-(CH ₂) ₄ -YLE-(CH ₂) ₃ -FIKELEKLL
11	HAib-(CH ₂) ₄ -YL-(CH ₂) ₃ -FIKELEKLL
12	HAib-(CH ₂) ₄ -Y-(CH ₂) ₃ -FIKELEKLL
13	HAib-(CH ₂) ₄ -FIKELEKLL
14	HAib-(CH ₂) ₅ -FIKELEKLL
15	HAib-(CH ₂) ₆ -FIKELEKLL
16	HAib-(CH ₂) ₈ -FIKELEKLL
17	HAib-(CH ₂) ₃ -VSSYLEGQ-(CH ₂) ₃ -KELEKLL
18	HAib-(CH ₂) ₃ -VSSYLEG-(CH ₂) ₃ -KELEKLL

19	HAib-(CH ₂) ₃ -VSSYLE-(CH ₂) ₄ -KELEKLL
20	HAib-(CH ₂) ₃ -SSYLE-(CH ₂) ₄ -KELEKLL
21	HAib-(CH ₂) ₃ -SYLE-(CH ₂) ₄ -KELEKLL
22	HAib-(CH ₂) ₃ -YLE-(CH ₂) ₄ -KELEKLL
23	HAib-(CH ₂) ₃ -YL-(CH ₂) ₄ -KELEKLL
24	HAib-(CH ₂) ₃ -Y-(CH ₂) ₄ -KELEKLL
25	HAib-(CH ₂) ₅ -KELEKLL
26	HAib-(CH ₂) ₆ -KELEKLL
27	HAib-(CH ₂) ₈ -KELEKLL

The peptidomimetics prepared as described above were tested for GLP-1 agonist activity in vitro using the cAMP cell-based assay described below. The GLP-1 mimetic peptide analog stimulated cAMP production in a dose response manner and the corresponding EC₅₀ value were determined for some of the selected peptidomimetics, which are active in vitro at 10 to 100 nM range. The EC₅₀ value of EX-4 was used as a positive control.

Cyclic AMP determination

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 adenylate cyclase and raises intracellular cAMP levels. To monitor agonism of peptide compounds in stimulating the GLP-1 receptor, adeny cyclase activity was monitored by assaying for cellular cAMP levels.

cAMP assay:

Stably transfected CHO/HGLP1R cells were assayed for cAMP generation in a semi high throughput platform using DiscoverX cAMP kit with Exendin-4 as a positive control. The activity of NCEs was determined as % Exendin-4 activity at 0.01 μM concentration. The positive compounds were further validated for cAMP generation using indirect cAMP ELISA kit (R & D systems) The activity of the compounds was expressed as fmol cAMP/μg of protein. EC₅₀ values of some of the representative compounds (I to IV) are shown in Figure 1.

Demonstration of in vivo efficacy of compounds:

The in- vivo glucose lowering properties of some of the representative compounds in animal models is described below. This test was used to examine in vivo efficacy of compounds of the present invention on blood glucose at hyperglycemia. The intra peritoneal glucose tolerance test (IPGTT) was performed in overnight fasted Swiss Albino Mice (SAM), weighing 25-30 g. Mice were given glucose load of 1.5g/

Kg/ 10 ml and blood was collected at different time intervals, via retroorbital plexus. Test compounds (peptidomimetics) 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.

- 5 Blood samples were drawn prior to Vehicle/Test compound/Glucose load (0 minute) and then at 15 min, 30 min, 60 min and 120 min. Vehicle/Test compound was administered 15 minutes prior to glucose load, via intra-peritoneal route of administration. Blood samples were centrifuged and the obtained serum was stored at - 20° C for analysis. Test compounds were examined along with a reference (positive control) and a vehicle control, with n = 6 animals per group. Glucose was determined by the GOD/POD method from serum. The mean value of duplicate results was calculated. The absolute values of glucose in serum levels were calculated using MS Excel software. The 0-minute base line corrected line graph were plotted using Graphpad prism software (ver 3.0). Area under the Curve (AUC) and Base line corrected area under the curve (BCAUC) were calculated and analyzed by performing One way ANOVA followed by Dunnett's post test using Graphpad prism software (ver 3.0).

- Using above experimental protocol, in vivo glucose lowering properties of some of the selected compounds, which showed in vitro EC₅₀, in CHO-GLP-1R cAMP assay, in the range of 1-50 nM range were determined. In Table 10, the in vivo glucose lowering potencies (ED₅₀ in IPGTT SAM model) of selected four representative compounds (Comp. I, II, III & IV) were given.

Table 10: In vivo potencies of compound I to IV (ED₅₀), in IPGTT SAM Model

Comp.	ED ₅₀ in IPGTT SAM Model (n = 6)
I	1 µmole / kg
II	500 nM / Kg
III	250 nM / kg
IV	100 nM / Kg

Several compounds of the present invention were screened in vivo, using other animal models, such as ob/ob, db/db and C57 and they showed in vivo efficacy and potency in varying degrees.

Utilities:

5 The present invention provides novel GLP-1 peptide mimics, with a preference for mimicking GLP-1, such that the compounds of the present invention have agonist activity for the GLP-1 receptor. Further, many of the GLP peptide mimics of the present invention exhibit increased stability to proteolytic cleavage as compared to GLP-1 native sequences.

10 Accordingly, the compounds of the present invention 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),
15 hyperglycemia, hyperinsulinemia, hypercholesterolemia, elevated blood levels of free fatty acids or glycerol, hyperlipidemia, hypertriglyceridemia, obesity, wound healing, tissue ischemia, atherosclerosis, hypertension, intestinal diseases (such as necrotizing enteritis, microvillus inclusion disease or celiac disease). The compound of the present invention may also be utilized to increase the blood levels of high density lipoprotein
20 (HDL).

In addition, the conditions, diseases 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 of the invention. The compounds of the present invention may optionally be used in combination with suitable DPP-IV
25 inhibitors for the treatment of some of the above disease states either by administering the compounds sequentially or as a formulation containing the compounds of the present invention along with a suitable DPP-IV inhibitors.

No adverse effects were observed for any of the mentioned compounds of invention. The compounds of the present invention showed good glucose serum-
30 lowering activity in the experimental animals used. These compounds are used for the testing/ prophylaxis of diseases caused by hyperinsulinaemia, hyperglycemia such as NIDDM, metabolic disorders and obesity since such diseases are inter-linked to each other.

We claim:

1. An isolated polypeptide having a sequence of Formula (I), including its tautomers, solvates and pharmaceutically acceptable salts



5 wherein,

A represents $-NH-R_1$, wherein R_1 represents hydrogen, groups selected from linear or branched (C_1-C_{15}) alkyl chain, an amino acid or peptide containing one, two or three natural amino acid residues, R_3-CO- group, $R_3O-C(O)-$ group, a sulfonyl group of formula R_3-SO_2- , each of these groups may be substituted; R_3 is selected from linear or
10 branched (C_1-C_{10}) alkyl, (C_3-C_6) cycloalkyl, aryl, heteroaryl, arylalkyl groups, each of these groups may be substituted;

B represents $-COOR_2$, $-CONHR_2$ or CH_2OR_2 , R_2 represents H, groups selected from linear or branched (C_1-C_{10}) alkyl, aryl groups selected from phenyl, naphthyl, indanyl, fluorenyl, biphenyl groups, aralkyl group, wherein the aryl groups are as defined
15 earlier, each of these groups may be substituted;

each of S_1 and S_2 may independently be a bond or independently represents a group $-NH-(CH_2)_n-COO-$, where, $n=1-9$;

Y represents a bond or $-CO-$, $-(CH_2)_m-$ ($m = 1-3$), 'O', 'S', $-CO-NH-$, $-CO-NR_4-$, or represents a short peptide containing one or two or three amino acids selected from
20 natural or non-natural amino acids; where R_4 represents H, optionally substituted groups selected from linear or branched (C_1-C_{10}) alkyl or aryl groups selected from phenyl, naphthyl, indanyl, fluorenyl, biphenyl groups; with the proviso that when S_1-Y-S_2 represents a bond,

X_1 is selected from the following amino acid sequences

25 HAEGTFTSD, HAEGTFTSDV, HAEGTFTSDVS, HAEGTFTSDVSS,
HAEGTFTSDVSSY, HAEGTFTSDVSSYL, HAEGTFTSDVSSYLE,
HAEGTFTSDVSSYLEG, HAEGTFTSDVSSYLEGQ, HAEGTFTSDVSSYLEGQA,
HAEGTFTSDVSSYLEGQAA, HAEGTFTSDVSSYLEGQAAK,
HAEGTFTSDVSSYLEGQAAKE, HAEGTFTSDVSSYLEGQAAKEF,

30 HAEGTFTSDVSSYLEGQAAKEFI, with the further option that one or more of these amino acids may be replaced by unnatural amino acids, and X_2 is selected from the following amino acid sequences

GPSSGAPPPS or

KELEKLL or

GPPS or

VKGR;

and when S_1 -Y- S_2 does not represent a bond

X_1 is selected from the following amino acid sequences

- 5 HA, HAE, HAEG, HAEGT, HAEGTF, HAEGTFT, HAEGTFTS, HAEGTFTSD with the further option that one or more of these amino acids may be replaced by unnatural amino acids;

X_2 is selected from

GPSSGAPPPS or

- 10 KELEKLL or

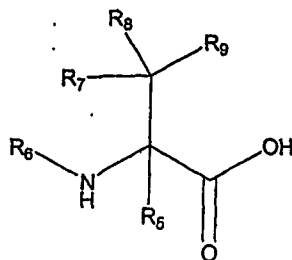
GPPS or

VKGR or

a dipeptide, selected from combination of two amino acids consisting of natural or unnatural amino acids, having a side chain containing an arylalkyl or heterorylalkyl

- 15 moieties selected from benzyl, naphthylmethyl, pyridylmethyl, thienylmethyl, furylmethyl, imidazolylmethyl, isooxazolylmethyl, quinolylmethyl, benzofuranylmethyl, benzothienylmethyl, indolylmethyl, indolylmethyl, dibenzofuranylmethyl, dibenzothienylmethyl, benzodihydrofuranylmethyl, benzodihydrothienylmethyl, thienopyrimidylmethyl, benzimidazolylmethyl, 20 phenanthrenylmethyl, dihydrophenanthrenylmethyl, fluorenylmethyl, dibenzofuranylmethyl, dibenzothiophenyl methyl groups, where each of these groups may be optionally substituted with (C_1-C_6) alkyl, (C_1-C_6) alkoxy, cyano, halo, hydroxy or optionally substituted aryl or heteroaryl groups, with the further provision that such aryl or heteroaryl substituents may further be optionally substituted with (C_1-C_6) alkyl, 25 (C_1-C_6) alkoxy, cyano, halo, hydroxy or aryl or heteroaryl groups.

2. A compound as claimed in claim 1 wherein the non-natural amino acids are represented by the general formula (IIa)



(IIa)

wherein R_5 is selected from H, F, (C₁-C₅) alkyl, the stereochemical configuration at the carbon bearing R_5 may be (R) or (S); R_6 is selected from H or (C₁-C₃) alkyl; each of R_7 and R_8 is independently selected from H, (C₁-C₂) alkyl or halogen atom, preferably fluorine atom; R_9 represents groups, selected from (C₁-C₅) alkyl, aryl or heteroryl moieties selected from phenyl, naphthyl, pyridyl, thienyl, furyl, imidazolyl, isooxazolyl, quinolyl, benzofuranyl, benzothienyl, indolyl, indolyl, dibenzofuranyl, dibenzothienyl, benzodihydrofuranyl, benzodihydrothienyl, thienopyrimidyl, benzimidazolyl, phenanthrenyl, dihydrophenanthrenyl, fluorenyl, dibenzofuranyl, dibenzothiophenyl groups, where each of these groups may be optionally substituted with (C₁-C₆) alkyl, (C₁-C₆) alkoxy, cyano, halo, hydroxy or optionally substituted aryl or heteroaryl groups, with the further provision that such aryl or heteroaryl substituents may further be optionally substituted with (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, halo, hydroxy or aryl or heteroaryl groups.

3. The isolated peptide as claimed in claim 1, wherein the dipeptide representing X_2 is preferably selected from Bip, Bip(2-Me), Bip(2-Et), Bip(2-Ipr), Bip(2-CN), Bip(2'-Et-4'-OMe), Bip(4'-fluoro), Bip(4'-Phenyl), 2-(9,10-Dihydro-phenanthrenyl]-Ala, 2-(Phenanthrenyl)-Ala, 4-(2-Naphthyl)-Phe, 4-(1-Naphthyl)-Phe, 2-Fluorenyl-Ala, 4-dibenzofuran-Phe, 4-dibenzothiophene-Phe, 4-(2'-methylphenyl)-3-pyridylalanine groups.

4. The isolated peptide as claimed in claim 1, wherein the substituents are selected from hydroxyl, oxo, halo, thio, nitro, amino, cyano, alkyl, haloalkyl, alkoxy, haloalkoxy, cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, carboxylic acid and its derivatives selected from esters and amides.

5. The isolated polypeptide of claim 1, wherein the isolated polypeptide is a compound selected from

HGEGTFTSD-(CH₂)₃-GPSSGAPPPS

HGEGTFTSD-(CH₂)₄-GPSSGAPPPS

HGEGTFTSD-(CH₂)₅-GPSSGAPPPS

HGEGTFTSD-(CH₂)₆-GPSSGAPPPS

HGEGTFTSD-(CH₂)₇-GPSSGAPPPS

- HEGTFTSD-(CH₂)₁₀-GPSSGAPPPS
 HEGTFTSD-(CH₂)₁₁-GPSSGAPPPS
 HEGTFTSDLSKQM-(CH₂)₃-GPSS
 HEGTFTSDLSKQM-(CH₂)₄-GPSS
 5 HEGTFTSDLSKQM-(CH₂)₅-GPSS
 HEGTFTSDLSKQM-(CH₂)₆-GPSS
 HEGTFTSDLSKQM-(CH₂)₇-GPSS
 HEGTFTSDLSKQM-(CH₂)₁₀-GPSS
 HEGTFTSDLSKQM-(CH₂)₁₁-GPSS
 10 HEGTFTSDLSKQME-G-GPSSGAPPPS
 HEGTFTSDLSKQME-(CH₂)₂-GPSSGAPPPS
 HEGTFTSDLSKQME-(CH₂)₃-GPSSGAPPPS
 HEGTFTSDLSKQME-(CH₂)₄-GPSSGAPPPS
 HEGTFTSDLSKQME-(CH₂)₅-GPSSGAPPPS
 15 HEGTFTSDLSKQME-(CH₂)₆-GPSSGAPPPS
 HEGTFTSDLSKQME-(CH₂)₇-GPSSGAPPPS
 HEGTFTSDLSKQME-(CH₂)₁₀-GPSSGAPPPS
 HEGTFTSDLSKQME-(CH₂)₁₁-GPSSGAPPPS
 HAEGTFTSD-(CH₂)₂-VKGR
 20 HAEGTFTSD-(CH₂)₃-VKGR
 HAEGTFTSD-(CH₂)₄-VKGR
 HAEGTFTSD-(CH₂)₅-VKGR
 HAEGTFTSD-(CH₂)₆-VKGR
 HAEGTFTSD-(CH₂)₁₀-VKGR
 25 HAibEGTFTSD-(CH₂)₂-VKGR
 HAibEGTFTSD-(CH₂)₃-VKGR
 HAibEGTFTSD-(CH₂)₄-VKGR
 HAibEGTFTSD-(CH₂)₅-VKGR
 HAibEGTFTSD-(CH₂)₆-VKGR
 30 HAibEGTFTSD-(CH₂)₁₀-VKGR
 HEGTFTSDLSKQMKELEKLL
 HAEGTFTSDKELEKLL
 HEGTFTSDKELEKLL
 HAibEGTFTSDGKELEKLL

- HGEGTFTSDGKELEKLL
HGEGTFTSDVSKELEKLL
HAEGTFTSDVSKELEKLL
HAEGTFTSDVSEKELEKLL
5 HAEGTFTSDVSGKELEKLL
HAEGTFTSDVSSYLEKELEKLL
HAEGTFTSDVSSYLEGKELEKLL
HGEGTFTSDVSSYLEGKELEKLL
HaEGTFTSDVSSYLEGKELEKLL
10 HAibEGTFTSDVSSYLEGKELEKLL
HAEGTFTSDVSSYLEGKELEKLLVKG
HAEGTFTSDVSSYLEPKKELEKLL
HAEGTFTSDVSSYLEGQAAKELEKLL
HAEGTFTSDVSSYLEGQAAKEFIKELEKLL
15 HAibEGTFTSDVSSYLEGQAAKEFIKELEKLL
HAibEGT-(α -Me)Phe(2-F)-TSDVSSYLEGQAAKEFIKELEKLL
Des-amino-HAibEGT-(α -Me)Phe(2-F)-TSDVSSYLEGQAAKEFIKELEKLL
HAEGTFTSD-(CH₂)₃-KELEKLL
HAEGTFTSD-(CH₂)₄-KELEKLL
20 HAEGTFTSD-(CH₂)₅-KELEKLL
HAEGTFTSD-(CH₂)₆-KELEKLL
HA-(CH₂)₃-DVSSYLEGQAAKEFIKELEKLL
HAib-(CH₂)₃-DVSSYLEGQAAKEFIKELEKLL
HAibEGTFTSDVSSYLEGQ-(CH₂)₂-KELEKLL
25 HAibEGTFTSDVSSYLEGQ-(CH₂)₃-KELEKLL
HAibEGTFTSDVSSYLE-(CH₂)₂-FIKELEKLL
HGEGTFTSD-(CH₂)₃-Bip-Bip
HAibEGTFTSD-(CH₂)₃-Bip-Bip
HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH₂)₃-Bip-Bip
30 HAEGTFTSD-G-Bip(2-Me)-Bip(2-Me)
HAibEGTFTSD-G-Bip(2-Me)-Bip(2-Me)
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Me)
HAEGTFTS-G-Bip(2-Me)-Bip(2-Me)
HAibEGTFTS-G-Bip(2-Me)-Bip(2-Me)

- HAibEGT-(α -Me)-Phe(2-F)-TS-G-Bip(2-Me)-Bip(2-Me)
HAEGTFTS-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEGTFTS-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
5 HAEGTFT-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEGTFT-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEGT-(α -Me)-Phe(2-F)-T-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAEGTF-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEGTF-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
10 HAibEGT-(α -Me)-Phe(2-F)-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAEGT-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEGT-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAEG-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEG-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
15 HAEGTFTSD-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEGTFTSD-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HAEGTFTSD-G-Bip-Bip(2-Me)
HAibEGTFTSD-G-Bip-Bip(2-Me)
20 HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip(2-Me)
HAEGTFTSD-G-Bip(2-Me)-Bip
HAibEGTFTSD-G-Bip(2-Me)-Bip
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip
HAEGTFTSD-G-Bip-Bip HAibEGTFTSD-G-Bip-Bip
25 HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip
HAEGTFTSD-G-Bip-Bip(2-Et)
HAibEGTFTSD-G-Bip-Bip(2-Et)
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip(2-Et)
HAEGTFTSD-G-Bip(2-Et)-Bip(2-Et)
30 HAibEGTFTSD-G-Bip(2-Et)-Bip(2-Et)
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Et)
HAEGTFTSD-G-Bip(2-Et)-Bip
HAibEGTFTSD-G-Bip(2-Et)-Bip

- HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip
HAEGTFTSD-G-Bip(2-Et)-Bip(2-Me)
HAibEGTFTSD-G-Bip(2-Et)-Bip(2-Me)
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Me)
5 HAEGTFTSD-G-Bip(2-Me)-Bip(2-Et)
HAibEGTFTSD-G-Bip(2-Me)-Bip(2-Et)
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Et)
HGEFTFTSD-G-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Me)
10 HGEFTFTSD-G-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
15 HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
20 HGEFTFTSD-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
25 HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₅-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₅-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₆-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₆-Bip(2-Et)-Bip(2-Et)
30 HGEFTFTSD-(CH₂)₁₀-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₁₀-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₁₁-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₁₁-Bip(2-Et)-Bip(2-Et)

- HGEGTFTS-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEGTFTS-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
5 HGEGTFTS-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEGTFTS-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HGEGTFTS-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
10 HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HGEGTFTS-(CH₂)₁₁-Bip(2-Me)-Bip(2-Me)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₁₁-Bip(2-Me)-Bip(2-Me)
HGEGTFTS-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
15 HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₅-Bip(2-Et)-Bip(2-Et)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₅-Bip(2-Et)-Bip(2-Et)
20 HGEGTFTS-(CH₂)₆-Bip(2-Et)-Bip(2-Et)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₆-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₁₀-Bip(2-Et)-Bip(2-Et)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₁₀-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₁₁-Bip(2-Et)-Bip(2-Et)
25 HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₁₁-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HGEGTFTS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HGE GT-(α-Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
30 HAEGTFTS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAibEGTFTS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAibEGT-(α-Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HGEGTFTSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)

- HGEET-(α -Me)-Phe(2-F)-TSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
 HAEGTFTSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
 HAibEGTFTSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
 HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
 5 HAEGTF-(CH₂)₂-Bip(2-Me)-Bip(2-Et)
 HAibEGTF-(CH₂)₂-Bip(2-Me)-Bip(2-Et)
 HAibEGT-(α -Me)-Phe(2-F)-(CH₂)₂-Bip(2-Me)-Bip(2-Et)
 HAEGTFTSD-G-TrPh-TrPh
 HAibEGTFTSD-G-TrPh-TrPh
 10 HAibEGT-(α -Me)-Phe(2-F)-TSD-G-TrPh-TrPh
 HAibEGT-(α -Me)-Phe(2-F)-(CH₂)₂-TrPh-TrPh
 HAibEG-(CH₂)₂-TrPh-TrPh
 HAibE-(CH₂)₂-TrPh-TrPh
 HAib-(CH₂)₃-TrPh-TrPh
 15 HAEGTFTSD-G-Nap-Nap
 HAibEGTFTSD-G-Nap-Nap
 HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Nap-Nap
 HAEGTFTSD-G-Bip(2-F)-Bip(2-F)
 HAibEGTFTSD-G-Bip(2-F)-Bip(2-F)
 20 AibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-F)-Bip(2-F)
 HAEGTFTSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEGTFTSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAEGTFTSD-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 25 HAibEGTFTSD-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAEGTFTS-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEGTFTS-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 30 HAibEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAEGTFT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEGTFT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala

- HAibEGT-(α -Me)-Phe(2-F)-T-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAEGTF-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEGTF-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEGT-(α -Me)-Phe(2-F)-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 5 HAEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAibEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAEG-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 10 HAibEG-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
 HAEGT-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
 HGEGT-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
 HGEGT-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
 HGEGT-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
 15 HGEGT-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
 HAEGT-(CH₂)₂-Bip(2-Me)-DBip(2-Me)
 HAEGT-(CH₂)₂-DBip(2-Me)-Bip(2-Me)
 HaEGT-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
 HGEG-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
 20 HAEG-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
 HGEG-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
 HGEG-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
 HGEG-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
 HAEG-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
 25 HAEG-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
 HAEG-(CH₂)₄-Bip(2-Me)-DBip(2-Me)
 HAEG-(CH₂)₅-Bip(2-Me)-DBip(2-Me)
 HGEG-(CH₂)₅-DBip(2-Me)-Bip(2-Me)
 HAE-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
 30 HAE-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
 HAE-(CH₂)₂-D-Bip(2-Me)-Bip(2-Me)
 HAE-(CH₂)₃-D-Bip(2-Me)-Bip(2-Me)
 HAE-(CH₂)₄-D-Bip(2-Me)-Bip(2-Me)
 HAE-(CH₂)₄-Bip(2-Me)-DBip(2-Me)

- HAE-(CH₂)₅-D-Bip(2-Me)-Bip(2-Me)
HAE-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
HAE-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
H-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
5 H-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
H-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
H-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₄-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₅-Bip(2-Et)-Bip(2-Me)
10 H-(CH₂)₆-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₁₀-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₅-Bip(2-Me)-DBip(2-Me)
H-(CH₂)₅-DBip(2-Me)-Bip(2-Me)
H-(CH₂)₅-DBip(2-Me)-DBip(2-Me)
15 HG-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HG-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HG-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
HG-(CH₂)₄-Bip(2-Et)-Bip(2-Me)
HG-(CH₂)₃-Bip(2-Et)-DBip(2-Me)
20 HG-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
FA-(CH₂)₃-DBip(2-Me)-Bip(2-Et)
FA-(CH₂)₃-DBip-Dbip
Ha-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
Ha-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
25 Ha-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
Ha-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
Ha-(CH₂)₃-Bip(2-Et)-DBip(2-Me)
Ha-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
Ha-(CH₂)₃-Bip(2-Et)-DBip(2-Et)
30 Ha-(CH₂)₃-Bip(2-Me)-Bip
Ha-(CH₂)₃-(N(Me))-DBip(2-Me)-Bip(2-Et)
Ha-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)
Ha-(CH₂)₃-(N(Me))-DBip-Bip(2-Et)
Ha-(CH₂)₃-DBip(2-Me)-Bip(2-Et)

- HA-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
5 HA-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₁₁-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Et)-DBip(2-Et)
HA-(CH₂)₃-DBip(2-Me)-DBip(2-Me)
10 HA-(CH₂)₃-DBip(2-Me)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
HA-(CH₂)₃-Bip(2-*l*pr)-Bip(2-*l*pr)
HA-(CH₂)₃-Bip(2-*l*pr)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Me)-Bip(2-*l*pr)
15 HA-(CH₂)₄-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Me)-DBip(2-Et)
HA-(CH₂)₂-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₅-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₆-Bip(2-Et)-Bip(2-Me)
20 HA-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₃-DBip(2-Et)-DBip(2-Me)
HA-(CH₂)₃-DBip(2-Et)-Bip(2-Me)
HA-(CH₂)₂-Bip(2-Me)-DBip(2-Me)
HA-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
25 HA-(CH₂)₃-DBip(2-Et)-DBip(2-Et)
HA-(CH₂)₃-DBip(2-Et)-Bip(2-Et)
HA-(CH₂)₃-DBip(2-Me)-DBip(2-Et)
HA-(CH₂)₃-Bip(2-Me)-Bip(2-Et)
HA-(CH₂)₃-DBip(2-Me)-Bip(2-Et)
30 HA-(CH₂)₃-Bip-Bip
HA-(CH₂)₃-Bip-D-Bip
HA-(CH₂)₃-DBip-D-Bip
HA-(CH₂)₃-DBip-Bip
HA-(CH₂)₃-Bip-Bip(2-Me)

- HA-(CH₂)₃-Bip(2-Me)-Bip
HA-(CH₂)₃-Bip(2-Et)-Bip
HA-(CH₂)₃-Bip-Bip(2-Et)
HA-(CH₂)₃-Bip(2-Ipr)-DBip(2-Ipr)
5 HA-(CH₂)₃-DBip(2-Ipr)-Bip(2-Ipr)
HA-(CH₂)₃-DBip(2-Ipr)-DBip(2-Ipr)
HA-(CH₂)₃-Bip(2-Me)-Bip(2-CN)
HA-(CH₂)₃-Bip-Bip(2-CN)
HA-(CH₂)₃-Bip(2-Et)-Bip(2-CN)
10 HA-(CH₂)₃-Bip(2-Ipr)-Bip(2-CN)
HA-(CH₂)₃-Bip(2-CN)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-CN)-Bip
HA-(CH₂)₃-Bip(2-CN)-Bip(2-Et)
HA-(CH₂)₃-Bip(2-CN)-Bip(2-Ipr)
15 HA-(CH₂)₃-Bip(2-CN)-Bip(2-CN)
HA-(CH₂)₂-F-(CH₂)₂-Bip(2-Et)-DBip(2-Et)
HA-(CH₂)₂-F-(CH₂)₂-Bip(2-Et)-DBip(2-Me)
HA-(CH₂)₅-Bip(2-Me)-DBip
HA-(CH₂)₃-Bip(2-Me)-DBip-R
20 HA-(CH₂)₃-DBip(2-Me)-DBip
HA-(CH₂)₅-Bip(2-Me)-DBip(2-Me)
HA-(CH₂)₅-DBip(2-Me)-Bip(2-Me)
HA-(CH₂)₄-D(Bip)-Bip(2-Et)
HA-(CH₂)₅-D(Bip)-Bip(2-Et)
25 HA-(CH₂)₄-Bip(2-Me)-DBip(2-Me)
HA-(CH₂)₅-Bip(2-Me)-DBip(2-Me)
HA-(CH₂)₃-(N(Me))-DBip-Bip(2-Et)
HA-(CH₂)₄-DBip(2-Me)-Bip(2-Et)
HA-(CH₂)₅-DBip(2-Me)-Bip(2-Et)
30 HA-(CH₂)₃-(N(Me))-DBip(2-Me)-Bip(2-Et)
HA-(CH₂)₄-Bip(2-Me)-DBip
HA-(CH₂)₅-Bip(2-Me)-DBip
HA-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)
HA-(N(Me))-(CH₂)₃-DBip(2-Me)-Bip(2-Et)

- HA-(N(Me))-(CH₂)₃-DBip-Bip(2-Et)
 HA-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
 HA-(N(Me))-(CH₂)₃-Bip(2-Me)-DBip
 HAE-(CH₂)₂-F-(CH₂)₂-Bip(2-Et)-DBip(2-Et)
 5 HAE-(CH₂)₂-F-(CH₂)₂-Bip(2-Et)-DBip(2-Me)
 HAib-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)

6. The isolated polypeptide of claim 1 wherein the isolated polypeptide is a compound selected from

- 10 HA-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 H-Aib-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 Ha-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 H-(N(Me))A-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 H-(N(Me))A-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 15 H-(N(Me))Aib-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 20 H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 25 Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
 30 H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
 H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃

- H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₆-NH-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 10 CH₃-(CH₂)₁₀-NH-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- HA-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-Aib-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- Ha-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))A-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 15 H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 20 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 25 Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 30 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃

- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 10 CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- HA-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-Aib-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-a-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))A-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 15 H-(N(Me))A-(N(Me))-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 20 H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 25 Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 30 H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃

- H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- CH₃-(CH₂)₆-NH-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 10 HAE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-Aib-E-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- HaE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 15 H-(N(Me))AE-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 20 H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 25 Des-amino-H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- Des-amino-H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 30 H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

- H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- 5 CH₃-(CH₂)₆-NH-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 10 CH₃-(CH₂)₁₀-NH-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- HAEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-Aib-EG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 15 HaEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AEG-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 20 H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 25 H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- Des-amino-H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 30 Des-amino-H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

- H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- 5 H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 10 CH₃-(CH₂)₁₀-NH-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 15 HAEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-Aib-EGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- HaEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AEGT-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 20 H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 25 H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- 30 Des-amino-H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
- Des-amino-H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

- H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 5 H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
- 10 CH₃-(CH₂)₆-NH-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- 15 CH₃-(CH₂)₁₀-NH-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
- HA-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
- H-Aib-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
- Ha-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
- 20 H-(N(Me))A-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-Bip(2-Me)-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-Bip(2-Me)-NH₂
- 25 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH₂
- Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH₂
- Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH₂
- 30 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃

- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₁₀-CH₃
- 5 CH₃-(CH₂)₆-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- 10 CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- HA-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
- H-Aib-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
- 15 Ha-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
- H-(N(Me))A-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)-NH₂
- 20 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH₂
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH₂
- Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH₂
- 25 Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH₂
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- 30 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₁₀-CH₃

- CH₃-(CH₂)₆-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
- 10 HA-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-Aib-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Ha-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 15 H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 20 H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 25 Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 30 H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃

- CH₃-(CH₂)₆-NH-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₁₀-NH-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 10 HA-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-Aib-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Ha-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 15 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 20 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 25 Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 30 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃

- CH₃-(CH₂)₆-NH-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- HA-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 10 H-Aib-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Ha-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-(N(Me))-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 15 H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 20 H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 25 Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 30 H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃

- CH₃-(CH₂)₆-NH-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- HAE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 10 H-Aib-E-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- HaE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AE-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 15 H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-
Ala-OH
- H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-
Pyr-Ala-OH
- H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-OH
- 20 H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-OH
- Des-amino-H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 25 Des-amino-H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 30 H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃

- CH₃-(CH₂)₆-NH-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₁₀-NH-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- HAEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 10 H-Aib-EG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- HaEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AEG-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-
- 15 OH
- H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-
Ala-OH
- H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-
Pyr-Ala-OH
- 20 H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-
Me-Ph)-3-Pyr-Ala-OH
- Des-amino-H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
- 25 (N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Des-amino-H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 30 H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-
Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-
Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃

- H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 5 CH₃-(CH₂)₆-NH-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 10 CH₃-(CH₂)₁₀-NH-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- HAEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-Aib-EGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- HaEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 15 H-(N(Me))AEGT-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 20 H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 25 H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Des-amino-H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- Des-amino-H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
- 30 H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃

- H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
- 5 CH₃-(CH₂)₆-NH-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₆-NH-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- 10 CH₃-(CH₂)₁₀-NH-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- CH₃-(CH₂)₁₀-NH-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
- HA-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-OH
- H-Aib-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-OH
- 15 Ha-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-OH
- H-(N(Me))A-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-OH
- H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-OH
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-OH
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-Bip(2-Me)-OH
- 20 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-Bip(2-Me)-OH
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
- Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
- 25 Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
- H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH₂)₆-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH₂)₆-CH₃
- 30 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH₂)₁₀-CH₃
- H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH₂)₁₀-CH₃

- CH₃-(CH₂)₆-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-
Bip(2-Me)-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-
Bip(2-Me)-COO-(CH₂)₆-CH₃
5 CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-
Bip(2-Me)-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-
Bip(2-Me)-COO-(CH₂)₆-CH₃
HA-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH
10 H-Aib-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH
Ha-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH
H-(N(Me))A-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH
H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH
H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH
15 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)-OH
H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)-OH
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-
20 OH
Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-
Me)-OH
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-
(CH₂)₆-CH₃
25 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-
(CH₂)₆-CH₃
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-
(CH₂)₁₀-CH₃
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- 30 $\text{HAib}-(\text{CH}_2)_6-\text{KELEKLL}$
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7. A pharmaceutical composition comprising compounds as claimed in claims 1-6 prepared according to the processes described herein and a suitable pharmaceutically acceptable carrier(s).
8. The compounds or their pharmaceutical compositions as claimed in claims 1-7, which possess the ability to mimic the biological activity of GLP-1, more preferably mimic the GLP-1R agonist activity.
9. The compounds or their pharmaceutical compositions as claimed in any of the claims 1-7, useful for the treatment or prevention of diseases wherein GLP-1R peptide plays a patho-physiological function.
10. A method of preventing or treating diseases caused by hyperlipidaemia, hypercholesteremia, hyperglycemia, hyperinsulinemia, elevated blood levels of free fatty acids or glycerol, hypertriglyceridemia, wound healing, obesity, impaired glucose tolerance, leptin resistance, insulin resistance, diabetic complications, such as nephropathy, retinopathy, neuropathy and cataracts, comprising administering an effective, non-toxic amount of compound of formula (I) as defined in any preceding claims to a patient in need thereof.
11. The method according to any preceding claims, wherein the disease is type 2 diabetes, impaired glucose tolerance, dyslipidaemia, hypertension, obesity, atherosclerosis, hyperlipidaemia, coronary artery disease, cardiovascular disorders and other diseases wherein insulin resistance is the underlying pathophysiological mechanism.
12. A medicine for treating/reducing any of the disease conditions described in any preceding claims which comprises administering a compound of formula (I), as defined in claims 1-7 and a pharmaceutically acceptable carrier, diluent, excipients or solvate to a patient in need thereof.
13. A medicine for treating/reducing any of the disease conditions described in any preceding claims which comprises administering a compound of formula (I), as defined in claims 1-7 in combination with a suitable DPP IV inhibitor, to a patient in need thereof.
14. Use of compounds of formula (I), alone or in combination with suitable DPP IV inhibitors, their pharmaceutical compositions and medicines containing them as defined in any previous claims as a medicament suitable for the treatment of diseases mentioned in any of the aforesaid claims.

CHL-558-645.ST25
SEQUENCE LISTING

<110> Cadila Healthcare Limited
Lohray, Braj Bhushan
Lohray, Vidya Bhushan
Bahekar, Rajesh H

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International Bureau



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(72) Inventors; and

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
20 September 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **NOVEL COMPOUNDS AS GLP-I AGONISTS**

A-X₁-S₁-Y-S₂-X₂-B

(I)

(57) Abstract: The present invention describes a group of novel peptidomimetics useful for the treatment of diabetes. These compounds are defined by the general formula (I) as given below. A-X₁-S₁-Y-S₂-X₂-B (I)

WO 2007/017892 A3

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 558-645-CHL	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/IN2006/000154	International filing date (day/month/year) 04/05/2006	(Earliest) Priority Date (day/month/year) 05/05/2005
Applicant CADILA HEALTHCARE LIMITED		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 9 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2006/000154

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☒ on paper
 - ☒ in electronic form
 - c. time of filing/furnishing
 - ☒ contained in the international application as filed
 - ☐ filed together with the international application in electronic form
 - ☒ furnished subsequently to this Authority for the purpose of search
2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2006/000154

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07K14/605

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data, PAJ, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/011892 A (US GOVERNMENT [US]; GREIG NIGEL H [US]; EGAN JOSEPHINE [US]; DOYLE MAI) 13 February 2003 (2003-02-13) the whole document page 13; figure 1; example 1	1-14
X	RUNGE S ET AL: "Different domains of the glucagon and glucagon-like peptide-1 receptors provide the critical determinants of ligand selectivity." BRITISH JOURNAL OF PHARMACOLOGY, vol. 138, no. 5, March 2003 (2003-03), pages 787-794, XP002427759 ISSN: 0007-1188 the whole document	1-14

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the international search

11 July 2007

Date of mailing of the international search report

26/07/2007

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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 Fax: (+31-70) 340-3016

Authorized officer

CERVIGNI, S

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2006/000154

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HINKE SIMON A ET AL: "In depth analysis of the N-terminal bioactive domain of gastric inhibitory polypeptide" LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 75, no. 15, 27 August 2004 (2004-08-27), pages 1857-1870, XP002387302 ISSN: 0024-3205 the whole document	1-14
P,X	WO 2006/024275 A (PHILIPPS UNI MARBURG [DE]; GOTTHARDT MARTIN [DE]; BEHE MARTIN [DE]; BE) 9 March 2006 (2006-03-09) the whole document	1-14
P,X	WO 2005/077072 A (AMYLIN PHARMACEUTICALS INC [US]; LEVY ODILE ESTHER [US]; HANLEY MICHAEL) 25 August 2005 (2005-08-25) the whole document	1-14
P,X	WO 2006/014287 A1 (SQUIBB BRISTOL MYERS CO [US]; EWING WILLIAM R [US]; MAPELLI CLAUDIO [U]) 9 February 2006 (2006-02-09) the whole document	1-14
X	WO 02/28438 A (KING S COLLEGE LONDON [GB]; BANSAL SUKHVINDER SINGH [GB]; HIDER ROBERT) 11 April 2002 (2002-04-11) the whole document examples 3-5	1-14
X	WO 2004/094461 A (SQUIBB BRISTOL MYERS CO [US]; NATARAJAN SESA IYER [US]; MAPELLI CLAUD) 4 November 2004 (2004-11-04) the whole document	1-14
X	AL-SABAH SULEIMAN ET AL: "A model for receptor-peptide binding at the glucagon-like peptide-1 (GLP-1) receptor through the analysis of truncated ligands and receptors" BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, vol. 140, no. 2, September 2003 (2003-09), pages 339-346, XP002437826 ISSN: 0007-1188 the whole document	1-14

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2006/000154

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHAHRAZAD MONTROSE-RAFIZADEH ET AL: "High Potency Antagonists of the Pancreatic Glucagon-like Peptide-1 Receptor" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOCHEMICAL BIOLOGISTS, BIRMINGHAM,, US, vol. 272, no. 34, 22 August 1997 (1997-08-22), pages 21201-21206, XP002247450 ISSN: 0021-9258 the whole document figure 3	1-14
X	DOYLE MAIRE E ET AL: "The importance of the nine-amino acid C-terminal sequence of exendin-4 for binding to the GLP-1 receptor and for biological activity." REGULATORY PEPTIDES, vol. 114, no. 2-3, 15 July 2003 (2003-07-15), pages 153-158, XP002441636 ISSN: 0167-0115 the whole document	1-14
X	US 5 545 618 A (BUCKLEY DOUGLAS I [US] ET AL) 13 August 1996 (1996-08-13) the whole document	1-14
X	XIAO Q ET AL: "Biological activities of glucagon-like peptide-1 analogues in vitro and in vivo" BIOCHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, PA, US, vol. 40, no. 9, 6 March 2001 (2001-03-06), pages 2860-2869, XP002277645 ISSN: 0006-2960 the whole document	1-14
X	GREEN B D ET AL: "STRUCTURALLY MODIFIED ANALOGUES OF GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AND GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP) AS FUTURE ANTIDIABETIC AGENTS" CURRENT PHARMACEUTICAL DESIGN, BENTHAM SCIENCE PUBLISHERS, SCHIPHOL, NL, vol. 10, no. 29, 2004, pages 3651-3662, XP009068381 ISSN: 1381-6128 the whole document	1-14
X	WO 03/058203 A (LILLY CO ELI [US]; GLAESNER WOLFGANG [US]; KOHN WAYNE DAVID [US]; MILL) 17 July 2003 (2003-07-17) the whole document	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2006/000154

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.

2. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is KELEKLL. Pharmaceutical compositions and use as a medicament.

3. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is GPPS. Pharmaceutical compositions and use as a medicament.

4. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is VKGR. Pharmaceutical compositions and use as a medicament.

5. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.

6. claims: 1-14 (all in part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is KELEKLL. Pharmaceutical compositions and use as a medicament.

7. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is GPPS. Pharmaceutical compositions and use as a medicament.

8. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is VKGR. Pharmaceutical compositions and use as a medicament.

9. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is a dipeptide as defined at page 55, lines 13-25. Pharmaceutical compositions and use as a medicament.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2006/000154

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03011892	A	13-02-2003	CA 2455963 A1 13-02-2003 EP 1411968 A2 28-04-2004 JP 2005501058 T 13-01-2005
WO 2006024275	A	09-03-2006	AU 2005279537 A1 09-03-2006 CA 2578252 A1 09-03-2006 DE 102004043153 A1 23-03-2006 EP 1784422 A2 16-05-2007
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WO 03058203	A	17-07-2003	AU 2003200839 A1 24-07-2003 BR PI0306706 A 27-03-2007 CA 2468700 A1 17-07-2003 EP 1585959 A2 19-10-2005 JP 2005528337 T 22-09-2005 MX PA04006679 A 10-11-2004

COMPUESTOS NOVEDOSOS COMO AGONISTAS GLP-1**Campo de la Invención**

La presente invención se relaciona con compuestos novedosos de la Fórmula general (I), sus formas tautoméricas, intermedios novedosos involucrados en su síntesis, sus sales farmacéuticamente aceptables y las composiciones farmacéuticas que las contienen.

A-X₁-S₁-Y-S₂-X₂-B (I)

En particular, la presente invención se relaciona con peptidomiméticos (peptidomimético) péptido-1 similar a glucagón novedosos (GLP-1), que actúan como Agonistas del receptor GLP-1 y exhiben la mayor actividad biológica del GLP-1 nativo. Adicionalmente, estos Peptidomiméticos GLP-1 exhiben estabilidad incrementada para clivaje proteolítico, especialmente contra La enzima DPP-IV (Dipeptidil peptidasa-IV) y se puede suministrar mediante varias rutas invasivas y no invasivas de administraciones tal como oral, nasal, bucal, pulmonar y ruta transdérmica de administración, para el tratamiento o prevención de la diabetes y trastornos relacionados.

La presente invención también se relaciona con un proceso para preparar compuestos de la Fórmula general (I), sus formas tautoméricas, sus sales farmacéuticamente aceptables, las composiciones farmacéuticas que las

contienen, e intermedios novedosos involucrados en sus síntesis.

Antecedente de la Invención

La amida GPL-I (7-36) es un producto del gen preproglucagón, que se secreta a partir de células L intestinales, en respuesta a la ingestión de alimento. La acción fisiológica del GLP-1 ha ganado considerable interés. El GLP-1 ejerce múltiple acción al estimular la secreción de insulina de las células β pancreáticas, en una forma dependiente de glucosa (acción insulínica). El GLP-1 también reduce la concentración de glucagón en plasma circulante al inhibir su secreción de las células α (Drucker D. J., Endocrinology, 142, 521-527, 2001). Más recientemente, se ha hecho claro que el GLP-1 también exhibe propiedades similares a la estimulación del crecimiento de células β , supresión de apetito, vaciado gástrico retrasado y estimulación de la sensibilidad de la insulina (Nauck, Horm. Metab. Res., 47, 1253-1258, 1997).

La vena del monstruo de Gila Heloderma Suspectum contiene un péptido de 39 aminoácidos llamado Exendin-4 (EX-4) que comparte aproximadamente 50 % de identidad de secuencia con el GLP-1 en sí mismo, exhibe una actividad agonista de GLP-1R muy potente (Glucagón similar al receptor péptido-1) (Thorens B., Diabetes, 42, 1678 - 1682, 1993). De hecho, se encontró que el EX-4 es mucho más potente que el péptido GLP-1 nativo, debido a su vida útil relativamente mayor (25 min., ruta de administración iv), comparado con el GLP-1 (2-5 min., ruta de administración iv). El Exendin-4 se

une con mayor afinidad al GLP-1R, debido a la presencia de las nueve secuencias extra C-terminal (Doyle M.E., Regulatory Peptide, 114, 153-158, 2003). Así, propiedades farmacológicas establecidas anteriormente de los agonistas GLP-1R lo hace un agente terapéutico altamente deseable para el tratamiento de diabetes.

El péptido GLP-1 nativo sintético se metaboliza rápidamente por las enzimas proteolíticas, tal como peptidasa-IV dipeptidilo (DPP-IV) en un metabolito inactivo, limitando por lo tanto el uso del GLP-1 como una droga. Actualmente, varios análogos de GLP-1 y EX-4, tal como Liraglutida/NN2211 (Novo Nordisk; fase-III; WO 1998 008871), BIM 51077 (Ipsen; Phase-II; WO 2000 034331), CJC-1131 (ConjuChem; fase-II; WO 2000 069911), ZP-10 (Zealand & Aventis; fase-II; WO 2001 004156) están en etapas de diferentes de desarrollo clínico (Nauck M. A., Regulatory Peptide, 115, 13-19, 2004). Sin embargo, todos estos péptidos requieren el suministro por vía parenteral de administración, que incluyen BYETTA® (Exendin-4, AC 2933; WO 2001 051078), Que se lanzó recientemente en el mercado (Amiloin & Lilly). Así, existe una necesidad crítica para desarrollar un mímico GLP-1 biológicamente activo que posea perfiles farmacodinámicos extendidos.

El GLP-1R es un receptor acoplado a las proteína G (GPCR) de dominio de transmembrana siete y se ubica en la membrana celular de células β pancreáticas. El sistema efector del GLP-1 R es la enzima ciclasa Adenililo (AC). La interacción del agonista GLP-1 con el GLP-1R origina la activación de AC, que convierte al ATP a cAMP. El incremento

en el nivel de cAMP intracelular eleva la proporción ADP/ATP, iniciando por lo tanto la despolarización celular (debido al cierre del canal K_{ATP}). El incremento en el nivel cAMP intracelular también activa la Cinasa Proteína (PK-A & PK-C), que eleva la concentración Ca^{2+} sistólica, al abrir el tipo L del canal Ca^{2+} . Un incremento en el Ca^{2+} intracelular conduce a la exocitosis de insulina, en células β pancreáticas (Fehmann, H.C., Endocr. Rev., 16, 390 - 410, 1995).

Un mecanismo general de interacción del ligando péptido con el GPCRs clase B ha surgido recientemente, denominado el modelo de "dos dominios" (Hoare S. R. J., Drug Discovery Today, Vol. 10 (6), 417-427, 2005). En este modelo de dos dominios, la porción del terminal C del péptido une el dominio N del receptor y la región del ligando de terminal N une a la región (transmembrana) de dominio J del GPCR. Esta interacción activa el receptor y estimula por lo tanto la señalización intracelular. La unión del receptor y la activación ocurren en dos dominios separados de Exendin, pero ellos se acoplan cercanamente en el GLP-1 (Eng J., J.B.C, 272 (34), 21291-21296, 1997).

Técnica Anterior

Bristol-Myers Squibb, (BMS), Princeton, NJ (US), reporta los mimicos GLP-1 humanos, con la Fórmula general Xaa1-Xaa11, en donde Xaa1-Xaa9 representan el primer residuo 1-9 del péptido GLP-1 con algunos análogos en donde Xaa2 representa Ala o se reemplaza opcionalmente con Aib, y Xaa6 representa Phe o se reemplaza opcionalmente con α -Me-Fe(2-F)-OH y Xaa10 & Xaa11 representa la combinación de derivados de bifenilo

alanina sustituidos o no sustituidos (Bip) (WO 03/ 033671A2; US 2004/ 0127423 A1; WO 2004/ 094461 A2; US 2006 / 0004222 A1 y WO 2006/ 014287 A1). La presente invención proporciona peptidomiméticos GLP-1 novedosos de formula (I) (referida aquí en adelante como peptidomiméticos), que actúan como un agonista GLP-1R y exhiben la mayor actividad biológica del péptido GLP-1 nativo. Adicionalmente, estos Peptidomiméticos GLP-1 exhiben estabilidad incrementada para clivaje proteolítico, especialmente contra enzima DPP-IV y por lo tanto, se encuentra sorprendentemente que tiene una vida útil incrementada que los hace adecuado para el tratamiento/mitigación/profilaxis de diabetes tipo 1 & tipo, trastornos metabólicos, obesidad y trastornos relacionados.

Resumen de la Invención

La presente invención describe un grupo de peptidomiméticos novedosos útiles para el tratamiento de diabetes. Estos compuestos se definen por la Fórmula general (I) como se muestra adelante. Los compuestos de la presente invención son útiles en el tratamiento del cuerpo humano o animal, mediante la regulación de la secreción de insulina. Los compuestos de esta invención son por lo tanto adecuados para el tratamiento/mitigación/regulación o profilaxis de diabetes tipo 1 & tipo 2 y obesidad.

Modalidades Preferidas

El objetivo principal de la presente invención es proporcionar compuestos novedosos de la Fórmula general (I), sus formas tautoméricas, intermedios novedosos involucrados en sus síntesis, sus sales farmacéuticamente aceptables, sus solvatos farmacéuticamente aceptables y las composiciones farmacéuticas que las contienen o sus mezclas, adecuadas para el tratamiento tratamiento/mitigación/regulación de diabetes.

En una modalidad se proporciona un proceso para la preparación de compuestos novedosos de la Fórmula general (I), sus formas tautoméricas, sus sales farmacéuticamente aceptables, solvatos farmacéuticamente aceptables y las composiciones farmacéuticas que las contienen.

En otra modalidad, se proporciona las composiciones farmacéuticas que contienen compuestos de la Fórmula general (I), sus formas tautoméricas, sus sales farmacéuticamente aceptables, solvatos y sus mezclas que tienen portadores farmacéuticamente aceptables, disolventes, diluyentes, excipientes y otros medios empleados normalmente en su fabricación.

En otra modalidad adicional se proporciona el uso de los compuestos novedosos de la presente invención como agente anti-diabéticos, al administrar una cantidad terapéuticamente efectiva y no tóxica del compuesto de formula (I), o sus composiciones farmacéuticamente aceptables a los mamíferos que están necesidad de tal tratamiento.

Abreviaturas Utilizadas

Se emplean las siguientes abreviaturas en los ejemplos y en cualquier parte aquí:

Aib = ácido α -Aminoisobutírico,
ACN o MeCN = Acetonitrilo,
Bip = residuo Bifenilalanina,
Bip(4-fluoro)= residuo 4-fluoro-bifenilalanina,
Bip(2-Me)= residuo 2-metil bifenilo,
Bip(2-Et)= residuo 2-etil bifenilo,
Bip(2-CN)= residuo 2-nitrilo bifenilo,
Bip(2-Ipr)= residuo 2-Isopropilo bifenilo,
Bip(2'-Et-4'-OMe)= residuo 2-etil-4-metoxi-bifenilo,
Bip(2-F)= residuo 2-fluoro-bifenilo,
Bn = Bencilo,
Boc = terc-Butoxicarbonilo,
But= grupo O-terc-butilo,
Adenosina 3',5'-monofosfato cíclico,
DCM = Diclorometano,
DMF = N,N-Dimetilformamida,
DIPCDI=Di-isopropilcarbodiimida,
DIPEA= Diisopropiloetilamina,
4-DBF= residuo 4-dibenzofuran-Fe-OH,
4-DBT= residuo 4-dibenzotiofeno-Fe-OH,
Dihidro-Fen= residuo 2-(9, 10-Dihidro-fenantrenil)-Ala-OH,
Et = Etilo,
Et₂O = Dietiléter,
Fmoc = Fluorenilmetoxicarbonilo,
2-Flu= residuo 2-Fluorenil-Ala-OH,
g = Gramo (s),
GTT = Ensayo de Tolerancia a la glucosa,
GLP-1R = Glucagón Similar al Receptor péptido-1,

h = Hora (s),

HOBt - Hidroxibenzotriazol,

HOAT= 7-Aza-hidroxibenzotriazol,

HBTU = hexafluorofosfato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametil amonio,

HPLC = Cromatografía Líquida de Alto Desempeño,

L - Litro,

LC /MS = Cromatografía líquida/Espectrometría de masa,

4-(2'-Me-Ph)-3-Pyr-Ala= residuo 4-(2'-metilfenil)-3-piridilalanina,

Me = Metilo,

Min = minuto (s),

ml = mililitro,

µl = microlitro,

mg = miligramo (s),

mmol = milimol (s),

fmol = fantomolar

MS= Espectrometría de masa,

Residuo 1-Naf=4-(1-Naftil)-Fe,

Residuo 2-Naf=4-(2-Naftil)-Fe,

Fen= residuo 2-(Fenantrenil)-Ala-OH,

Pbf= Pentametilbenzofuran-5 -sulfonilo,

PiBOP = hexafluorofosfato de Benzotriazol-1-il-oxi-tris-pirrolidino-fosfonio,

SPPS = Síntesis de Péptido de Fase Sólida,

Sc = sub-cutáneo,

TrF= residuo 4-fenil-bifenilalanina,

TMS = Trimetilsililo,

TIPS = Triisopropilosilano,

TFA = ácido trifluoroacético,

TBTU= tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametilamonio,

Trt= grupo Tritilo,

(α -Me)Fe(2-F)- residuo α -metil-2-fluoro-fenilalanina,

(N(Me))- = enlace amida N-metilada,

D-Alanina representada mediante 'a' y D-Bip representa el residuo alanina 'D'-Bifenilo,

ip = intra-peritoneal,

Secuencia de Péptido GLP-1 = NH₂-HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR-CONH₂ (aminoácidos 30). Los 30 aminoácidos de dicho Péptido GLP-1 se muestran en la Seq ID 1.

HAEGTFTSDVSSYLEGQAAKEFIAWLVKGR -Seq ID 1 Secuencia de Extendin-4 = NH₂-HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-CONH₂ (39 aminoácidos). Los 39 aminoácidos de Extendin -4 se muestran en la Seq ID 2.
HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS -Seq ID 2

Descripción Detallada

De acuerdo con la presente invención, se proporcionan peptidomiméticos/péptidos análogos GLP-1 sintéticos, que tiene la formula estructural (I),



en donde,

A representa -NH-R₁, en donde R₁ representa hidrógeno, grupos seleccionados de cadena alquilo (C₁-C₁₅) lineal o ramificado, tal como grupos metilo, etilo, propilo, isopropilo, n-butilo, iso- butilo, t-butilo, pentilo,

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isopentilo, hexilo, heptilo, octilo, decilo y similares, un aminoácido o péptido que contienen uno, dos, o tres residuos de aminoácidos naturales, grupo $R_3\text{-CO-}$, tal como el grupo, (2-Hidroxifenil)-acetil y similares, grupo $R_3\text{O-C(O)-}$ tal como el grupo Fmoc y similares, un grupo sulfonilo de fórmula $R_3\text{-SO}_2\text{-}$, cada uno de estos grupos se puede sustituir, en donde R_3 es seleccionado de alquilo ($C_1\text{-}C_{10}$) lineal o ramificado, tal como grupos metilo, etilo, propilo, isopropilo, n-butilo, iso-butilo, t-butilo, pentilo, isopentilo, hexilo, heptilo, octilo, decilo y similares, cicloalquilo ($C_3\text{-}C_6$), tal como grupos ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y similares, grupos arilo seleccionados de fenilo, naftilo, indanilo, fluorenilo, bifenilo y similares, grupos heteroarilo seleccionados de piridilo, tienilo, furilo, imidazolilo, benzofuranilo y similares, grupos arilalquilo seleccionados de bencilo, naftilmetilo y similares, cada uno de estos grupos se puede sustituir;

B representa grupos -COOR_2 , -CONHR_2 o CH_2OR_2 , R_2 representa H, seleccionados del grupo alquilo ($C_1\text{-}C_{10}$) lineal o ramificado, tal como metilo, etilo, propilo, isopropilo, n-butilo, iso-butilo, t-butilo, pentilo, isopentilo, hexilo, heptilo, octilo, grupos decilo y similares, grupos arilo seleccionados de fenilo, naftilo, indanilo, fluorenilo, bifenilo y similares, grupos aralquilo, cada uno de estos grupos se pueden sustituir, cada uno de S_1 y S_2 puede ser independientemente un enlace y representa independientemente un grupo $\text{'-NH-(CH}_2\text{)}_n\text{-COO-}'$, en donde, $n=1\text{-}9$; tal como derivados de aminoácido acético, aminoácido propiónico, aminoácido butanoico, aminoácido pentanoico, aminoácido

hexanoico, aminoácido heptanoico, aminoácido octanoico, aminoácido-nonanoico, aminoácido-decanoico y similares;

Y representa un enlace o $-\text{CO}-$, $-(\text{CH}_2)_m-$ ($m = 1-3$), 'O', 'S', $-\text{CO}-\text{NH}-$, $-\text{CO}-\text{NR}_4-$, o representa un péptido corto que contienen uno o dos o tres aminoácidos seleccionados de aminoácidos naturales o no naturales; en donde R_4 representa H, grupos opcionalmente sustituidos seleccionados del grupo alquilo (C_1-C_{10}) lineal o ramificado tal como metilo, etilo, propilo, isopropilo, n-butilo, isorbutilo, t-butilo, pentilo, isopentilo, hexilo, heptilo, octilo, decilo grupos y similares, arilo grupos seleccionados de fenilo, naftilo, indanilo, fluorenilo, bifenilo y similares; con la condición que

i) cuando $\text{S}_1-\text{Y}-\text{S}_2$ representa un enlace, X_1 es seleccionado de las siguientes secuencias de aminoácido HAEGTFTSD (Seq ID 3), HAEGTFTSDV (Seq ID 4), HAEGTFTSDVS (Seq ID 5), HAEGTFTSDVSS (Seq ID 6), HAEGTFTSDVSSY (Seq ID 7), HAEGTFTSDVSSYL (Seq ID 8), HAEGTFTSDVS SYLE (Seq ID 9), HAEGTFTSDVSSYLEG (Seq ID 10), HAEGTFTSDVS SYLEGQ (Seq ID 11), HAEGTFTSDVSSYLEGQA (Seq ID 12), HAEGTFTSDVS SYLEGQAA (Seq ID 13), HAEGTFTSDVSSYLEGQAAK (Seq ID 14), HAEGTFTSDVS S YLEGQAAKE (Seq ID 15), HAEGTFTSDVSSYLEGQAAKEF (Seq ID 16), HAEGTFTSDVSSYLEGQAAKEFI (Seq ID 17), con la opción adicional que uno de estos aminoácidos se pueden colocar o aminoácidos no naturales, y X_2 se selecciona de las siguientes secuencias de aminoácido G PSSGAPPPS (Seq ID 18) o KELEKLL (Seq ID 19) o GPPS o (Seq ID 20)

VKGR (Seq ID 21);

ii) y cuando SpY-S₂ no representa un enlace

X₁ se selecciona de las siguientes secuencias de aminoácido
HA (Seq ID 22), HAE (Seq ID 23), HAEG (Seq ID 24), HAEGT (Seq
ID 25), HAEGTF (Seq ID 26), HAEGTFT (Seq ID 27), HAEGTFTS
(Seq ID 28), HAEGTFTSD (Seq ID 29) con la opción adicional de
que uno o más de estos aminoácidos se pueden colocar
mediante aminoácidos no naturales;

X₂ se selecciona de

GPSSGAPPPS (Seq ID 18) o

KELEKLL (Seq ID 19) o

GPPS (Seq ID 20) o

VKGR (Seq ID 21) o

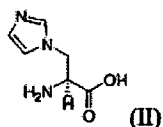
un dipéptido, seleccionado de la combinación de dos
aminoácidos, que consiste de aminoácidos naturales o no
naturales, que tienen una cadena lateral que contienen un
arilalquilo o una cantidad de heteroarilalquilo seleccionada
de bencilo, naftilmetilo, piridilmetilo, tienilmetilo,
furilometilo, imidazolilmetilo, isooxazolilmetilo,
quinolilmetilo, benzofuranilometilo, benzotienilmetilo,
indolinilmetilo, indolilmetilo, dibenzofuranilometilo,
dibenzotienilmetilo, benzodihidrofuranilometilo,
benzodihidrotienilmetilo, tienopirimidilmetilo,
benzimidazolilmetilo, fenantrenilmetilo,
dihidrofenantrenilmetilo, fluorenilmetilo,
dibenzofuranilometilo, grupos metil dibenzotiofenilo y
similares, en donde cada uno de estos grupos se pueden
sustituir opcionalmente con grupo alquilo (C₁-C₆) tal como

metilo, etilo, propilo, isopropilo, n-butilo, iso-butilo, t-butilo, pentilo, isopentilo, grupos hexilo y similares, grupo alcoxi (C₁-C₆) tal como metoxi, etoxi, propoxi, butoxi, pentoxi, grupos hexanoxi, ciano, grupo halo tal como cloro, bromo, yodo, grupos fluoro, hidroxilo o arilo opcionalmente sustituido o grupos heteroarilo seleccionados de fenilo, naftilo, piridilo, tienilo, furilo, imidazolilo, isooxazolilo, quinolilo, benzofuranilo, benzotienilo, indolinilo, indolilo, dibenzofuranilo, dibenzotienilo, benzodihidrofuranilo, benzodihidrotienilo, tienopirimidilo, benzimidazolilo, fenantrenilo, dihidrofenantrenilo, fluorenilo, dibenzofuranilo, dibenzotiofenilo y similares, con la condición adicional de que tales sustituyentes arilo o heteroarilo puede opcionalmente sustituirse con alquilo (C₁-C₆), ciano, halo, hidroxilo o arilo o grupos heteroarilo.

En una modalidad preferida, la secuencia dipéptido puede comprender uno o más aminoácidos seleccionados de Bip, Bip(2-Me), Bip(2-Et), Bip(2-Ipr), Bip(2-CN), Bip(2'-Et-4'-OMe), Bip(4'-fluoro), Bip(4'-Fenil), 2-(9,10-Dihidro-fenantrenil)-Ala, 2-(Fenantrenil)-Ala, 4-(2-Naftil)-Fe, 4-(1-Naftil)-Fe, 2-Fluorenil-Ala, 4-dibenzofuran-Fe, 4-dibenzotiofeno-Fe, 4-(2'-metilfenil)-3-piridilalanina; El término aminoácidos naturales' indica todos aquellos 20 aminoácidos, que están presentes en la naturaleza.

El término "aminoácidos no naturales" o "aminoácidos no naturales" representan el reemplazo de los L-aminoácidos con aminoácidos D correspondientes tal como el reemplazo de L-Ala con D-Ala o L-Pro con D-Pro y similares o modificaciones adecuadas de los aminoácidos L o D, aminoalquilácidos, por

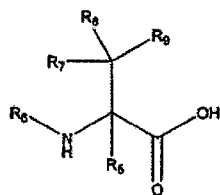
- α -alquilación tal como sustitución de Ala con α -metil Ala (Aib), el reemplazo de Phe con α -metil Phe, el reemplazo de Bip sustituido con α -metil Bip;
- N-alquilación con grupos seleccionados de grupos alquilo (C_1-C_6) o cicloalquilo (C_3-C_6);
- Modificación de cadena lateral tal como el reemplazo de His con análogos de histidina tal como 1-imidazolil-alanina (II) o des-amino-His,



o el reemplazo de anillo fenilo de Phe con grupos piridilo, naftilo, bifenilo;

- sustitución de un amino ácido de cadena lateral tal como sustitución de cadena lateral de aminoácido aromático con halógeno, grupos alquilo (C_1-C_3), arilo, más específicamente el reemplazo de Phe con 2 & 4-halo Phe;

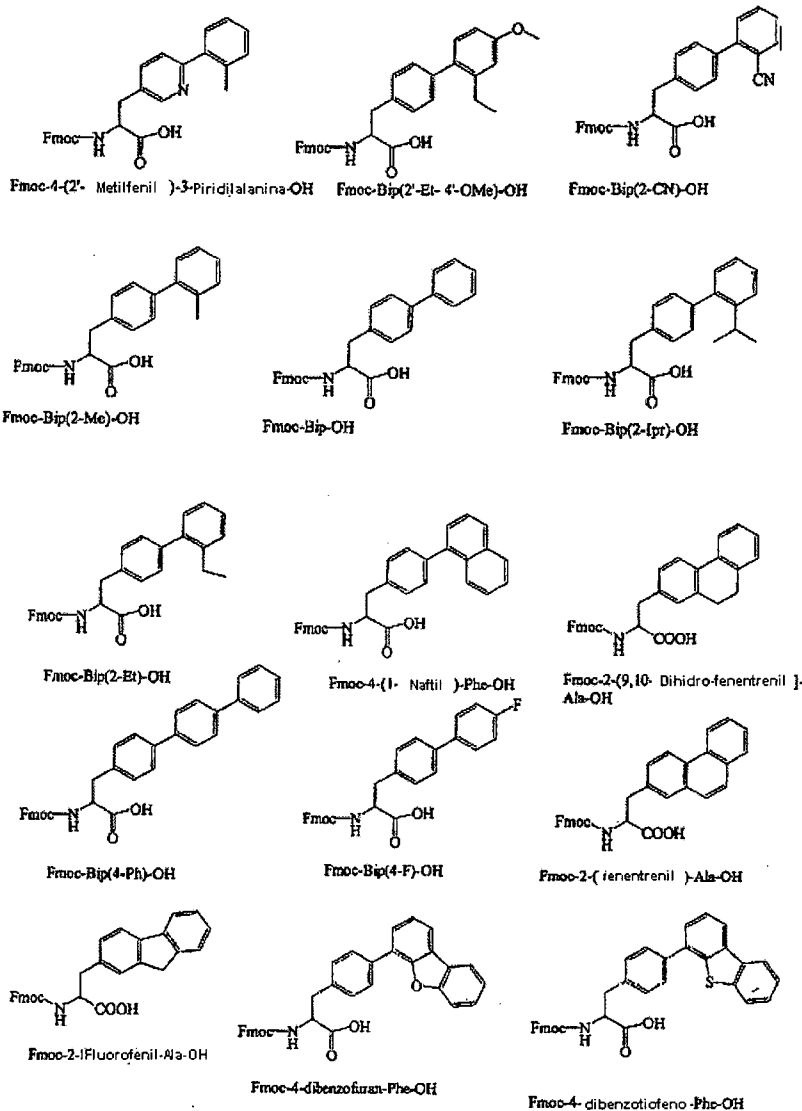
Tales "aminoácidos no naturales" o "aminoácidos no naturales" se pueden representar de forma general por la siguiente estructura:



(IIa)

en donde R_5 se selecciona de H, F, alquilo (C_1-C_5), la configuración estereoquímica en el carbono que lleva R_5 puede ser (R) o (S); R_6 se selecciona de H o alquilo (C_1-C_3); cada uno de R_7 y R_8 se selecciona independientemente de H, alquilo (C_1-C_3), tal como metilo y etilo o átomo de halógeno, preferiblemente átomo fluor; R_9 representa grupos, seleccionados de grupos alquilo (C_1-C_5), arilo o la cantidad heterorilo se selecciona de fenilo, naftilo, piridilo, tienilo, furilo, imidazolilo, isooxazolilo, quinolilo, benzofuranilo, benzotienilo, indolinilo, indolilo, dibenzofuranilo, dibenzotienilo, benzodihidrofuranilo, benzodihidrotienilo, tienopirimidilo, benzimidazolilo, fenantrenilo, dihidrofenantrenilo, fluorenilo, dibenzofuranilo, dibenzotiofenilo, en donde cada uno de estos grupos se pueden sustituir opcionalmente con alquilo (C_1-C_6), alcoxi (C_1-C_6), ciano, halo, hidroxilo o arilo opcionalmente sustituido o grupos heteroarilo, con la condición adicional de que tales sustituyentes arilo o heteroarilo puede opcionalmente sustituirse con grupos alquilo (C_1-C_6), alcoxi (C_1-C_6), ciano, halo, hidroxilo o arilo o heteroarilo.

Lista de análogos Bip Fmoc protegidos utilizados para la síntesis de Peptidomiméticos GLP-1



Los sustituyentes adecuados incluyen, pero no se limitan a los siguientes radicales, solos o en combinación con otros radicales - hidroxilo, oxo, halo, tio, nitro, amino, ciano, alquilo, haloalquilo, alcoxi, haloalcoxi, cicloalquilo, arilo, ariloxi, aralquilo, aralcoxi, heteroarilo, heteroaralquilo, heteroariloxi, heteroaralcoxi, acilo,

aciloxi, ácido carboxílico y sus derivados tal como ésteres y amidas;

Los varios grupos, radicales y sustituyentes utilizados en cualquier parte en la especificación se describen en los siguientes párrafos.

El término "alquilo" utilizado aquí, solo o en combinación con otros radicales, denota un radical lineal o ramificado que contienen uno a diez carbonos, tal como metilo, etilo, n-propilo, iso-propilo, n-butilo, sec-butilo, terc-butilo, amilo, t-amilo, n-pentilo, n-hexilo, iso-hexilo, heptilo, octilo, decilo y similares.

El término "cicloalquilo" utilizado aquí, solo o en la combinación con otros radicales, denota un radical que contiene tres a siete carbonos, tal como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y similares.

El término "arilo" o "aromático" utilizado aquí, solo o en la combinación con otros radicales, denota un sistema aromático que contienen uno, dos, o tres anillos en donde tales anillos se pueden unir en una forma pendiente o se pueden fusionar, tal como fenilo, naftilo, tetrahidronaftilo, indano, bifenilo, y similares.

El término "arilalquilo" denota un grupo alquilo, como se definió anteriormente, unido a un arilo, tal como bencilo, feniletilo, naftilmetilo, y similares. El término "ariloxi" denota un radical arilo, como se definió

anteriormente, unido a un grupo alcoxi, tal como fenoxi, naftiloxi y similares, que se pueden sustituir.

El término "aralcoxi" denota una porción arilalquilo, como se definió anteriormente, tal como benciloxi, fenotiloxi, naftilmetiloxi, fenilpropilooxi, y similares, que se puede sustituir.

El término "heteroarilo" o "heteroaromático" utilizado aquí, solo o en la combinación con otros radicales, denota un sistema aromático que contiene uno, dos, o tres anillos en donde tales anillos se pueden unir en una forma pendiente o se pueden fusionar que contienen uno o más hetero átomos seleccionados de O, N o S, tal como piridilo, tienilo, furilo, pirrolilo, oxazolilo, tiazolilo, isotiazolilo, imidazolilo, isoxazolilo, oxadiazolilo, tiadiazolilo, triazolilo, tetrazolilo, benzopiranilo, benzopiranonilo, benzofuranilo, benzotienilo, indolinilo, indolilo, azaindolilo, azaindolinilo, benzodihidrofuranilo, benzodihidrotienilo, pirazolopirimidinilo, pirazolopirimidonilo, azaquinazolinilo, azaquinazolinoilo, piridofuranilo, piridotienilo, tienopirimidilo, tienopirimidonilo, quinolinilo, pirimidinilo, pirazolilo, quinazolinilo, quinazolonilo, pirimidonilo, piridazinilo, triazinilo, benzoxazinilo, benzoxazinonilo, benzotiazinilo, benzotiazinonilo, benzoxazolilo, benzotiazolilo, benzimidazolilo, benzotriazolilo, ftalazinilo, naftilidinilo, purinilo, carbazolilo, fenotiazinilo, fenoxazinilo, y similares.

El término "heteroaralquilo" utilizado aquí, solo o en combinación con otros radicales, denota un grupo heteroarilo, como se definió anteriormente, unido a una cadena de carbono saturada recta o ramificada que contienen 1 a 6 carbonos, tal como (2-furil)metilo, (3-furil)metilo, (2-tienil)metilo, (3-tienil)metilo, (2-piridil)metilo, 1-metil-1-(2-pirimidil)etil y similares. Los términos "heteroariloxi", "heteroaralcoxi", "heterocicloxi" denotan grupos heteroarilo, heteroarilalquilo, respectivamente, como se definió anteriormente, unidos a un átomo de oxígeno.

El término "acilo" utilizado aquí, solo o en combinación con otros radicales, denota un radical que contienen uno a ocho carbonos tal como formilo, acetilo, propanoilo, butanoilo, iso-butanoilo, pentanoilo, hexanoilo, heptanoilo, benzoilo y similares, que se pueden sustituir.

El término "ácido carboxílico" utilizado aquí, solo o en combinación con otros radicales, denota un grupo -COOH, e incluye derivados de ácido carboxílico tal como ésteres y amidas. El término "éster" utilizado aquí, solo o en combinación con otros radicales, denota el grupo -COO-, e incluye derivados de ácido carboxílico, en donde las porciones éster son alcóxicarbonilo, tal como metoxicarbonilo, etoxicarbonilo, y similares, que se pueden sustituir.

A menos que se indique otra cosa, el término 'amino ácido' como se emplea aquí solo o como parte de otros grupos incluye, sin limitación, un grupo amino y un grupo carboxilo ligado al mismo carbono, referido como carbono ' α '.

La configuración absoluta 'S' en el carbono ' α ' es se refiere comúnmente como una configuración 'L' o natural. La configuración 'R' en el carbono ' α ' se refiere comúnmente como el aminoácido 'D'. En el caso en donde los 'sustituyentes- α ' sean iguales, tal como hidrógeno o metilo, los aminoácidos son GIy o Aib y no son quirales.

El término "modulador del receptor" se refiere a un compuesto que actúa en el receptor GLP-1 para alterar su capacidad de regular los eventos de señalización descendentes. Ejemplos de moduladores receptores incluyen agonistas, agonistas parciales, agonistas inversos, potenciadores alostéricos.

Preferiblemente, los peptidomiméticos aislados son 3-30 mer y tales péptidos se unen a y activan el receptor GLP-1.

De acuerdo con la presente invención, los peptidomiméticos aislados sintéticos descritos aquí poseen la capacidad para imitar la actividad biológica del Péptido GLP-1, con preferencia para actividad agonista en GLP-1R. Estos peptidomiméticos GLP- 1 exhiben propiedades in vivo deseables, haciéndolos candidatos terapéuticos ideales para administración parenteral y oral.

La presente invención proporciona compuestos de las composiciones farmacéuticas de formula (I) que emplean tales compuestos solos o en combinación y para métodos de utilización de tales compuestos. En particular, la presente invención una composición farmacéutica que comprende a una

cantidad terapéuticamente efectiva de un compuesto de formula (I), solo o en la combinación(s), con un portador farmacéuticamente aceptable.

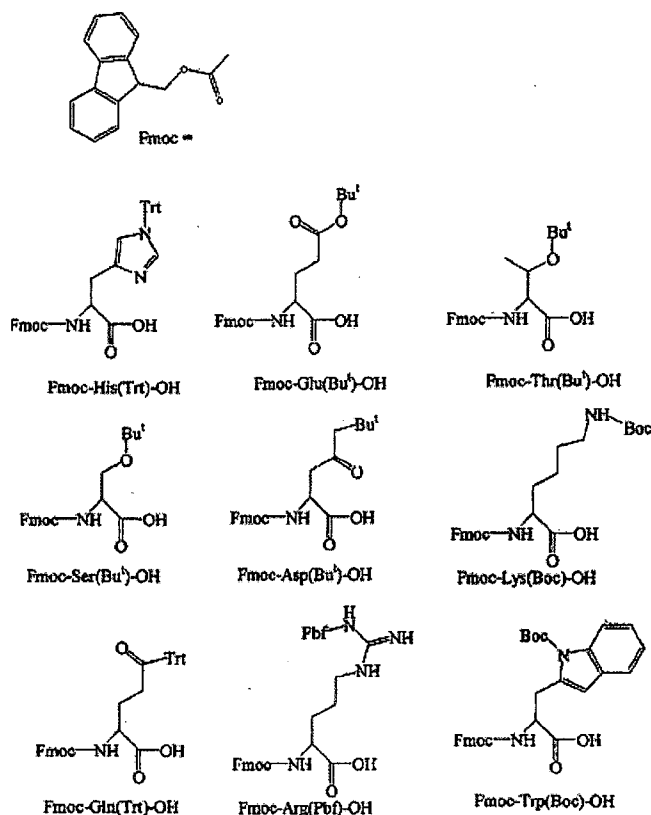
Se proporciona adicionalmente un método para tratar y retrasar la progresión del inicio de la diabetes, especialmente diabetes tipo II, que incluye complicaciones de diabetes, que incluyen retinopatía, neuropatía, nefropatía y cicatrización de heridas retrasadas y enfermedades relacionadas tales como resistencia a la insulina (homeostasis de glucosa lesionadas), hiperglicemia, hiperinsulinemia, niveles sanguíneos elevados de ácidos grasos o glicerol, obesidad, hiperlipidemia que incluye hipertrigliceridemia, síndrome X, aterosclerosis e hipertensión, en donde una cantidad terapéuticamente efectiva de un compuesto de formula (I) o sus combinaciones a un mamífero, ejemplo, humano, un paciente en necesidad de tratamiento.

Se pueden emplear varias rutas sintéticas para preparar los compuestos de la presente invención bien conocidas por aquellos expertos en la técnica de la síntesis de péptidos. Los compuesto de la fórmula (I), en donde todos los símbolos son como se definió antes se pueden sintetizar utilizando los métodos descritos adelante, junto con técnicas convencionales bien conocidas por aquellos expertos en la técnica de la síntesis de péptidos, o variaciones de estos como se aprecia por el experto en la técnica. Los métodos referidos incluyen, pero no se limitan a aquellos descritos adelante.

Los peptidomiméticos de estos descritos aquí se pueden producir por síntesis química utilizando variaciones adecuadas de varias técnicas de fase sólida conocidas generalmente como aquellas descritas en G. Barany & R. B. Merrifield, "The peptides: Analysis, synthesis, Biology"; Volume 2- "Special methods in peptide synthesis, Part A", pp. 3- 284, E. Gross & J. Meienhofer, Eds., Academic Press, New York, 1980; y en J. M. Stewart y J. D. Young, "Solid-phase peptide synthesis " 2nd Ed., Pierce chemical Co., Rockford, II, 1984.

La estrategia preferida para preparar los peptidomiméticos de esta invención se basa en el uso de enfoque spps basado en Fmoc, en donde el grupo Fmoc (9-Fluorenil-metil-metiloxycarbonil) se utiliza para protección temporal del grupo α -amino, en combinación con los grupos protectores de ácido labil, tal como grupo t-butiloxi carbonil (Boc), terc-butilo (Bu^T), Tritilo (Trt) para protección temporal de las cadenas laterales de aminoácidos (ver, por ejemplo, E. Atherton & R.C. Sheppard, "The Fluorenilmetoxycarbonil amino protecting group", en "The peptides: Analysis, synthesis, Biology"; Volume 9 - "Special methods in peptide synthesis, Part C", pp. 1-38, S. Udenfriend & J. Meienhofer, Eds., Academic Press, San Diego, 1987).

Ejemplos de aminoácidos ortogonalmente protegidos utilizados en la síntesis de péptido de Fase Sólida Fmoc para síntesis de peptidomiméticos



Los peptidomiméticos se pueden sintetizar en una forma similar a etapas en un soporte de polímero insoluble (resina), partiendo del terminal C del péptido. En una modalidad, la síntesis se inicia al anexar el aminoácido del terminal C del péptido a la resina a través de la formación de una amida, éster o enlace éter. Esto permite la liberación eventual del péptido resultante como una amida C-terminal, ácido carboxílico o alcohol, respectivamente.

En el SPPS basado en Fmoc, el aminoácido de terminal C y todos los otros aminoácidos utilizados en la síntesis se requiere que tengan sus grupos α -amino y funcionalidades de cadena lateral (si están presentes) protegidas diferencialmente (protección ortogonal), de tal forma que el grupo protector α -amino grupo se pueda remover selectivamente

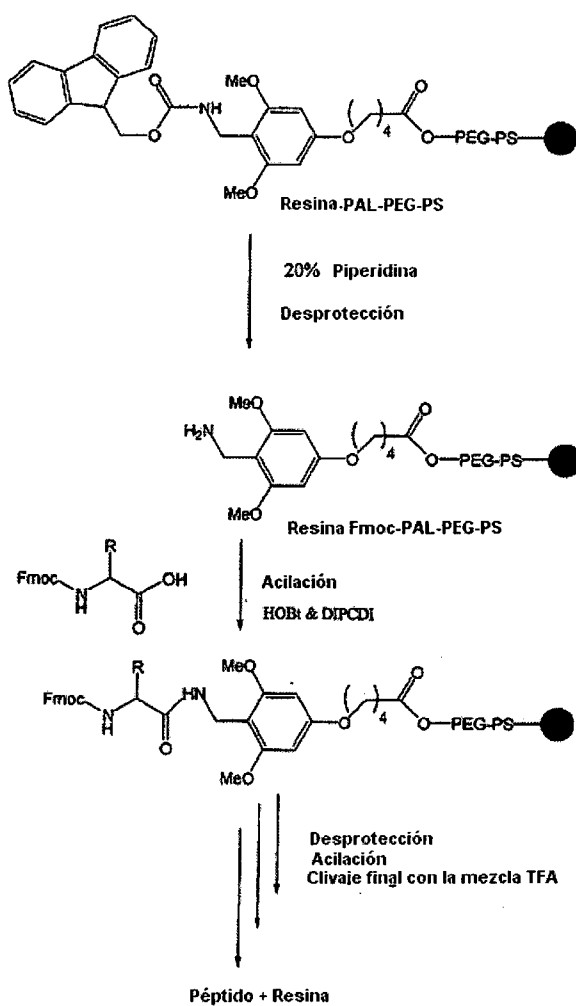
durante la síntesis, utilizando una base adecuada tal como 20% de solución de piperidino, sin ningún clivaje prematuro del péptido de resina o desprotección de grupos protectores de cadena lateral, usualmente protegidos con grupos protectores de ácido labil.

El acoplamiento de un aminoácido se desarrolla por la activación de su grupo carboxilo como un éster activo y la reacción de este con grupos α -amino no bloqueados del aminoácido de terminal N unido a la resina. Después de cada acoplamiento y desprotección, la resina peptidilo se lava con el exceso de disolventes, tal como DMF, DCM y dietil éter. La secuencia de desprotección del grupo α -amino y el acoplamiento se repiten hasta que se ensambla la secuencia de péptido deseada. El péptido luego se cliva de la resina con la desprotección concomitante de las funcionalidades de cadena lateral, utilizando una mezcla de clivaje apropiado, usualmente en la presencia de secuestrantes apropiados para limitar las reacciones laterales. El péptido resultante se purifica finalmente por HPLC de fase inversa.

La síntesis de las resinas-peptidilo requiere como precursores para los péptidos finales utilizar resinas de polímero de poliestireno reticulado disponibles comercialmente (Novabiochem, San Diego, CA). Se prefiere para uso en esta invención resina Fmoc-PAL-PEG-PS, resina de bencihidrilamina 4-(2',4'-dimetoxifenil-Fmoc-aminometil)-fenoxiacetil-p-metilo (resina MBHA amida Fmoc-Rink), resina 2-cloro-Tritil-cloruro o resina de alcohol p-benciloxibencilo (resina HMP) a la que el aminoácido del terminal C puede o no se puede ya unir. Si el aminoácido del

terminal C no se une, esta unión se puede lograr mediante el éster activo HOBt del aminoácido Fmoc protegido formado por su reacción con DIPCDI. En el caso de la resina 2-Cloro-tritil, el acoplamiento del primer aminoácido Fmoc protegido se logra, utilizando DIPEA. Para el ensamble al siguiente aminoácido, la protección del terminal N de la resina peptidilo se desprotege selectivamente utilizando una solución de 10-20% de piperidina. Después de cada acoplamiento y desprotección, el exceso de reactivos de acoplamiento y aminoácidos se remueve por lavado con un DMF, DCM y éter. El acoplamiento de los aminoácidos posteriores se puede lograr utilizando ésteres activos HOBt o HOAT producidos de DIPCDI/ HOBt o DIPCDI/HOAT, respectivamente. En el caso de algunos acoplamientos difíciles, especialmente acoplamiento de aquellos aminoácidos, que son hidrófobos o aminoácidos con protecciones de cadena lateral de masa, el acoplamiento completo se puede lograr utilizando una combinación de agentes de acoplamiento altamente eficientes tales como HBTU, PyBOP o TBTU, con aditivos tal como DIPEA.

Esquema general para SPPS basado en Fmoc



La síntesis de los análogos de péptidos descritos aquí se pueden llevar a cabo al utilizar aparatos de síntesis de péptidos de flujo continuo o en forma de tandas. Los aminoácidos no comerciales no naturales presentes en posiciones diferentes se incorporan en la cadena del péptido, utilizando uno o más de los métodos conocidos en la técnica. En un enfoque, se prepara un aminoácido no natural Fmoc- protegido en la solución, utilizando los procedimientos apropiados en la literatura. Por ejemplo, los análogos Bip Fmoc protegidos, descritos anteriormente, se preparan utilizando el método de acoplamiento cruzado Suzuki

modificado, conocido en la literatura (por ejemplo, Tetrahedron Letter 58, 9633-9695, 2002). Los aminoácidos α -metilados Fmoc protegidos se preparan utilizando la síntesis Strecker asimétrica, como se describe para por ejemplo, en Org. Letters 3(8), 1121-1124, 2001. Los aminoácidos N-metilados Fmoc protegidos se preparan utilizando un método en la literatura como se describe en por ejemplo, JOC, 2005, 70, 6918-6920. El derivado resultante luego se utiliza en la síntesis en forma de etapas del péptido. Alternativamente, los aminoácidos no naturales requeridos constituyen la resina directamente utilizando los procedimientos de química orgánica sintética y se constituye una cadena de péptido lineal.

Los precursores de péptido-resina para sus respectivos peptidomiméticos se pueden clivar y desproteger utilizando variaciones adecuadas de cualquiera de los procedimientos de clivaje estándar descritos en la literatura (ver, por ejemplo, D. S. King et al. Int. J. peptide Protein res. 36, 1990, 255 - 266). Un método preferido para uso en esta invención es el uso de la mezcla de clivaje TFA, en la presencia de agua y TIPS como secuestrantes. Típicamente, la resina peptidilo se incuba en TFA / Agua /TIPS (94:3:3; V: V: V; 10 ml / 100 mg de resina peptidilo) durante 1.5-2 horas a temperatura ambiente. La resina clivada luego se filtra, la solución de TFA se concentra o seca bajo presión reducida. El producto crudo resultante se precipita o se lava con Et₂O o se redisuelve directamente en DMF o 50 % se ácido acético acuoso para purificación por HPLC preparativo. Los Peptidomiméticos con la pureza deseada se pueden obtener mediante purificación utilizando HPLC preparativo. La

solución de péptido crudo se inyecta en una columna semi-prep (Luna 10 μ ; C₁₈; 100 Å), dimensión 250 X 50 mm y se eluye con un gradiente lineal de ACN en agua, ambos amortiguados con 0.1 % de TFA, utilizando un índice de flujo de 15 -50 ml /min con monitoreo de efluente mediante detector PDA en 220 nm. Las estructuras de los peptidomiméticos purificados se puede confirmar por análisis espectroscopia de masa de electro rociado (ES-MS).

Todos los péptidos preparadas se aíslan como sal de trifluoro-acetato, con TFA como un contra ión, después de la purificación por prep-HPLC. Sin embargo, algunos péptidos se someten a desalinización, al pasar a través de un lecho de resina de intercambio de ión adecuado, preferiblemente a través de una resina de intercambio de anión Dowex SBR P(Cl) o una resina de intercambio de anión equivalente básica. En algunos casos, los contraiones TFA se reemplazan con iones de acetato, al pasar a través de resinas de intercambio de ión adecuadas, eluidas con solución de ácido acético diluido. Para la preparación de la sal de clorhidrato de péptidos, en la última etapa de fabricación, los péptidos seleccionados, con la sal de acetato se tratan con 4 M de HCl. La solución resultante se filtra a través de un filtro de membrana (0.2 μ m) y se liofiliza posteriormente para producir el blanco para la sal HCL blanca. Luego de técnicas similares y/o de tales modificaciones adecuadas, que están bien dentro del alcance de las personas expertas en la técnica, otras sales farmacéuticamente aceptables adecuadas de los peptidomiméticos de la presente invención se preparan.

En una modalidad preferida, la presente invención proporciona un método para elaborar unos peptidomiméticos que imitan la actividad de un agonista GLP-1R de polipéptido endógeno. En otra modalidad preferida, el agonista del receptor de polipéptido es GLP-1.

Los compuestos novedosos de la presente invención se pueden formular en composiciones farmacéuticamente adecuadas al combinar con excipientes adecuados como es bien sabido.

La composición farmacéutica se proporciona al emplear técnicas convencionales. Preferiblemente la composición está en forma de dosis unitaria que contiene una cantidad efectiva del componente activo, que es, los compuestos de fórmula (I) solos o en combinación, de acuerdo con esta invención.

La cantidad de componente activo, que es, compuestos de fórmula (I) de acuerdo con esta invención, en la composición farmacéutica y la forma de dosis unitaria de esta se pueden variar o ajustar ampliamente dependiendo del método de aplicación particular, la potencia del compuesto particular y la concentración deseada. Por vía de guía, la dosis oral diaria del ingrediente activo, cuando se utiliza para los efectos indicados variará entre aproximadamente 0.001 a 1000 mg/kg de peso corporal, preferiblemente entre aproximadamente 0.01 a 100 mg/kg de peso corporal por día y más preferiblemente entre aproximadamente 0.6 a 20 mg/kg/día.

Método general de preparación de preparación de peptidomiméticos, utilizando enfoque SPPS:

Ensamble de peptidomiméticos en resina:

Una cantidad suficiente (50-100 mg) de resina Fmoc-PAL-PEG-PS o resina MBHA Fmoc-Rink amida, carga: 0.5-0.6 mmol / g se sumerge en DMF (1-10 ml / 100 mg de resina) durante 2-10 minutos. El grupo Fmoc en la resina luego se remueve mediante la incubación de la resina con 10-30 % de piperidina en DMF (10-30 ml / 100 mg de resina), durante 10-30 minutos. La resina desprotegida se filtra y se lava el exceso de DMF, DCM y éter (50 ml X 4). La resina lavada se incuba en DMF destilado fresco (1 ml / 100 mg de resina), bajo atmósfera de nitrógeno durante 5 minutos. 0.5 M de solución del primer aminoácido Fmoc protegido (1-3 eq.), pre-activado con HOBt (1-3 eq.) y DIPCDI (1-2 eq.) en DMF se agrega a la resina, y luego la resina se agita durante 1-3 horas, bajo atmósfera de nitrógeno. La terminación de acoplamiento se monitorea utilizando una prueba de ninhidrina cualitativa. Después del acoplamiento de los primeros aminoácidos, la resina se lava con DMF, DCM y Dietil éter (50 ml X 4). Para el acoplamiento de los siguientes aminoácidos, en primer lugar, la protección Fmoc del primer aminoácido acoplado con la resina se desprotege, utilizando 10-20% de solución de piperidina, seguido por el segundo aminoácido Fmoc protegido utilizando unos agentes de acoplamiento adecuados, y según lo descrito anteriormente. Los ciclos repetidos de desprotección, lavado, acoplamiento y lavado se desarrollan hasta que la cadena de péptido deseada se ensambla en la resina, como lo mostrado por el esquema general anterior.

Finalmente, la resina peptidilo Fmoc-protegida anterior se desprotege mediante el tratamiento de 20% piperidina como

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se describió anteriormente y las resinas peptidilo se lavan con DMF, DCM y Dietil éter (50 ml X 4). La Resina que contiene el péptido deseado se seca bajo presión de nitrógeno durante 10-15 minutos y se someten a clivaje/desprotección:

Clivaje y desprotección:

Los peptidomiméticos deseados se clivan y desprotegen a partir de sus resinas peptidilo respectivas mediante tratamiento con mezcla de clivaje TFA como sigue. Una solución de TFA / Agua / Triisopropilosilano (95: 2.5: 2.5) (10 ml / 100 mg de resina peptidilo) se agregan a resinas peptidilo y la mezcla se mantiene a temperatura ambiente con agitación ocasional. La resina se filtra, se lava con una mezcla de clivaje y el filtrado combinado se evapora hasta secado. El residuo obtenido se disuelve en 10 ml de agua y la capa acuosa se extrae tres veces con éter (20 ml cada una) y finalmente la capa acuosa se seca por congelamiento. El producto crudo obtenido después de secado por congelamiento se purifica mediante HPLC preparativo como sigue:

Purificación por HPLC de los peptidomiméticos crudos:

Se lleva a cabo HPLC preparativo en un cromatógrafo líquido LC-8A Shimadzu. Una solución de péptido crudo disuelta en DMF o agua se inyecta en una columna semi-prep (Luna 10 μ ; C₁₈; 100 Å⁰), dimensión 250 X 50 mm y se eluye con un gradiente lineal de ACN en agua, amortiguada con 0.1 % TFA, utilizando un índice de flujo de 15 -50 ml / min, con monitoreo de efluente mediante detector PDA en 220 nm. Un gradiente típico de 20 % a 70 % de agua- mezcla ACN,

amortiguada con 0.1 % TFA se utiliza, durante un periodo de 50 minutos, con 1% de cambio de gradiente por minuto. El producto deseado eluido se recolecta en una única fracción de 10-20 ml y se obtienen peptidomiméticos puros como polvos blancos amorfos mediante liofilización respectiva de las fracciones HPLC.

Análisis HPLC de los peptidomiméticos purificados

Después de purificación por HPLC preparativo como se describió anteriormente, cada péptido se analiza mediante RP-HPLC analítico en un sistema HPLC analítico LC-10AD Shimadzu. Para el análisis HPLC analítico de peptidomiméticos, se utiliza la columna Luna 5 μ ; C₁₈; 100 Å, dimensión 250 X 4.6 mm de 0.1% TFA y amortiguador ACN y la adquisición del cromatograma se lleva a cabo en 220 nm, utilizando un detector PDA.

Caracterización por espectrometría de masa

Cada péptido se caracteriza por Espectrometría de masa de ionización por electro rociado (ESI-MS), en inyección de flujo o modo LC/MS. Los espectrómetros de masa triple cuadrupolo (API-3000 (MDS-SCIEX, Canada) se utilizan en todos los análisis en modo de electro rociado de ión positivo y negativo. Los datos de exploración completa se adquieren sobre el rango de masa del cuadrupolo, se operan en resolución de unidad. En todos los casos, el peso molecular medido experimentalmente está dentro de 0.5 Daltons de del peso molecular monoisotópico calculado. La cuantificación de

cromatograma de masa se hace utilizando el software Analyst 1.4.1.

La utilización de los métodos sintéticos descritos aquí junto con otras técnicas comúnmente conocidas y variaciones adecuadas de estas, se preparan los siguientes peptidomiméticos GLP-1. Esta lista es indicadora de los varios grupos de peptidomiméticos, que se pueden preparar de acuerdo con la presente invención, y se espera para por lo menos incluir variaciones obvias de estos compuestos. Sin embargo, tal descripción no se debe constituir como limitante del alcance de la invención en ninguna forma.

S. No.	Secuencia
1	HGEGTFTSD-(CH ₂) ₃ -GPSSGAPPPS
2	HGEGTFTSD-(CH ₂) ₄ -GPSSGAPPPS
3	HGEGTFTSD-(CH ₂) ₅ -GPSSGAPPPS
4	HGEGTFTSD-(CH ₂) ₆ -GPSSGAPPPS
5	HGEGTFTSD-(CH ₂) ₇ -GPSSGAPPPS
6	HGEGTFTSD-(CH ₂) ₁₀ -GPSSGAPPPS
7	HGEGTFTSD-(CH ₂) ₁₁ -GPSSGAPPPS

8	HGEGTFTSDLSKQM-(CH ₂) ₃ -GPSS
9	HGEGTFTSDLSKQM-(CH ₂) ₄ -GPSS
10	HGEGTFTSDLSKQM-(CH ₂) ₅ -GPSS
11	HGEGTFTSDLSKQM-(CH ₂) ₆ -GPSS
12	HGEGTFTSDLSKQM-(CH ₂) ₇ -GPSS
13	HGEGTFTSDLSKQM-(CH ₂) ₁₀ -GPSS
14	HGEGTFTSDLSKQM-(CH ₂) ₁₁ -GPSS
15	HGEGTFTSDLSKQME-G-GPSSGAPPPS
16	HGEGTFTSDLSKQME-(CH ₂) ₂ -GPSSGAPPPS
17	HGEGTFTSDLSKQME-(CH ₂) ₃ -GPSSGAPPPS
18	HGEGTFTSDLSKQME-(CH ₂) ₄ -GPSSGAPPPS
19	HGEGTFTSDLSKQME-(CH ₂) ₅ -GPSSGAPPPS
20	HGEGTFTSDLSKQME-(CH ₂) ₆ -GPSSGAPPPS
21	HGEGTFTSDLSKQME-(CH ₂) ₇ -GPSSGAPPPS
22	HGEGTFTSDLSKQME-(CH ₂) ₁₀ -GPSSGAPPPS
23	HGEGTFTSDLSKQME-(CH ₂) ₁₁ -GPSSGAPPPS

Tabla 2:

S. No.	Secuencia
1	HAEGTFTSD-(CH ₂) ₂ -VKGR
2	HAEGTFTSD-(CH ₂) ₃ -VKGR
3	HAEGTFTSD-(CH ₂) ₄ -VKGR
4	HAEGTFTSD-(CH ₂) ₅ -VKGR
5	HAEGTFTSD-(CH ₂) ₆ -VKGR
6	HAEGTFTSD-(CH ₂) ₁₀ -VKGR
7	HAibEGTFTSD-(CH ₂) ₂ -VKGR
8	HAibEGTFTSD-(CH ₂) ₃ -VKGR
9	HAibEGTFTSD-(CH ₂) ₄ -VKGR
10	HAibEGTFTSD-(CH ₂) ₅ -VKGR
11	HAibEGTFTSD-(CH ₂) ₆ -VKGR
12	HAibEGTFTSD-(CH ₂) ₁₀ -VKGR

Tabla 3:

S. No.	Secuencia
1	HGEGTFTSDLKQMKELEKLL
2	HAEGTFTSDKELEKLL
3	HGEGTFTSDKELEKLL
4	HAibEGTFTSDGKELEKLL
5	HGEGTFTSDGKELEKLL
6	HGEGTFTSDVSKELEKLL
7	HAEGTFTSDVSKELEKLL
8	HAEGTFTSDVSEKELEKLL
9	HAEGTFTSDVSGKELEKLL
10	HAEGTFTSDVSSYLEKELEKLL
11	HAEGTFTSDVSSYLEGKELEKLL
12	HGEGTFTSDVSSYLEGKELEKLL
13	HAEGTFTSDVSSYLEGKELEKLL
14	HAibEGTFTSDVSSYLEGKELEKLL
15	HAEGTFTSDVSSYLEGKELEKLLVKG
16	HAEGTFTSDVSSYLEPKKELEKLL
17	HAEGTFTSDVSSYLEGQAAKELEKLL
18	HAEGTFTSDVSSYLEGQAAKEFIKELEKLL
19	HAibEGTFTSDVSSYLEGQAAKEFIKELEKLL
20	HAibEGT-(α -Me)Phe(2-F)- TSDVSSYLEGQAAKEFIKELEKLL
21	Des-amino-HAibEGT-(α -Me)Phe(2-F)- TSDVSSYLEGQAAKEFIKELEKLL
22	HAEGTFTSD-(CH ₂) ₃ -KELEKLL
23	HAEGTFTSD-(CH ₂) ₄ -KELEKLL
24	HAEGTFTSD-(CH ₂) ₅ -KELEKLL
25	HAEGTFTSD-(CH ₂) ₆ -KELEKLL
26	HA-(CH ₂) ₃ -DVSSYLEGQAAKEFIKELEKLL
27	HAib-(CH ₂) ₃ -DVSSYLEGQAAKEFIKELEKLL
28	HAibEGTFTSDVSSYLEGQ-(CH ₂) ₂ -KELEKLL
29	HAibEGTFTSDVSSYLEGQ-(CH ₂) ₃ -KELEKLL
30	HAibEGTFTSDVSSYLE-(CH ₂) ₂ -FIKELEKLL

Tabla 4:

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S. No.	Secuencia
1	HGEGTFTSD-(CH ₂) ₃ -Bip-Bip
2	HAibEGTFTSD-(CH ₂) ₃ -Bip-Bip
3	HAibEGT-(α-Me)-Phe(2-F)-TSD-(CH ₂) ₃ -Bip-Bip
4	HAEGTFTSD-G-Bip(2-Me)-Bip(2-Me)
5	HAibEGTFTSD-G-Bip(2-Me)-Bip(2-Me)
6	HAibEGT-(α-Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Me)
7	HAEGTFTS-G-Bip(2-Me)-Bip(2-Me)
8	HAibEGTFTS-G-Bip(2-Me)-Bip(2-Me)
9	HAibEGT-(α-Me)-Phe(2-F)-TS-G-Bip(2-Me)-Bip(2-Me)
10	HAEGTFTS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
11	HAibEGTFTS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
12	HAibEGT-(α-Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
13	HAEGTFT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
14	HAibEGTFT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
15	HAibEGT-(α-Me)-Phe(2-F)-T-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
16	HAEGTF-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
17	HAibEGTF-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
18	HAibEGT-(α-Me)-Phe(2-F)-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
19	HAEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
20	HAibEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
21	HAEG-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
22	HAibEG-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
23	HAEGTFTSD-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
24	HAibEGTFTSD-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)

25	HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
26	HAEGTFTSD-G-Bip-Bip(2-Me)
27	HAibEGTFTSD-G-Bip-Bip(2-Me)
28	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip(2-Me)
29	HAEGTFTSD-G-Bip(2-Me)-Bip
30	HAibEGTFTSD-G-Bip(2-Me)-Bip
31	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip
32	HAEGTFTSD-G-Bip-Bip
33	HAibEGTFTSD-G-Bip-Bip
34	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip
35	HAEGTFTSD-G-Bip-Bip(2-Et)
36	HAibEGTFTSD-G-Bip-Bip(2-Et)
37	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip-Bip(2-Et)
38	HAEGTFTSD-G-Bip(2-Et)-Bip(2-Et)
39	HAibEGTFTSD-G-Bip(2-Et)-Bip(2-Et)
40	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Et)
41	HAEGTFTSD-G-Bip(2-Et)-Bip
42	HAibEGTFTSD-G-Bip(2-Et)-Bip
43	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip
44	HAEGTFTSD-G-Bip(2-Et)-Bip(2-Me)
45	HAibEGTFTSD-G-Bip(2-Et)-Bip(2-Me)
46	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Me)
47	HAEGTFTSD-G-Bip(2-Me)-Bip(2-Et)
48	HAibEGTFTSD-G-Bip(2-Me)-Bip(2-Et)
49	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Et)
50	HGEGTFTSD-G-Bip(2-Me)-Bip(2-Me)
51	HGEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Me)
52	HGEGTFTSD-G-Bip(2-Et)-Bip(2-Et)
53	HGEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Et)
54	HGEGTFTSD-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
55	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
56	HGEGTFTSD-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)

57	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
58	HGEGIFTSD-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
59	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
60	HGEGIFTSD-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
61	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
62	HGEGIFTSD-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
63	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
64	HGEGIFTSD-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)
65	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)
66	HGEGIFTSD-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
67	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
68	HGEGIFTSD-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
69	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
70	HGEGIFTSD-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Et)
71	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Et)
72	HGEGIFTSD-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)
73	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)
74	HGEGIFTSD-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)
75	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)
76	HGEGTFTS-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
77	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
78	HGEGTFTS-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
79	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
80	HGEGTFTS-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
81	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
82	HGEGTFTS-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
83	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
84	HGEGTFTS-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
85	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
86	HGEGTFTS-(CH ₂) ₁₁ -Bip(2-Me)-Bip(2-Me)
87	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₁₁ -Bip(2-Me)-Bip(2-Me)
88	HGEGTFTS-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)

89	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)
90	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
91	HGEGTFTS-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
92	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)
93	HGEGTFTS-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
94	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)
95	HGEGTFTS-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Et)
96	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Et)
97	HGEGTFTS-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)
98	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)
99	HGEGTFTS-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)
100	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)
101	HGEGTFTS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
102	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
103	HGEGTFTS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
104	HGEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
105	HAEGTFTS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
106	HAibEGTFTS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
107	HAibEGT-(α -Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
108	HGEGTFTSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
109	HGEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
110	HAEGTFTSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
111	HAibEGTFTSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
112	HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Et)
113	HAEGTF-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Et)
114	HAibEGTF-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Et)
115	HAibEGT-(α -Me)-Phe(2-F)-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Et)
116	HAEGTFTSD-G-TrPh-TrPh
117	HAibEGTFTSD-G-TrPh-TrPh
118	HAibEGT-(α -Me)-Phe(2-F)-TSD-G-TrPh-TrPh
119	HAibEGT-(α -Me)-Phe(2-F)-(CH ₂) ₂ -TrPh-TrPh
120	HAibEG-(CH ₂) ₂ -TrPh-TrPh

121	HAibE-(CH ₂) ₂ -TrPh-TrPh
122	HAib-(CH ₂) ₃ -TrPh-TrPh
123	HAEGTFTSD-G-Nap-Nap
124	HAibEGTFTSD-G-Nap-Nap
125	HAibEGT-(α-Me)-Phe(2-F)-TSD-G-Nap-Nap
126	HAEGTFTSD-G-Bip(2-F)-Bip(2-F)
127	HAibEGTFTSD-G-Bip(2-F)-Bip(2-F)
128	HAibEGT-(α-Me)-Phe(2-F)-TSD-G-Bip(2-F)-Bip(2-F)
129	HAEGTFTSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
130	HAibEGTFTSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
131	HAibEGT-(α-Me)-Phe(2-F)-TSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
132	HAEGTFTSD-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
133	HAibEGTFTSD-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
134	HAibEGT-(α-Me)-Phe(2-F)-TSD-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
135	HAEGTFTS-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
136	HAibEGTFTS-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
137	HAibEGT-(α-Me)-Phe(2-F)-TS-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
138	HAEGTFT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
139	HAibEGTFT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
140	HAibEGT-(α-Me)-Phe(2-F)-T-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
141	HAEGTF-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
142	HAibEGTF-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
143	HAibEGT-(α-Me)-Phe(2-F)-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
144	HAEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
145	HAibEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
146	HAEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
147	HAibEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
148	HAEG-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
149	HAibEG-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala

Tabla 5:

S. No.	Secuencia
1	HAEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
2	HGEGT-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
3	HGEGT-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
4	HGEGT-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
5	HGEGT-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
6	HAEGT-(CH ₂) ₂ -Bip(2-Me)-DBip(2-Me)
7	HAEGT-(CH ₂) ₂ -DBip(2-Me)-Bip(2-Me)
8	HAEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
9	HGEG-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
10	HAEG-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
11	HGEG-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
12	HGEG-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
13	HGEG-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
14	HAEG-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
15	HAEG-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
16	HAEG-(CH ₂) ₄ -Bip(2-Me)-DBip(2-Me)
17	HAEG-(CH ₂) ₅ -Bip(2-Me)-DBip(2-Me)
18	HGEG-(CH ₂) ₅ -DBip(2-Me)-Bip(2-Me)
19	HAE-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
20	HAE-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
21	HAE-(CH ₂) ₂ -D-Bip(2-Me)-Bip(2-Me)
22	HAE-(CH ₂) ₃ -D-Bip(2-Me)-Bip(2-Me)
23	HAE-(CH ₂) ₄ -D-Bip(2-Me)-Bip(2-Me)
24	HAE-(CH ₂) ₄ -Bip(2-Me)-DBip(2-Me)
25	HAE-(CH ₂) ₅ -D-Bip(2-Me)-Bip(2-Me)
26	HAE-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
27	HAE-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)

Tabla 6:

S. No.	Secuencia
1	H-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
2	H-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
3	H-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
4	H-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
5	H-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Me)
6	H-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Me)
7	H-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Me)
8	H-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Me)
9	H-(CH ₂) ₅ -Bip(2-Me)-DBip(2-Me)
10	H-(CH ₂) ₅ -DBip(2-Me)-Bip(2-Me)
11	H-(CH ₂) ₅ -DBip(2-Me)-DBip(2-Me)
12	HG-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
13	HG-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
14	HG-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
15	HG-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Me)
16	HG-(CH ₂) ₅ -Bip(2-Et)-DBip(2-Me)
17	HG-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
18	FA-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Et)
19	FA-(CH ₂) ₃ -DBip-DBip
20	Ha-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
21	Ha-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
22	Ha-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
23	Ha-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
24	Ha-(CH ₂) ₃ -Bip(2-Et)-DBip(2-Me)
25	Ha-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
26	Ha-(CH ₂) ₃ -Bip(2-Et)-DBip(2-Et)
27	Ha-(CH ₂) ₃ -Bip(2-Me)-Bip
28	Ha-(CH ₂) ₃ -(N(Me))-DBip(2-Me)-Bip(2-Et)

29	HA-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)
30	HA-(CH ₂) ₃ -(N(Me))-DBip-Bip(2-Et)
31	HA-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Et)
32	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)
33	HA-(CH ₂) ₄ -Bip(2-Me)-Bip(2-Me)
34	HA-(CH ₂) ₅ -Bip(2-Me)-Bip(2-Me)
35	HA-(CH ₂) ₆ -Bip(2-Me)-Bip(2-Me)
36	HA-(CH ₂) ₁₀ -Bip(2-Me)-Bip(2-Me)
37	HA-(CH ₂) ₁₁ -Bip(2-Me)-Bip(2-Me)
38	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
39	HA-(CH ₂) ₃ -Bip(2-Et)-DBip(2-Et)
40	HA-(CH ₂) ₃ -DBip(2-Me)-DBip(2-Me)
41	HA-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Me)
42	HA-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Me)
43	HA-(CH ₂) ₃ -Bip(2- <i>l</i> pr)-Bip(2- <i>l</i> pr)
44	HA-(CH ₂) ₃ -Bip(2- <i>l</i> pr)-Bip(2-Me)
45	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2- <i>l</i> pr)
46	HA-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Me)
47	HA-(CH ₂) ₃ -Bip(2-Me)-DBip(2-Et)
48	HA-(CH ₂) ₂ -Bip(2-Et)-Bip(2-Me)
49	HA-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Me)
50	HA-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Me)
51	HA-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)
52	HA-(CH ₂) ₃ -DBip(2-Et)-DBip(2-Me)
53	HA-(CH ₂) ₃ -DBip(2-Et)-Bip(2-Me)
54	HA-(CH ₂) ₂ -Bip(2-Me)-DBip(2-Me)
55	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Et)
56	HA-(CH ₂) ₃ -DBip(2-Et)-DBip(2-Et)
57	HA-(CH ₂) ₃ -DBip(2-Et)-Bip(2-Et)
58	HA-(CH ₂) ₃ -DBip(2-Me)-DBip(2-Et)
59	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Et)
60	HA-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Et)
61	HA-(CH ₂) ₃ -Bip-Bip

62	HA-(CH ₂) ₃ -Bip-DBip
63	HA-(CH ₂) ₃ -DBip-DBip
64	HA-(CH ₂) ₃ -DBip-Bip
65	HA-(CH ₂) ₃ -Bip-Bip(2-Me)
66	HA-(CH ₂) ₃ -Bip(2-Me)-Bip
67	HA-(CH ₂) ₃ -Bip(2-Et)-Bip
68	HA-(CH ₂) ₃ -Bip-Bip(2-Et)
69	HA-(CH ₂) ₃ -Bip(2- <i>l</i> pr)-DBip(2- <i>l</i> pr)
70	HA-(CH ₂) ₃ -DBip(2- <i>l</i> pr)-Bip(2- <i>l</i> pr)
71	HA-(CH ₂) ₃ -DBip(2- <i>l</i> pr)-DBip(2- <i>l</i> pr)
72	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-CN)
73	HA-(CH ₂) ₃ -Bip-Bip(2-CN)
74	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-CN)
75	HA-(CH ₂) ₃ -Bip(2- <i>l</i> pr)-Bip(2-CN)
76	HA-(CH ₂) ₃ -Bip(2-CN)-Bip(2-Me)
77	HA-(CH ₂) ₃ -Bip(2-CN)-Bip
78	HA-(CH ₂) ₃ -Bip(2-CN)-Bip(2-Et)
79	HA-(CH ₂) ₃ -Bip(2-CN)-Bip(2- <i>l</i> pr)
80	HA-(CH ₂) ₃ -Bip(2-CN)-Bip(2-CN)
81	HA-(CH ₂) ₂ -F-(CH ₂) ₂ -Bip(2-Et)-DBip(2-Et)
82	HA-(CH ₂) ₂ -F-(CH ₂) ₂ -Bip(2-Et)-DBip(2-Me)
83	HA-(CH ₂) ₅ -Bip(2-Me)-DBip
84	HA-(CH ₂) ₃ -Bip(2-Me)-DBip-R
85	IIA-(CII ₂) ₃ -DBip(2-Mc)-DBip
86	HA-(CH ₂) ₅ -Bip(2-Me)-DBip(2-Me)
87	HA-(CH ₂) ₅ -DBip(2-Me)-Bip(2-Me)
88	HA-(CH ₂) ₄ -D(Bip)-Bip(2-Et)
89	IIA-(CH ₂) ₅ -D(Bip)-Bip(2-Et)
90	HA-(CH ₂) ₄ -Bip(2-Me)-DBip(2-Me)
91	HA-(CH ₂) ₅ -Bip(2-Me)-DBip(2-Me)
92	HA-(CH ₂) ₅ -(N(Me))-DBip-Bip(2-Et)
93	HA-(CH ₂) ₄ -DBip(2-Me)-Bip(2-Et)
94	HA-(CH ₂) ₅ -DBip(2-Me)-Bip(2-Et)

95	HA-(CH ₂) ₃ -(N(Me))-DBip(2-Me)-Bip(2-Et)
96	HA-(CH ₂) ₄ -Bip(2-Me)-DBip
97	HA-(CH ₂) ₅ -Bip(2-Me)-DBip
98	HA-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)
99	HA-(N(Me))-(CH ₂) ₃ -DBip(2-Me)-Bip(2-Et)
100	HA-(N(Me))-(CH ₂) ₃ -DBip-Bip(2-Et)
101	HA-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)
102	HA-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-DBip
103	HAE-(CH ₂) ₂ -F-(CH ₂) ₂ -Bip(2-Et)-DBip(2-Et)
104	HAE-(CH ₂) ₂ -F-(CH ₂) ₂ -Bip(2-Et)-DBip(2-Me)
105	HAib-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)

Los siguientes compuestos se pueden preparar de acuerdo con los procesos generales descritos anteriormente y se incluyen dentro del alcance de la presente invención (Tablas 7-9)

Tabla 7:

S. No.	Secuencia
1	HA-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
2	H-Aib-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
3	Ha-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
4	H-(N(Me))A-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
5	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
6	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
7	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
8	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
9	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
10	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂

11	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
12	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
13	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
14	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
15	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
16	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
17	CH ₃ -(CH ₂) ₆ -NH-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
18	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
19	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
20	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
21	HA-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
22	H-Aib-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
23	HA-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
24	H-(N(Me))A-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
25	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
26	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
27	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
28	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
29	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-

	Me-Ph)-3-Pyr-Ala-NH ₂
30	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
31	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
32	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
33	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
34	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
35	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
36	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
37	CH ₃ -(CH ₂) ₆ -NH-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
38	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
39	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
40	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
41	HA-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
42	H-Aib-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
43	H-a-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
44	H-(N(Me))A-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
45	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
46	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
47	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂

48	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
49	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
50	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
51	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
52	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
53	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
54	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
55	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
56	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
57	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
58	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
59	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
60	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
61	HA-E-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
62	H-Aib-E-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
63	HA-E-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
64	H-(N(Me))AE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
65	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
66	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-

	Ala-NH ₂
67	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
68	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
69	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
70	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
71	Des-amino-H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
72	Des-amino-H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
73	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
74	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
75	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
76	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
77	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
78	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
79	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
80	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
81	HAEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
82	H-Aib-EG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
83	HAEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
84	H-(N(Me))AEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂

85	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
86	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
87	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
88	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
89	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
90	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
91	Des-amino-H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
92	Des-amino-H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
93	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
94	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
95	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
96	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
97	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
98	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
99	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
100	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
101	HAEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂

102	H-Aib-EGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
103	HaEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
104	H-(N(Me))AEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
105	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
106	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
107	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
108	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
109	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
110	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
111	Des-amino-H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
112	Des-amino-H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH ₂
113	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
114	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
115	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
116	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₁₀ -CH ₃
117	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
118	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
119	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃

120	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH ₂) ₆ -CH ₃
121	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
122	H-Aib-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
123	Ha-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
124	H-(N(Me))A-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
125	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
126	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-NH ₂
127	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-Bip(2-Me)-NH ₂
128	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-Bip(2-Me)-NH ₂
129	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH ₂
130	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH ₂
131	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH ₂
132	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH ₂
133	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
134	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
135	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₁₀ -CH ₃
136	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₁₀ -CH ₃
137	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
138	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
139	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
140	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃

141	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
142	H-Aib-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
143	Ha-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
144	H-(N(Me))A-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
145	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
146	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-NH ₂
147	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)-NH ₂
148	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)-NH ₂
149	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH ₂
150	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH ₂
151	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH ₂
152	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH ₂
153	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
154	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
155	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₁₀ -CH ₃
156	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₁₀ -CH ₃
157	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
158	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
159	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃
160	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH ₂) ₆ -CH ₃

Tabla 8:

S. No.	Secuencia
1	HA-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
2	H-Aib-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
3	Ha-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
4	H-(N(Me))A-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
5	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
6	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
7	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
8	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
9	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
10	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
11	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
12	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
13	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
14	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
15	H-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
16	H-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
17	CH ₃ -(CH ₂) ₆ -NH-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
18	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃

19	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))A-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
20	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
21	HA-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
22	H-Aib-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
23	HA-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
24	H-(N(Me))A-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
25	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
26	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
27	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
28	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
29	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
30	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
31	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
32	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
33	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
34	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
35	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
36	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
37	CH ₃ -(CH ₂) ₆ -NH-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃

38	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
39	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
40	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
41	HA-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
42	H-Aib-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
43	Ha-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
44	H-(N(Me))A-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
45	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
46	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
47	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
48	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
49	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
50	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
51	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
52	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
53	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
54	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
55	H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
56	H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃

57	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
58	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
59	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
60	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₄ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
61	HAE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
62	H-Aib-E-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
63	HA-E-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
64	H-(N(Me))AE-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
65	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
66	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
67	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
68	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
69	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
70	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
71	Des-amino-H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
72	Des-amino-H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
73	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
74	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
75	H-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-

	Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
76	H-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
77	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
78	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
79	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AE-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
80	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-E-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
81	HAEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
82	H-Aib-EG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
83	HAEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
84	H-(N(Me))AEG-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
85	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
86	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
87	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
88	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
89	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
90	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
91	Des-amino-H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
92	Des-amino-H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
93	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃

94	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
95	H-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
96	H-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
97	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
98	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
99	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AEG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
100	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-EG-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
101	HAEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
102	H-Aib-EGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
103	HAEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
104	H-(N(Me))AEGT-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
105	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
106	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
107	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
108	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
109	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
110	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
111	Des-amino-H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
112	Des-amino-H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-

	(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
113	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
114	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
115	H-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
116	H-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₁₀ -CH ₃
117	CH ₃ -(CH ₂) ₆ -NH-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
118	CH ₃ -(CH ₂) ₆ -NH-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
119	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))AEGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
120	CH ₃ -(CH ₂) ₁₀ -NH-(N(Me))Aib-EGT-(N(Me))-(CH ₂) ₂ -(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH ₂) ₆ -CH ₃
121	HA-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
122	H-Aib-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
123	Ha-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
124	H-(N(Me))A-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
125	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
126	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2-Me)-Bip(2-Me)-OH
127	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-Bip(2-Me)-OH
128	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-Bip(2-Me)-OH
129	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
130	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
131	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
132	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH
133	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃

134	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
135	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₁₀ -CH ₃
136	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₁₀ -CH ₃
137	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
138	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
139	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
140	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
141	HA-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
142	H-Aib-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
143	Ha-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
144	H-(N(Me))A-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
145	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
146	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -Bip(2-Et)-Bip(2-Me)-OH
147	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)-OH
148	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-Bip(2-Me)-OH
149	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
150	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
151	Des-amino-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
152	Des-amino-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-OH
153	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
154	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
155	H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-

	(CH ₂) ₁₀ -CH ₃
156	H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₁₀ -CH ₃
157	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
158	CH ₃ -(CH ₂) ₆ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
159	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))A-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃
160	CH ₃ -(CH ₂) ₁₀ -NH-H-(N(Me))Aib-(N(Me))-(CH ₂) ₃ -(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-COO-(CH ₂) ₆ -CH ₃

Tabla 9:

S. No.	Secuencia
1	HA-(CH ₂) ₃ -DVSSYLEGQAAKEFIKELEKLL
2	HAib-(CH ₂) ₃ -DVSSYLEGQAAKEFIKELEKLL
3	HAibEGTFTSDVSSYLEGQ-(CH ₂) ₂ -KELEKLL
4	HAibEGTFTSDVSSYLEGQ-(CH ₂) ₃ -KELEKLL
5	HAibEGTFTSDVSSYLE-(CH ₂) ₂ -FIKELEKLL
6	HAibEGT-(α-Me)Phe(2-F)-TSDVSSYLE-(CH ₂) ₂ -FIKELEKLL
7	HAib-(CH ₂) ₃ -VSSYLE-(CH ₂) ₂ -FIKELEKLL
8	HAib-(CH ₂) ₃ -VSSYLE-(CH ₂) ₃ -FIKELEKLL
9	HAib-(CH ₂) ₃ -YLE-(CH ₂) ₃ -FIKELEKLL
10	HAib-(CH ₂) ₄ -YLE-(CH ₂) ₃ -FIKELEKLL
11	HAib-(CH ₂) ₄ -YL-(CH ₂) ₃ -FIKELEKLL
12	HAib-(CH ₂) ₄ -Y-(CH ₂) ₃ -FIKELEKLL
13	HAib-(CH ₂) ₄ -FIKELEKLL
14	HAib-(CH ₂) ₅ -FIKELEKLL
15	HAib-(CH ₂) ₆ -FIKELEKLL
16	HAib-(CH ₂) ₈ -FIKELEKLL
17	HAib-(CH ₂) ₃ -VSSYLEGQ-(CH ₂) ₃ -KELEKLL
18	HAib-(CH ₂) ₃ -VSSYLEG-(CH ₂) ₃ -KELEKLL

19	HAib-(CH ₂) ₃ -VSSYLE-(CH ₂) ₄ -KELEKLL
20	HAib-(CH ₂) ₃ -SSYLE-(CH ₂) ₄ -KELEKLL
21	HAib-(CH ₂) ₃ -SYLE-(CH ₂) ₄ -KELEKLL
22	HAib-(CH ₂) ₃ -YLE-(CH ₂) ₄ -KELEKLL
23	HAib-(CH ₂) ₃ -YL-(CH ₂) ₄ -KELEKLL
24	HAib-(CH ₂) ₃ -Y-(CH ₂) ₄ -KELEKLL
25	HAib-(CH ₂) ₅ -KELEKLL
26	HAib-(CH ₂) ₆ -KELEKLL
27	HAib-(CH ₂) ₈ -KELEKLL

Los peptidomiméticos preparados como se describió anteriormente se prueban para actividad agonista GLP-1 in Vitro utilizando el ensayo basado en células cAMP descrito adelante. El análogo de peptidomimético GLP-1 estimula la producción cAMP en una forma de respuesta de dosis y el valor correspondiente EC₅₀ se determina para algunos de los peptidomiméticos seleccionados, que son activos in vitro en un rango de 10 a 100 nm. El valor EC₅₀ del EX-4 se utiliza como un control positivo.

Determinación de AMP cíclico

El receptor GLP-1 es un receptor acoplado a la proteína G. El GLP-1 (7-36)-amida, la forma biológicamente activa, se une al receptor GLP-1 y a través de la transducción de señal origina la activación de la ciclasa adenilato y eleva los niveles de cAMP intracelulares. Para monitorear el agonismo de los Compuestos de péptido en la estimulación del receptor GLP-1, se monitorea la actividad ciclasa adenilo al ensayar los niveles de cAMP celulares.

Ensayo cAMP:

Se ensayan células CHO/HGLP1R transfectadas de forma estable para generación de cAMP en una plataforma de semi alto rendimiento utilizando el kit discoverX cAMP con Exendin-4 como un control positivo. La actividad del NCE se determina como porcentaje de actividad Exendin-4 en concentración 0.01 μM . Los compuestos positivos se validan adicionalmente para generación de cAMP utilizando el kit ELISA cAMP (R & D Systems). La actividad de los compuestos se expresa como fmol cAMP/ μg de proteína. Los valores EC_{50} de algunos de los compuestos representativos (I a IV) se muestran en la figura 1.

Demostración de eficacia in vivo de compuestos:

Las propiedades de reducción de glucosa in vivo de algunos de los compuestos representativos en modelos animales se describe adelante. Esta prueba se utiliza para examinar la eficacia in vivo de compuestos de la presente invención en glucosa sanguínea en glucosa en hiperglicemia. La prueba de tolerancia a la glucosa intraperitoneal (IPGTT) se desarrollan en ratones suizos albinos (SAM), que pesan 25-30 g. A los ratones se les da una carga de glucosa de 1.5 g/kg/10 ml y se recolecta la sangre en diferentes intervalos de tiempo, por vía del plexo retro orbital. Los compuestos de ensayo (peptidomiméticos) se disuelven en un vehículo apropiado en una concentración en nmol/ml equivalente a la dosis que se administra en nmol/kg, de tal manera que cada ratón podría recibir el mismo volumen/peso de solución de dosificación.

Las muestras de sangre se retiran antes para vehículo/compuesto de prueba/carga de glucosa (0 minutos) y luego en 15 min, 30 min, 60 min, y 120 min. El compuesto de vehículo/ensayo se administra 15 minutos antes para carga de glucosa, por vía de ruta intraperitoneal de administración. Se centrifugan las muestras sanguíneas y el suero obtenido se almacena a -20°C para análisis. Los compuestos de ensayo se examinan junto con una referencia (control positivo) y un vehículo de control con $n=6$ animales por grupos. La glucosa se determina por el método GOD/POD de suero. El valor medio de los resultados duplicados se calcula. Los valores absolutos de la glucosa en los niveles de suero se calculan utilizando el software MS Excel. La gráfica de línea corregida de línea base de 0 minutos se grafica utilizando el software Graphpad prism (ver 3.0). El área bajo la curva (AUC) y el área de línea base corregida bajo la curva (BCAUC) se calculan y analizan al desarrollar un ANOVA de una vía seguido por el ensayo Dunnett utilizando el software Graphpad prism (ver 3.0).

Utilizando el anterior protocolo experimental, las propiedades de reducción de glucosa in vivo de algunos de los compuestos seleccionados, que muestran que EC_{50} in Vitro, en ensayo cAMP CHO/GLP-1R, en el rango de 1-50 nm se determinan. En la tabla 10, se dan las potencias de reducción de glucosa in vivo (ED_{50} en el modelo SAM IPGTT) de cuatro compuestos representativos seleccionados (Comp. I, II, III y IV).

Tabla 10: Potencias in vivo de los compuestos I a IV (ED_{50}), en modelo IPGTT SAM

Comp.	ED50 en Modelo IPGTT SAM (n = 6)
I	1 μ mol / kg
II	500 nM / Kg
III	250 nM / kg
IV	100 nM / Kg

Varios compuestos de la presente invención se seleccionan in vivo, utilizando otros modelos animales, tal como ob/ob, db/db y C57 y ellos muestran eficacia in vivo y potencia en varios grados.

Utilidad:

La presente invención proporciona peptidomiméticos novedosos GLP-1 con una preferencia para imitar el GLP-1, de tal manera que los compuestos de la presente invención tienen actividad agonista del receptor GLP-1. Adicionalmente, muchos de los peptidomiméticos GLP de la presente invención exhiben estabilidad incrementada para clivaje proteolítico como se compara con las secuencias GLP-1 nativas.

De acuerdo con esto, los compuestos de la presente invención se pueden administrar a mamíferos, preferiblemente humanos, para el tratamiento de una variedad de condiciones y trastornos que incluyen, pero no se limitan a, tratar o retrasar la progresión o inicio de la diabetes (preferiblemente tipo II, deficiencia de tolerancia a la glucosa, resistencia a la insulina y complicaciones diabéticas, tal como nefropatía, retinopatía, neuropatía y

cataratas), hiperglicemia, hiperinsulinemia, hipercolesterolemia, niveles sanguíneos elevados de ácidos grasos libres o glicerol, hiperlipidemia, hipertrigliceridemia, obesidad, mala cicatrización, isquemia de tejido, aterosclerosis, hipertensión, enfermedades intestinales (tal como enteritis necrotizante, enfermedad de inclusión de microbillus o enfermedad célica). El compuesto de la presente invención también se puede utilizar para incrementar los niveles sanguíneos de lipoproteína de alta densidad (HDL).

Adicionalmente, las condiciones, enfermedades referenciadas colectivamente como "síndrome X" o síndrome metabólico como se detalla en Johannsson J., Clin. Endocrinol. Metab., 82, 727-34, 1997, se pueden tratar empleando los compuestos de la invención. Los compuestos de la presente invención se pueden utilizar convencionalmente en combinación con inhibidores DPP-IV adecuados para tratamiento de algunos de los estados de enfermedad anteriores ala administrar los compuestos secuencialmente o como una formulación que contiene los compuestos de la presente invención junto con un inhibidor DPP-IV adecuado.

No se observan efectos adversos para cualquiera de los compuestos mencionados de la invención. Los compuestos de la presente invención muestran buena actividad de reducción de suero en glucosa en los animales experimentales utilizados. Estos compuestos se utilizan para el ensayo/profilaxis de enfermedades originadas por hiperinsulinemia, hiperglicemia tal como NIDDM, trastornos metabólicos y obesidad en razón a que tales enfermedades se entrelazan la una a la otra.

Reivindicaciones

1. Un polipéptido aislado que tiene una secuencia de fórmula (I), que incluye sus tautómeros, solvatos y sales farmacéuticamente aceptables.

A-X₁-S₁-Y-S₂-X₂-B (I)

En donde,

A representa -NH-R₁, en donde R₁ representa hidrógeno, grupos seleccionados de cadena alquilo (C₁-C₁₅) lineal o ramificada, un aminoácido o péptido que contiene uno, dos o tres residuos aminoácidos naturales, un Grupo R₃O-C(O)-, un grupo sulfonil de fórmula R₃-SO₂-, cada uno de estos grupos se puede sustituir; R₃ se selecciona de alquilo (C₁-C₁₀) lineal o ramificado, cicloalquilo (C₃-C₆), arilo, heteroarilo, grupos arilalquilo, cada uno de estos grupos se pueden sustituir;

B representa -COOR₂, -CONHR₂ o CH₂OR₂, R₂ representa H, seleccionados de grupos alquilo (C₁-C₁₀) lineal o ramificado, grupos arilo seleccionados de fenilo, naftilo, indanilo, fluorenilo, grupos bifenilo, grupo aralquilo, en donde los grupos arilo son como se definió anteriormente, cada uno de estos grupos se puede sustituir;

cada uno de S₁ y S₂ pueden independientemente estar unidos o independientemente representan un grupo '-NH-(CH₂)_n-COO-', en donde , n=1-9;

Y representa un enlace o -CO-, -(CH₂)_m- (m = 1-3), 'O', 'S', -CO-NH-, -CO-NR₄-, o representa un péptido corto que contiene

uno o dos o tres aminoácidos seleccionados de aminoácidos naturales o no naturales; en donde R_4 representa H, opcionalmente sustituidos seleccionados de grupos alquilo (C_1-C_{10}) lineal o ramificado o grupos arilo seleccionados de grupos fenilo, naftilo, indanilo, fluorenilo, bifenilo; con la condición que cuando S_1-Y-S_2 representan un enlace, X_1 se selecciona de las siguientes secuencias de aminoácido

HAEGTFTSD, HAEGTFTSDV, HAEGTFTSDVS, HAEGTFTSDVSS, HAEGTFTSDVSSY, HAEGTFTSDVSSILO, HAEGTFTSDVSSILE, HAEGTFTSDVSSILEG, HAEGTFTSDVSSILEGQ, HAEGTFTSDVSSILEGQA, HAEGTFTSDVSSILEGQAA, HAEGTFTSDVSSILEGQAAK, HAEGTFTSDVSSILEGQAAICE, HAEGTFTSDVSSILEGQAAKEF, HAEGTFTSDVSSILEGQAAKEFI, con la opción adicional que uno o más de estos aminoácidos se pueden reemplazar por aminoácidos no naturales, y X_2 se selecciona de las siguientes secuencias de aminoácidos

GPSSGAPPPS o

KELEKLL o

GPPS o

VKGR; y cuando S_1-Y-S_2 no representan un enlace X_1 se selecciona de las siguientes secuencias de aminoácido HA, HAE, HAEG, HAEGT, HAEGTF, HAEGTFT, HAEGTFTS, HAEGTFTSD con la opción adicional que uno o más de estos aminoácidos se pueden reemplazar por aminoácidos no naturales;

X_2 se selecciona de

GPSSGAPPPS o

KELEKLL o

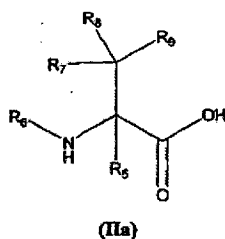
GPPS o

VKGR o

un dipéptido, seleccionado de la combinación de dos aminoácidos que consisten de aminoácidos naturales o no

naturales, que tienen una cadena lateral que contiene unas porciones arilalquilo o heterorilalquilo seleccionadas de grupos bencilo, naftilmetilo, piridilmetilo, tienilmetilo, furilmetilo, imidazolilmetilo, isooxazolilmetilo, quinolilmetilo, benzofuranilmetilo, benzotienilmetilo, indolinilmetilo, indolilmetilo, dibenzofuranilmetilo, dibenzotienilmetilo, benzodihidrofuranilmetilo, benzodihidrotienilmetilo, tienopirimidilmetilo, benzimidazolilmetilo, fenantrenilmetilo, dihidrofenantrenilmetilo, fluorenilmetilo, dibenzofuranilmetilo, dibenzotiofenilo metilo, en donde cada uno de estos grupos se pueden sustituir opcionalmente con alquilo (C₁-C₆), alcoxi (C₁-C₆), ciano, halo, hidroxilo o grupos arilo o heteroarilo opcionalmente sustituidos, con la condición adicional de que tales sustituyentes arilo o heteroarilo pueden opcionalmente y adicionalmente sustituirse con alquilo (C₁-C₆), alcoxi (C₁-C₆), ciano, halo, hidroxilo o arilo o grupos heteroarilo.

2. Un compuesto como se reivindica en la reivindicación 1 en donde los aminoácidos no naturales se representan mediante la fórmula general (IIa)



en donde R₅ se selecciona de H, F, alquilo (C₁-C₅), la configuración estereoquímica en el R₅ que lleva carbono puede

ser (R) o (S); R_6 se selecciona de H o alquilo (C_1-C_3); cada uno de R_7 y R_8 se selecciona independientemente de H, alquilo (C_1-C_2) o un átomo de halógeno, preferiblemente un átomo de fluor; R_9 representa grupos, seleccionados de alquilo (C_1-C_6), porciones arilo o heteroarilo seleccionadas de grupos fenilo, naftilo, piridilo, tienilo, furilo, imidazolilo, isooxazolilo, quinolilo, benzofuranilo, benzotienilo, indolinilo, indolilo, dibenzofuranilo, dibenzotienilo, benzodihidrofuranilo, benzodihidrotienilo, tienopirimidilo, benzimidazolilo, fenantrenilo, dihidrofenantrenilo, fluorenilo, dibenzofuranilo, dibenzotiofenilo, en donde cada uno de estos grupos se pueden opcionalmente sustituir con alquilo (C_1-C_6), alcoxi (C_1-C_5), ciano, halo, hidroxilo o grupos arilo o heteroarilo opcionalmente sustituidos, con la condición adicional de que tales sustituyentes arilo o heteroarilo pueden opcionalmente y adicionalmente ser sustituidos con alquilo (C_1-C_6), alcoxi (C_1-C_5), ciano, halo, hidroxilo o arilo o grupos heteroarilo.

3. El péptido aislado como se reivindica en la reivindicación 1, en donde el dipéptido que representa X_2 es preferiblemente seleccionado de grupos Bip, Bip(2-Me), Bip(2-Et), Bip(2-Ipr), Bip(2-CN), Bip(2'-Et-4'-OMe), Bip(4'-fluoro), Bip(4'-Fenilo), 2-(9,10-Dihidro-fenantrenil)-Ala, 2-(Fenantrenil)-Ala, 4-(2-Naftil)-Phe, 4-(1-Naftil)-Phe, 2-Fluorenil-Ala, 4-dibenzofuran-Phe, 4-dibenzotiofeno-Phe, 4-(2'-metilfenil)-3-piridilalanina.

4. El péptido aislado como se reivindica en la reivindicación 1, en donde los sustituyentes se seleccionan de hidroxilo, oxo, halo, tio, nitro, amino, ciano, alquilo,

haloalquilo, alcoxi, haloalcoxi, cicloalquilo, arilo, ariloxi, aralquilo, aralcoxi, heteroarilo, heteroaralquilo, heteroarilooxi, heteroaralcoxi, acilo, aciloxi, ácido carboxílico y sus derivados seleccionados de ésteres y amidas.

5. El polipéptido aislado de la reivindicación 1, en donde el polipéptido aislado es un compuesto seleccionado de

HGEGTFTSD-(CH₂)₃-GPSSGAPPPS
HGEGTFTSD-(CH₂)₄-GPSSGAPPPS
HGEGTFTSD-(CH₂)₅-GPSSGAPPPS
HGEGTFTSD-(CH₂)₆-GPSSGAPPPS
HGEGTFTSD-(CH₂)₇-GPSSGAPPPS
HGEGTFTSD-(CH₂)₁₀-GPSSGAPPPS
HGEGTFTSD-(CH₂)_n-GPSSGAPPPS
HGEGTFTSDLSKQM-(CH₂)₃-GPSS
HGEGTFTSDLSKQM-(CH₂)₄-GPSS
HGEGTFTSDLSKQM-(CH₂)₅-GPSS
HGEGTFTSDLSKQM-(CH₂)₆-GPSS
HGEGTFTSDLSKQM-(CH₂)₇-GPSS
HGEGTFTSDLSKQM-(CH₂)₁₀-GPSS
HGEGTFTSDLSKQM-(CH₂)₁₁-GPSS
HGEGTFTSDLSKQME-G-GPSSGAPPP₁S
HGEGTFTSDLSKQME-(CH₂)₂-GPSSGAPPPS
HGEGTFTSDLSKQME-(CH₂)₃-GPSSGAPPPS
HGEGTFTSDLSKQME-(CH₂)₄-GPSSGAPPPS
HGEGTFTSDLSKQME-(CH₂)₅-GPSSGAPPPS
HGEGTFTSDLSKQME-(CH₂)₆-GPSSGAPPPS
HGEGTFTSDLSKQME-(CH₂)₇-GPSSGAPPPS
HGEGTFTSDLSKQME-(CH₂)₁₀-GPSSGAPPPS
HGEGTFTSDLSKQME-(CH₂)₁₁-GPSSGAPPPS
HAEGTFTSD-(CH₂)₂-VKGR
HAEGTFTSD-(CH₂)₃-VKGR
HAEGTFTSD-(CH₂)₄-VKGR
HAEGTFTSD-(CH₂)₅-VKGR
HAEGTFTSD-(CH₂)₆-VKGR
HAEGTFTSD-(CH₂)₁₀-VKGR

HAibEGTFTSD- (CH₂)₂-VKGR
HAibEGTFTSD- (CH₂)₃-VKGR
HAibEGTFTSD- (CH₂)₄-VKGR
HAibEGTFTSD- (CH₂)₅-VKGR
HAibEGTFTSD- (CH₂)₆-VKGR
HAibEGTFTSD- (CH₂)₁₀-VKGR
HGETFTSDLSKQMKLEKLL
HAEGTFTSDKELEKLL
HGETFTSDKELEKLL
HAibEGTFTSDGKELEKLL
HGETFTSDGKELEKLL
HGETFTSDVSKELEKLL
HAEGTFTSDVSKELEKLL
HAEGTFTSDVSEKELEKLL
HAEGTFTSDVSGKELEKLL
HAEGTFTSDVSSYLEKELEKLL
HAEGTFTSDVSSYLEGKELEKLL
HGETFTSDVSSYLEGKELEKLL
HaEGTFTSDVSSYLEGKELEKLL
HAibEGTFTSDVSSYLEGKELEKLL
HAEGTFTSDVSSYLEGKELEKLLVKG
HAEGTFTSDVSSYLEPKLEKLL
HAEGTFTSDVSSYLEGQAAKELEKLL
HAEGTFTSDVSSYLEGQAAKEFIKELEKLL
HAIBEGTFTSDVSSYLEGQAAKEFIKELEKLL
HAibEGT- (α-Me) Phe (2-F) -TSDVSSYLEGQAAKEFIKELEKLL
Des-amino-HAibEGT- (α-Me) Phe (2-F) -TSDVSSYLEGQAAKEFIKELEKLL
HAEGTFTSD- (CH₂)₃-KELEKLL
HAEGTFTSD- (CH₂)₄-KELEKLL
HAEGTFTSD- (CH₂)₅-KELEKLL
HAEGTFTSD- (CH₂)₆-KELEKLL
HA- (CH₂)₃-DVSSYLEGQAAKEFIKELEKLL
HAib- (CH₂)₃-DVSSYLEGQAAKEFIKELEKLL
HAibEGTFTSDVSSYLEGQ- (CH₂)₂-KELEKLL
HAibEGTFTSDVSSYLEGQ- (CH₂)₃-KELEKLL
HAibEGTFTSDVSSYLE- (CH₂)₂-FIKELEKLL
HGETFTSD- (CH₂)₃-Bip-Bip
HAibEGTFTSD- (CH₂)₃-Bip-Bip
HAibEGT- (α-Me) -Phe (2-F) -TSD- (CH₂)₃-Bip-Bip
HAEGTFTSD-G-Bip (2-Me) -Bip (2-Me)
HAibEGTFTSD-G-Bip (2-Me) -Bip (2-Me)

HAibEGT- (α -Me) -Phe (2-F) -TSD-G-Bip (2-Me) -Bip (2-Me)
HAEGTFTS-G-Bip (2-Me) -Bip (2-Me)
HAibEGTFTS-G-Bip (2-Me) -Bip (2-Me)
HAibEGT- (α -Me) -Phe (2-F) -TS-G-Bip (2-Me) -Bip (2-Me)
HAEGTFTS- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGTFTS- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGT- (α -Me) -Phe (2-F) -TS- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAEGTFT- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGTFT- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGT- (α -Me) -Phe (2-F) -T- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAEGTF- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGTF- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGT- (α -Me) -Phe (2-F) - (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAEGT- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGT- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAEG- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEG- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAEGTFTSD- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGTFTSD- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAibEGT- (α -Me) -Phe (2-F) -TSD- (CH_2)₂-Bip (2-Me) -Bip (2-Me)
HAEGTFTSD-G-Bip-Bip (2-Me)
HAibEGTFTSD-G-Bip-Bip (2-Me)
HAibEGT- (α -Me) -Phe (2-F) -TSD-G-Bip-Bip (2-Me)
HAEGTFTSD-G-Bip (2-Me) -Bip
HAibEGTFTSD-G-Bip (2-Me) -Bip
HAibEGT- (α -Me) -Phe (2-F) -TSD-G-Bip (2-Me) -Bip
HAEGTFTSD-G-Bip-Bip HAibEGTFTSD-G-Bip-Bip
HAibEGT- (α -Me) -Phe (2-F) -TSD-G-Bip-Bip
HAEGTFTSD-G-Bip-Bip (2-Et)
HAibEGTFTSD-G-Bip-Bip (2-Et)
HAibEGT- (α -Me) -Phe (2-F) -TSD-G-Bip-Bip (2-Et)
HAEGTFTSD-G-Bip (2-Et) -Bip (2-Et)
HAibEGTFTSD-G-Bip (2-Et) -Bip (2-Et)
HAibEGT- (α -Me) -Phe (2-F) -TSD-G-Bip (2-Et) -Bip (2-Et)
HAEGTFTSD-G-Bip (2-Et) -Bip
HAibEGTFTSD-G-Bip (2-Et) -Bip
HAibEGT- (α -Me) -Phe (2-F) -TSD-G-Bip (2-Et) -Bip
HAEGTFTSD-G-Bip (2-Et) -Bip (2-Me)
HAibEGTFTSD-G-Bip (2-Et) -Bip (2-Me)
HAibEGT- (α -Me) -Phe (2-F) -TSD-G-Bip (2-Et) -Bip (2-Me)
HAEGTFTSD-G-Bip (2-Me) -Bip (2-Et)

HAibEGTFTSD-G-Bip(2-Me)-Bip(2-Et)
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Et)
HGEFTFTSD-G-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-G-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HGEFTFTSD-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₅-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₅-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₆-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₆-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₁₀-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)₁₀-Bip(2-Et)-Bip(2-Et)
HGEFTFTSD-(CH₂)₁₁-Bip(2-Et)-Bip(2-Et)
HGEFT-(α -Me)-Phe(2-F)-TSD-(CH₂)_n-Bip(2-Et)-Bip(2-Et)
HGEFTFTS-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TS-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEFTFTS-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TS-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HGEFTFTS-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TS-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEFTFTS-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TS-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HGEFTFTS-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TS-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HGEFTFTS-(CH₂)₁₁-Bip(2-Me)-Bip(2-Me)
HGEFT-(α -Me)-Phe(2-F)-TS-(CH₂)_n-Bip(2-Me)-Bip(2-Me)
HGEFTFTS-(CH₂)₃-Bip(2-Et)-Bip(2-Et)

HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGEGLTTS-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₄-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₅-Bip(2-Et)-Bip(2-Et)
HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₅-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₆-Bip(2-Et)-Bip(2-Et)
HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₆-Bip(2-Et)-Bip(2-Et)
I-IGEGTFTS-(CII₂)₁₀-Bip(2-Et)-Bip(2-Et)
HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₁₀-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₁₁-Bip(2-Et)-Bip(2-Et)
HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)_j-Bip(2-Et)-Bip(2-Et)
HGEGTFTS-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HGEGTFTS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HGEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAEGTFTS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAibEGTFTS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAibEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HGEGTFTSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HGEGT-(α -Me)-Phe(2-F)-TSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAEGTFTSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAibEGTFTSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH₂)₂-Bip(2-Et)-Bip(2-Et)
HAEGTF-(CH₂)₂-Bip(2-Me)-Bip(2-Et)
HAibEGTF-(CH₂)₂-Bip(2-Me)-Bip(2-Et)
HAibEGT-(α -Me)-Phe(2-F)-(CH₂)₂-Bip(2-Me)-Bip(2-Et)
HAEGTFTSD-G-TrPh-TrPh
HAibEGTFTSD-G-TrPh-TrPh
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-TrPh-TrPh
HAibEGT-(α -Me)-Phe(2-F)-(CH₂)₂-TrPh-TrPh
HAibEG-(CH₂)₂-TrPh-TrPh
HAibE-(CH₂)₂-TrPh-TrPh
HAib-(CH₂)₃-TrPh-TrPh
HAEGTFTSD-G-Nap-Nap
HAibEGTFTSD-G-Nap-Nap
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Nap-Nap
HAEGTFTSD-G-Bip(2-F)-Bip(2-F)
HAibEGTFTSD-G-Bip(2-F)-Bip(2-F)
AibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2-F)-Bip(2-F)
HAEGTFTSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala

HAibEGTFTSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGT-(α -Me)-Phe(2-F)-TSD-G-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-
3-Pyr-Ala
HAEGTFTSD-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGTFTSD-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGT-(α -Me)-Phe(2-F)-TSD-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-
Ph)-3-Pyr-Ala
HAEGTFTS-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGTFTS-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGT-(α -Me)-Phe(2-F)-TS-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-
Ph)-3-Pyr-Ala
HAEGTFT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGTFT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGT-(α -Me)-Phe(2-F)-T-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-
Ph)-3-Pyr-Ala
HAEGTF-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGTF-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGT-(α -Me)-Phe(2-F)-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-
3-Pyr-Ala
HAEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAEG-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAibEG-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala
HAEGT-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HGEGT-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEGT-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HGEGT-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEGT-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HAEGT-(CH₂)₂-Bip(2-Me)-DBip(2-Me)
HAEGT-(CH₂)₂-DBip(2-Me)-Bip(2-Me)
HaEGT-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HGEG-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HAEG-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HGEG-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HGEG-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HGEG-(CH₂)₉-Bip(2-Me)-Bip(2-Me)
HAEG-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
HAEG-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
HAEG-(CH₂)₄-Bip(2-Me)-DBip(2-Me)

HAEG-(CH₂)₅-Bip(2-Me)-DBip(2-Me)
HGEG-(CH₂)₅-DBip(2-Me)-Bip(2-Me)
HAE-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HAE-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
HAE-(CH₂)₂-D-Bip(2-Me)-Bip(2-Me)
HAE-(CH₂)₃-D-Bip(2-Me)-Bip(2-Me)
HAE-(CH₂)₄-D-Bip(2-Me)-Bip(2-Me)
HAE-(CH₂)₄-Bip(2-Me)-DBip(2-Me)
HAE-(CH₂)₅-D-Bip(2-Me)-Bip(2-Me)
HAE-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
HAE-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
H-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
H-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
H-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
H-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₄-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₅-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₆-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₁₀-Bip(2-Et)-Bip(2-Me)
H-(CH₂)₅-Bip(2-Me)-DBip(2-Me)
H-(CH₂)₅-DBip(2-Me)-Bip(2-Me)
H-(CH₂)₅-DBip(2-Me)-DBip(2-Me)
HG-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HG-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HG-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
HG-(CH₂)₄-Bip(2-Et)-Bip(2-Me)
HG-(CH₂)₃-Bip(2-Et)-DBip(2-Me)
HG-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
FA-(CH₂)₃-DBip(2-Me)-Bip(2-Et)
FA-(CH₂)₃-DBip-Dbip
Ha-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
Ha-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
Ha-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
Ha-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
Ha-(CH₂)₃-Bip(2-Et)-DBip(2-Me)
Ha-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
Ha-(CH₂)₃-Bip(2-Et)-DBip(2-Et)
Ha-(CH₂)₃-Bip(2-Me)-Bip
Ha-(CH₂)₃-(N(Me))-DBip(2-Me)-Bip(2-Et)
Ha-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)
Ha-(CH₂)₃-(N(Me))-DBip-Bip(2-Et)

Ha-(CH₂)₃-DBip(2-Me)-Bip(2-Et)
HA-(CH₂)₃-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₄-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₅-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₆-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₁₀-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₁₁-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Et)-DBip(2-Et)
HA-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
HA-(CH₂)₃-DBip(2-Me)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Me)-DBip(2-Me)
HA-(CH₂)₃-Bip(2-*Isopropyl*)-Bip(2-*Isopropyl*)
HA-(CH₂)₃-Bip(2-*Isopropyl*)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Me)-Bip(2-*Isopropyl*)
HA-(CH₂)₄-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Me)-DBip(2-Et)
HA-(CH₂)₂-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₅-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₆-Bip(2-Et)-Bip(2-Me)
HA-(CH₂)₂-Bip(2-Me)-Bip(2-Me)
HA-(CH₂)₃-DBip(2-Et)-DBip(2-Me)
HA-(CH₂)₃-DBip(2-Et)-Bip(2-Me)
HA-(CH₂)₂-Bip(2-Me)-DBip(2-Me)
HA-(CH₂)₃-Bip(2-Et)-Bip(2-Et)
HA-(CH₂)₃-DBip(2-Et)-DBip(2-Et)
HA-(CH₂)₃-DBip(2-Et)-Bip(2-Et)
HA-(CH₂)₃-DBip(2-Me)-DBip(2-Et)
HA-(CH₂)₃-Bip(2-Me)-Bip(2-Et)
HA-(CH₂)₃-DBip(2-Me)-Bip(2-Et)
HA-(CH₂)₃-Bip-Bip
HA-(CH₂)₃-Bip-D-Bip
HA-(CH₂)₃-DBip-D-Bip
HA-(CH₂)₃-DBip-Bip
HA-(CH₂)₃-Bip-Bip(2-Me)
HA-(CH₂)₃-Bip(2-Me)-Bip
HA-(CH₂)₃-Bip(2-Et)-Bip
HA-(CH₂)₃-Bip-Bip(2-Et)
HA-(CH₂)₃-Bip(2-*Isopropyl*)-DBip(2-*Isopropyl*)
HA-(CH₂)₃-DBip(2-*Isopropyl*)-Bip(2-*Isopropyl*)
HA-(CH₂)₃-DBip(2-*Isopropyl*)-DBip(2-*Isopropyl*)

HA-(CH₂)₃-Bip(2-Me)-Bip(2-CN)
 HA-(CH₂)₃-Bip-Bip(2-CN)
 HA-(CH₂)₃-Bip(2-Et)-Bip(2-CN)
 HA-(CH₂)₃-Bip(2-Ipr)-Bip(2-CN)
 HA-(CH₂)₃-Bip(2-CN)-Bip(2-Me)
 HA-(CH₂)₃-Bip(2-CN)-Bip
 HA-(CH₂)₃-Bip(2-CN)-Bip(2-Et)
 HA-(CH₂)₃-Bip(2-CN)-Bip(2-Ipr)
 HA-(CH₂)₃-Bip(2-CJN)-Bip(2-CN)
 HA-(CH₂)₂-F-(CH₂)₂-Bip(2-Et)-DBip(2-Et)
 HA-(CH₂)₂-F-(CH₂)₂-Bip(2-Et)-DBip(2-Me)
 HA-(CH₂)₅-Bip(2-Me)-DBip
 HA-(CH₂)₃-Bip(2-Me)-DBip-R
 HA-(CH₂)₃-DBip(2-Me)-DBip
 HA-(CH₂)₅-Bip(2-Me)-DBip(2-Me)
 HA-(CH₂)₅-DBip(2-Me)-Bip(2-Me)
 HA-(CH₂)₄-D(Bip)-Bip(2-Et)
 HA-(CH₂)₅-D(Bip)-Bip(2-Et)
 HA-(CH₂)₄-Bip(2-Me)-DBip(2-Me)
 HA-(CH₂)₅-Bip(2-Me)-DBip(2-Me)
 HA-(CH₂)₃-(N(Me))-DBip-Bip(2-Et)
 HA-(CH₂)₄-DBip(2-Me)-Bip(2-Et)
 HA-(CH₂)₅-DBip(2-Me)-Bip(2-Et)
 HA-(CH₂)₃-(N(Me))-DBip(2-Me)-Bip(2-Et)
 HA-(CH₂)₄-Bip(2-Me)-DBip
 HA-(CH₂)₅-Bip(2-Me)-DBip
 HA-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)
 HA-(N(Me))-(CH₂)₃-DBip(2-Me)-Bip(2-Et)
 HA-(N(Me))-(CH₂)₃-DBip-Bip(2-Et)
 HA-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)
 HA-(N(Me))-(CH₂)₃-Bip(2-Me)-DBip
 HAE-(CH₂)₂-F-(CH₂)₂-Bip(2-Et)-DBip(2-Et)
 HAE-(CH₂)₂-F-(CH₂)₂-Bip(2-Et)-DBip(2-Me)
 HAib-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)

6. El polipéptido aislado de la reivindicación 1 en donde el polipéptido aislado es un compuesto seleccionado de:

HA-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 H-Aib-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
 Ha-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))A-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))Aib-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
CH₃-(CH₂)₆-NH-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
HA-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-Aib-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
Ha-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))A-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₅-CH₃

H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃

H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃

CH₃-(CH₂)₆-NH-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃ CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

HA-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-Aib-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-a-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))A-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))A-(N(Me))-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))Aib-(N(Me))-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-
(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-
(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
CH₃-(CH₂)₆-NH-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃ CH₃-(CH₂)₆-
NH-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-H-N(Me)Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
HAE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-Aib-E-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
HAE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))AE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-
NH₂
H-(N(Me))AE-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-
Pyr-Ala-NH₂
H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-
3-Pyr-Ala-NH₂
H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-
Ph)-3-Pyr-Ala-NH₂
H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-
Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
Des-amino-H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

Des-amino-H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₅-CH₃

H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃

H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃

CH₃-(CH₂)₆-NH-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

CH₃-(CH₂)₆-NH-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

CH₃-(CH₂)₁₀-NH-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

CH₃-(CH₂)₁₀-NH-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

HAEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-Aib-EG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

HaEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))AEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))AEG-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

Des-amino-H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

Des-amino-H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂

H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃

H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
CH₃-(CH₂)₆-NH-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-
4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-
4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
HAEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-Aib-EGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
HaEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))AEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-
NH₂
H-(N(Me))AEGT-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-
Pyr-Ala-NH₂
H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-
Ph)-3-Pyr-Ala-NH₂
H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-
Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-
(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
Des-amino-H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
Des-amino-H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-
4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH₂
H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
H-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃

H-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₁₀-CH₃
CH₃-(CH₂)₆-NH-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-
4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))AEGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))Aib-EGT-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-
4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-NH-(CH₂)₆-CH₃
HA-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
H-Aib-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
Ha-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
H-(N(Me))A-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-Bip(2-Me)-NH₂
H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-Bip(2-Me)-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-
NH₂
H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-
Me)-NH₂
Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-
Bip(2-Me)-NH₂
Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-
(N(Me))-Bip(2-Me)-NH₂
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-
NH-(CH₂)₆-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-
Me)-NH-(CH₂)₆-CH₃
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-
NH-(CH₂)₁₀-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-
Me)-NH-(CH₂)₁₀-CH₃ CH₃-(CH₂)₅-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-
(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-
(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-
(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-
(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃

HA-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
 H-Aib-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
 Ha-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
 H-(N(Me))A-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
 H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
 H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-NH₂
 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)-NH₂
 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-Bip(2-Me)-NH₂
 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH₂
 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH₂
 Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH₂
 Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH₂
 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
 H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₁₀-CH₃
 H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₁₀-CH₃
 CH₃-(CH₂)₆-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
 CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
 CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
 CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Et)-(N(Me))-Bip(2-Me)-NH-(CH₂)₆-CH₃
 HA-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
 H-Aib-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
 Ha-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
 η-(N(Me))A-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
 H-(N(Me))A-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
 H-(N(Me))Aib-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
 H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH .

Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH

Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₅-CH₃

H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃

H-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃

H-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃

CH₃-(CH₂)₆-NH-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃

CH₃-(CH₂)₆-NH-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃ CH₃-(CH₂)₁₀-NH-(N(Me))A-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃

CH₃-(CH₂)₁₀-NH-(N(Me))Aib-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃

HA-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-Aib-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

Ha-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))A-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))Aib-(N(Me))-(CH₂)₃-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH

H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃ CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
HA-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-Aib-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
Ha-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))A-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))A-(N(Me))-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))Aib-(N(Me))-(CH₂)₄-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
Des-amino-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH

Des-amino-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
CH₃-(CH₂)₆-NH-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃ CH₃-(CH₂)₁₀-NH-H-(N(Me))A-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-H-(N(Me))Aib-(N(Me))-(CH₂)₄-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
HAE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH H-Aib-E-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
HaE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))AE-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))AE-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
Des-amino-H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
Des-amino-H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃

H-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
H-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
CH₃-(CH₂)₆-NH-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₆-NH-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))AE-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))Aib-E-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-
4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
HAEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-Aib-EG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
HAEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))AEG-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-
OH
H-(N(Me))AEG-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-
Pyr-Ala-OH
H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-
3-Pyr-Ala-OH
H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-(2'-
Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-4-
(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
Des-amino-H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
Des-amino-H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-
OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-
4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
H-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-
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4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃
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(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₁₀-CH₃

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CH₃-(CH₂)₁₀-NH-(N(Me))AEG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
CH₃-(CH₂)₁₀-NH-(N(Me))Aib-EG-(N(Me))-(CH₂)₂-(N(Me))-Bip(2'-Et-4'-OMe)-(N(Me))-4-(2'-Me-Ph)-3-Pyr-Ala-COO-(CH₂)₆-CH₃
HAEGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
H-Aib-EGT-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
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H-(N(Me))AEGT-(N(Me))-(CH₂)₂-Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala-OH
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Ha-(CH₂)₃-Bip(2-Me)-Bip(2-Me)-OH

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H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-Bip(2-Me)-OH

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H-(N(Me))Aib-(N(Me))-(CH₂)₃-(N(Me))-Bip(2-Me)-(N(Me))-Bip(2-Me)-OH

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H-Aib-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH

Ha-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH

H-(N(Me))A-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH

H-(N(Me))A-(N(Me))-(CH₂)₃-Bip(2-Et)-Bip(2-Me)-OH

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HAibEGTFTSDVSSYLEGQ- (CH₂)₂-KELEKLL
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HAibEGT- (α-Me) Phe(2-F)-TSDVSSYLE- (CH₂)₂-FIKELEKLL
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HAib-(CH₂)₆-KELEKLL
HAib-(CH₂)₈-KELEKLL

7. Una composición farmacéutica que comprende compuestos como se reivindica en las reivindicaciones 1-6 preparadas de acuerdo con el proceso descrito aquí y portadores farmacéuticamente aceptables.

8. Los compuestos o sus composiciones farmacéuticas como se reivindica en las reivindicaciones 1-7, que poseen la capacidad para imitar la actividad biológica de GLP-1, más preferiblemente imita la actividad del agonista GLP-1R.

9. Los compuestos o sus composiciones farmacéuticas como se reivindica en una cualquiera de las reivindicaciones 1-7, útiles para el tratamiento o prevención de enfermedades en donde el péptido GLP-1R juega una función patofisiológica.

10. Un método para tratar o prevenir enfermedades causadas por hiperlipidemia, hipercolesteremia, hiperglicemia, hiperinsulinemia, niveles sanguíneos elevados de ácidos grasos libres o glicerol, hipertrigliceridemia, mala cicatrización, obesidad, eficiencia de tolerancia a la

glucosa, resistencia a la leptina, resistencia a la insulina, complicaciones diabéticas, tal como nefropatía, retinopatía, neuropatía y cataratas, que comprende administrar una cantidad efectiva, no tóxica del compuesto de la fórmula (I) como se define en cualquiera de las reivindicaciones precedentes a un paciente que lo necesita.

11. El método de acuerdo con cualquiera de las reivindicaciones precedentes, en donde la enfermedad es diabetes tipo 2, eficiencia de tolerancia a la glucosa, dislipidemia, hipertensión, obesidad, aterosclerosis, hiperlipidemia, enfermedad de arteria coronaria, trastornos cardiovasculares y otras enfermedades en donde la resistencia a la insulina es el mecanismo patofisiológico subyacente.

12. Una medicina para tratar/reducir cualquiera de las condiciones de enfermedad descritas en cualquiera de las reivindicaciones precedentes que comprende administrar un compuesto de la fórmula (I), como se define en las reivindicaciones 1-7 y un portador farmacéuticamente aceptable, diluyente, excipiente o solvato a un paciente en necesidad de este.

13. Una medicina para tratar/reducir cualquiera de las condiciones de enfermedad descritas en cualquiera de las reivindicaciones precedentes que comprende administrar un compuesto de la fórmula (I), como se define en las reivindicaciones 1-7 en combinación con un inhibidor DPP IV adecuado, a un paciente en necesidad de este.

14. Uso de los compuestos de la fórmula (I), solo o en combinación con inhibidores DPP IV adecuados, sus composiciones farmacéuticas y medicinas que los contienen como se define en una cualquiera de las reivindicaciones anteriores como un medicamento adecuado para el tratamiento de las enfermedades mencionadas en cualquiera de las reivindicaciones anteriores.

COMPUESTOS NOVEDOSOS COMO AGONISTAS GLP-1**Resumen**

La presente invención describe un grupo de peptidomiméticos novedosos útiles para el tratamiento de la diabetes. Estos compuestos se definen por la Fórmula general (I) como se muestra adelante. A-X₁-S₁-Y-S₂-X₂-B (I)

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Lohray, Vidya Bhushan
Bahekar, Rajesh H

<120> Compuestos novedosos como agonistas GLP-1

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only	
International Application No.	
International Filing Date	
Name of receiving Office and "PCT International Application"	
Applicant's or agent's file reference (if desired) (12 characters maximum) 558-645-CHL	

Box No. I TITLE OF INVENTION NOVEL COMPOUNDS AS GLP-1 AGONISTS	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) CADILA HEALTHCARE LIMITED Zydus Tower, Satellite Cross Roads Ahmedabad 380 015 Gujarat INDIA	
Telephone No. +91 11 79 2686 8100	
Facsimile No. +91 11 79 2686 2362	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) LOHRAY, Braj Bhushan CADILA HEALTHCARE LIMITED Zydus Tower, Satellite Cross Roads Ahmedabad 380 015 Gujarat, INDIA	
This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) SUBRAMANIAM, Hariharan; NATARAJ, Guruswamy; AHUJA, Shalina; PRITHVIRAJ, Susheela Subramaniam, Nataraj & Associates E-556, Greater Kailash-II New Delhi-110 048, INDIA	
Telephone No. +91 11 2921 5603	
Facsimile No. +91 11 2922 6005	
Teleprinter No.	
Agent's registration No. with the Office	
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) LOHRAY, Vidya Bhushan CADILA HEALTHCARE LIMITED Zydus Tower, Satellite Cross Roads Ahmedabad 380 015 Gujarat, INDIA	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BAHEKAR, Rajesh H CADILA HEALTHCARE LIMITED Zydus Tower, Satellite Cross Roads Ahmedabad 380 015 Gujarat, INDIA	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicant's and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ KR Republic of Korea is not designated for any kind of national protection
- ☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 05.05.2005 (05 May 2005)	558/MUM/2005	IN		
item (2) 31.05.2005 (31 May 2005)	645/MUM/2005	IN		
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☒ item (1) ☒ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / .EP

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | | |
|---|--|---|---|
| ☐ Box No. VIII (i) | Declaration as to the identity of the inventor | : | |
| ☒ Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : | 1 |
| ☐ Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : | |
| ☐ Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : | |
| ☐ Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : | |

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Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212 (see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No VIII (ii)). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)) in a case where the declaration under Rule 4.17(iv) is not appropriate.

in relation to this International Application

CADILA HEALTHCARE LIMITED, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, INDIA is entitled to apply for and be granted a patent by virtue of the following:

1. LOHRAY, Braj Bhushan; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India.
2. LOHRAY, Vidya Bhushan; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India.
3. BAHEKAR, Rajesh H; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads Ahmedabad 380 015, Gujarat, India.

are the inventors for the subject matter for which protection is sought by way of this International application; and is entitled as employer of all said inventors:

1. LOHRAY, Braj Bhushan; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India.
2. LOHRAY, Vidya Bhushan; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India.
3. BAHEKAR, Rajesh H; Cadila Healthcare Limited, Zydus Tower, Satellite Cross Roads Ahmedabad 380 015, Gujarat, India.

☐ This declaration is continued on the following sheet. "Continuation of Box No. VIII (ii)".

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:	This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):	Number of items
(a) on paper, the following number of sheets:	1. ☒ fee calculation sheet	1
request (including declaration sheets) : 5	2. ☐ original separate power of attorney	:
description (excluding sequence listing and/or tables related thereto) : 53	3. ☐ original general power of attorney	:
claims : 31	4. ☐ copy of general power of attorney; reference number, if any:	:
abstract : 1	5. ☐ statement explaining lack of signature	:
drawings :	6. ☐ priority document(s) identified in Box No. VI as item(s):	:
Sub-total number of sheets : 90	7. ☐ translation of international application into (language):	:
sequence listing :	8. ☐ separate indications concerning deposited microorganism or other biological material	:
tables related thereto :	9. ☐ sequence listing in electronic form (indicate type and number of carriers)	:
(for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below)	(i) ☒ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) :	1
Total number of sheets : 90	(ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter :	:
(b) ☐ only in electronic form (Section 801(a)(i))	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column :	:
(i) ☐ sequence listing	10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers)	:
(ii) ☐ tables related thereto	(i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) :	:
(c) ☐ also in electronic form (Section 801(a)(ii))	(ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) :	:
(i) ☐ sequence listing	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column :	:
(ii) ☐ tables related thereto	11. ☐ other (specify):	:
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the		
☐ sequence listing: 1		
☐ tables related thereto:		
(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)		
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: English	

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Hariharan SUBRAMANIAM
Patent Attorney & Patent Agent for the Applicant
(Regn. No. IN PA/93)

For receiving Office use only		2. Drawings: ☐ received: ☐ not received:
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 11(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference

558-645-CHL

Applicant

CADILA HEALTHCARE LIMITED

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE

INR 8000.00 T

2. SEARCH FEE

USD 2075.00 S

International search to be carried out by

EP

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FILING FEE

Where items (b) and/or (c) of Box No. IX apply, enter Sub-total number of sheets } 90

Where items (b) and (c) of Box No. IX do not apply, enter Total number of sheets }

i1 first 30 sheets

1211.00 i1

i2

60

number of sheets
in excess of 30

x

13

fee per sheet

=

780.00 i2

i3

additional component (only if a sequence listing and/or tables
related thereto are filed in electronic form under Section 801(a)(i),
or both in that form and on paper, under Section 801(a)(ii):

400 x

fee per sheet

=

i3

Add amounts entered at i1, i2 and i3 and enter total at I

USD 1911.00 I

(Applicants from certain States are entitled to a reduction of 75% of the international filing fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the international filing fee.)

4. FEE FOR PRIORITY DOCUMENT (if applicable)

INR 8000.00 P

5. TOTAL FEES PAYABLE

INR 16000 + USD 4066

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

MODE OF PAYMENT (Not all modes of payment may be available at all receiving Offices)

☐ authorization to charge
deposit account (see below)

☐ postal money order

☐ cash

☐ coupons

☐ cheque

☐ bank draft

☐ revenue stamps

☐ other (specify):

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/

Deposit Account No.:

Date:

Name:

Signature:

☐ Authorization to charge the total fees indicated above.

☐ (This check-box may be marked only if the conditions for deposit accounts
of the receiving Office so permit) Authorization to charge any deficiency
or credit any overpayment in the total fees indicated above.

☐ Authorization to charge the fee for priority document.

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PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:
SUBRAMANIAM, Hariharan
Subramaniam, nataraj & Associates,
E-556, Greater Kailash-II,
New Delhi-110 048.

NOTIFICATION CONCERNING PAYMENT OF PRESCRIBED FEES

(PCT Rules 14, 15 and 16 and Administrative
Instructions, Sections 102bis(c), 304,
323(b), 707(b) and 803)

Date of mailing
(day/month/year) 25 MAY, 2006

Applicant's or agent's file reference
558-645-CHL

PAYMENT DUE
see item 3 for time limits

International application No.
PCT/IN06/00154

International filing date/Date of receipt
(day/month/year)
04 MAY 2006 (04.05.06)

Priority date (day/month/year)
05.05.2005 & 31.05.2005

Applicant CADILA HEALTHCARE LIMITED, et al

1. The applicant is hereby notified that this receiving Office has received:

- ☐ the payment of all the prescribed fees, and ☐ an overpayment, which will be refunded in due course.
- ☒ no or insufficient payment of the prescribed fees and the applicant is hereby invited to pay the balance due, as summarized under item 2, within the time limit(s) indicated under item 3.

2. Fees and payment calculation:

INR 16000 + USD 3815	-	INR 16000+ NIL	=	NIL+ USD 3815
Total fees payable		Amount paid		Balance

☒ The details of the calculation are given in the Annex.

3. Time limit(s) for payment and amount(s) payable (Rules 14.1, 15.4 and 16.1(f)):

- ☒ within ONE MONTH from the date of receipt of the international application (for the transmittal fee (if any), the search fee and the international filing fee). The amount payable for each fee is the amount applicable on the date of receipt of the international application.
- ☐ within 16 MONTHS from the priority date (only for the fee for priority document). The applicant's attention is drawn to the fact that the request made by the applicant under Rule 17.1(b) will be considered not to have been made unless the fee is paid within that time limit.

4. Additional observations (if necessary):

- ☒ The search copy will not be transmitted to the International Searching Authority until the search fee is paid (therefore the start of the international search will be delayed) (Rule 23.1(a) and (b)).

Name and mailing address of the receiving Office
The Patent Office,
Boudhik Sampada Bhavan, Near Antop Hill Post Office,
S.M. Road, Antop Hill, MUMBAI-400 037, Maharashtra, INDIA.
Facsimile No. (91) (22) 2413 0387

Authorized officer
N. K. MOHANTY
R. BHATTACHARYA
Telephone No. (91) (22) 2413 7701

ANNEX TO FORM PCT/RO/102
CALCULATION OF THE PRESCRIBED FEES

International application No.

PCT/IN06/00154

T Transmittal Fee

Prescribed amount: INR 8000 **T**
Amount paid: INR 8000
Balance: NIL

☒ correct amount
☐ overpayment
☐ balance due

S Search Fee

Prescribed amount: USD 1925 **S**
Amount paid: NIL
Balance: USD 1925

☐ correct amount
☐ overpayment
☒ balance due

I International Filing Fee

Fixed amount for first 30 sheets: USD 1086 **i1**
67 x USD 12 = USD 804 **i2**
Number of sheets Fee per sheet
in excess of 30
Additional
component: . . . 400 x . . . = . . . - **i3**
Fee per sheet

Reduction where the international application is filed
(See PCT Applicant's Guide, Volume I, General Part,
for details on the availability of this reduction):

using the PCT-EASY software: - **r**

or

in electronic form where the text of the
description, claims and abstract is not in
character coded format: - **r**

in electronic form where the text of the
description, claims and abstract is in character
coded format: - **r**

Sub-total: = USD 1890 **i1+i2+i3-r**

Prescribed total amount (The amount to be entered at **i** is the sub-total
entered at (i1+i2+i3-r), except where the applicant is (or all applicants
are) entitled to a reduction of 75%, in which case the amount to be
entered at **i** is 25% of the sub-total (i1+i2+i3-r); certain applicants from
certain States are entitled to a reduction of 75% of the international
filing fee; see Notes to the Fee Calculation Sheet as annexed to the
Request Form, PCT/RO/101, for details): =

Amount paid: NIL
Balance: USD 1890

☐ correct amount
☐ overpayment
☒ balance due

P Fee for Priority Document

Prescribed amount: INR 8000 **P**
Amount paid: INR 8000
Balance: NIL

☒ correct amount
☐ overpayment
☐ balance due

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:
SUBRAMANIAM, Hariharan
Subramaniam, nataraj & Associates,
E-556, Greater Kailash-II,
New Delhi-110 048.

INVITATION TO CORRECT DEFECTS IN
THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(i) and 14(1) and Rule 26)

Applicant's or agent's file reference 558-645-CHL	Date of mailing (day/month/year) 25 MAY, 2006
International application No. PCT/IN06/00154	International filing date (day/month/year) 04 MAY 2006 (04.05.06)
Applicant CADILA HEALTHCARE LIMITED, et al	

1. ☒ The applicant is hereby invited, within the time limit indicated above, to correct, in the international application as filed, the defects specified on the attached:
 - ☒ Annex A
 - ☒ Annex B1 (text matter of the international application as filed)
 - ☐ Annex C1 (drawings of the international application as filed)
2. ☐ The applicant is hereby invited, within the time limit indicated above, to correct, in the translation of the international application furnished under Rule 12.3 or 12.4, the defects specified on the attached:
 - ☐ Annex A
 - ☐ ~~Annex B2 (text matter of the translation of the international application)~~
 - ☐ Annex C2 (drawings of the translation of the international application)

Additional observations (if necessary):

HOW TO CORRECT THE DEFECTS?

Correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. A correction may be stated in a letter only if it is of such a nature that it can be transferred from the letter to the record copy without adversely affecting the clarity and direct reproducibility of the sheet onto which the correction is to be transferred (Rule 26.4).

ATTENTION

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this invitation and any attachments has been sent to the International Bureau

☒ and the International Searching Authority

Name and mailing address of the receiving Office The Patent Office, Boudhik Sampada Bhavan, Near Antop Hill Post Office, S.M. Road, Antop Hill, MUMBAI-400 037, Maharashtra, INDIA. Facsimile No. (91)(22) 2413 0387	Authorized officer N. K. MOHANTY R. BHATTACHARYA Telephone No. (91) (22) 2413 7701
--	--

The receiving Office has found the following defects in the international application as filed:

1. As to signature of the international application (Rules 4.15, 26.2bis(a) and 90.4), the request:

- a. ☐ is not signed* by the applicant or, if there is more than one applicant, by at least one of them
- b. ☐ is not accompanied by the statement referred to in the check list in Box No. IX of the request explaining the lack of the signature of an applicant for the designation of the United States of America
- c. ☒ is signed by what appears to be an agent/common representative but:
 - ☒ the international application is not accompanied by a power of attorney appointing him
 - ☐ the power of attorney accompanying the international application is not signed by all the applicants
- d. ☐ other (specify):

* Although Rule 4.15 requires that all applicants must sign the request (e.g. including all inventors/applicants for the designation of the United States of America), for the purposes of Article 14(1)(a)(i), if there is more than one applicant, it shall be sufficient that the request be signed by one of them (Rule 26.2bis(a)).

However, the applicant's attention is drawn to the fact that the national law applied by each designated Office may require, in connection with the processing of the international application in the national phase, that the applicant furnish the confirmation of the international application by the signature of any applicant for the designated State who has not signed the request (Rule 51bis.1(a)(vi)).

2. As to indications concerning the applicant* who is entitled, according to Rule 19.1, to file the international application with the receiving Office, the request (Rules 4.4, 4.5 and 26.2bis(b)):

- a. ☐ does not properly indicate the applicant's name (specify):
- b. ☐ does not indicate the applicant's address
- c. ☐ does not properly indicate the applicant's address (specify):
- d. ☐ does not indicate the applicant's nationality
- e. ☐ does not indicate the applicant's residence

☐ Further observations about indications concerning other applicants (if applicable):

* Although Rules 4.4 and 4.5 require indications concerning the applicant, or if there are several applicants, of each of them, for the purposes of Article 14(1)(a)(ii), if there is more than one applicant, it shall be sufficient that the indications required under Rule 4.5(a)(ii) and (iii) be provided in respect of one of them who is entitled according to Rule 19.1 to file the international application with the receiving Office (Rule 26.2bis(b)).

However, the applicant's attention is drawn to the fact that the national law applied by each designated Office may require, in connection with the processing of the international application in the national phase, that the applicant furnish any missing indication required under Rule 4.5(a)(ii) and (iii) in respect of any applicant for the designated State (Rule 51bis.1(a)(vii)).

3. As to the language of certain elements of the international application, other than the description and claims (Rules 12.1(c) and 26.3ter(a) and (c)):

- a. ☐ the request is not in a language of publication accepted by this receiving Office; (the) language(s) accepted by this receiving Office is/are:
- b. ☐ the text matter of the drawings is not in the language in which the international application is to be published, which is:
- c. ☐ the abstract is not in the language in which the international application is to be published, which is:

4. The title of the invention:

- a. ☐ is not indicated in Box No. I of the request (Rule 4.1(a))
- b. ☐ is not indicated at the top of the first sheet of the description (Rule 5.1(a))
- c. ☐ as appearing in Box No. I of the request is not identical with the title heading the description (Rule 5.1(a))

5. As to the abstract (Rules 8 and 26.1(b)):

- ☐ the international application does not contain an abstract

ANNEX B1 TO FORM PCT/RO/106

International application No.

PCT/IN06/00154

This receiving Office has found that, with regard to the presentation of the text matter of the international application as filed, the physical requirements are not complied with to the extent that compliance therewith is necessary for:

1. ☒ reasonably uniform international publication (Rules 11 and 26.3(a)(i)) (*defects to be specified*):

	Request	Description	Claims	Abstract
a. ☐ the sheets do not admit of direct reproduction	☐	☐	☐	☐
b. ☐ the element does not commence on a new sheet	☐	☐	☐	☐
c. ☐ sheets are not free from creases, cracks, folds	☐	☐	☐	☐
d. ☐ sheets are not used in the upright position	☐	☐	☐	☐
e. ☐ one side of the sheets is not left unused	☐	☐	☐	☐
f. ☐ the paper of the sheets is not flexible/strong/white/smooth/non-shiny/durable	☐	☐	☐	☐
g. ☐ the sheets are not connected as prescribed (Rule 11.4(b))	☐	☐	☐	☐
h. ☐ sheets are not A4 size (29.7cm x 21cm)	☐	☐	☐	☐
i. ☐ the minimum margins on the sheets are not as prescribed (top: 2cm; left side: 2.5cm; right side: 2cm; bottom: 2cm)		☐	☐	☐
j. ☐ the file reference number indicated on the sheets does not appear in the left-hand corner of the sheets, within 1.5 cm of the top of the sheets		☐	☐	☐
k. ☐ the file reference number exceeds the maximum of 12 characters	☐	☐	☐	☐
l. ☐ the sheets of the description, claims and abstract are not numbered in consecutive Arabic numerals		☐	☐	☐
m. ☐ the sheet numbers are not centered at the top or bottom of the sheets	☐	☐	☐	☐
n. ☐ the sheet numbers are in the margin (see i. above for the size of the margins)		☐	☐	☐
o. ☐ the text matter is not typed or printed	☐	☐	☐	☐
p. ☐ the typing on the sheets is not 1½-spaced		☐	☐	☐
q. ☐ the characters in the text matter on the sheets are less than 0.21 cm high in capital letters	☐	☐	☐	☐
r. ☐ the text matter on the sheets is not in dark, indelible color	☐	☐	☐	☐
s. ☐ the element contains drawings	☐	☐	☐	☐
t. ☐ the sheets contain alterations/overwritings/interlineations/too many erasures	☐	☐	☐	☐
u. ☐ the sheets contain photocopy marks	☐	☐	☐	☐

2. ☐ satisfactory reproduction (Rules 11 and 26.3(b)(i))

Further observations (if necessary):

Declaration to claim the priority of earlier application should be submitted.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

NOTIFICATION OF RECEIPT OF SEARCH COPY

(PCT Rule 25.1)

To:

SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E 556 Greater Kailash II
New Delhi 110 048
INDE

Date of mailing
(day/month/year)

21/12/2006

Applicant's or agent's file reference

558-645-CHL

IMPORTANT NOTIFICATION

International application No.

PCT/IN2006/000154

International filing date (day/month/year)

04/05/2006

Priority date (day/month/year)

05/05/2005

Applicant

CADILA HEALTHCARE LIMITED

1. Where the International Searching Authority and the receiving Office are not the same office:

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the receiving Office are the same office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

05/12/2006 (date of receipt).

2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing or tables related thereto in electronic form.
3. ☐ The search copy contained a nucleotide and/or amino acid sequence listing or tables related thereto in electronic form.

4. Time limit for establishment of international search report and written opinion of the International Searching Authority

The applicant is informed that the time limit for establishing the international search report and the written opinion of the International Searching Authority is three months from the date of receipt indicated above or nine months from the priority date, whichever time limit expires later (Rules 42.1 and 43bis.1(a))

5. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the receiving Office.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

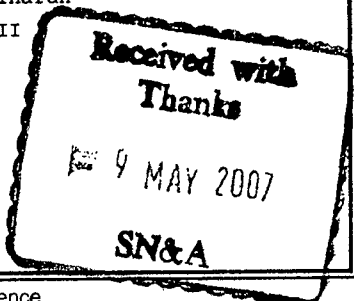
ISA/EP

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E 556 Greater Kailash II
New Delhi 110 048
INDE



INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

REGISTERED MAIL

Applicant's or agent's file reference 558-645-CHL	Date of mailing (day/month/year) 04/05/2007
International application No. PCT/IN2006/000154	International filing date (day/month/year) 04/05/2006
Applicant CADILA HEALTHCARE LIMITED	

1. This International Searching Authority

- (i) considers that there are 9 (number of) inventions claimed in the international application covered by the claims indicated ~~below~~ on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~ on the extra sheet:

- (ii) ☒ has carried out a partial international search (see Annex) ☐ will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:

see annex

- (iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby invited, within the time limit indicated above, to pay the amount indicated below:

EUR 1.615,00 x 8 = EUR 12.920
 Fee per additional invention number of additional inventions total amount of additional fees

Or, _____ x _____ = _____

The applicant is informed that, according to Rule 40.2(c), the payment of any additional fee may be made under protest, i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. ☒ Claim(s) Nos. see annex have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Stefanie Büchler
--	---

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.

2. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is KELEKLL. Pharmaceutical compositions and use as a medicament.

3. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is ~~GPSSGAPPPS~~ GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.

4. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is VKGR. Pharmaceutical compositions and use as a medicament.

5. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.

6. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is KELEKLL. Pharmaceutical compositions and use as a medicament.

7. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is GPPS. Pharmaceutical compositions and use as a medicament.

8. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is VKGR. Pharmaceutical compositions and use as a medicament.

9. claims: 1-14 (all in part)

An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is a dipeptide as defined at page 55, lines 13-25. Pharmaceutical compositions and use as a medicament.

The closest prior art with respect to the present patent application can be exemplified by document D1 (W003/011892), which discloses a number of chimeric peptides incorporating a portion of the GLP-1 sequence at their N-terminal end (cf. D1, page 26). In the light of this prior art, the problem underlying the present application can be regarded as the provision of further GLP-1 peptide mimics. The proposed solution consists of polypeptides having the sequence of Formula (I), claim 1, comprising (X1) an N-terminal fragment of GLP-1 bound via an optional linker (S1-Y-S2) to an oligopeptide (X2) corresponding to the C-terminus of exendin-4, to the C-terminus of GLP-1, to KELEKLL, to GPPS or to any dipeptide.

A single general concept covering all such polypeptides could only be defined in that they all are chimeric oligopeptides containing a fragment of GLP-1 at their N-terminus. However, compounds having all these structural properties are known from D1 (but also from D2 and D3), which discloses a number of these peptides and investigates their structure-function relationship. Since no further technical features could be identified which could serve as same or corresponding technical features in the sense of Rule 13.2 PCT to restore unity of invention, the

search division considers that the following separate inventions are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT.

A distinction of separate subjects is made, based on structural relationship. Nine different groups of inventions have been identified. Only invention 1 has been searched. Since each invention identified above requires a separate search in databases and in the classified documentation, the ISA considers the PCT guidelines VII, 12, regarding the provision of a complete search with negligible additional work, as not applicable to the present application.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Although claims 10-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

**Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH**

International Application No
PCT/IN2006/000154

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
- see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/011892 A (US GOVERNMENT [US]; GREIG NIGEL H [US]; EGAN JOSEPHINE [US]; DOYLE MAI) 13 February 2003 (2003-02-13) the whole document page 13; figure 1; example 1 -----	1-14
X	RUNGE S ET AL: "Different domains of the glucagon and glucagon-like peptide-1 receptors provide the critical determinants of ligand selectivity." BRITISH JOURNAL OF PHARMACOLOGY, vol. 138, no. 5, March 2003 (2003-03), pages 787-794, XP002427759 ISSN: 0007-1188 the whole document -----	1-14
X	HINKE SIMON A ET AL: "In depth analysis of the N-terminal bioactive domain of gastric inhibitory polypeptide" LIFE SCIENCES, PERGAMON PRESS, OXFORD, GB, vol. 75, no. 15, 27 August 2004 (2004-08-27), pages 1857-1870, XP002387302 ISSN: 0024-3205 the whole document -----	1-14
P, X	WO 2006/024275 A (PHILIPPS UNI MARBURG [DE]; GOTTHARDT MARTIN [DE]; BEHE MARTIN [DE]; BE) 9 March 2006 (2006-03-09) the whole document ----- -/--	1-14

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS
OF THE PARTIAL INTERNATIONAL SEARCH

International Application No

PCT/IN2006/000154

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/077072 A (AMYLIN PHARMACEUTICALS INC [US]; LEVY ODILE ESTHER [US]; HANLEY MICHAEL) 25 August 2005 (2005-08-25) the whole document -----	1-14

Patent Family Annex

Information on patent family members

International Application No.

PCT/IN2006/000154

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03011892	A	13-02-2003	CA 2455963 A1	13-02-2003
			EP 1411968 A2	28-04-2004
			JP 2005501058 T	13-01-2005
WO 2006024275	A	09-03-2006	DE 102004043153 A1	23-03-2006
WO 2005077072	A	25-08-2005	AU 2005211755 A1	25-08-2005
			CA 2555877 A1	25-08-2005
			EP 1718665 A2	08-11-2006

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E 556 Greater Kailash II
New Delhi-110 048
INDE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 558-645-CHL	Date of mailing (day/month/year) 26/07/2007
International application No. PCT/IN2006/000154	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant CADILA HEALTHCARE LIMITED	International filing date (day/month/year) 04/05/2006

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Sabine Oblinger
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

~~The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).~~

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SUBRAMANIAM, NATARAJ & ASSOCIATES
Attn. Subramaniam, Hariharan
E 556 Greater Kailash II
New Delhi 110 048
INDE

INVITATION TO FURNISH NUCLEOTIDE AND/OR
AMINO ACID SEQUENCE LISTING AND/OR TABLES
RELATED THERETO COMPLYING WITH STANDARD
AND/OR TECHNICAL REQUIREMENTS

(PCT Rule 13ter.1(a) to (d) and Administrative Instructions,
Sections 208 and 802 and Annexes C and C-bis)

Date of mailing
(day/month/year) 22/02/2007

Applicant's or agent's file reference

558-645-CHL

REPLY DUE

within 1 months ~~24~~
from the above date of mailing

International application No.

PCT/IN2006/000154

International filing date
(day/month/year)

04/05/2006

Applicant

CADILA HEALTHCARE LIMITED

1. The applicant is hereby **invited**, within the time limit indicated above, to furnish to this Authority:

- ☐ a nucleotide and/or amino acid sequence listing **on paper** complying with the standard provided for in Annex C of the Administrative Instructions, accompanied by a **statement** to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
- ☐ a **statement** to the effect that the sequence listing on paper, already furnished to this Authority, does not go beyond the disclosure in the international application as filed.
- ☒ a nucleotide and/or amino acid sequence listing and/or tables related thereto in **electronic form** complying with the standard and/or technical requirements provided for in Annex C and/or Annex C-bis of the Administrative Instructions, **accompanied by a statement that the information recorded in electronic form is identical to the sequence listing and/or tables related thereto on paper.**
- ☐ a **statement** that the information recorded in electronic form (that electronic form having already been furnished to this Authority) is identical to the sequence listing and/or tables related thereto on paper.

2. The applicant is hereby invited, within the time limit indicated above, to pay to this Authority:

- ☐ a late furnishing fee in the amount of _____ (currency/amount).

3. **Failure to comply with this invitation** may result in this Authority only carrying out the international search to the extent that a meaningful search can be carried out without the sequence listing.

4. Further observations (if necessary):

IMPORTANT REMARK: The statements are legally required [See Suppl.No.2 to Official Journal No.11/1998 (page 14, § 40 and page 64, § III.2)]

Name and mailing address of the International Searching Authority
 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Nina Vercio



Europäisches PatentAmt
Office Européen des Brevets
European Patent Office

DG1
DG1
DG1

Storage and Retrieval of Amino acid and Nucleotide Data

Nina Vercio
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk

Tel: +31 70 340 2842
Fax: +31 70 340 3992

ANNEX

Dear applicant/representative,

Present application discloses amino acid/nucleotide sequences.

According to our verification the Sequence Listing which has been sent to us is not complete. Namely, the IN Receiving Office has not yet provided the Sequence Listing on electronic medium as originally filed.

Therefore, the applicant is herewith invited to file the Sequence Listing in computer readable form, accompanied by the appropriate statements.

According to Supplement 2 to the Official Journal Nr.11/98 of the EPO [& Rule 5.2. PCT], if nucleotide / amino acid sequences are disclosed in a European/International patent application, the description shall contain a *sequence listing* complying with **WIPO standard ST. 25**.

Relating to this, we remind you that if these requirements are not met or not met in due time, the EPO does not perform the international search where a meaningful search cannot be carried out (Rule 13^{ter}.1(c)PCT). In this case the international search report is replaced in full or in part by the statement under Article 17(2)(a)(ii)PCT.

Moreover Rule 13^{ter}(f) prescribes that a subsequently filed sequence listing, which is not a correction within the meaning of rule 26.4PCT and which is not a rectification within the meaning of Rule 91.1.PCT of a sequence listing, shall not form part of the international application. In accordance herewith, the furnishing of a subsequently filed sequence listing does not give rise to an opportunity either to amend the description, claims and figures with a view to refer to said subsequently filed sequence listing or add it to the application as originally filed. The subsequently furnished listing will therefore normally not be forwarded to the international Bureau for publication purposes.

We strongly recommend the applicant to use the **PatentIn** software to submit the sequence listing.

(If problems arise with the download of the PatentIn software, a CD-ROM copy can be obtained from the EPO via e-mail :dochelp@epo.org), free of charge; Internet:
<http://www.european-patent-office.org>.

The computer readable form of the Sequence Listing in ASCII format (text only) is mandatory. For further questions do not hesitate to contact us.

Please send sequence listing on paper and in computer-readable form preferably to the European Patent Office, Strand Program, Directorate Documentation, Ms.Nina Vercio, Room S00 E45, Patentlaan 2, NL 2288 EE Rijswijk, The Netherland

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

To: see form PCT/ISA/220		Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/IN2006/000154	International filing date (day/month/year) 04.05.2006	Priority date (day/month/year) 05.05.2005	
International Patent Classification (IPC) or both national classification and IPC INV. C07K14/605			
Applicant CADILA HEALTHCARE LIMITED			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu cl Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer CERVIGNI, S Telephone No. +49 89 2399-2835
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IN2006/000154

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ on paper
 - ☒ in electronic form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 10-14 (IA)

because:

☒ the said international application, or the said claims Nos. 10-14 (IA) relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos. 1-14

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☒ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/N2006/000154

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☒ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>5-6</u>
	No: Claims	<u>1-4,7-14</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-14</u>
Industrial applicability (IA)	Yes: Claims	<u>1-9</u>
	No: Claims	<u>10-14</u>

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IN2006/000154

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and /or
2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

SECTION III

- 1 Claims 10-14 relate at least in part to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Therefore, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION IV

- 2 This authority considers that the present application relates to multiple inventions not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT.
 - 2.1 The closest prior art with respect to the present patent application can be exemplified by document D1 (WO03/011892), which discloses a number of chimeric peptides incorporating a portion of the GLP-1 sequence at their N-terminal end (cf. D1, figure 1). In the light of this prior art, the problem underlying the present application can be regarded as the provision of further GLP-1 peptide mimics. The proposed solution consists of polypeptides having the sequence of Formula (I), claim 1, comprising an N-terminal fragment (X_1) of GLP-1, covalently coupled via optional linkers (S_1 -Y- S_2) to an oligopeptide (X_2) corresponding to the C-terminus of exendin-4, to the C-terminus of GLP-1, to oligopeptides of sequence KELEKLL or GPPS, or to a dipeptide.
 - 2.2 A single general concept covering all such peptides could only be defined in that they all are chimeric oligopeptides containing a fragment of GLP-1 at their N-terminus. However, compounds having all these structural properties are known from D1 (and also from D2 to D6) which discloses a number of these peptides and discusses their structure-function relationship. Since no further technical features can be identified which could serve as same or corresponding technical features in the sense of Rule 13.2 PCT to restore unity of invention, the search division considers that the following separate inventions are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT.
 - 2.3 A distinction of separate subjects is made, based on structural relationship. Nine different groups of inventions have been identified as listed below.

- 2.3.1 *Invention 1:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.
- 2.3.2 *Invention 2:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is KELEKLL. Pharmaceutical compositions and use as a medicament.
- 2.3.3 *Invention 3:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is GPPS. Pharmaceutical compositions and use as a medicament.
- 2.3.4 *Invention 4:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 represents a bond, X1 is a N-terminal ~~fragment of~~ GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI (cf. page 54, lines 25-30) and X2 is VKGR. Pharmaceutical compositions and use as a medicament.
- 2.3.5 *Invention 5:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is GPSSGAPPPS. Pharmaceutical compositions and use as a medicament.
- 2.3.6 *Invention 6:* claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is KELEKLL. Pharmaceutical compositions and use as a

medicament.

- 2.3.7 *Invention 7*: claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is GPPS. Pharmaceutical compositions and use as a medicament.
- 2.3.8 *Invention 8*: claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is VKGR. Pharmaceutical compositions and use as a medicament.
- 2.3.9 *Invention 9*: claim 1-14 (all in part). An isolated polypeptide having a sequence of formula (I) in claim 1, wherein S1-Y-S2 does not represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD (cf. page 55, line 5) and X2 is a dipeptide "selected from combination of two amino acids consisting of natural or unnatural amino acids, having a side chain containing an arylalkyl or heterorylalkyl", as defined at page 55, lines 13-25. Pharmaceutical compositions and use as a medicament.
- 2.4 Since all further fees have been paid within the fixed time limit, an international search report and the present written opinion are issued covering all inventions 1 to 9.

SECTION V

3 Reference is made to the following documents:

- D1: WO 03/011892 A (US GOVERNMENT [US]; GREIG NIGEL H [US]; EGAN JOSEPHINE [US]; DOYLE MAI) 13 February 2003;
- D2: RUNGE S ET AL: "Different domains of the glucagon and glucagon-like peptide-1 receptors provide the critical determinants of ligand selectivity." BRITISH JOURNAL OF PHARMACOLOGY, vol. 138, no. 5, March 2003, pages 787-794;

- D3: HINKE SIMON A ET AL: "In depth analysis of the N-terminal bioactive domain of gastric inhibitory polypeptide" LIFE SCIENCES, vol. 75, no. 15, 27 August 2004, pages 1857-1870;
- D4: AL-SABAH SULEIMAN ET AL: "A model for receptor-peptide binding at the glucagon-like peptide-1 (GLP-1) receptor through the analysis of truncated ligands and receptors" BRITISH JOURNAL OF PHARMACOLOGY, vol. 140, no. 2, September 2003, pages 339-346;
- D5: CHAHRZAD MONTROSE-RAFIZADEH ET AL: "High Potency Antagonists of the Pancreatic Glucagon-like Peptide-1 Receptor" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 34, 22 August 1997, pages 21201-21206;
- D6: WO 2004/094461 A (SQUIBB BRISTOL MYERS CO [US]; NATARAJAN SESHAIYER [US]; MAPELLI CLAUD) 4 November 2004;

- 3.1 Document D1 discloses "a series of chimeric peptides [which] incorporate fundamental features of exendin-4 and GLP-1" (cf. D1, example 1 and figure 1). Such analogues were designed to solve the same problem addressed by the present application, that is *i.a.* to provide GLP-1 agonists having an increased stability against proteolytic cleavage from DPP-IV. These analogues "include one or more amino acid residues present in GLP-1 and one or more amino acid residues presents in exendin-4. The modifications also include truncations of either GLP-1 or Exendin-4 or the chimeric polypeptides" (cf. D1, page 13). "Lateral spacers", closely resembling to the definitions of S₁ and S₂ of the present application, are contemplated as well (cf. D1, page 14).
- 3.2 Document D2 to D6 are cited here as examples of documents disclosing peptides which contain a fragment of GLP-1 at their N-terminus. The oligopeptides described in D6 are considered to be detrimental to the novelty of invention 9 as defined above. More in detail, D6 discloses various N-terminal GLP-1 fragments exhibiting an increased stability to proteolytic cleavage and having a Bip-Bip dipeptide (or its derivatives) at its C-terminus (cf. D6, examples 11 and 12).
- 3.3 As a result, the present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-4 and 7-14 is not new in respect of prior art as defined in the regulations (Rule 64 PCT).

- 4 Concerning inventive step, the problem to be solved by the present application may be regarded in view of the prior art as the provision of further analogues of GLP-1 having an increased resistance to proteolysis.
- 4.1 The 9 proposed solutions above are respectively the provision of the compounds embraced by formula (I), claim 1, wherein S_1 -Y- S_2 represents a bond, X_1 is a N-terminal fragment of GLP-1 spanning the sequence from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI of natural GLP-1 (or analogues thereof where "one or more of these amino acid may be replaced by an unnatural amino acids") and X_2 is GPSSGAPPPS, the C-terminus of exendin-4 (*invention 1*), KELEKLL (*invention 2*), GPPS (*invention 3*) or VKGR (*invention 4*), the C-terminus of GLP-1. Alternatively, S_1 -Y- S_2 does not represent a bond (and each of these three entities is defined at lines 16-22), X_1 is a N-terminal fragment of GLP-1 spanning the sequence from HA to HAEGTFTSD of natural GLP-1 (or analogues thereof where "one or more of these amino acid may be replaced by an unnatural amino acids") and X_2 is GPSSGAPPPS, the C-terminus of exendin-4 (*invention 5*), KELEKLL (*invention 6*), GPPS (*invention 7*), VKGR, the C-terminus of GLP-1 (*invention 8*) or a dipeptide as defined in claim 1, lines 13-25 (*invention 9*).
- 4.2 ~~This authority is of the opinion that none of the solutions proposed involves an inventive step.~~
- 4.3 As discussed above, the subject-matter of claims 1-14 consists in the selection of a series of peptides obtainable by (specific) combinations of structural motifs.
- 4.4 It is however reminded that it does not involve an inventive step to select a number of compounds without showing any advantageous effect compared to known compounds, such as those of D1-D5 (*inventions 1 to 8*) or D6 (*invention 9*), apparently having the same activity and very similar structure. Such an arbitrary design selection of chimeric GLP-1 peptides cannot involve an inventive step, because, in order to fulfil the requirements of Article 33(3) PCT, a selection must be justified by a technical purpose, *i.e.* by a hitherto unknown or unexpected technical effect resulting from those structural features which distinguish the compound

claimed from all other possible solutions.

- 4.5 The same reasoning applies to each and every polypeptide claimed: no unexpected effects or properties are indicated in the application, other than the ones which the person skilled in the art, being aware of the disclosures of D1 or D6, would have expected *a priori* such compounds to possess.
- 4.6 As a matter of fact, this authority notes that no experimental data whatsoever have been provided regarding any of polypeptides claimed. Although reference is made in the description to four "representative compounds (I to IV) [...] shown in Figure 1", which allegedly display an activity *in vivo* (cf. page 51 and Table 10), the chemical structure of such prophetic compounds is not disclosed and Figure 1 is not present in the application as filed.
- 4.7 The applicant is informed that any further provision of data concerning compounds I to IV or any other peptide would not be allowable under Article 34(2)(b) PCT.
- 4.8 As a result, all compounds of claims 1-9 must be considered to merely be an arbitrary selection among several straightforward possibilities from which the skilled person would have chosen, without the exercise of inventive skill, in order to solve the problem posed.
- 4.9 The present application does not satisfy the criterion set forth in Article 33(3) PCT, because the subject-matter of claims 1-14 does not involve an inventive step (Rule 65 PCT).

SECTION VI

Certain documents cited:

Application No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2006/024275	09.03.2006	26.08.2005	03.09.2004
WO 2005/077072	25.08.2005	11.02.2005	11.02.2004
WO 2006/014287	09.02.2006	30.06.2005	02.07.2004 26.05.2005

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15 September 2007

Authorized officer: Sabine Oblinger, esq

Dear Sir,

Re: CADILA HEALTHCARE LIMITED
PCT International Application
No. PCT/IN2006/000154
Filed on: 04 May 2006
Priority: 05 May 2005 (IN: 558/MUM/2005)
31-May 2005 (IN: 645/MUM/2005)

We refer to the Written Opinion mailed along with Form PCT/ISA/220 on 26 July 2007. The due date for response is **26 October 2007**.

The applicants have also considered the Hon'ble Examiner's comments. The applicants humbly submit as follows:

In the present invention, the applicants have described novel peptidomimetics of Formula I as GLP-1 agonist. Though the search authority has stated that there are 9 different set of inventions, the applicants would humbly submit that there is a fundamental uniform concept across all the compounds described and claimed in this application.

In class B GPCR family, which include GLP-1 receptor as well, a concept of two-domain model has been proposed. In this two-domain model, the C-terminal portion of the peptide ligand binds to the N-domain of the receptor and the N-terminal ligand region binds to the J-domain region of receptor (Drug Discovery Today, Vol 10 (6), 417, 2005). This is a general concept known and based on this, several peptidomimetics have been proposed which are/were expected to overcome some of the problems associated with Exendin-4 or GLP-1 peptides.

The problems associated with both Exendin-4 and GLP-1 relates to either

- unstability/less stability to proteolytic enzymes, mainly DPP-IV enzyme.
- short half-life, due to rapid metabolism and renal clearance.
- non-availability of oral dosage forms, due to unstability in GIT and poor oral absorption.
- currently peptide based GLP-1 agonist which are available in the market or which are in the different phase of clinical development and mainly delivered by parenteral route of administration, which most of the patients do not prefer.

Knowing the limitation of currently available GLP-1 peptide based therapy, in the present application, in order to overcome some of the problems associated with Exendin-4 &/or GLP-1

peptides, and keeping in mind the above general concept of two-domain model for the GPCR class, we have disclosed a series of peptidomimetics, having the following features:

- one class of peptidomimetics comprises first 9-23 residues of N-terminal region of GLP-1 peptide combined with selected C-terminal residues of Exendin-4 (GPSSGAPPS) with or without a spacer 'S1-Y-S2';
- the second class of peptidomimetics comprises first 9-23 residues of N-terminal region of GLP-1 peptide combined with last four residues of N-terminal region of GLP-1 peptide with or without a spacer S1-Y-S2;
- the third class of peptidomimetics comprises first 9-23 residues of N-terminal region of GLP-1 peptide combined with the residue KELEKLL with or without a spacer S1-Y-S2.
- the fourth class of peptidomimetics comprises first 9-23 residues of N-terminal residues of GLP-1 peptide combined with the tetrapeptide GPPS with or without a spacer S1-Y-S2.
- the fifth class of peptidomimetics comprises first 2-9 residues of N-terminal residues of GLP-1 peptide combined with the dipeptide (Bip-Bip) with a spacer S1-Y-S2.

with the further restriction that

- when S1-Y-S2 is defined as a bond, we have restricted the selection of N-terminal residues of GLP-1 peptide to minimal length of first 1-9 residues to a maximum length of first 1-23 residues;
- when S1-Y-S2 is not a bond, in that case, we have restricted the selection of the N-terminal residues of GLP-1 peptide to only first 2-9 residues.

Hence, it is clear that the present invention actually discloses a class of peptidomimetics which comprises a rational combination of certain key sequences of N-terminal of GLP-1 (not the full length peptide, which is 29 amino acid long) with certain key sequences of either C-terminal of Exendin-4 or tetrapeptide GPPS or GLP-1 or the sequence KELEKLL or a dipeptide (Bip-Bip, with S1-Y-S2 spacer), in a way which provides the peptidomimetics with some unique features not known before and which the applicants have described in the specification. These classes of peptidomimetics are novel and have properties stated in the specification which makes them candidates with potential superior beneficial properties over other known peptidomimetics as discussed below.

As described the applicants in their specification, the compounds of the invention "exhibit increased stability to proteolytic cleavage, especially against DPP-IV enzyme and therefore, surprisingly found to have an increased half-life". These statements are not speculative statements but based on data and facts. With due respects, the applicants submit that unless there is any evidence to the contrary, ignoring such statements made by the inventors in the specification will amount to not giving due credit when it is due, for something which can at best be described as an aberration from the norm while drafting the specification by the inventors. The applicants respectfully submit that their data clearly backs the statements made by them.

The applicants have discussed earlier the rational behind designing the compounds of the present invention. It is very clear that the compounds were neither designed arbitrarily nor was the rational behind designing the compounds an extension of any of the existing concepts known for developing peptidomimetics as modulators of GLP-1. The mere fact that the

applicants have used the same broad designing principle for designing such class of peptidomimetics does not render the present class of compounds non-inventive over the cited references. The beneficial effect of the class of compounds has been described quite clearly in the specification and to provide data only to further substantiate those beneficial effect should not be considered as bringing in new matter but as an explanation and validation of the effects described and claimed. It is well established that for being inventive, it is not required for a class of compounds to necessarily have a 'superior beneficial effect' (Decision of The Board of Appeals of the European Union; T 0154/87-3.2.1). Such a criterion may be considered in the absence of other criterion to differentiate the inventive merit of an invention from the prior art. From the discussion below it will be clear that the compounds of the present invention are sufficiently different and unique over all the cited documents to be considered inventive per se. The judgment of inventive merit should not be limited to showing of superior efficacy alone particularly, when the structural features and the underlying rational is unique. The applicants have discussed the biological activities of the compounds in the specification and also provided data for four of the compounds described in the specification, which shows that they are biologically active. Showing of superior activity may be considered as further proof of beneficial effect and therefore better probability of success (for e.g. commercially) but should not be considered as limiting factor for determining non-obviousness. To establish further beneficial effect the applicants are submitting herewith additional data as evidence of inventive merit.

To further clarify the inventive merit of the present class of compounds, the applicants will first go on to differentiate the present compounds from each of the cited documents below. Subsequently the applicants will provide data which will establish some of the beneficial effects described and claimed in the specification, which will go towards further establishing the enhanced probability of success of these classes of compounds.

The Hon'ble Examiner has stated that the present applications consist of nine different inventions. The applicants are listing down them below but most humbly disagree that they relate to distinct inventions.

Claims classification:

1st invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI and X2 is GPSSGAPPPS.

2nd invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI and X2 is KELEKLL.

3rd invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI and X2 is GPPS.

4th invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 represent a bond, X1 is a N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI and X2 is VKGR.

5th invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 **does not represent a bond**, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD and X2 is GPSSGAPPPS.

6th invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 **does not represent a bond**, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD and X2 is KELEKLL.

7th invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 **does not represent a bond**, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD and X2 is GPPS.

8th invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 **does not represent a bond**, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD and X2 is VKGR.

9th invention: An isolated polypeptide having a sequence of formula (I) wherein S1-Y-S2 **does not represent a bond**, X1 is a N-terminal fragment of GLP-1 selected from HA to HAEGTFTSD and X2 is a dipeptide as defined at page 55.

As discussed earlier, the novelty of the present invention include selective combination of activation and binding domain, with or without spacer, which is not reported in literature published till date. The invention is also restricted as follows:

When S1-Y-S2 is defined as a bond, the applicants have restricted the selection of N-terminal residues of GLP-1 peptide to minimal length of first 1-9 residues (Seq ID 3) to maximum length of first 1-23 residues (Seq ID 17).

When S1-Y-S2 is not defined as a bond, the applicants have restricted the selection of the N-terminal residues of GLP-1 peptide to only first 2-9 residues (Seq ID 22 to 29).

In class B GPCR family, which include GLP-1 receptor as well, a concept of two-domain model has been proposed. In this two-domain model, the C-terminal portion of the peptide ligand binds to the N-domain of the receptor and the N-terminal ligand region binds to the J-domain region of receptor. Primarily, for the GLP-1 agonistic activity, few N-terminal and C-terminal residues (amino acids) are important for binding of ligand and activation of receptor.

In the present investigation, series of peptidomimetics were reported with general formula I, which includes combination of selected N-terminal residues of GLP-1 peptide with the C-terminal residues of Exendin-4 (GPSSGAPPPS; Seq. ID 18)/ GPPS (Seq. ID 20)/ last 4 residues of N-terminal region of GLP-1 peptide (VKGR; Seq ID 21)/ helix forming sequence KELEKLL (Seq ID 19), dipeptide (Bip-Bip), with or without optional spacer of S1-Y-S2.

The Hon'ble Examination authority has classified them into 9 different inventions, of which first 4 inventions differs in the selection of various X2, inventions 5-8 resembles with inventions 1-4 except that S1-Y-S2 does not represent a bond and in invention 9, X2 represent a dipeptide, with S1-Y-S2 as spacer.

The applicants respectfully submit that all the claims classified above fits in Formula I and the apparent multiplicity/ variety of claims 1-9 occurred due to variation of X2 mainly and overall, it represent a single general inventive concept, in which for the first time the applicants are reporting selective combination of N and C terminal residues, which represent binding and activation component, basically required for the GLP-1 agonistic activity.

Cited documents:

D1: WO03/011892:

D1 has been cited against this application as the closest prior art. This document discloses chimeric peptides generated by combining GLP-1 or Ex-4 peptide sequences. However, it is the applicants' contention that this document does not teach the present invention nor provide any guidance to a person skilled in the art to derive the present invention from this document either alone or in combination with any other document.

The cited document describes chimeric peptides in which either,

- selected residues of full length GLP-1 peptide were replaced by equivalent residues from exendin-4 peptide sequence; or
- to a full length GLP-1 peptide (1-29 amino acids) to which the C-terminal residues of exendin-4 peptide (either GPSSGAPPS/PSSGAPP/PSSGA/PSS) were attached; or
- the C-terminal of GLP-1 or exendin-4 peptides were truncated; or
- a spacer '-NH-(CH₂)_n-COO-' was selectively incorporated next to Histidine residue at 2nd position.

The present application totally differs from this concept, as this cited document does not report a full-length GLP-1 peptide attached to C-terminal residues of exendin-4. As per the present invention, in general formula I, when S1-Y-S2 represent a bond (claims 1-4), the applicants are selectively combining X2, which represent either

- the C-terminal residues of Exendin-4 (GPSSGAPPPS; Seq. ID 18)/ GPPS (Seq. ID 20);
- or last 4 residues of N-terminal reg on of GLP-1 peptide (VKGR; Seq ID 21); or
- helix forming sequence KELEKLL (Seq ID 19)

with selected C-terminal residues of GLP-1 peptide sequence, restricted from HAEGTFTSD (first nine residues) to HAEGTFTSDVSSYLEGQAAKEFI (first 23 residues) (Seq ID 3 to 17) and not the full length GLP-1 peptide sequence as reported in WO03/011892.

In claims 5-8, the applicants have incorporated additional feature of S1-Y-S2 as a spacer (which does not represent a bond) represented by an amino alkyl acid (-NH-(CH₂)_n-COO-) and while incorporating this spacer, we have restricted the N-terminal GLP-1 peptide sequence (X1) from HA to HAEGTFTSD (first 2-9 residues of GLP-1) (Seq ID 22-29) while X2 represents sequences as described above, which totally differs from the claims cited in WO 03/011892.

In claim 9, the applicants have disclosed S1-Y-S2 representing an amino alkyl acid (-NH-(CH₂)_n-COOH-), X1 represents sequence from HA to HAEGTFTSD (first 2-9 residues of GLP-1) (Seq ID 22-29) while X2 represent a dipeptide specifically Bip-Bip. Although the concept of combining first 1-9 residues of GLP-1 peptide (sequence HAEGTFTSD) with direct amide bond

attachment with Bip-Bip has been reported in WO2006/014287A1, WO2004/094461 A etc., but the concept of incorporation of S1-Y-S2 spacer as disclosed in the present specification is not covered in any of these applications.

As mention earlier, our sequence design feature is based upon the concept of having only the binding and activation component and deletion of middle residues of GLP-1 peptide or replacement with S1-Y-S2 spacer. Over all, this concept is totally novel and additional incorporation of S1-Y-S2 spacer lead to significant improvement in the biological activity and also due to short length of these novel peptidomimetics, it has the potential to be able to deliver the peptides orally, mainly due to their metabolic stability. Based upon above explanation, it is clear that all the sequences have been designed logically and should not be considered as arbitrary selection.

Thus, it is the applicants' humble position that the cited document D1 does not in any way teach the inventive concept of the present application.

D2: WO 2006/024275A; (Chimer of GLP-1 full length with EX-4)

In this cited document, chimeric peptides of 75 amino acids were prepared by combining 37 residues of GLP-1 (1-37) with exendin-3 /exendin-4 (1-39). Hence, this document describes a combination of atleast one full-length peptide with another peptide, either of whose residues are far greater than those described in the present application. The present invention differs from D2 because the applicants are not reporting full length chimeric peptides but on the contrary, are reporting short chain peptidomimetics.

D3: WO2005/077072A; (Hybrid polypeptides)

In this document, hybrid polypeptides are described by covalently linking different peptides of class B GPCR such as amylin, adrenomodullin, calcitonin, CCK, leptin, PPY, GLP-1, GLP-2, oxyntomodulin with exendin-4. The difference of the teachings of D3 with the present invention is quite obvious. The present application does not report hybrid peptides of class B-GPCR subfamilies and none of the sequence reported in D3 remotely resembles with the applicants' sequences.

D4: WO2006/014287A1 & D6: WO2004/094461A; (9+2 Bip combination)

These documents describe direct attachment of first 1-9 residues of GLP-1 peptide (HAEGTFTSD) with dipeptide Bip-Bip. The applicants have acknowledged both these documents in their present application.

The present invention, especially claim 9 differs from both these two cited documents with respect to incorporation of additional spacer S1-Y-S2 between 1-9 residues of GLP-1 and dipeptide Bip-Bip. Also the length of X1 in our patent application varies from HA to HAEGTFTSD (two to nine residues of GLP-1), while in both the applications the corresponding sequences is restricted to first 9 amino acids of GLP-1 peptide, without any spacer.

E5: WO02/28438A (KELEKLL seq. as absorption enhancer)

This cited document described synthesis of peptide based absorption enhancer, consisting of a helix forming linear peptide KELEKLL, attached to alkyl chains of different length *via* the biodegradable linker, glutamic acid.

The present application differs both in terms of sequence designing and biological activity, because as cited in claims 2 and 6, the applicants have also attached this helix forming sequence (KELEKLL), with or without S1-Y-S2 spacer to the N-terminal residues of GLP-1 peptide, which is not at all covered in this document.

D7: US 5545618A (truncated peptides)

This document describes preparation of analogs of GLP-1 peptide, mainly by truncation of C-terminal residues of GLP-1 peptide, substitution of residues at position 7 and 8 with D-amino acids to improve metabolic stability or N-alkylation. The concept of combining active sequences of GLP-1 with therapeutically useful sequences of Exendin-4 with or without a spacer is not taught in this document.

The present application differs from this patent because the applicants are not describing the truncated GLP-1 peptide analog as described in this patent.

D8: WO03/ 058203A (extended GLP-1 peptide)

This document describes preparation of extended GLP-1 peptide analogs, in which additional 21 residues were added to the C-terminal region of full-length GLP-1 peptide and long peptides upto 50 amino acids were prepared.

None of our peptide sequence reported is having total length more than 30 amino acids.

The International Search Authority has also cited the following non-patent literature to be novelty destroying for the present application. The applicants will now go on to distinguish the present application from each of these cited references thereby establishing that the present application is not taught by any of these documents also either alone or in combination.

D9: Brit. J. Pharmacol., 138(5), 2003, 787-794;

In this article, chimeric glucagon/GLP-1 peptides were prepared to generate the SAR. The applicants' invention differs from this reference because the applicants are not reporting chimeric glucagon/GLP-1 peptides.

D10: Life Sciences, 75(15), 2004, 1857-1870;

The document examines the N-terminal bioactive domain of GIP (Gastric Inhibitory Polypeptide) residing in residues 1-14, by Ala scan mutagenesis. Some chimeras of GIP and GLP were also prepared, to improve their metabolic stability.

The present invention differs from this review article because the applicants are neither reporting Ala scan of GIP nor the chimeric peptides of GIP and GLP.

D11: Brit. J. Pharmacol., 140(2), 2003, 339-346; (truncated GLP-1)

In this article, receptor-peptide interactions of GLP-1 peptide were studied by designing truncated GLP-1 and Exendin peptides. GLP-1 / Exendin peptides were truncated both from N and C terminal, to see agonistic / antagonistic activities.

The applicants' invention differs with the fact that the applicants are not reporting N and C terminal truncated peptide. All peptidomimetics disclosed in the present application contains the first N-terminal amino acid (His) of GLP-1 peptide.

D12: JBC, 272(34), 1997, 21201-21206; (Antagonist of GLP)

This paper mainly describes SAR of GLP-1R antagonist, designed by N-terminal truncation of first 1-9 residues of Exendin or GLP-1 peptide sequence. A set of Exendin/GLP-1 chimeric peptides were also reported in this article, mainly by substitution of GLP-1 sequences into N-terminally truncated Exendin (3-39).

The present invention differ from this paper because in all the applicants' sequences listed in Table 1-9, the N-terminal amino acids of GLP-1 sequence is intact, atleast first two residues HA, which is absent in all the peptide sequences listed in this paper.

D13: Regulatory Peptides, 114(2-3), 2003, 153-158; (similar as WO03/011892A)

In this paper, the importance of C-terminal 9 amino acids (PSSGAPPPS) of Exendin for its biological activity were studied. Series of peptides were prepared either by stepwise truncation of 1-9 residues from the C-terminal side of Exendin peptide or by addition of PSSGAPPPS/PSSGAP/PSS to the full length GLP-1 peptide.

The present invention differs from the teachings of this paper because the applicants are not reporting N-terminal truncation of Exendin nor the applicants are adding the Seq. GPSSGAPPPS to full length GLP-1 sequence but the applicants have restricting X1 to N-terminal fragment of GLP-1 selected from HAEGTFTSD to HAEGTFTSDVSSYLEGQAAKEFI and X2 as either GPSSGAPPPS/ GPPS/ VKGR, with or without S1-Y-S2 spacer.

D14: Biochemistry, 40(9), 2001, 2860-2869

In this article, the N and C terminal of GLP-1 peptide were kept as it is and the middle residues were replaced with a series of secretin-class chimeric peptides, such as replacement of N-terminal 1-5 residues of GLP-1 peptide with 1-5 residues of Glucagon/ PACAP/PHI/Secretin/VIP peptides etc. Some sequences are also reported with the substitution of 8, 11, 12 and 16th residues of GLP-1 peptide with Ala.

The present invention differs from this paper because the applicants are not reporting Ala scan of GLP-1 peptide or synthesis of chimeric peptides designed by the replacement of N-terminal 1-5 residues of GLP-1 peptide with 1-5 residues of Glucagon/ PACAP/PHI/Secretin/VIP peptides.

This review article discusses mainly about SAR of various GLP-1 and GIP peptide analogues designed by structural modification at N-terminal Histidine of GLP-1 peptide or Tyr of GIP. The N-terminal NH₂ group of both the peptides were protected so as to prolong the half life of peptides, mainly by improving resistance against DPP IV enzyme. In another set of peptides, modification were also carried out at 2nd position by replacing Ala with amino acids such as Aib, Val, Ser and Abu, mainly to improve metabolic stability against DPP IV enzyme.

The difference with the present invention is quite clear. The applicants' invention differs from this paper because the present invention includes selective modification at N-terminal region of intact GLP/GIP peptides at position 1 and 2, mainly to improve its half life and resistance against DPP IV enzyme.

Concluding Remarks

Thus, from the above discussion it is quite evident that the concept of preparing chimeric peptides as GLP-1 agonist is known by using different combination of GLP-1 and /or Exendin-4 either full length or truncated with or without other suitable groups. However, the novelty and inventiveness lies in the particular combination, the sequences which have been used, the rational for combining such peptides and the beneficial (not necessarily superior) effects of such combination.

From the above discussion and explanation, it is clear that the compounds claimed in the applicants' patent application are novel and inventive (the unique peptidomimetics are neither taught by any of the cited documents nor can be derived in a non-inventive way from the teachings of the documents either alone or in combination) and according to the specification they have a biologically beneficial effect. Therefore, it is the applicants' humble contention that the peptidomimetics disclosed in the present application are novel and inventive. However, to further substantiate the novelty and inventive merit of the applicants' invention and show that many of the compounds described and claimed have potential superior benefits, the applicants are providing data for several compounds. These data indicates that several compounds reported in the applicants' application have improved stability against DPP-IV enzymes, exhibit longer half-life (with respect to exendin-4 and GLP-1 peptide), better or comparable insulin secretion (in vitro in RIN cell assay), better or comparable cAMP production (in vitro HGLP-1 R assay), improved Pharmacokinetic parameter (cMax) and significant glucose reduction (in vivo, in C57 mice), compared to both Exendin-4 and GLP-1 peptides. Moreover, compared to Exendin-4 and GLP-1 peptides, some of sequences reported are very short in length and in *in-vitro* assay, they were found to be stable against various proteolytic enzymes, making them ideal candidate for oral delivery, mainly due to short chain amino acid length. Such potential superior beneficial properties indeed makes these class of compounds (as disclosed in the present application) as probable candidates for the development, especially as an oral GLP-1 modulator, which will go a long way in satisfying a huge unmet medical need *i.e.* an orally active GLP-1 modulator which will be useful for the prevention and mitigation of type 2 diabetes and various other associated metabolic disorders.

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S. No	Sequences	In vitro stability against DPP-IV enzyme reported as % degraded	In vitro glucose dependent insulin secretion (pg/μg/h) in RIN5F cells at 100 nM conc. of test compounds	EC ₅₀ ; CAMP production in HGLP-1 R assay (in vitro); nM conc. used	Pharmacokinetic parameters after subcut administration of test compounds at 1 μM/kg dose in C57 mice, 24h		ED ₅₀ in IPGTT SAM Model (n = 6); nM/kg dose used, via ip route of admn (in vivo)
					C _{max} (μg/ml)	t _{1/2} (h)	
	HGEGTFTSDLS KQMEEEAVRL FIEWLKNGGP SSGAPPPS	42	36.2±0.11	0.09	0.23	0.50	0.1
	HAEGTFTSDV SSYLEGQAAK EFIAWLVKGR	59	33.7±0.13	0.1	0.09	0.09	2
1	HGEGTFTSD- (CH ₂) ₃ - GPSSGAPPPS	10	23.8±0.12	10	0.6	0.9	100
2	HGEGTFTSD- (CH ₂) ₄ - GPSSGAPPPS	12	11.1±0.17	16	0.7	1	95
3	HGEGTFTSDLS KQM-(CH ₂) ₃ - GPSS	9	23.4±0.22	22	0.6	1.3	200
4	HGEGTFTSDLS KQM-(CH ₂) ₄ - GPSS	6	16.7±0.16	2	0.5	1.6	126
5	HGEGTFTSDLS KQME-(CH ₂) ₂ - GPSSGAPPPS	2	34.6±0.10	1	1	4.2	1
6	HGEGTFTSDLS KQME-(CH ₂) ₃ - GPSSGAPPPS	2	36.1±0.19	0.1	1.2	5.9	0.5
7	HGEGTFTSDLS KQME-(CH ₂) ₁₀ - GPSSGAPPPS	14	33.4±0.18	0.2	1.1	2.4	6
8	HGEGTFTSDLS KQME-(CH ₂) ₁₁ - GPSSGAPPPS	2	12.6±0.33	6	0.3	2.6	300
9	HAEGTFTSD- (CH ₂) ₂ -VKGR	9	18.3±0.12	8	0.2	2.9	340
10	HAEGTFTSD- (CH ₂) ₃ -VKGR	3	30.9±0.11	1	0.3	1.5	320

11	HAEGTFTSD- (CH ₂) ₄ -VKGR	00	22.7±0.19	2	0.4	3.2	400
12	HGEGTFTSDLS KQMKELEKLL	12	11.2±0.33	23	1.4	3.4	475
13	HAEGTFTSDK ELEKLL	11	09.1±0.22	42	1.2	3.9	600
14	HaEGTFTSDVS SYLEGKELEKL L	6	35.5±0.45	0.03	1.1	2.1	0.6
15	HAibEGTFTSD VSSYLEGKELE KLL	1	37.2±0.13	0.01	1.2	7.9	0.5
16	HAEGTFTSDV SSYLEGQAAK EFIKELEKLL	12	31.3±0.22	0.2	0.7	4.6	2
17	HAibEGTFTSD VSSYLEGQAA KEFIKELEKLL	14	29.6±0.23	2	0.9	4.3	10
18	Des-amino- HAibEGT-($\odot$ - Me)Phe(2-F)- TSDVSSYLEGQ AAKEFIKELEK LL	13	33.4±0.45	0.2	0.8	3.9	8
19	HA-(CH ₂) ₃ - DVSSYLEGQA AKEFIKELEKL L	2	28.5±0.42	0.3	0.9	6.1	15
20	HAib-(CH ₂) ₃ - DVSSYLEGQA AKEFIKELEKL L	00	31.2±0.33	0.2	1.1	6.4	20
21	HAibEGTFTSD -(CH ₂) ₃ -Bip-Bip	2	26.3±0.42	0.5	1.1	6.1	25
22	HAibEGT-($\odot$ - Me)-Phe(2-F)- TSD-G-Bip(2- Me)-Bip(2-Me)	3	33.8±0.12	0.1	1.4	5.2	20
23	HAibEGT-($\odot$ - Me)-Phe(2-F)- TS-(CH ₂) ₂ - Bip(2-Me)- Bip(2-Me)	6	29.9±0.16	0.3	1.0	2.1	21
24	HAibEGT-($\odot$ - Me)-Phe(2-F)- (CH ₂) ₂ -Bip(2- Me)-Bip(2-Me)	00	31.2±0.15	0.2	1.1	2.5	12
25	HAEG-(CH ₂) ₂ - Bip(2-Me)- Bip(2-Me)	4	30.7±0.11	0.3	1.0	4.5	24

26	HAibEGT-($\odot$ -Me)-Phe(2-F)-TSD-G-Bip-Bip(2-Me)	5	18.1 $\pm$ 0.05	2	0.3	3.4	56
27	HAEGTFTSD-G-Bip-Bip(2-Et)	2	17.3 $\pm$ 0.06	4	0.4	3.9	97
28	HAibEGTFTSD-G-Bip-Bip(2-Et)	00	22.2 $\pm$ 0.09	2	0.4	2.1	67
29	HGEGT-($\odot$ -Me)-Phe(2-F)-TSD-(CH ₂) ₄ -Bip(2-Et)-Bip(2-Et)	00	11.7 $\pm$ 0.11	10	0.2	4.9	345
30	HGEGTFTSD-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)	0.5	17.5 $\pm$ 0.22	09	0.2	4.6	340
31	HGEGT-($\odot$ -Me)-Phe(2-F)-TS-(CH ₂) ₅ -Bip(2-Et)-Bip(2-Et)	0.3	06.3 $\pm$ 0.15	77	0.02	4.3	1000
32	HGEGTFTS-(CH ₂) ₆ -Bip(2-Et)-Bip(2-Et)	0.4	09.4 $\pm$ 0.06	72	0.04	3.9	1200
33	HGEGT-($\odot$ -Me)-Phe(2-F)-TS-(CH ₂) ₁₀ -Bip(2-Et)-Bip(2-Et)	0.3	12.6 $\pm$ 0.02	40	0.3	1.6	29
34	HGEGTFTS-(CH ₂) ₁₁ -Bip(2-Et)-Bip(2-Et)	0.2	17.1 $\pm$ 0.22	36	0.4	0.9	43
35	HAEGTFTSD-G-Nap-Nap	0.1	26.2 $\pm$ 0.17	12	0.6	1.9	56
36	HAibEGTFTSD-G-Nap-Nap	1	24.7 $\pm$ 0.11	13	0.8	2.1	65
37	HAEGTF-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala	0.1	22.6 $\pm$ 0.16	12	0.5	3.4	45
38	HAibEGTF-(CH ₂) ₂ -Bip(2'-Et-4'-OMe)-4-(2'-Me-Ph)-3-Pyr-Ala	00	23.4 $\pm$ 0.15	14	1.0	3.9	47
39	HAEGT-(CH ₂) ₂ -Bip(2-Me)-Bip(2-Me)	00	15.1 $\pm$ 0.33	14	1.1	2.1	110

40	HGEGT-(CH ₂) ₃ - Bip(2-Me)- Bip(2-Me)	00	22.3±0.36	12	1.0	4.9	46
41	HGEG-(CH ₂) ₃ - Bip(2-Me)- Bip(2-Me)	0.1	04.5±0.12	68	1.1	4.6	750
42	HAEG-(CH ₂) ₃ - Bip(2-Me)- Bip(2-Me)	0.2	12.9±0.11	15	1.2	4.3	345
43	HAE-(CH ₂) ₃ - Bip(2-Et)-Bip(2- Me)	0.3	19.2±0.18	18	1.0	3.9	230
44	HAE-(CH ₂) ₂ - Bip(2-Me)- Bip(2-Me)	00	28.7±0.03	09	0.9	2.1	126
45	H-(CH ₂) ₄ -Bip(2- Et)-Bip(2-Me)	00	26.6±0.06	06	0.8	2.7	129
46	H-(CH ₂) ₅ -Bip(2- Et)-Bip(2-Me)	00	25.3±0.09	07	1.0	4.9	132
47	HG-(CH ₂) ₃ - Bip(2-Et)-Bip(2- Me)	00	27.7±0.44	07	1.1	5.2	135
48	HG-(CH ₂) ₄ - Bip(2-Et)-Bip(2- Me)	00	28.5±0.14	07	1.2	5.7	137
49	Ha-(CH ₂) ₃ - Bip(2-Me)- Bip(2-Me)	00	22.4±0.18	09	0.9	5.6	136
50	Ha-(CH ₂) ₃ - (N(Me))- DBip(2-Me)- Bip(2-Et)	00	27.2±0.17	04	0.8	4.6	134
51	HA-(CH ₂) ₃ - Bip(2-Me)- DBip(2-Et)	00	26.8±0.07	03	1.0	3.2	145
52	HA-(CH ₂) ₃ - DBip(2-Et)- Bip(2-Et)	00	25.9±0.09	04	0.9	3.1	142
53	HA-(CH ₂) ₃ - DBip(2-Me)- DBip(2-Et)	00	28.6±0.11	02	0.8	1.1	151
54	HA-(CH ₂) ₃ -Bip- Bip	00	11.1±0.13	28	1.0	3.4	22
55	HA-(CH ₂) ₃ - DBip-DBip	00	16.2±0.15	25	1.1	3.9	24
56	HA-(CH ₂) ₃ - DBip-Bip	00	18.6±0.17	26	1.2	2.1	26
57	HA-(CH ₂) ₃ - Bip(2-Ipr)- DBip(2-Ipr)	00	17.4±0.19	29	0.9	4.9	28

58	HA-(CH ₂) ₃ - Bip(2-Ipr)- Bip(2-CN)	00	19.1±0.22	24	0.8	4.6	28
59	HA-(CH ₂) ₃ - Bip(2-CN)- Bip(2-Me)	00	17.2±0.23	27	0.7	4.3	29
60	HA-(CH ₂) ₃ - Bip(2-CN)- Bip(2-Ipr)	00	22.5±0.34	22	0.9	3.9	34
61	HA-(CH ₂) ₂ -F- (CH ₂) ₂ -Bip(2- Et)-DBip(2-Et)	00	24.3±0.36	24	0.7	0.9	32
62	HA-(CH ₂) ₅ - D(Bip)-Bip(2- Et)	00	19.8±0.12	28	1.0	0.4	31
63	HA-(N(Me))- (CH ₂) ₃ -DBip(2- Me)-Bip(2-Et)	00	28.6±0.16	14	0.9	1.9	14
64	HA-(N(Me))- (CH ₂) ₃ -DBip- Bip(2-Et)	00	29.4±0.19	12	0.8	1.8	26
	HAEGTFTSDV SEKELEKLL	6	12.3±0.22	19	1.0	2.1	245
66	HAEGTFTSDV SGKELEKLL	9	22.8±0.33	22	1.1	2.3	112
67	HAEGTFTSDV SSYLEKELEKL L	12	29.2±0.45	12	1.2	1.7	116
68	HAEGTFTSDV SSYLEGKELEK LL	11	31.6±0.09	04	0.9	1.4	3
69	HGEGTFTSDV SSYLEGKELEK LL	2	32.5±0.08	03	0.8	2.1	2
70	HAEGTFTSD- (CH ₂) ₄ - KELEKLL	2	14.3±0.07	25	0.3	2.5	126

In view of the submissions presented above, the applicants respectfully submit that the present invention is novel and inventive.

The applicants respectfully request the Hon'ble Examiner to take the submissions on record and issue a favourable IPER.

Yours faithfully,

Hari Subramaniam

SUBRAMANIAM, NATARAJ & ASSOCIATES

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558-645-CHL

16 October 2007

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NETHERLANDS

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Kind Attn: Sabine Oblinger esq.
Authorized Officer

BY FACSIMILE & COURIER

No. of pages: 04

Dear Sirs,

Re: **CADILA HEALTHCARE LIMITED**
PCT International Application No. PCT/IN2006/000154
Filed on : 04 May 2006
Priority : 05 May 2005 (IN: 558/MUM/2005)
 31 May 2005 (IN: 645/MUM/2005)
SUPPLEMENTARY RESPONSE TO WRITTEN OPINION
Due Date: : 26 October 2007

It is respectfully submitted that a response to the written opinion dated 15 September 2007 is already on record. A copy of the response is enclosed herewith.

It is humbly submitted that due to an inadvertent mistake our response dated 15 September 2007 did not address objection on paragraph 4.6 of the written opinion.

The Learned Examiner is respectfully requested to take this supplementary response on record.

To meet the Learned Examiner's objection on paragraph 4.6 it is respectfully submitted that Figure 1 was omitted during the filing of the PCT Application due to a typographical error. A copy of Figure 1 is enclosed herewith.

It is further submitted that Table 10 on Page 52 has been amended to meet the Learned Examiner's objection. A copy of amended page 52 is enclosed herewith. In the amended Table 10 the Sequences of Compounds I to IV have been incorporated. It is humbly submitted that no new matter has been added. These sequences are already disclosed in the specification. Sequence of compound I is disclosed in Table 4 (94 Seq.), sequence II, III and IV are disclosed in Table 3 (1 Seq.), Table 1 (8 Seq.) and Table 1 (1 Seq.) respectively.

The Learned Examiner is respectfully requested to take the enclosed Figure 1 and amendments of page 52 on record. The amendments fall within the scope of the invention. No new matter has been added.

It is respectfully submitted that the supplementary response along with the response dated 15 September 2007 is duly considered and a favorable Examination Report is established.

Yours truly,

H. Subramaniam

Enclosures:

Figure 1 (Fax + courier)

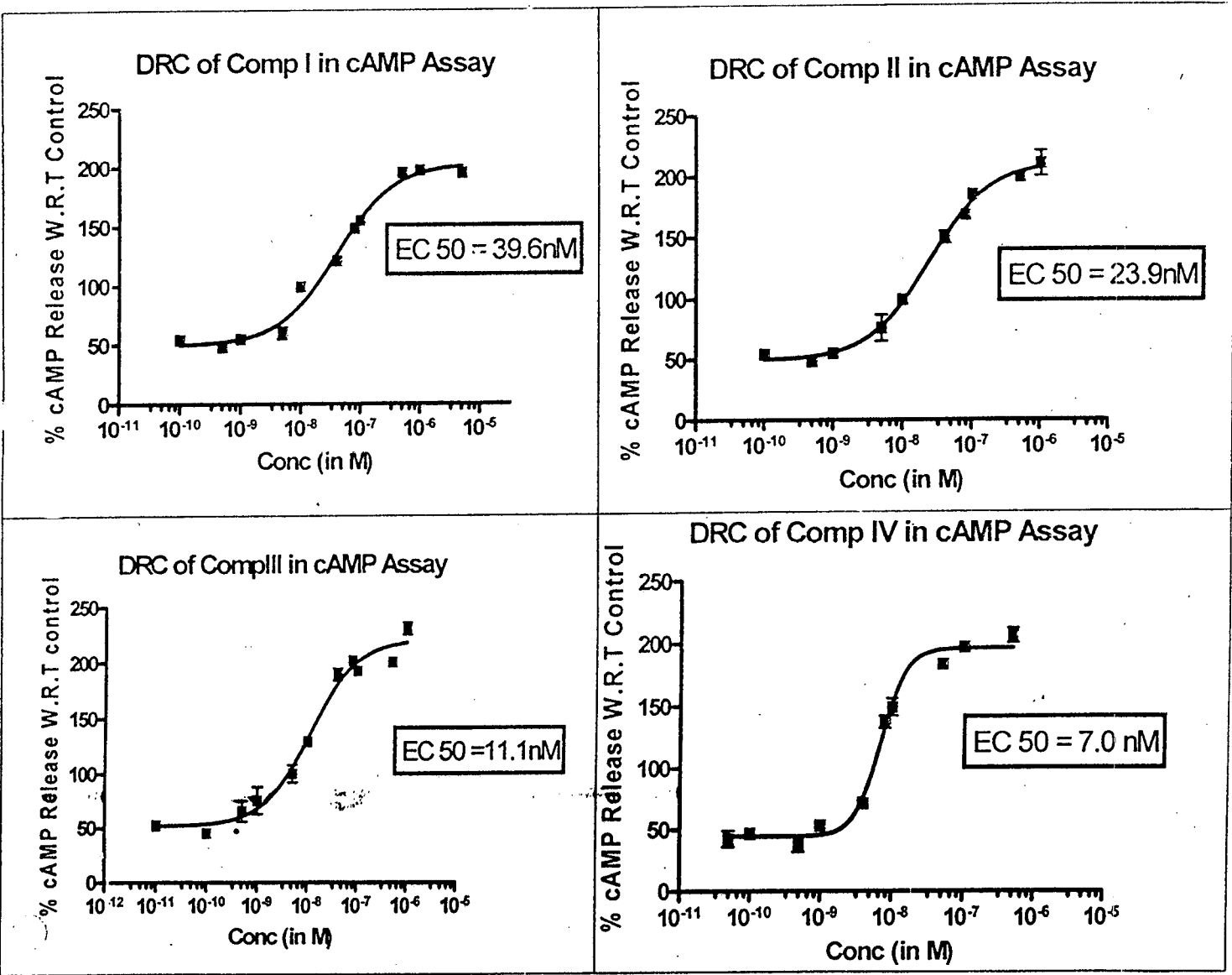
Amended page 52 with track changes (Fax + courier)

Amended page 52 (Fax + courier)

Copy of response dated 15 September 2007 (14 pages) (by courier only)

240

Figure: 1- EC₅₀ values ('S'-Curves) for some of the representative compounds (in vitro cAMP assay)



Kg/ 10 ml and blood was collected at different time intervals, via retroorbital plexus. Test compounds (peptidomimetics) 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.

5 Blood samples were drawn prior to Vehicle/Test compound/Glucose load (0 minute) and then at 15 min, 30 min, 60 min and 120 min. Vehicle/Test compound was administered 15 minutes prior to glucose load, via intra-peritoneal route of administration. Blood samples were centrifuged and the obtained serum was stored at - 20° C for analysis. Test compounds were examined along with a reference (positive control) and a vehicle control, with n = 6 animals per group. Glucose was determined by the GOD/POD method from serum. The mean value of duplicate results was calculated. The absolute values of glucose in serum levels were calculated using MS Excel software. The 0-minute base line corrected line graph were plotted using Graphpad prism software (ver 3.0). Area under the Curve (AUC) and Base line corrected area under the curve (BCAUC) were calculated and analyzed by performing One way ANOVA followed by Dunnett's post test using Graphpad prism software (ver 3.0).

Using above experimental protocol, in vivo glucose lowering properties of some of the selected compounds, which showed in vitro EC₅₀, in CHO-GLP-1R cAMP assay, in the range of 1-50 nM range were determined. In Table 10, the in vivo glucose lowering potencies (ED₅₀ in IPGTT SAM model) of selected four representative compounds (Comp. I, II, III & IV) were given.

Table 10: In vivo potencies of compound I to IV (ED₅₀), in IPGTT SAM Model

Comp.	Sequence	ED ₅₀ in IPGTT SAM Model (n = 6)
I	<u>HGEGT-(α-Me)-Phe(2-F)-TS-(CH₂)₅-Bip(2-Et)-Bip(2-Et)</u> Table 4 (94 Seq.)	1 μmole / kg
II	<u>HGEGTFTSDLSKQMKELEKLL</u> Table 3 (1 Seq.)	500 nM / Kg
III	<u>HGEGTFTSDLSKC M-(CH₂)₃-GPSS</u> Table 1 (8 Seq.)	250 nM / kg
IV	<u>HGEGTFTSD-(CH₂)₃-GPSSGAPPS</u> Table 1 (1 1 Seq.)	100 nM / Kg

Kg/ 10 ml and blood was collected at different time intervals, via retroorbital plexus. Test compounds (peptidomimetics) 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.

- 5 Blood samples were drawn prior to Vehicle/Test compound/Glucose load (0 minute) and then at 15 min, 30 min, 60 min and 120 min. Vehicle/Test compound was administered 15 minutes prior to glucose load, via intra-peritoneal route of administration. Blood samples were centrifuged and the obtained serum was stored at - 20° C for analysis. Test compounds were examined along with a reference (positive control) and a vehicle control, with n = 6 animals per group. Glucose was determined by the GOD/POD method from serum. The mean value of duplicate results was calculated. The absolute values of glucose in serum levels were calculated using MS Excel software. The 0-minute base line corrected line graph were plotted using Graphpad prism software (ver 3.0). Area under the Curve (AUC) and Base line corrected area under the curve (BCAUC) were calculated and analyzed by performing One way ANOVA followed by Dunnett's post test using Graphpad prism software (ver 3.0).

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II	<u>HGEGTFTSDLSKOMKELEKLL</u> Table 3 (1 Seq.)	500 nM / Kg
III	<u>HGEGTFTSDLSKOM-(CH₂)₃-GPSS</u> Table 1 (8 Seq.)	250 nM / kg
IV	<u>HGEGTFTSD-(CH₂)₃-GPSSGAPPPS</u> Table 1 (1 Seq.)	100 nM / Kg

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDE

Date of mailing (day/month/year) 11 December 2006 (11.12.2006)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 558-645-CHL	International application No. PCT/IN2006/000154

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

CADILA HEALTHCARE LIMITED (for all designated States except US)
LC-HRAY, Braj, Bhushan et al (for US)

International filing date: 04 May 2006 (04.05.2006)
Priority date(s) claimed: 05 May 2005 (05.05.2005)
31 May 2005 (31.05.2005)
Date of receipt of the record copy by the International Bureau: 05 December 2006 (05.12.2006)
List of designated Offices:

AP: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW

EA: AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR

OA: BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

National: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

ATTENTION: The applicant should carefully check the data appearing in this notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau. In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- time limits for entry into the national phase - see updated important information (as of April 2002)
- requirements regarding priority documents (if applicable)

A copy of this notification is being sent to the receiving Office and to the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Birchen Mireille
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 87 40 Telephone No. +41 22 338 83 45

INFORMATION ON ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 19 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see *PCT Gazette* No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the *PCT Newsletter*, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette* ("Section IV" part published on a weekly basis), to the *PCT Newsletter* (on a monthly basis) and to the relevant National Chapters in Volume II of the *PCT Applicant's Guide* (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages of the site, including those of the *Gazette*, *Newsletter* and *Guide*, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the *PCT Applicant's Guide*, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before the date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau and if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 2(xi)(b)).

From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDE

Date of mailing (day/month/year) 14 December 2006 (14.12.2006)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 558-645-CHL	
International application No. PCT/IN2006/000154	
International filing date (day/month/year) 04 May 2006 (04.05.2006)	
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 05 May 2005 (05.05.2005)
Applicant CADILA HEALTHCARE LIMITED et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable)* The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable)* An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
05 May 2005 (05.05.2005)	558/MUM/2005	IN	05 December 2006 (05.12.2006)
31 May 2005 (31.05.2005)	645/MUM/2005	IN	05 December 2006 (05.12.2006)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Dorothee Mülhausen

Facsimile No. +41 22 338 87 40
Telephone No. +41 22 338 96 72

Facsimile No. +41 22 338 82 70

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDE

Date of mailing (day/month/year) 07 September 2007 (07.09.2007)		IMPORTANT NOTICE	
Applicant's or agent's file reference 558-645-CHL			
International application No. PCT/IN2006/000154	International filing date (day/month/year) 04 May 2006 (04.05.2006)	Priority date (day/month/year) 05 May 2005 (05.05.2005)	
Applicant CADILA HEALTHCARE LIMITED et al			

- ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does not apply**, please see Form PCT/IB/308(First Notice) issued previously.
- Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
15 February 2007 (15.02.2007)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, NG, PG, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KM, KN, KZ, LC, LK, LR, LS, LT, LV, LY, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, RO, SC, SD, SG, SK, SL, SM, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZM, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **30 MONTHS** from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For **regular updates on the applicable time limits** (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pc/en/index.html>.

It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Dorothee Mülhausen
Facsimile No. +41 22 338 82 70	e-mail: pt01.pct@wipo.int

From the INTERNATIONAL BUREAU

PCT**NOTIFICATION CONCERNING
AVAILABILITY OF THE PUBLICATION
OF THE INTERNATIONAL APPLICATION**

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDE

Thanks

Date of mailing (day/month/year) 15 February 2007 (15.02.2007)		
Applicant's or agent's file reference 558-645-CHL		
International application No. PCT/IN2006/000154	International filing date (day/month/year) 04 May 2006 (04.05.2006)	Priority date (day/month/year) 05 May 2005 (05.05.2005)
Applicant CADILA HEALTHCARE LIMITED et al		

IMPORTANT NOTICE

SN&A

The applicant is hereby notified that the International Bureau:



has published the above-indicated international application on 15 February 2007 (15.02.2007) under No. WO 2007/017892



has republished the above-indicated international application on under No. WO

For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48) or (88) (as the case may be) on the front page of the published international application.

A copy of the international application is available for viewing and downloading on WIPO's website at the following address:
<http://www.wipo.int/pctdb> (under "Query" enter the PCT or WO number).

The applicant may also request a paper copy of the published international application from the International Bureau by submitting a written request to PatentScope@wipo.int or to the address provided below.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Dorothee Mülhausen
Facsimile No. +41 22 338 82 70	e-mail: pt01.pct@wipo.int

From the INTERNATIONAL BUREAU

PCTNOTIFICATION CONCERNING
AVAILABILITY OF THE PUBLICATION
OF THE INTERNATIONAL APPLICATION

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDEDate of mailing (day/month/year)
20 September 2007 (20.09.2007)Applicant's or agent's file reference
558-645-CHL

IMPORTANT NOTICE

International application No.
PCT/IN2006/000154International filing date (day/month/year)
04 May 2006 (04.05.2006)Priority date (day/month/year)
05 May 2005 (05.05.2005)

Applicant

CADILA HEALTHCARE LIMITED et al

The applicant is hereby notified that the International Bureau:

has published the above-indicated international application on under
No. WOhas republished the above-indicated international application on 20 September 2007 (20.09.2007) under
No. WO 2007/017892For an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48)
or (88) (as the case may be) on the front page of the published international application.A copy of the international application is available for viewing and downloading on WIPO's website at the following address:
<http://www.wipo.int/pctdb> (under "Query" enter the PCT or WO number).The applicant may also request a paper copy of the published international application from the International Bureau by submitting a written
request to PatentScope@wipo.int or to the address provided below.The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Dorothee Mülhausen

Facsimile No. +41 22 338 82 70

e-mail: pt01.pct@wipo.int

From the INTERNATIONAL BUREAU

PCTINFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Article 31(7) and Rule 61.3)

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDEDate of mailing (day/month/year)
15 February 2007 (15.02.2007)Applicant's or agent's file reference
558-645-CHL**IMPORTANT INFORMATION**International application No.
PCT/IN2006/000154International filing date (day/month/year)
04 May 2006 (04.05.2006)Priority date (day/month/year)
05 May 2005 (05.05.2005)

Applicant

CADILA HEALTHCARE LIMITED et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR**National:** BG, CA, CN, CZ, DE, JP, KM, KN, KP, KR, LY, MN, NG, NO, PL, RO, RU, SK, SM, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW**EA:** AM, AZ, BY, KG, KZ, MD, RU, TJ, TM**OA:** BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG**National:** AE, AG, AL, AM, AT, AU, AZ, BA, BB, BR, BW, BY, BZ, CH, CO, CR, CU, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, ~~MX~~, ~~MW~~, ~~MX~~, ~~MZ~~, NA, NI, NZ, ~~OM~~, ~~PG~~, ~~PH~~, PT, SC, SD, SE, SG, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

3. Since the election(s) was (were) made before the expiration of 19 months from the priority date, the applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary report on patentability (Chapter II of the Patent Cooperation Treaty) (Article 36(3)(b) and Rule 74.1).

Some Offices have fixed time limits expiring later than the above-mentioned time limit. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters, the *PCT Newsletter* and the WIPO Internet site, updated regularly.The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Dorothee Mülhausen

Facsimile No. +41 22 338 82 70

e-mail: pt01.pct@wipo.int

From the INTERNATIONAL BUREAU

PCT

**INVITATION TO CORRECT
DECLARATIONS MADE IN THE REQUEST
UNDER PCT RULE 4.17**

(PCT Rules 4.17 and 26ter.2(a))

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDE

Date of mailing (day/month/year) 11 December 2006 (11.12.2006)	
Applicant's or agent's file reference 558-645-CHL	REPLY DUE See below
International application No. PCT/IN2006/000154	International filing date (day/month/year) 04 May 2006 (04.05.2006)
Applicant CADILA HEALTHCARE LIMITED et al	

1. The applicant is hereby invited to submit to the International Bureau a corrected declaration within the time limit indicated below and as explained in the Annex. The applicant's attention is drawn to the fact that the declaration has not been examined for compliance with national law requirements of the designated State(s) for which that declaration is made.

When? Within 16 months from the priority date, provided that any corrected declaration which is received by the International Bureau after the expiration of that time limit shall be considered to have been received on the last day of that time limit if it reaches it before the technical preparations for international publication have been completed (Rule 26ter.1).

How? By submitting a replacement sheet containing a corrected declaration accompanied by a letter explaining the correction (see Section 216). See Sections 211 to 215 for the applicable standardized wording.

Where? ~~Directly to the~~ International Bureau at the address indicated below.
If the corrected declaration is submitted to the receiving Office, that Office shall mark the date of receipt on it and transmit it promptly to the International Bureau. The declaration shall be considered to have been submitted to the International Bureau on the date marked (see Section 317).

2. Failure to correct the declaration within the time limit will result in the declaration, as originally filed, being published as part of the international application (Rule 48.2(a)(x)).

Any declaration received after the expiration of the time limit under Rule 26ter.1 will have to be submitted by the applicant directly to the designated Offices concerned; it is only in the case of a signed declaration of inventorship for the purposes of the designation of the United States of America (Rule 4.17(iv)) that the original declaration will be returned to the applicant (see Section 419(d)).

3. In respect of national phase processing, the applicant's attention is drawn to Rule 51bis.2 which provides that the designated Office shall not, unless it may reasonably doubt the veracity of the declaration concerned, require any document or evidence relating to the subject matter of any declaration complying with Rule 4.17(i) to (iv) which is contained in the request or submitted to the International Bureau or directly to the designated Office. Note, however, that Rule 51bis.2 may not apply in respect of certain States. For further information, see Notes to the request form, Box No. VIII.

4. A copy of this Invitation is being sent to the receiving Office.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Birchen Mireille
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 87 40 Telephone No. +41 22 338 83 45

The International Bureau has found the following defect(s) in the declaration(s) listed below:

1. ☐ declaration as to the identity of the inventor (Rules 4.17(i) and 51bis.1(a)(i) and Section 211), in respect of:
2. ☒ declaration as to the applicant's entitlement, as at the international filing date, to apply for or be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii) and Section 212), in respect of:
 - a. (name(s) included in the declaration): LOHRAY, Braj, Bhushan; LOHRAY, Vidya, Bhushan; BAHEKAR, Rajesh, H.
 - ☒ is not in the prescribed wording
 - ☒ other (specify): As from April 1, 2006, the declarations should not include the text concerning the States for which they have been made and this is now considered as a defect. Please resend declaration with correct wording.
3. ☐ declaration as to the applicant's entitlement, as at the international filing date, to claim priority of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii) and Section 213), in respect of:
4. ☐ declaration of inventorship (only for the purposes of the designation of the United States of America) (Rules 4.17(iv) and 51bis.1(a)(iv) and Section 214), in respect of:
5. ☐ declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51bis.1(a)(v) and Section 215), in respect of:

From the INTERNATIONAL BUREAU

PCTNOTIFICATION RELATING TO
DECLARATION MADE UNDER PCT RULE 4.17(PCT Rules 26ter and 48.2(a)(x)
and Administrative Instructions, Section 419)

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDE

Date of mailing (day/month/year) 11 January 2007 (11.01.2007)	Received with Thanks	
Applicant's or agent's file reference 558-645-CHL	7 : JA	IMPORTANT NOTIFICATION
International application No. PCT/IN2006/000154	SN&A	International filing date (day/month/year) 04 May 2006 (04.05.2006)
Applicant CADILA HEALTHCARE LIMITED et al		

- The applicant is hereby notified of the following regarding the declaration indicated below in respect of **CADILA HEALTHCARE LIMITED** :
 - ☐ declaration as to the identity of the inventor (Rules 4.17(i) and 51bis.1(a)(i) and Section 211)
 - ☒ declaration as to the applicant's entitlement, as at the international filing date, to apply for or be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii) and Section 212)
 - ☐ declaration as to the applicant's entitlement, as at the international filing date, to claim priority of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii) and Section 213)
 - ☐ declaration of inventorship (for the purposes of the designation of the United States of America) (Rules 4.17(iv) and 51bis.1(a)(iv) and Section 214)
 - ☐ declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51bis.1(a)(v) and Section 215)
- ☒ **Addition or correction of the declaration within the time limit under Rule 26ter.1.**
 The added or corrected declaration was received on 05 September 2006 (05.09.2006), which was within the time limit under Rule 26ter.1.
 Any declaration referred to under items 1(i) to (v), whether or not the declaration complies with Rule 4.17, will be published as part of the international application pursuant to Rule 48.2(a)(x).
- ☐ **Failure to add or correct the declaration within the time limit under Rule 26ter.1.**
 The declaration was received on which was after the expiration of the time limit under Rule 26ter.1; therefore, that declaration, as added or corrected, referred to under items 1(i) to (v) will not be published as part of the international application, and any signed declaration referred to under item 1(iv) is attached. Such declaration should be submitted by the applicant directly to the designated Office(s) concerned.
- The applicant's attention is drawn to Rule 51bis.2 which provides that the designated Office shall not, unless it may reasonably doubt the veracity of the declaration concerned, require any document or evidence relating to the subject matter of any declaration complying with Rule 4.17(i) to (iv) which is contained in the request or submitted to the International Bureau or directly to the designated Office. Note, however, that Rule 51bis.2 may not apply in respect of certain States. For further information, see Notes to the request form, Box No. VIII.
- A copy of this notification is being sent to the receiving Office and the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Sevillano Carine
Facsimile No. +41 22 338 82 70	Facsimile No. +41 22 338 87 40
	Telephone No. +41 22 338 92 54

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference 558-645-CHL	
International application No. PCT/IN2006/00154	International filing date (day/month/year) 04 May 2006 (04.05.2006)
(Earliest) Priority date (day/month/year) 05.05. 2005 & 31.05.2005	
Title of invention NOVEL COMPOUNDS AS GLP-1 AGONISTS	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) CADILA HEALTHCARE LIMITED Zydus Tower, Satellite Cross Roads Ahmedabad 380 015, Gujarat, India (applicant for all designated states except U.S.A.)	
Telephone No. +91 79 2686 8100	
Facsimile No. +91 79 2686 8144	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LOHRAY, Braj Bhushan CADILA HEALTHCARE LIMITED Zydus Tower, Satellite Cross Roads Ahmedabad 380 015, Gujarat, India (inventor and applicant for U.S.A. only)	
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LOHRAY, Vidya Bhushan CADILA HEALTHCARE LIMITED Zydus Tower, Satellite Cross Roads Ahmedabad 380 015, Gujarat, India (inventor and applicant for U.S.A. only)	
State (that is, country) of nationality: IN	State (that is, country) of residence: IN
☒ Further applicants are indicated on a continuation sheet.	

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

BAHEKAR, Rajesh H
CADILA HEALTHCARE LIMITED
Zydus Tower, Satellite Cross Roads
Ahmedabad 380 015,
Gujarat, India
(inventor and applicant for U.S.A. only)

State (that is, country) of nationality:

IN

State (that is, country) of residence:

IN

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐

Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE: OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)SUBRAMANIAM, Hariharan; NATARAJ, Guruswamy;
AHUJA, Shalina; PRITHVIRAJ, Susheela
Subramaniam, Nataraj & Associates
E-556, Greater Kailash-II
New Delhi-110 048, INDIA

Telephone No.

+91 11 2921 5603

Facsimile No.

+91 11 2922 6005

Teleprinter No.

Agent's registration No. with the Office
IN/PA-93☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☒ as originally filed☐ as amended under Article 34the claims ☒ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34the drawings ☐ as originally filed☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA to postpone the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**

The filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | |
|--|----------|
| 1. translation of international application | sheets |
| 2. amendments under Article 34 | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | sheets |
| 5. letter | 1 sheets |
| 6. other (<i>specify</i>) | sheets |

For International Preliminary Examining Authority use only
received not received

☐	☐
☐	☐
☐	☐
☐	☐
☐	☐
☐	☐

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in electronic form |
| 3. ☐ original general power of attorney | 7. ☐ tables in electronic form related to a sequence listing |
| 4. ☐ copy of general power of attorney; reference number, if any: | 8. ☐ other (<i>specify</i>): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Hari Subramaniam
Patent Agent

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the time limit of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.

7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.

8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/IN2006/00154	For International Preliminary Examining Authority use only	
Applicant's or agent's file reference 558-645-CHL	Date stamp of the IPEA	
Applicant ÇADILA HEALTHCARE LIMITED		
CALCULATION OF PRESCRIBED FEES		
1. Preliminary examination fee	EUR 1530.00	P
2. Handling fee (<i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i>)	EUR 129.00	H
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1659.00	
TOTAL		
MODE OF PAYMENT		
☐ authorization to charge deposit account with the IPEA (see below)	☐ cash	
☐ cheque	☐ revenue stamps	
☐ postal money order	☐ coupons	
☐ bank draft	☐ other (specify):	
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT <i>(This mode of payment may not be available at all IPEAs)</i>		
☐ Authorization to charge the total fees indicated above.	IPEA/ _____	
☐ <i>(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)</i> Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Deposit Account No.: _____	
	Date: _____	
	Name: _____	
	Signature: _____	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence
and Administrative Instructions, Section 601(a))

Date of mailing
(day/month/year)

09-01-2007

Applicant's or agent's file reference

558-645-CHL

IMPORTANT NOTIFICATION

International application No.

PCT/IN2006/000154

International filing date (day/month/year)

04/05/2006

Priority date (day/month/year)

05/05/2005

Applicant

CADILA HEALTHCARE LIMITED et al

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

30/11/2006

2. This date of receipt is:

- ☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- ☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- ☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ **ATTENTION:** That date of receipt is after the expiration of 19 months from the priority date. Consequently, in respect of some Offices, the demand does not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)) and the acts for entry into the national phase must therefore be performed within 20 months from the priority date (or later in some Offices). However, in respect of some other Offices, the time limit of 30 months (or later) may nevertheless apply. See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

- ☐ (If applicable) This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/

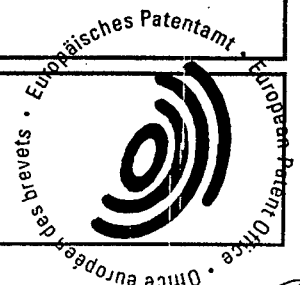


European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

BACHER M

Tel. (+49-89) 2399-8615



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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

SUBRAMANIAM, Hariharan
Subramaniam, Nataraj & Associates
E-556, Greater Kailash II
New Delhi 110 048
INDE

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

Date of mailing (day/month/year)	09-01-2007
-------------------------------------	------------

Applicant's or agent's file reference 558-645-CHL	REPLY DUE See paragraph 1 below
--	------------------------------------

International application No. PCT/IN2006/000154	International filing date (day/month/year) 04/05/2006
--	--

Applicant

CADILA HEALTHCARE LIMITED et al

1. ☐ REPLY DUE within _____, months/days from the above date of mailing
☐ NO REPLY DUE

2. COMMUNICATION:

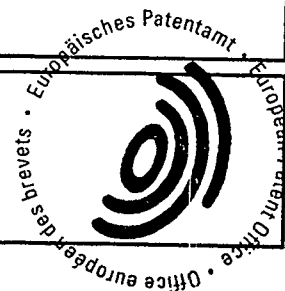
**NOTIFICATION CONCERNING PAYMENT OF
THE PRELIMINARY EXAMINATION AND HANDLING FEE**

The International Preliminary Examining Authority invites the applicant to pay the prescribed fees:
EUR 1595,-- (examination fee) and EUR 129,-- (handling fee).

The handling and examination fee shall be paid within one month form the date on which
the demand was submitted or 22 months form the (earliest) priority date,
whichever expires later (Rule 57.3, Rule 58.1 PCT).

Please note that the Form IPEA/403 is not any longer used because it is not adopted
to the current time limits for the payment of fees.

Name and mailing address of the IPEA/  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	Authorized officer Bacher, Martin ++49 89 2399 8615
---	---



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TRADUCCIÓN OFICIAL No. 02/329 de un documento escrito en inglés, el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Juan Pablo Piedrahita Aguilera, Traductor e Intérprete Oficial debidamente reconocido de conformidad con el Certificado de Idoneidad Profesional No. 0045 expedido por la Universidad Nacional de Colombia.

(Se traducen los sellos sobre un poder otorgado por la compañía CADILA HEALTHCARE LIMITED con fecha Septiembre 21, 2002, escrito en inglés y español, y Legalización No. 516875 Ministerio de Relaciones Exteriores).

(En ingles y español, poder)

(Sello: No. de Serie 313, 2002, (Firma) R. J. BRAHMBHATT, NOTARIO, GOBIERNO DE GUJARAT)

(Sello Notarial a Tinta, Mi Comisión vence 10/07/2007, (Firmado) R.J. BRAHMBHATT, Notario, Gobierno de Gujarat)

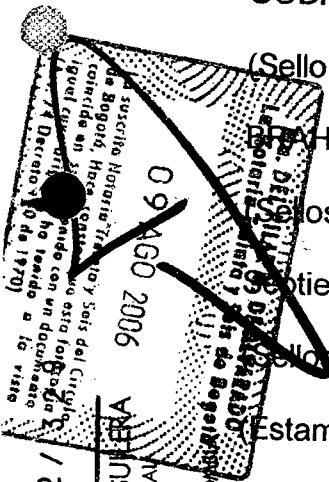
(Sellos a tinta de la Cámara de Comercio e Industria de Nueva Delhi, 26 de Septiembre 2002)

(Sellos a Notariales a tinta del Gobierno de Gujarat, 21 de Septiembre 2002)

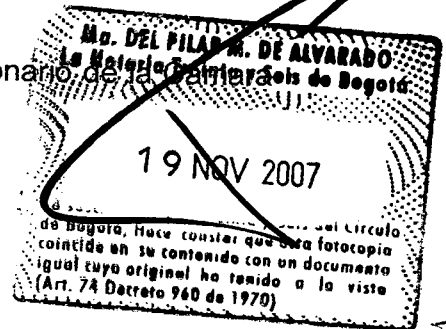
(Estampillas)

(Sello Notarial a Tinta, Ante mi, (Firmado) R.J. BRAHMBHATT, Notario, Gobierno de Gujarat)

Al respaldo: (Sellos a Tinta autenticando la firma del Funcionario de la Embajada de Bogotá)



TRADUCCION OFICIAL No. 02/329
JUAN PABLO PIEDRAHITA AGUILERA
C. IDONEIDAD 045
UNIVERSIDAD NACIONAL DE COLOMBIA



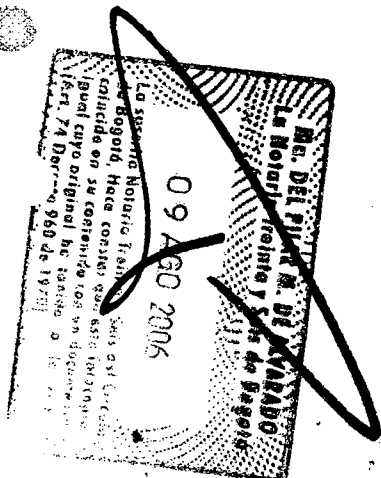
de Comercio, Septiembre 27, 2002)

En Español, legalización de la firma anterior por el Consulado de Colombia en Nueva Delhi, India No. 19/2002 de Octubre 3, 2002. Pagado el Impuesto de Timbre y los Derechos Consulares por US\$ 108.00.

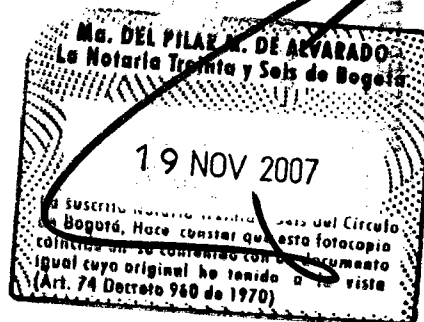
Legalización de la firma del Cónsul por el Jefe de Legalizaciones del Ministerio de Relaciones Exteriores de Colombia No. 516875, con fecha Octubre 17, 2002.

ES TRADUCCIÓN FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito.

Bogotá, Octubre 25 de 2002.



Juan Pablo Piedrahita Aguilera
0 2 3 3 2 9
TRADUCCION OFICIAL No. _____
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
C. IDONEIDAD 045
UNIVERSIDAD NACIONAL DE COLOMBIA



Ma. DEL PILAR M. DE AGUIRRE
La Notaria Treinta y Seis del Bogotá

19 NOV 2007

suscrita Notaria Treinta y Seis del Circulo
de Bogotá. Hace constar que esta fotocopia
coincide en su contenido con el documento
igual cuyo original ha sido a la vista
(Art. 74 Decreto 940 de 1970)

COLOMBIA

Carrera 11 n° 93-43, Of. 404 Bogotá Colombia Tel: (57 1) 6350813-Fax: (57 1) 6350824 Email: clarkemodetclarkemodet.com.co

R. J. BRAHMBHAT
NOTARY
GOVT. OF GUJARAT

PODER

Yo (nosotros), abajo firmante(s)

Arun Madhusudan Parikh

en mi (nuestro) carácter de representante(s) legales de

Cadila Healthcare Limited

una sociedad organizada y existente de acuerdo con las leyes de *India*.

y en actual cumplimiento de su objeto social, con domicilio en *Zydus tower Satellite Road, Ahmedabad, India*
Pin 380015

por el presente instrumento confiero (conferimos) poder especial a favor de DILIA MARIA RODRIGUEZ D'ALEMAN, con Cédula de Ciudadanía No. 41.654.882 de Bogotá, y tp. 20824 y CLAUDIA LUCIA CARO RAMIREZ, con Cédula de Ciudadanía No. 40.017.374 de Tunja, y tp. 36448, con domicilio en Bogotá, Colombia, para que actuando en su orden en nombre del (de la) otorgante le (la) representen ante cualquier entidad, autoridad y/o persona, especialmente ante las del orden Administrativo, Contencioso Administrativo, Judicial, Tribunales de Arbitramento y/o cualquier otro en lo referente a los siguientes asuntos:

- 1) Solicitar, tramitar, obtener y/o registrar cualquiera de las modalidades de Propiedad Industrial, tales como: patentes de invención, modelos de utilidad; diseños industriales, variedades vegetales; marcas, lemas, nombres y enseñanzas comerciales y denominaciones de origen; así como sus renovaciones, prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 2) Solicitar, tramitar, obtener y/o registrar derechos de autor, cualquiera de sus presentaciones así como la protección de secretos industriales y know-how.
- 3) Solicitar, tramitar, obtener y/o registrar registros sanitarios, permisos y/o licencias de funcionamiento; así como sus renovaciones o prórrogas, transferencias, cambios de nombre y/o domicilio, contratos y licencias.
- 4) Ejercer acciones de oposición, observación,

POWER OF ATTORNEY

I (we), the undersigned

ARUN MADHUSUDAN PARIKH

legal representative(s) of

CADILA HEALTHCARE LIMITED

an organization existing under the laws of INDIA

and in present execution of its business activity, domiciled at

ZYDUS TOWER, SATELLITE ROAD, AHMEDABAD, GUJARAT, INDIA.
PIN: 380015

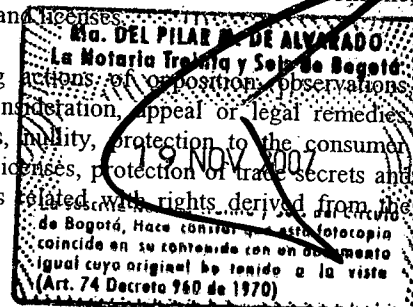
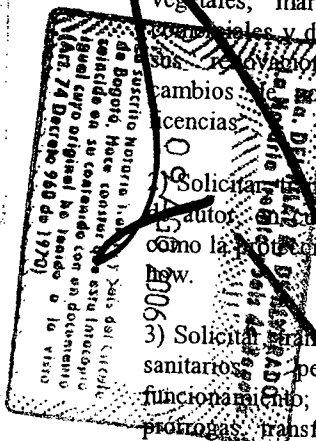
do hereby grant POWER OF ATTORNEY to DILIA MARIA RODRIGUEZ D'ALEMAN, identification card No. 41.654.882 of Bogotá, and tp. 20824 and CLAUDIA LUCIA CARO RAMIREZ, tp. 36448, identification card No. 40.017.374 of Tunja, residing in Bogotá, Colombia, to act in the order of their appointment in behalf of grantor before any entity, authority and/or natural or juridical person, specially before those Administrative, Administrative-Contentious, Judicial, arbitration courts, and/or any other, in all matters concerning the following:

To apply, process, obtain and/or register any of the modalities of Industrial Property, such as: Patents of Invention, Utility Models; Designs, plant varieties; Marks, Slogans, Trade Names and emblems and appellations of Origin; as well as their renewals, extensions, assignments, changes of name and/or domicile, agreements and licenses.

2) To apply, process, obtain and/or register copyrights of any kind as well as protection of industrial secrets or know-how.

3) To apply, process, obtain and/or register sanitary registrations, operating authorizations and/or licenses; as well as their renewals or extensions, assignments, changes of name and/or domicile, agreements and licenses.

4) To bring actions of opposition, observations, claims, reconsideration, appeal or legal remedies, cancellations, nullity, protection of the consumer granting of licenses, protection of trade secrets and other actions related with rights derived from the



02 / 329

TRADUCCION OFICIAL No. 02 / 329
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCCION OFICIAL
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reclamós, reconsideración, reposición, apelación, cancelación administrativa o judicial, nulidad, protección al consumidor, concesión de licencias, protección de secretos industriales y demás acciones y recursos relacionados con derechos derivados de los asuntos arriba indicados y en contra de la competencia desleal, acciones derivadas de la obtención o explotación de licencias, acciones de indemnización de perjuicios. También podrá(n) intervenir en juicios civiles, comerciales, penales, contencioso-administrativos, tutelas y de policía; en acciones o juicios promovidos por el (la) mandante o en contra el (ella).

5) Registrar nombres de dominio ante la entidad competente.

6) En el ejercicio de este mandato los mandatarios arriba mencionados quedan facultados para: conciliar, cancelar, transigir, comprometer en árbitros, desistir, recibir y tomar posesión de la cosa objeto de litigio y renunciar o desistir a derechos concedidos o en curso de concesión, admitir los hechos del proceso.

7) Ratificar o no la agencia oficiosa.

8) Así mismo faculto (facultamos) a los mencionados apoderados para recibir notificaciones y designar apoderados judiciales o extrajudiciales, sustituir el presente poder y revocar las sustituciones que hicieren.

Dado y firmado en

a los 21 días de Sept. 2002

competition, actions resulting from the obtaining or exploitation of licenses, recovering damages actions. They can also intervene or participate in Civil, Commercial, Criminal or Contentious-Administrative Trials; the actions for writ mandamus, police actions; in actions, lawsuits or litigations instituted by the grantor or against him.

5) To register domain names before the competent entity.

6) To the effect of this mandate the above-named proxy are empowered to: conciliate, cancel, settle, submit to arbitration, withdraw and to receive and take possession of the litigation related object and waive or renounce the rights granted or in process of granting, admit the facts of the case.

7) To ratify or not the officious agency.

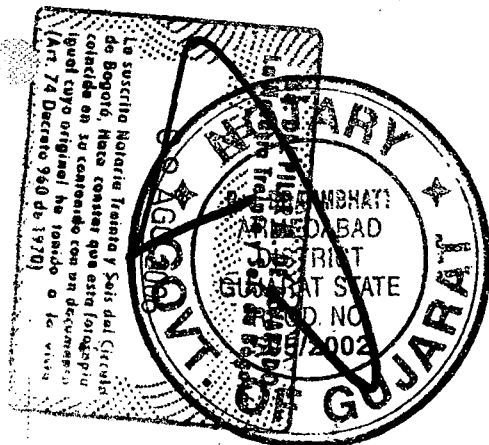
8) I (we) hereby appoint the afore mentioned attorneys with powers to receive notifications and to designate judicial and extra-judicial attorneys, substitute this Power of Attorney and to revoke such substitutions.

Granted and signed at

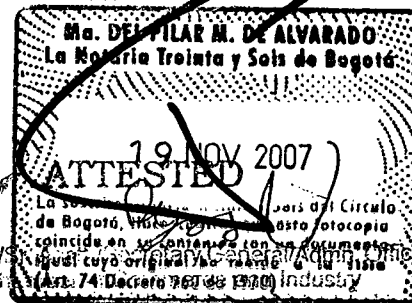
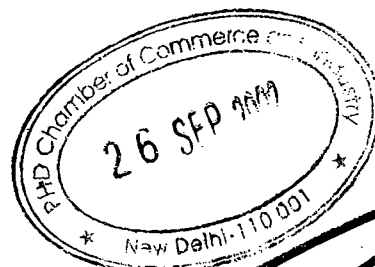
on this 21st day of SEPTEMBER, 2002.

Firma/ Signature

[Handwritten Signature]



BEFORE ME
[Signature]
R.J. BRAHMBHATT
NOTARY
DIST. OF GUJARAT



Addl./Joint/Dy. Notary Public/General Admin. Officer
PHD Chamber of Commerce and Industry
New Delhi

TRADUCCION OFICIAL No. 101329
JUAN PABLO PIEDRAHITA AGUILERA
TRADUCTOR E INTERPRETE OFICIAL
C. IDONEIDAD 045
UNIVERSIDAD NACIONAL DE COLOMBIA

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02329
TRANSMISION OFICIAL No.
JU GUILERA
 OFICIAL
 S
 DE COLOMBIA

09 ABO 2006
La suscrita Notaria Treinta y Seis del Circulo de Bogotá, Hace constar que esta fotocopia coincide en su contenido con el documento original de fecha 7 de Diciembre de 1970.

No. 13927 Fecha 27 SEP 2007
La suscrita Notaria Treinta y Seis del Circulo de Bogotá, Hace constar que esta fotocopia coincide en su contenido con el documento original de fecha 7 de Diciembre de 1970.
The Signature of Assn. Secretary
Equity Secretary / Secretary of Change
19 NOV 2007
La suscrita Notaria Treinta y Seis del Circulo de Bogotá, Hace constar que esta fotocopia coincide en su contenido con el documento original de fecha 7 de Diciembre de 1970.
Section Officer (O.I.)



विदेश मंत्रालय, नई दिल्ली
Ministry of External Affairs
New Delhi



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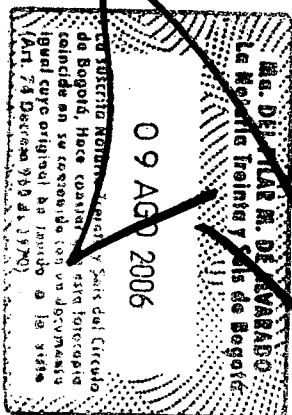
No.19/2002

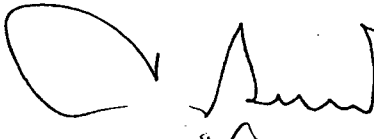
EL SUSCRITO MINISTRO PLENIPOTENCIARIO ENCARGADO DE LAS
FUNCIONES CONSULARES ANTE LA EMBAJADA DE COLOMBIA EN NUEVA
DELHI INDIA,
VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS

CERTIFICA:

QUE EL SEÑOR A.K. GHOSH, FUNCIONARIO CONSULAR DEL
MINISTERIO DE RELACIONES EXTERIORES DE INDIA, QUIEN
AUTENTICO LA FIRMA DEL SEÑOR ARUN MADHUSUDAN PARIKH,
FIRMANTE DEL PRESENTE DOCUMENTO, EJERCIÓ EN LA FECHA
LAS FUNCIONES INDICADAS Y SU FIRMA CORRESPONDE A LA
REGISTRADA EN ESTE CONSULADO; QUE LA COMPAÑIA CADILA
HEALTHCARE LIMITED" ESTA CONSTITUIDA DE ACUERDO CON LAS
LEYES DE LA INDIA Y CUMPLE SU OBJETO CONFORME A LAS
MISMAS. DOMICILIADA EN AHMEDABAD GUJARAT, INDIA; QUE EL
SEÑOR ARUN MADHUSUDAN PARIKH, EN SU CARACTER DE VICE-
PRESIDENTE Y REPRESENTANTE LEGAL DE LA EMPRESA ARRIBA
MENTIONADA, ESTA FACULTADO PARA FIRMAR EL PRESENTE
DOCUMENTO.

DADO EN NUEVA DELHI A LOS TRES (3) DIAS DEL MES DE OCTUBRE
DE DOS MIL DOS (2002).




LUIS GUILLERMO BECERRA
Ministro Plenipotenciario
Cónsul de Colombia



518875
Luis G. Becerra
COTA FIRMA ADECUADA EN EL
DOCUMENTO DESEMPAÑA
LAS FUNCIONES INDICADAS

MINISTERIO DE RELACIONES
EXTERIORES

PAGADO IMPUESTO DE TIMBRE Y
DERECHOS CONSULARES: US \$108.00
(Ciento ocho Dólares Americanos)



2002 OCT 17 A 10:13

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

285



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Act. 411 PRESENTACION Folios: 285

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION []

MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Descripción de la invención []
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Firma Responsable

Fecha _____

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia