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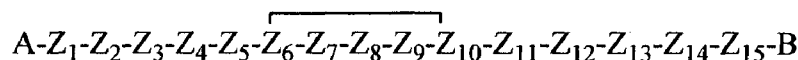— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

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(54) **Title**: CYCLIC SHORT CHAIN PEPTIDES

$$A\text{-}Z_1\text{-}Z_2\text{-}Z_3\text{-}Z_4\text{-}Z_5\text{-}Z_6\text{-}Z_7\text{-}Z_8\text{-}Z_9\text{-}Z_{10}\text{-}Z_{11}\text{-}Z_{12}\text{-}Z_{13}\text{-}Z_{14}\text{-}Z_{15}\text{-}B$$
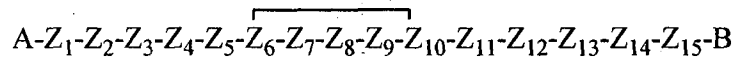
(I)

(57) **Abstract**: The present invention provides novel cyclic short-chain peptideshaving pharmaceutically beneficial properties. The invention also provides a process for preparing such short chain peptides and pharmaceutical compositions containing the cyclic peptides of the present invention. $A\text{-}Z_1\text{-}Z_2\text{-}Z_3\text{-}Z_4\text{-}Z_5\text{-}Z_6\text{-}Z_7\text{-}Z_8\text{-}Z_9\text{-}Z_{10}\text{-}Z_{11}\text{-}Z_{12}\text{-}Z_{13}\text{-}Z_{14}\text{-}Z_{15}\text{-}B$ (I)

CYCLIC SHORT CHAIN PEPTIDES

Field of Invention:

The present invention relates to novel cyclic short chain peptides of general
formula (I) having beneficial pharmacological properties, their pharmaceutically
acceptable salts and pharmaceutical compositions containing them.

$$\overline{A\text{-}Z_1\text{-}Z_2\text{-}Z_3\text{-}Z_4\text{-}Z_5\text{-}Z_6\text{-}Z_7\text{-}Z_8\text{-}Z_9\text{-}Z_{10}\text{-}Z_{11}\text{-}Z_{12}\text{-}Z_{13}\text{-}Z_{14}\text{-}Z_{15}\text{-}B}$$

(I)

The present invention also relates to processes for preparing compounds of
general formula (I), their pharmaceutically acceptable salts and pharmaceutical
compositions containing them.

Background to the invention:

Osteoporosis is a skeletal disorder characterised by diminished bone mass,
decreased bone mineral density (BMD), decreased bone strength and associated with an
increased risk of bone fracture (Lane J. M., et al., Clin. Orthop. Relat. Res., 372, 2000,
139-150). Osteoporotic fractures most often occur in the vertebrae, hips or the femoral
neck. These fractures severely impair the quality of life because of pain, long-lasting
immobility and poor recovery. Bone comprises of several different cell types.
Osteoblast (bone formation) lays down new bone from the mineral present in the
extracellular milieu around the cells. Osteoclasts (bone loss) remove old bones,
releasing the minerals compiled within bone back into the extracellular matrix. The
balance between adequate new bone being deposited and old bone being removed is
what gives bone its extremely beneficial properties. Osteoporosis occurs when the rate
of the bone resorption is greater than the rate of bone formation (Seeman E., et al., N.
Engl. J. Med., 354(21), 2006, 2250-2261). Postmenopausal estrogen deficiency is the
most common cause of osteoporosis in women, as estrogen puts a break on osteoclast
lifespan. Other major risk factors in the development of osteoporosis include: low
calcium intake, vitamin D deficiency, type-1 diabetes, rheumatoid arthritis, long-term
use of medication such as anticonvulsants and corticosteroids and low levels of
testosterone in men (Cole Z. A., et al., Curr. Rheumatol. Rep., 10(2), 2008, 92-96;
Harvey, N., et al., Curr. Rheumatol. Rep., 5(1), 2003, 75-81).

Patients with osteoporosis would benefit from new therapies designed to promote fracture repair or from therapies designed to prevent or lessen the fractures associated with the disease (Lindsay R., Lancet, 341(8848), 1993, 801-805). At present, there is no effective cure for osteoporosis, though estrogen, raloxifene (oestrogen receptor modulators), calcitonin and the bisphosphonates (etidronate, alendronate and risedronate) are used to treat the disease with varying levels of success through their action to decrease bone resorption (Recker R. R., J. Clin. Endocrinol. Metab. 1993, 76(1), 14-16).

Native human Parathyroid Hormone (PTH) is an 84 amino acids polypeptide that acts as the most important regulator of calcium homeostasis in the human body through its direct action on bone and kidneys (Kronenberg H. M., Bringhurst F. R., Nussbaum S. R., Jüppner H., Abou-Samra A. B., In Handbook of Experimental Pharmacology, Mundy, G. R., and Martin, T. J., (eds), pp. 185-201, Springer-Verlag, Heidelberg (1993)). PTH synthesis and release from the parathyroid glands are controlled principally by the serum calcium level; a low level stimulates and a high level suppresses both hormone synthesis and release. PTH in-turn, maintains the serum calcium level by directly or indirectly promoting calcium entry into the blood. PTH contributes to net gastrointestinal absorption of calcium by favouring the renal synthesis of the active form of vitamin D. PTH promotes calcium reabsorption from bone, indirectly by stimulating differentiation of the osteoclasts (bone-resorbing cells). Administration of PTH via parenteral route efficiently increases bone mineral density (BMD), bone strength and reduces the incidence of new osteoporotic fractures in osteoporotic patients (Greenspan S. L., et al., Ann. Intern. Med., 146(5), 2007, 326-339; Neer R. M., et al., N. Engl. J. Med., 344, 2001, 1434-1441).

PTH exerts all these effects primarily through its interaction with a cell surface PTH receptor, which is expressed in numerous tissues, most abundantly in kidney, bone and growth plate chondrocytes (Lanske B., et al., Crit. Rev. Eukaryot. Gene Expr., 8, 1998, 297-320). The PTH receptor is homologous in primary structure to a number of other receptors that bind peptide hormones, such as secretin, calcitonin and glucagon; together, these receptors form a distinct family called G-protein coupled receptors (GPCR/ GPCRs) family B (Kolakowski L. F., Receptor Channels, 2, 1994, 1-7). The GPCR comprise an extracellular N-terminal domain of 100-160 residues, connected to a juxtamembrane domain (J-domain) of seven membrane-spanning α-helices with intervening loops and a C-terminal tail (Donnelly D., FEBS Letts., 409, 1997, 431-

436). The Class B GPCRs are activated by endogenous peptide ligands of intermediate
size, typically 30-40 amino acids (Hoare, S. R. J., Drug Discovery Today, 10, 2005,
423-427). A general mechanism of peptide ligand interaction with class B GPCRs has
emerged and is termed as the 'two-domain' model. The C-terminal portion of the
5   peptide binds the N-domain of the receptor, confirm binding of ligand with the receptor
and the N-terminal ligand region binds the J-domain, an interaction that activates the
receptor and stimulates intracellular signalling (Ji T. H., et al., J. Biol. Chem., 273,
1988, 17299-17302; Hjorth, S. A., et al., Regulatory Peptides, 64, 1996, 70).

PTH binds to the PTH receptor with affinity in the nM range; the ligand-
10   occupied receptor transmits a signal across the cell membrane to intracellular effector
enzymes through a mechanism that involves intermediary heterotrimeric GTP-binding
proteins (G proteins). The primary intracellular effector enzyme activated by the PTH
receptor in response to PTH peptide is adenylyl cyclase (AC) (Goltzman D., J. Bone
Miner. Res., 15(3), 2000, 605-608). Thus PTH induces increase in the second
15   messenger, cyclic adenosine monophosphate (cAMP) which regulates the poorly
characterized downstream cellular processes involved in bone remolding (Juppner H.,
et al., Science, 254, 1991, 1024-1026). Other signalling pathways of this receptor, such
as elevation of intracellular calcium, phospholipase C-dependent and independent
activation of protein kinase C, have been described. Since PTH regulates blood calcium
20   and the phosphate levels and exhibit potent anabolic (bone-forming) effects, the
parathyroid hormone and its derivatives represent potential therapeutic agent for the
treatment of osteoporosis (Slovik D. M., et al., J. Bone Miner. Res., 1, 1986, 377-381;
Dempster D. W., et al., Endocr. Rev., 14, 1993, 690-709).

Synthetic PTH (1-34) exhibits full bioactivity in most cell-based assay systems,
25   has potent anabolic effects on bone mass in animals and has recently been shown to
reduce the risk of bone fracture in postmenopausal osteoporotic women. In human trials
on postmenopausal women, daily subcutaneous injections of low doses of PTH (1-34)
were shown to result in impressive bone formation in the spine and femoral neck with
significant reduction in incidence of vertebral fractures (Neer R. M., et al., N. Engl. J.
30   Med., 344, 2001, 1434-1441; Dempster D. W., et al., Endocr. Rev., 14, 1993, 690-709).
These clinical data reveal PTH as one of the most efficacious agents tested for
osteoporosis. Under the brand name Forteo (Eli Lilly), PTH (1-34) in the form of
teriparatide acetate has been approved for the treatment of osteoporosis.

PTH derivatives include polypeptides that have amino acid substitutions or are truncated relative to the full-length molecule. Both the N and C-terminal truncated forms of PTH (1-34) has been studied. Additionally, amino acid substitutions within the truncated polypeptides have also been investigated. (Azurani A., et al., J. Biol. Chem.,

5   271, 1996, 14931-14936). It has been known that residues in the 15-34 domain of PTH peptide contribute importantly to receptor binding affinity, while N-terminal 1-14 amino acids of PTH peptide are responsible for the activation of receptor (Naussbaum S. R., et al., J. Biol. Chem., 255, 1980, 10183-10187; Gardella T. J., et al., Endocrinology, 132, 1993, 2024-2030; Takasu H., et al., Biochemistry, 38, 1999,

10   13453-13460; Hoare S. R. J., et al., J. Biol. Chem., 276, 2001, 7741-7753; Luck M. D., et al., Molecular Endocrinology, 13, 1999, 670-680). Truncated PTH (1-34) derivatives such as cyclised PTH (1-17), PTH (1-28), PTH (1-31) and PTH (1-11) are active in most assay systems and promote bone-formation (Whitfield J. F., et al., J. Bone Miner. Res., 12, 1997, 1246-1252; WO 2007 / 130113 A2; WO 2008 / 068487; Whitefild J. F.,

15   et al., Calcif. Tissue Int., 56, 1995, 227-231; Rixon R. H., et al., J. Bone Miner. Res., 9, 1994, 1179-1189; Whitfield J. F., et al., Trends Pharmacol. Sci., 16, 1995, 372-386; Whitfield J. F., et al., Calcif. Tissue Int., 58, 1996, 81-87); Andrea C., et al., J.M.C., 53, 2010, 8072-8079. But these peptides are still too large for efficient non-parenteral delivery. The discovery of an even smaller and metabolically stable PTH agonist would

20   be an important advance in the effort to develop new treatments for osteoporosis.

Unfortunately, due to the large molecular weight of PTH peptide, its therapeutic application has been limited, since its synthesis is technically difficult and therefore expensive and the only possible administration mode is the injection route. Moreover, PTH is highly susceptible to protease attack and must be stored at low temperature due

25   to its low stability. In addition to these technical limitations, tolerability is limited by transient mobilization of calcium and hypercalcemia also the toxicological data and in particular the unfavourable results of cancerogenesis studies (dose and treatment duration dependent increased risk of osteosarcoma) induce a cautious use of PTH (1-34) (Vahle J. L., Toxicol. Pathos., 32(4), 2004, 426-438; Whitfiel J. F., Medscape

30   Womens Health, 6(5), 2001, 7; Kuijpers G., BMJ, 324(7335), 2002, 435-436). On the other hand, low molecular weight peptides, for instance those consisting of the first 14 or 11 amino acids of PTH (PTH (1-14) and PTH (1-11)), proved to be inactive or exhibited very low biological activity, in animal models (Tregear G. W., et al.,

Endocrinology, 93, 1973, 1349-1353; Gardella T. J., et al., J. Biol. Chem., 266, 1991, 13141-13146).

    Therefore, during last decade, investigation has focused on development of PTH-derived low molecular weight peptides with improved biological profile, preferably orally bioavailable, protease resistant, easy to synthesis and exhibit a greater safety index. Recently, it was found that the activity of low molecular weight peptides can be improved by introducing helix stablising unnatural amino acids at specific positions. For example, PTH(1-11) analogs ([Ala_3, Gln_{10}, Arg_{11}]-PTH(1-11), [Ala_3, Gln_{10}, Har_{11}]-PTH(1-11) and [$Aib_{1,3}$; Gln_{10}; Har_{11}]-PTH(1-11)) and PTH (1-14) analogs, such as [AC_5C_1, Aib_3, Gln_{10}, Har_{11}, Ala_{12}, Trp_{14}]PTH(1-14) stimulate cAMP, in nM range (WO 03/009804; WO 04/093902). Several studies were carried out to find low molecular weight peptides with PTH-like activity (Reidhaar-olson J. F., et al., Mol. Cell. Endocrinology., 160, 2000, 135-147; Shimizu M., et al., J. Biol. Chem., 275, 2000, 21836-21843; Shimizu M., et al., Endocrinology, 142, 2001, 3068-3074; Shimizu N., et al., J. Biol. Chem., 276, 2001, 49003-49012; WO 03/009804). Although short chain peptide analogues consisting of 11 amino acids (derivatives of first 1-11 residues of PTH peptide, Seq. ID. No.2) can activate the PTH receptor (in vitro) with low potency (WO 04/067021), however, in animal models (in vivo) bone-anabolic activity of these analogues has not been reported. In conclusion, agonistic activity on cAMP-signalling pathway of the PTH receptor (in vitro) alone is not at all predictive for bone-anabolic activity in vivo.

    To enhance the duration of action and stability against proteolytic enzyme, in the present investigation, we have site-specifically cyclised the side chains of Z_6 and Z_{10} of these short-chain peptides ($A-Z_1-Z_2-Z_3-Z_4-Z_5-Z_6-Z_7-Z_8-Z_9-Z_{10}-Z_{11}-Z_{12}-Z_{13}-Z_{14}-Z_{15}-B$) either with diester or lactam bridge and surprisingly, succeeded in identifying highly metabolically stable and potent cyclic short chain peptides, having PTH-1 receptor agonistic activity. Due to increased metabolic stability, most of these cyclic peptides showed improved oral bioavailability, while retaining PTH-1 receptor agonistic activities.

PTH (1-34) sequences alignment shown below represents the primary structural relationships:

PTH (1-34): ^{1}**SVSEIQLMHNLGKH**^{14}**LNSMERVEWLRKKLQDVHNF**^{34} (Seq. ID No: 1).

PTH (1-14): ^{1}**SVSEIQLMHNLGKH**^{14} (Seq. ID No: 2)

PTH (1-15): ^{1}SVSEIQLMHNLGKHL^{15} (Seq. ID No: 3)

Single-letter abbreviations for amino acids can be found in Zubay, G., Biochemistry 2nd ed., 1988, MacMillan Publishing, New York, p. 33.

Prior art

5   A series of conformationally constrained parathyroid hormone peptide (PTH) analogs and derivatives, have been reported with general formula Xaa1-Xaa14 and / or Xaa1-Xaa15, wherein Xaa1-Xaa14 and / or Xaa1-Xaa15 represent the first 1-14 and / or 1-15 N-terminal residues of PTH peptide (SVSEIQLMHNLGKH; Seq. ID No. 2 and SVSEIQLMHNLGKHL; Seq. ID No. 3), with some analogs wherein Xaa1 and Xaa3

10   represent either Aib or AC$_5$C, Xaa8 represent Nle; Xaa10 represent S & E, Xaa11 represent Har, Xaa12 represent Ala and Xaa14 represent W (WO 03 / 009804 A2; US 2006 / 7153951 B2; US 2007 / 0117157 A1; US 2007 / 0203071 A1; US 2006 / 0019902 A1; US 2007 / 0161569 A1; US 2007 / 0111946 A1; Gardella T. J., et al., J. Biol. Chem. 2000, 275, 21836-21843; Gardella T. J., et al., Endocrinology, 2001, 142,

15   3068-3074; Gardella T. J., et al., J. Biol. Chem., 2001, 52, 49003-49012). Earlier, Caporale et al., reported in vitro PTH1r agonistic activity of novel cyclic analogue of PTH fragment (11 amino acid cyclic peptides), containing lactam or diester bridge (J. Med. Chem., 2010, 53, 8072-8079). Recently, some non-peptide PTH agonist are also reported in literature but none of them were found to have potential in *in-vivo* animal

20   models (US 2007 / 0099940 A1; WO 2005 / 077918 A1)

       Recently, we found that homologous substitution of N-terminal sequence of PTH (1-34) peptide (first 1-14 or 1-15 residues) with unnatural amino acids resulted in the identification of novel class of short-chain peptides (A-Z_1-Z_2-Z_3-Z_4-Z_5-Z_6-Z_7-Z_8-Z_9-Z_{10}-Z_{11}-Z_{12}-Z_{13}-Z_{14}-Z_{15}-B) having potent PTH-1 receptor agonistic activity, with

25   varying degree of selectivity and most of the short-chain peptides showed bioavailability even by oral route of administration, while retaining PTH-1 receptor agonistic activities (WO2010/128521).
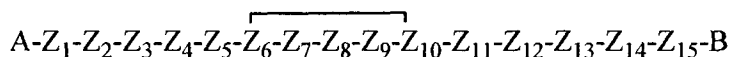
Summary of the invention

       The present invention describes a group of novel cyclic short chain peptides that

30   function as agonist of the PTH receptor, having different degree of affinity towards the PTH / PTH-1 receptor and useful for the treatment of osteoporosis. These cyclic peptides are defined by the general formula (I) as given below. The cyclic peptides of the present invention are useful for the treatment or prevention of hypoparathyroidism

and diseases characterized by bone mass reduction or bone loss, such as osteoporosis, postmenopausal osteoporosis and for stimulating bone repair.

The present invention provides novel cyclic peptides of formula (I), which primarily act as a PTH/ PTH-1 receptor agonist. These cyclic peptides exhibit increased

5   metabolic stability against proteolytic enzymes. Most of these cyclic peptides were found to be stable in rat plasma upto 24 hours (*in vitro*), showed increased stability against GIT enzymes such as pepsin and acidic stomach pH and also against liver microsomes (*in vitro*). Due to increased metabolic stability, other than parenteral route of administration, most of these cyclic peptides can also be delivered by oral route of

10 administration.

Preferred embodiments

A preferred embodiment of the present invention is to provide novel cyclic peptides of general formula (I), novel intermediates involved in their synthesis, their pharmaceutically acceptable salts and pharmaceutical compositions containing them or

15 their mixtures, suitable for the treatment/mitigation/regulation of bone disorders.

$$\overline{A\text{-}Z_1\text{-}Z_2\text{-}Z_3\text{-}Z_4\text{-}Z_5\text{-}Z_6\text{-}Z_7\text{-}Z_8\text{-}Z_9\text{-}Z_{10}\text{-}Z_{11}\text{-}Z_{12}\text{-}Z_{13}\text{-}Z_{14}\text{-}Z_{15}\text{-}B}$$

(I)

In a further preferred embodiment, is provided pharmaceutical compositions containing cyclic peptides of general formula (I), their pharmaceutically acceptable

20 salts, solvates and their mixtures having pharmaceutically acceptable carriers, solvents, diluents, excipients and other components normally employed in their manufacture.

In a still further preferred embodiment is provided the use of the novel cyclic peptides of the present invention as agents for stimulating new bone formation and treating and / or preventing osteoporosis and related bone disorders, by administering a

25 therapeutically effective and non-toxic amount of the cyclic peptides of formula (I), or their pharmaceutically acceptable compositions to the mammals those are in need of such treatment.

Abbreviations used

The following abbreviations are employed in the examples and elsewhere

30 herein:

Aib = α-Amino-isobutyric acid,

Ala= Alanine,

αMe-APPA= 2-amino-2-methyl-5-phenylpentanoic acid,

7

αMe-Bip(OMe)= alpha-methylated Bip(OMe),

αMe-Pro= alpha-methyl-Proline,

αMe-Phe = alpha-methyl-phenylalanine,

αMe-2F-Phe = alpha-methyl-2-fluorophenylalanine,

5   αMe-2,6-F-Phe = alpha-methyl-2,6-diflurophenylalanine,

αMe-Trp = alpha-methyl-Tryptophan,

αMe-Tyr = alpha-methyl-Tyrosine,

αMe-Val = alpha-methyl-Valine,

AC_5C= 1-amino-cyclopentanecarboxylic acid,

10   ACN = Acetonitrile,

APPA = 2-amino-5-phenylpentanoic acid,

Arg= Arginine,

Asp= Aspartate,

Asn= Asparagine,

15   Boc = tert-Butoxycarbonyl,

Bip(OMe)= 2'-ethyl-4'-methoxy-biphenylalanine,

Bu^t= O-tert-butyl group,

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

Cit = Citrulline,

20   DCM = Dichloromethane,

DMF = N,N-Dimethylformamide,

DIPCDI= Di-isopropylcarbodiimide,

DIPEA= Diisopropylethylamine,

Et = Ethyl,

25   Et_2O = Diethyl ether,

Fmoc = Fluorenylmethoxycarbonyl,

2F-Phe = 2-fluorophenylalanine,

g = Gram (s),

Gly= Glycine,

30   Glu= Glutamate,

Gln= Glutamine,

Ile= Isoleucine,

h = Hour (s),

His= Histidine,

Har = Homoarginine,

HoSer = Homoserine,

HOBt = 1-Hydroxybenzotriazole,

5   HOAt= 7-Aza-hydroxybenzotriazole,

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,

10   Lys= Lysine,

Me = Methyl,

Met= Methionine,

Min = minute (s),

mL = milliliter,

15   μl = microliter,

mg = milligram (s),

mmol = millimole (s),

MS= Mass Spectrometry,

Nle = Norleucine,

20   Orn = Ornithine,

po: per-oral administration,

Phe= Phenylalanine,

PTH= Parathyroid Hormone,

PTH-1r agonist = Parathyroid Hormone receptor agonist,

25   PyBOP = Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate,

Pyr= Pyroglutamic acid,

Pro= Proline,

sc= Subcutaneous route of administration,

SPPS = Solid Phase Peptide Synthesis,

30   TMS = Trimethylsilyl,

TIPS = Triisopropylsilane,

TFA = Trifluoroacetic acid,

TBTU= 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate,

Trt= Trityl group,

Trp= Tryptophan,

Tyr= Tyrosine,

Val= Valine,

WR= Wistar Rats.

Brief description of the drawings

Figure 1: Examples of orthogonally protected amino acids used in Fmoc based-solid phase peptide synthesis (SPPS) of short-chain peptides.

Figure 2: *In vitro* DRC and EC_{50} determination of PTH(1-34) **(Figure A)** and **Seq. ID No. 133 (Figure B)**, in Rat PTH-1 R assay (agonistic activity, measured by amount of cAMP released).
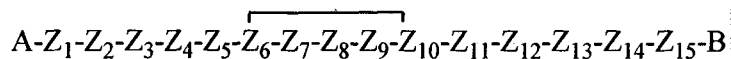
Figure 3: *In vivo* DRC study with **Seq. ID No. 168 (Figure A:** % increase in serum Ca^{2+} levels; **Figure B:** % decrease in serum PO_4 levels), in OVX Female Rat.

Figure 4: Changes in biochemical parameters and femur weight, in OVX Rat after 6 weeks treatment with **Seq. ID No. 247** and **PTH(1-34).**

Detailed description of the invention

In accordance with the present invention, synthetic cyclic short chain peptides having the structural formula (I), which showed PTH-1 receptor agonistic activity, are disclosed. These cyclic short chain peptides exhibit increased metabolic stability to proteolytic cleavage, as most of cyclic peptides were found to be stable in rat plasma upto 24 hours (*in vitro*), showed increased stability against GIT enzymes such as pepsin and acidic stomach pH and also against liver microsomes (*in vitro*). Due to increased metabolic stability, some of these cyclic peptides can also be delivered by oral routes of administration, for the treatment / prevention of hypoparathyroidism and diseases characterized by bone mass reduction, such as osteoporosis, postmenopausal osteoporosis and for stimulating bone repair.

The present invention thus discloses novel cyclic short chain peptides as PTH receptor agonist having the following structure (I).

$$\text{A-}Z_1\text{-}Z_2\text{-}Z_3\text{-}Z_4\text{-}Z_5\text{-}\overline{Z_6\text{-}Z_7\text{-}Z_8\text{-}Z_9\text{-}Z_{10}\text{-}Z_{11}\text{-}Z_{12}\text{-}Z_{13}}\text{-}Z_{14}\text{-}Z_{15}\text{-B}$$

(I)

wherein,

'A' represents the groups $-NH-R_1$ or $R_3-CO-NH-$ wherein R_1 represents hydrogen or optionally substituted linear (C_{1-18}) alkyl chain, or suitable amino acids preferably

selected from pyroglutamic acid (Pyr), Pro (P), alpha-methyl-Proline (αMe-P), Val (V), alpha-methyl-Valine (αMe-V); R_3 is selected from optionally substituted linear (C_{1-18}) alkyl chain, (C_{1-6})alkoxy, (C_3-C_6) cycloalkyl, aryl, heteroaryl or arylalkyl groups;

5   In a preferred embodiment, the aryl group is selected from phenyl, napthyl, indanyl or biphenyl, groups; the heteroaryl group is selected from pyridyl, thienyl, furyl, imidazolyl, benzofuranyl groups; the arylalkyl groups represent groups wherein the aryl group is attached to an alkyl groups as defined elsewhere in the specification.

'B' represents –$COOR_2$, -$CONHR_2$ or CH_2OR_2, wherein R_2 represents H or suitable
10   amino acids. Preferred amino acids may be selected from the group comprising of Val (V), alpha-methyl-Valine (αMe-V), and the like;
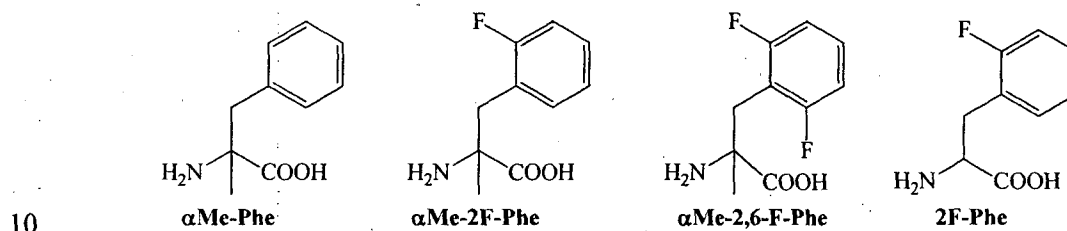
          Each of Z_1, Z_3 & Z_{12} may be same or different and independently represents a naturally or unnaturally occurring amino acids selected from the group comprising of Ser (S), Val (V), Pro (P), alpha-methyl-Proline (αMe-P), Gly (G), Ala (A), α-amino-
15   isobutyric acid (Aib), 1-amino cyclopropane carboxylic acid (AC_3C), 1-amino-cyclopentanecarboxylic acid (AC_5C), 1-amino-cyclohexanecarboxylic acid (AC_6C); preferably, each of Z_1, Z_3 & Z_{12} represents amino acid selected from Ala (A), α-amino-isobutyric acid (Aib), 1-amino cyclopropane carboxylic acid (AC_3C) or 1-amino-cyclopentanecarboxylic acid (AC_5C);

20   Z_2 represents either a Val (V) or alpha-methyl-valine (αMe-V);

Z_4 represents a naturally or unnaturally occurring amino acids selected from the group comprising of Glu(E), Asp(D).

          Each of Z_6 & Z_{10}, may be same or different and independently represents a naturally or unnaturally occurring amino acid selected from the group comprising of
25   Ser (S), Homoserine (HoSer), Lys (K), Orn (Ornithine), Glu (E), Homoglutamic acid (HoGlu), Asp (D); wherein, the side chains of Z_6 and Z_{10} having acidic or basic group such as Lys (K), Glu (E) or Asp (D) lead to the formation of lactam bridge or the side chain of Z_6 and Z_{10} having alcohol group such as Ser (S) or Homoserine (HoSer) are cross-linked as a diester bridge, with dicarboxylic acids, such as succinic acid, glutaric
30   acid, adipic acid, pimelic acid, suberic acid, azelaic acid or sebacic acid; preferably each of Z_6 & Z_{10} represents amino acid selected from Ser (S), Lys (K), Glu (E) or Asp (D);

Each of Z_5, Z_7 & Z_9 may be same or different and independently represents a naturally or unnaturally occurring amino acid selected from the group comprising of Leu (L), Ile (I), Nle (Norleucine), HoLeu (Homoleucine), His (H), Phe (F), alpha-methyl-phenylalanine (αMe-Phe-), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-

5   ), alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-) or 2-fluorophenylalanine (2F-Phe-); preferably amino acid selected from Ile (I), Nle (Norleucine), His (H), Phe(F), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-) or alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-);

10

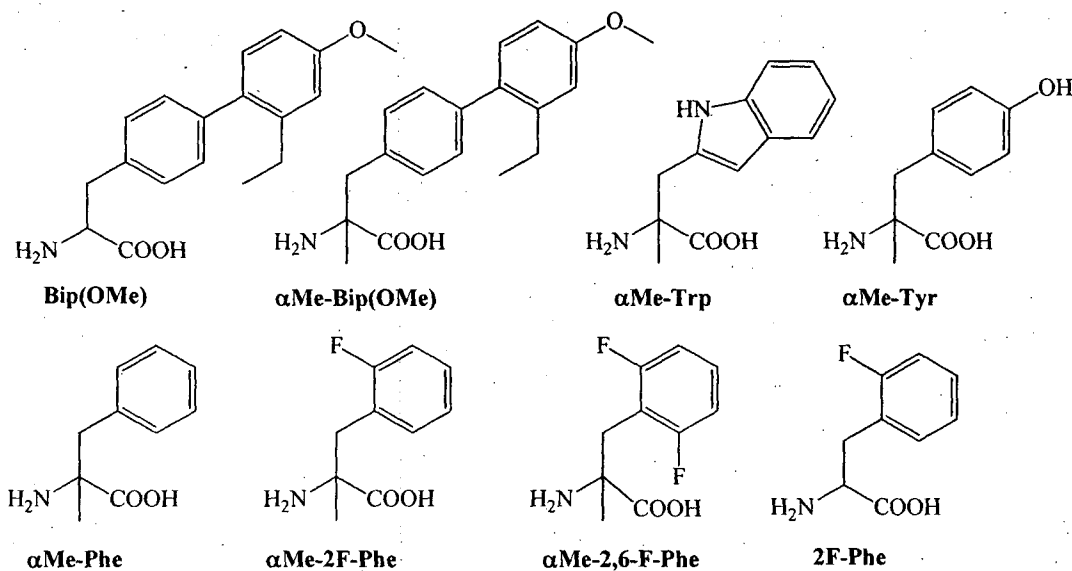αMe-Phe αMe-2F-Phe αMe-2,6-F-Phe   2F-Phe

Z_8 represents a naturally or unnaturally occurring amino acid selected from the group comprising of Met, alpha-methyl-Valine (αMe-V), Leu, Nle, HoLeu, Val; preferably Z_8 represents amino acid selected from Met, Leu or Val;
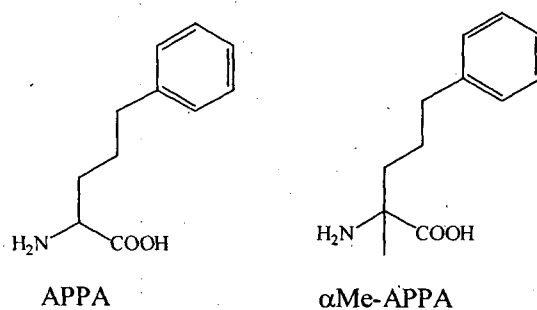
Z_{11} & Z_{13} may be same or different and independently represents a naturally or

15   unnaturally occurring amino acid selected from the group comprising of Lysine (K), Arginine (R), Homoarginine (Har), Ornithine (Orn), Citrulline (Cit), Phenyl alanine (F), alpha-methyl-phenylalanine (αMe-Phe-), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-) or alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-) or 2-fluorophenylalanine (2F-Phe-); preferably, each of Z_{11} & Z_{13} represents amino acid

20   selected from Lysine (K), Arginine (R), Homoarginine (Har) or Citrulline (Cit);

Z_{14} may be present or absent. Z_{14} when present represents a naturally or unnaturally occurring amino acid selected from the group comprising of 2'-ethyl-4'-methoxy-biphenylalanine (Bip(OMe)), α-methylated Bip(OMe) [αMe-Bip(OMe)], alpha-methyl-tryptophan (αMe-Trp), alpha-methyl-tyrosine (αMe-Tyr), Tryptophan

25   (W), Tyrosine (Y), D-Tryptophan (dW), D-Tyrosine (dY), alpha-methyl-phenylalanine (αMe-Phe-), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-), alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-) or 2-fluorophenylalanine (2F-Phe-); preferably Z_{14} represents amino acid selected from Tryptophan (W), Tyrosine (Y), D-Tryptophan

12

(*d*W), D-Tyrosine (*d*Y), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-), or alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-);

Bip(OMe)   αMe-Bip(OMe)   αMe-Trp   αMe-Tyr

αMe-Phe   αMe-2F-Phe   αMe-2,6-F-Phe   2F-Phe

Z_{15} may be present or absent. Z_{15} when present represents a naturally or unnaturally occurring amino acid selected from the group comprising of 2-amino-5-phenylpentanoic acid (APPA) or 2-amino-2-methyl-5-phenylpentanoic acid (αMe-APPA);

APPA   αMe-APPA

The term 'natural amino acids' indicates all those twenty amino acids, which are present in nature.

The term 'unnatural amino acids' or 'non-natural amino acids' preferably represents either replacement of L-amino acids with corresponding D-amino acids such as replacement of L-Ala with D-Ala 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 Met with α-methyl Met;

- substitution on the side chain of amino acid such as substitution of aromatic amino acid side chain with halogen, (C_1-C_3) alkyl, aryl groups, more specifically the replacement of Phe with halo Phe;

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

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

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.

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 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.

While the invention has been primarily exemplified in relation to cyclic peptides, it will also be understood that the peptide linkage between the residues may be replaced by a non-peptide bond provided that the ability to mimic PTH agonist activity is retained. The person skilled in the art will be aware of such suitable modifications, such as α-methylation, N-methylation of amide bonds and the like.

Sequences encompassing conservative substitutions of amino acids are also within the scope of the invention, provided that the biological activity is retained.

It is to be clearly understood that the compounds of the invention include peptide amides and non-amides and peptide analogues, including but not limited to the following:

a) Compounds in which one or more amino acids is replaced by its corresponding D-amino acid. The skilled person will be aware that retro-inverso amino acid sequences can be synthesised by standard methods; see for example, Chorev M., Acc. Chem. Res., 26, 1993, 266-273;

b) Peptidomimetic compounds, in which the peptide bond is replaced by a structure more resistant to metabolic degradation. See for example, Olson G. L., et al., J. Med. Chem., 36(21), 1993, 3039-3049 and

c) Compounds in which individual amino acids are replaced by analogous structures

5   for example Ala with Aib; Met with αMe-Met.

In general, the use of such alternative structures can provide significantly longer half-life in the body, since they are more resistant to breakdown under physiological conditions or to improve bioavailability.

Throughout the description the conventional one-letter and three-letter code for

10   natural amino acids are used as well as generally acceptable three-letter codes for other unnatural amino acids such as Har (homoarginine), Nle (norleucine), α-amino isobutanoic acid (Aib) are used.

The term 'PTH receptor modulator or agonist' refers to a compound that acts at the PTH-1 and/or PTH-2 receptor to alter its ability to regulate downstream signaling

15   events, such as cAMP production. Example of receptor modulators includes agonist, partial agonist, inverse agonist and allosteric potentiators.

In accordance with the present invention, the synthetic isolated cyclic peptides described herein primarily acts as PTH receptor agonists. These synthetic cyclic peptides exhibit desirable *in vitro* PTH receptor agonist activity in UMR-106 cells, in

20   the range of 1-1000 nM concentration. PTH receptor agonistic activity is assessed by estimation of amount of cAMP released by the test compounds. Some of the cyclic peptides prepared showed increase in BMD and / or bone strength, when tested *in vivo*, in OVX rat model, thus making them ideal therapeutic candidates for the treatment and prevention of osteoporosis. These new classes of cyclic peptides can be administered

25   by oral or other non-invasive routes or parenteral routes of administration.

The present invention provides cyclic short chain peptides of formula (I) pharmaceutical compositions employing such cyclic short chain peptides either alone or in combination and for methods of using such cyclic peptides. In particular, the present invention provides a pharmaceutical composition comprising a therapeutically effective

30   amount of cyclic peptides 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 osteoporosis, especially primary osteoporosis, endocrine osteoporosis, postmenopausal osteoporosis, hereditary and congentinal forms

of osteoporosis, wherein, therapeutically effective amount of cyclic peptides of formula (I) or their combination(s) can be administered to a mammal, example, human and a patient in need of treatment.

Preparation of the cyclic short chain peptides:

5   Several synthetic routes can be employed to prepare the cyclic short chain peptides of the present invention. The cyclic peptides 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,

10   but not limited to those described below.

The cyclic short chain peptides thereof described herein may be produced by chemical synthesis using suitable variations of both the solution-phase (preferably, using Boc-chemistry; as generally described in M. Bodansky, A. Bodansky, "The practice of peptide synthesis", Springer-Verlag, Berlim, 1984; E. Gross, J. Meinhofer, "The

15   peptide synthesis, analysis, biology", Vol. 1, Academic Press, London, 1979) and or solid-phase techniques, such as those described generally 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

20   synthesis" 2nd Ed., Pierce chemical Co., Rockford, Il, 1984.

The preferred strategy for preparing the cyclic peptides of this invention is based on the use of Fmoc-based SPPS approach, wherein Fmoc (9-fluorenylmethoxycarbonyl) group is used for temporary protection of the α-amino group, in combination with the acid labile protecting groups, such as tert-

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

30   1987).

The cyclic short chain peptides 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 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

5   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.

10   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

15   peptide sequence is assembled (Scheme 1). 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

20   utilizes commercially available cross-linked polystyrene polymer resins (Novabiochem, San Diego, CA). Preferred for use in this invention is 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

25   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 10-20 %

30   piperidine solution. After every coupling and deprotection, excess of amino acids and coupling reagents were removed by washing with 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 protection; 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   The synthesis of the cyclic peptides described herein can be carried out by using batchwise or continuous flow peptide synthesis apparatus, such as CS-Bio or AAPPTEC peptide synthesizer, utilizing the Fmoc/trityl protection strategy. 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, Fmoc-

10   protected non-natural amino acid was prepared in solution, using appropriate literature procedures. For example, the Fmoc-protected APPA analogs, described above, were prepared from L-pyroglutamic acid, in good enantiomeric purity, using modified literature procedure (Betsbrugge J.V., et al., Tetrahedron, 54, 1988, 1753-1762).

The Fmoc-protected α-methylated amino acids were prepared using asymmetric

15   Strecker synthesis (Boesten, W.H.J., et al., Org. Lett., 3(8), 2001, 1121-1124; Cativiela C., Diaz-de-villegas M. D., Tetrahedran Asymmetry, 9, 1988, 3517-3599). 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 building.

20   Side chain cyclization of linear peptide was carried out by selective deprotection of side chain protecting group of Z_6 and Z_{10} residues. After the side chain deprotection, the diester bridge formation was carried out using dicarboxylic acid, HBTU, HOAt, and collidine, while lactam bridge was prepared by treating the peptide resin, with solution of HBTU, HOBt, and DIPEA (Andrea C., et al., JMC., 53, 2010,
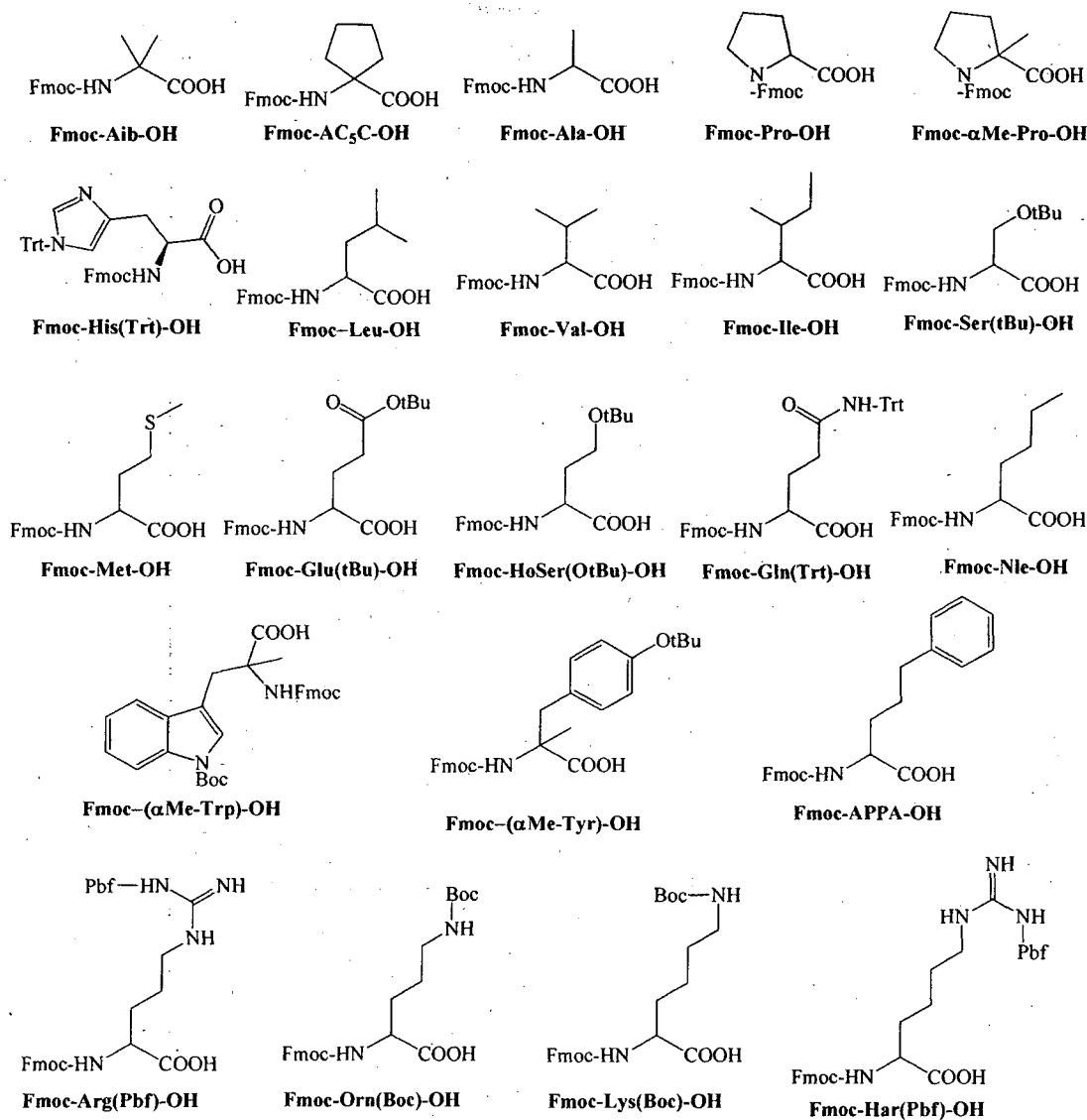
25   8072-79).

Fmoc-HN—COOH
Fmoc-Aib-OH

Fmoc-HN—COOH
Fmoc-AC₅C-OH

Fmoc-HN—COOH
Fmoc-Ala-OH

COOH
N-Fmoc
Fmoc-Pro-OH

COOH
N-Fmoc
Fmoc-αMe-Pro-OH

Trt-N, FmocHN, OH
Fmoc-His(Trt)-OH

Fmoc-HN—COOH
Fmoc-Leu-OH

Fmoc-HN—COOH
Fmoc-Val-OH

Fmoc-HN—COOH
Fmoc-Ile-OH

OtBu
Fmoc-HN—COOH
Fmoc-Ser(tBu)-OH

Fmoc-HN—COOH
Fmoc-Met-OH

O, OtBu
Fmoc-HN—COOH
Fmoc-Glu(tBu)-OH

OtBu
Fmoc-HN—COOH
Fmoc-HoSer(OtBu)-OH

O, NH-Trt
Fmoc-HN—COOH
Fmoc-Gln(Trt)-OH

Fmoc-HN—COOH
Fmoc-Nle-OH

COOH, NHFmoc, N-Boc
Fmoc-(αMe-Trp)-OH

OtBu
Fmoc-HN—COOH
Fmoc-(αMe-Tyr)-OH

Fmoc-HN—COOH
Fmoc-APPA-OH

Pbf—HN, NH, NH
Fmoc-HN—COOH
Fmoc-Arg(Pbf)-OH

Boc, NH
Fmoc-HN—COOH
Fmoc-Orn(Boc)-OH

Boc—NH
Fmoc-HN—COOH
Fmoc-Lys(Boc)-OH

NH, HN, NH, Pbf
Fmoc-HN—COOH
Fmoc-Har(Pbf)-OH

Figure 1: Examples of some of the protected amino acids used in Fmoc based-solid phase peptide synthesis (SPPS) of short-chain peptides.

The peptide-resin precursors for their respective cyclic peptides may be cleaved and deprotected using suitable variations of any of the standard cleavage procedures described in the literature (King D.S., et al., Int. J. Peptide Protein Res., 1990, 36, 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, the peptidyl-resin was incubated in TFA / Water /TIPS (95:2.5:2.5) for 1.5 - 4 hrs at room temperature. The cleaved resin is then filtered off and the TFA solution is concentrated or dried under reduced pressure. The resulting crude peptide is either precipitated or washed with Et₂O
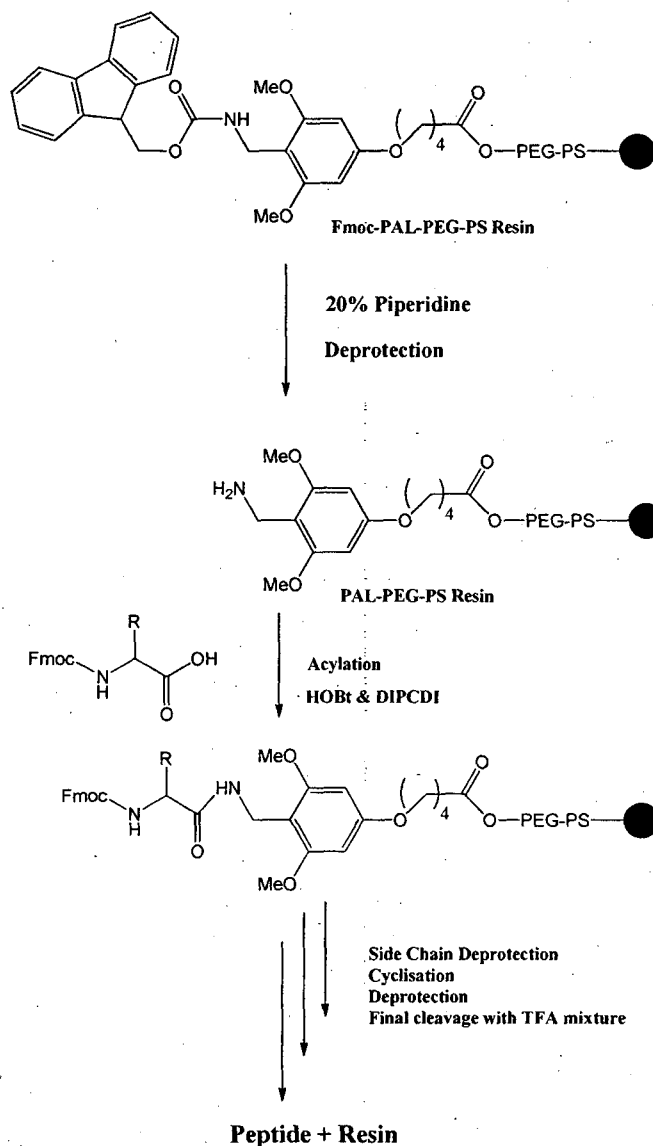
or is re-dissolved directly into DMF or 50 % aqueous acetic acid for purification by preparative HPLC.

The cyclic short chain peptides 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 10µ; C_{18}; 100 A°), 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 40 mL /min with effluent monitoring by PDA detector at 220 nm. The structures of the purified cyclic peptides 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 buffer. 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 µm) 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 cyclic short chain peptides of the present invention were prepared.

Scheme 1: General Scheme for Fmoc-Based SPPS

General method of preparation of cyclic short chain peptides, using SPPS approach:

Assembly of short chain peptides on resin:

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 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. 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 (1-3 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.

5   After the coupling of first amino acid, the resin was washed with DMF, DCM and Diethyl ether. 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,

10   coupling and washing were performed until the desired peptide chain was assembled on resin, as per general **Scheme 1** above.

Side chain cyclization of linear peptide was carried out by selective deprotection of side chain protecting group of Z_6 and Z_{10} residues. After the side chain deprotection, the diester bridge formation was carried out using dicarboxylic acid (1-2

15   eq.), HBTU (4-6 eq.), HOAt (4-6 eq.), and collidine (6-8 eq.), while lactam bridge was prepared by treating the peptide resin, with solution of HBTU (4-6 eq.), HOBt (4-6 eq.), and DIPEA (8-10 eq.). 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. Resin containing desired

20   peptide was dried under nitrogen pressure for 10-15 minutes and subjected for cleavage/ deprotection.

Representative example of automated solid phase synthesis of peptide sequence ID. No. 185:

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe)

25   The   Cyclic   short-chain   peptide,

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe)   was   assembled   on   an automated CS-Bio 536 PepSynthesiser™ using Fmoc solid phase peptide synthesis (SPPS) approach (**Scheme 2**). The Fmoc amino acids and the 2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate (TBTU) were packed together in vials

30   and positioned in the amino acid module of the synthesizer.

A stock solution of diisopropylethylamine (DIPEA; 0.9 M) and DMF were stored in reagent bottles, under dry nitrogen atmosphere. The resin, Fmoc-PAL-PEG-PS (0.38 mmol/g; 1g) was dried over P_2O_5, *in vacuo* (1 hr) and swollen in freshly

distilled DMF (5 mL). The swollen resin was slurry packed into a glass column and positioned in the synthesizer. All the synthetic cycles were carried out at a flow rate of 5 mL min^{-1}, **Table 1**. The resin was washed with freshly distilled DMF for 10 minutes. Deprotection of Fmoc group was performed with 20% piperidine in DMF for 10 minutes and the deprotection was monitored by UV detection of the column effluent at 304 nm.

Table 1. Automated cycles for solid phase peptide synthesis

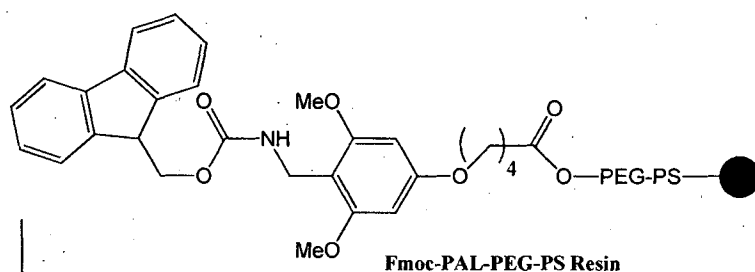| Step	Function	Reagent/ Solvent	Number of cycles	Time (Minute)
1	Wash	Dimethylformamide (DMF)	1	10
2	Deprotection	20 % piperidine in DMF	2	15
3	Wash	DMF	3	15
4	Acylation	Amino acid; TBTU and diisopropylethylamine (in DMF)	Recycle	120
5	Wash	Dimethylformamide	4	10

Excess piperidine was removed by three auxiliary wash cycles and a distilled DMF wash cycle, with each cycle of 15 minutes. The amino group was treated with Fmoc-amino acid (4 equivalent), preactivated with TBTU (3.9 equivalent) in the presence of DIPEA (8 equivalent) and recycled for 120 minutes. The excess amino acid and soluble by-products were removed from column and loop by four auxiliary wash cycles and distilled DMF wash cycles, with each cycle of 10 minutes. Furthermore, synthetic cycles (deprotection, wash, acylation and wash) were repeated for complete assembly of linear peptide. Side chain cyclization of linear peptide was carried out by

selective deprotection of side chain protecting group of Z_6 and Z_{10} residues. After the side chain deprotection, the diester bridge formation was carried out using dicarboxylic acid (1-2 eq.), HBTU (4-6 eq.), HOAt (4-6 eq.), and collidine (6-8 eq.), while lactam bridge was prepared by treating the peptide resin, with solution of HBTU (4-6 eq.),

5   HOBt (4-6 eq.), and DIPEA (8-10 eq.).

Final deprotection cycle was performed with 20% piperidine in DMF for 15 minutes to remove the terminal Fmoc group, followed by wash cycle (10 X 4 minutes). Completed peptide-resin was filtered through sintered glass filter, washed three times successively with DMF, DCM, methanol, DMF and diethyl ether (100 mL each).

10 Peptide-resin was dried *in vacuo* over P_2O_5 (2 hr) and stored at -20 °C.

Fmoc-PAL-PEG-PS Resin

1) Piperidine (Fmoc deprotection)
2) Fmoc-αMe-2F-Phe-OH (4 eq.); DMF; TBTU (3.9 eq.); DIPEA (8 eq); 2 h
3) Washing with DMF and DCM
4) Repeat step 1-3, with follwoing amino acids:
Fmoc-Cit-OH
Fmoc-Ala-OH
Fmoc-Har(Pbf)-OH
Fmoc-Glu(allyl)-OH
Fmoc-His(Trt)-OH
Fmoc-Nle-OH
Fmoc-αMe-2F-Phe-OH
Fmoc-Lys(alloc)-OH
Fmoc-Ile-OH
Fmoc-Glu(OtBu)-OH
Fmoc-Aib-OH
Fmoc-Val-OH
Fmoc-Aib-OH
5) Pd(PPh₃)₄ (0.3 eq.); PhSiH₃ (24 eq.); DCM (side chain deprotection)
6) HBTU (5 eq.); HOBt (5 eq.); DIPEA (10 eq.); DMF; 3h (cyclisation)
7) Piperidine (Fmoc deprotection)
8) TFA cleavage
9) RP-HPLC purification

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe)

(Seq. ID. No.185)

Scheme 2: SPPS of Seq. ID. No. 185

Ninhydrin resin test was carried out to check the *N*-terminal free amino group of resin bound peptide. Appearance of blue-purple colouration of the solution and the resin beads indicates the presence of free amino group on resin bound peptide and was considered to be a positive test.

5   Small-scale cleavage was carried out to assess the purity of resin bound peptide. The dried Peptide-resin (ca 10-mg) was treated with mixture (1 mL) of TFA, water, triisopropylsilane (95: 2.5: 2.5 v/v), for 90 minutes at room temperature with gentle occasional swirling. The resin was filtered, washed thoroughly with neat TFA (1 mL) and the entire filtrate was evaporated under reduced pressure. Residual TFA was

10   azeotroped three times with diethyl ether (2 mL). Residue obtained was suspended in distilled water (2 mL) and the aqueous layer was extracted three times with diethyl ether (3 mL). The aqueous layer was separated and freeze-dried to yield the crude peptide Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe).

The lyophilised peptide Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe)

15   was dissolved in 0.1% aqueous TFA (ca 1mg /1 mL) and its purity was analyzed by analytical RP-HPLC and characterized by electrospray ionisation mass spectrometry (ESI-MS). Percent purity: 90 % (crude peptide). ESI-MS; Calcd. For

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe);

1774 (M^+), 1796 $(M+Na^+)$ and 1812 $(M+K^+)$; Found (m/z): 1774 (M^+), 1796 $(M+Na^+)$

20   and 1812 $(M+K^+)$.

Using above protocol and suitable variations thereof which are within the scope of a person skilled in the art, the cyclic short-chain peptides designed in the present invention were prepared, using Fmoc-SPPS approach. Furthermore, resin bound cyclic short-chain peptides were cleaved and deprotected, purified and characterized using

25   following protocol.

Cleavage and deprotection:

The desired cyclic short-chain peptides 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-

30   resin) was added to peptidyl-resins and the mixture was kept at room temperature with occasional starring. 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 cyclic short-chain peptides:

5   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 10μ; C_{18}; 100 A^0), 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

10   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 cyclic short-chain peptides were obtained as amorphous white powders by lyophilisation of respective HPLC fractions.

HPLC analysis of the purified cyclic short-chain peptides

15   After purification by preparative HPLC as described above, each peptide was analyzed by analytical RP-HPLC on a Shimadzu LC-10AD analytical HPLC system. For analytical HPLC analysis of cyclic short-chain peptides, Luna 5μ; C_{18}; 100 A°, 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

20   PDA detector.

Characterization by Mass Spectrometry

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-SCIES, Canada) was used in all analyses in positive

25   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 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.

30   Utilizing the synthetic methods described herein along with other commonly known techniques and suitable variations thereof, the following novel cyclic short chain peptides were prepared. This list is indicative of the various groups of cyclic short chain peptides, which can be prepared according to the present invention, and are

expected to at least include obvious variations of these cyclic short chain peptides. However, such disclosure should not be construed as limiting the scope of the invention in any way. In **Table 2 (i-xvi)**, novel cyclic short chain peptides of present invention are listed along with their corresponding Seq. ID. No.

Table 2 (i): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
4	Aib-V-Aib-EISLMHS-Har-AK-(αMe-Phe)	1723 (98.60%)
5	Aib-V-Aib-EISL-Nle-HS-Har-AK-(αMe-Phe)	
6	Aib-V-Aib-EISLMHS-Har-Aib-K-(αMe-Phe)	
7	Aib-V-Aib-EISL-Nle-HS-Har-Aib-K-(αMe-Phe)	1763 (97.13%)
8	Aib-V-(AC₅C)-EISLMHS-Har-Aib-K-(αMe-Phe)	
9	Aib-V-(AC₅C)-EISL-Nle-HS-Har-Aib-K-(αMe-Phe)	1789 (98.22%)
10	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-Phe)	
11	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-Phe)	1814 (96.10%)
12	Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-Phe)	
13	Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-Phe)	1840 (97.78%)
14	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-Phe)	
15	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-Phe)	

Table 2 (ii): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
16	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-2F-Phe)	1818 (99.02%)
17	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-2F-Phe)	
18	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-2F-Phe)	1844 (95.67%)
19	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-2F-Phe)	
20	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2F-Phe)	1836 (98.06%)
21	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2F-Phe)	
22	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2F-Phe)	1870 (98.89%)
23	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2F-Phe)	

Table 2 (iii): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
24	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe)	1836 (96.34%)
25	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe)	
26	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe)	1870 (94.33%)
27	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe)	
28	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe)	1854 (98.78%)

29	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe)	
30	Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe)	1888 (99.12%)
31	Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe)	
32	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe)	
33	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe)	

Table 2 (iv): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
34	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)	1847 (97.10%)
35	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)	
36	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)	1873 (98.78%)
37	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)	
38	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)	
39	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)	
40	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)	1899 (98.08%)
41	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)	
42	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)	
43	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)	
44	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)	1899 (98.36%)

45	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)	
46	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)	1883 (97.66%)
47	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)	
48	(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)	
49	(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)	

Table 2 (v): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
50	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Aib-(αMe-2F-Phe)	1775 (96.88%)
51	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2F-Phe)	
52	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Aib-(αMe-2F-Phe)	1801 (98.11%)
53	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2F-Phe)	
54	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe)	
55	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe)	
56	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe)	1819 (99.22%)
57	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe)	
58	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe)	
59	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe)	
60	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe)	1837 (97.15%)

61	Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe)	
62	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe)	1837 (98.18%)
63	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe)	

Table 2 (vi): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
64	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)-(APPA)	2022 (96.78%)
65	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)-(APPA)	
66	Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)-(APPA)	2048 (96.44%)
67	Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)-(APPA)	
68	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)-(APPA)	2048 (98.08%)
69	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)-(APPA)	
70	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)-(APPA)	2064 (95.65%)
71	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)-(APPA)	
72	Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)-(APPA)	2110 (95.78%)
73	Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)-(APPA)	
74	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)-(APPA)	2110 (96.03%)
75	(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)-(APPA)	

5   **Table 2 (vii): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.**

Seq.	Sequence of cyclic peptide	Mass

ID No.		(%Purity)
76	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe)	1860 (97.43%)
77	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe)	1886 (96.79%)
78	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe)	
79	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe)	
80	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe)	1878 (98.70%)
81	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe)	
82	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe)	1904 (95.38%)
83	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe)	
84	(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe)	1904 (99.05%)
85	(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe)	
86	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe)	
87	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-2,6-F-Phe)	
88	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe)	
89	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2,6-F-Phe)	1896 (97.07%)
90	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe)	
91	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2,6-F-Phe)	1922 (98.09%)
92	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe)	
93	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-H-S-Har-A-Har-(αMe-2,6-F-Phe)	
94	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe)	

| 95 | (AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2,6-F-Phe) | |
| 96 | (AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe) | |

Table 2 (viii): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
97	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-dY	
98	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-dY	1830 (96.89%)
99	Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-dY	
100	Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-dY	1856 (98.77%)
101	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-dY	
102	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-dY	
103	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-dY	
104	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-dY	1856 (99.06%)
105	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-dY	
106	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-dY	1849 (97.10%)
107	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-dY	
108	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-dY	1875 (98.65%)
109	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-dY	
110	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-dY	

| 111 | (AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-dY | |
| 112 | (AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-dY | 1875 (98.21%) |

Table 2 (ix): List of cyclic peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
113	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-W	1839 (97.78%)
114	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-W	1853 (96.69%)
115	Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-W	
116	Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-W	1879 (98.88%)
117	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-W	
118	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-W	1905 (99.12%)
119	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-W	
120	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-W	
121	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-W	
122	Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-W	1872 (95.34%)
123	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-W	
124	Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-W	1898 (97.70%)
125	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HSHar-A-Har-W	
126	(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-W	

127	(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-W	
128	(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-W	1898 (96.62%)

Table 2 (x): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
129	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AR-(αMe-2F-Phe)	1818 (96.75%)
130	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-R-(αMe-2F-Phe)	1832 (98.20%)
131	Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-AR-(αMe-2F-Phe)	
132	Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-R-(αMe-2F-Phe)	1858 (97.48%)
133	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AR-(αMe-2F-Phe)	
134	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-R-(αMe-2F-Phe)	
135	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-dK-(αMe-2F-Phe)	
136	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-dK-(αMe-2F-Phe)	1804 (98.78%)
137	Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-dK-(αMe-2F-Phe)	
138	Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-dK-(αMe-2F-Phe)	1830 (97.09%)
139	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-dK-(αMe-2F-Phe)	
140	(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-dK-(αMe-2F-Phe)	1830 (99.21%)

5   **Table 2 (xi): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.**

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
141	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Trp)	1853 (98.63%)
142	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp)	1867 (98.12%)
143	Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Trp)	
144	Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp)	1893 (96.89%)
145	(AC₅C)-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Trp)	
146	(AC₅C)-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp)	
147	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Trp)	
148	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp)	1893 (97.78%)
149	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Tyr)	
150	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Tyr)	1844 (96.33%)
151	Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Tyr)	
152	Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Tyr)	1870 (97.90%)
153	(AC₅C)-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Tyr)	
154	(AC₅C)-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Tyr)	
155	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Tyr)	1870 (98.03%)
156	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Tyr)	

Table 2 (xii): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
157	Aib-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer( )-Har-A-Cit-(αMe-2F-Phe)	1847 (96.89%)
158	Aib-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2F-Phe)	1861 (98.77%)
159	(AC₅C)-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2F-Phe)	
160	(AC₅C)-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2F-Phe)	1887 (97.88%)
161	Aib-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2F-Phe)	
162	Aib-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2F-Phe)	
163	(AC₅C)-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2F-Phe)	1887 (99.32%)
164	(AC₅C)-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2F-Phe)	
165	Aib-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe)	
166	Aib-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe)	1880 (97.46%)
167	(AC₅C)-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe)	
168	(AC₅C)-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe)	1906 (99.05%)
169	Aib-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe)	1899 (97.78%)
170	Aib-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe)	
171	Aib-V-(AC₅C)-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe)	1925 (96.56%)
172	Aib-V-(AC₅C)-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe)	
173	(AC₅C)-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe)	1925 (98.98%)

| 174 | (AC₅C)-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe) | |

Table 2 (xiii): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
175	Aib-V-Aib-EIS-(αMe-2F-Phe)-MHS-Har-Aib-Har-(αMe-Bip(OMe))-(APPA)	2159 (99.04%)
176	Aib-V-Aib-EIS-(αMe-2F-phe)-Nle-HS-Har-Aib-Har-(αMe-Bip(OMe))-(APPA)	2141 (97.44%)
177	Aib-V-Aib-EIS-(αMe-2F-Phe)-MHS-Har-Aib-Har-(Bip(OMe))-(αMe-APPA)	
178	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(Bip(OMe))-(αMe-APPA)	2141 (98.43%)
179	Aib-V-Aib-EIS-(αMe-2F-Phe)-MHS-Har-Aib-Har-(αMe-Trp)-(APPA)	
180	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp)-(APPA)	
181	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har	1653 (97.15%)
182	Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har	
183	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har	
184	(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har	1693 (95.78%)

Table 2 (xiv): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
185	Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe)	1774 (98.03%)

186	Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe)	1788 (97.87%)
187	Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe)	
188	Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe)	1814 (96.89%)
189	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe)	
190	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe)	1814 (98.78%)
191	Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har-(αMe-2F-Phe)	
192	Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har-(αMe-2F-Phe)	1801 (99.22%)
193	Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har-(αMe-2F-Phe)	
194	Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har-(αMe-2F-Phe)	1827 (95.68%)
195	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har-(αMe-2F-Phe)	
196	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har-(αMe-2F-Phe)	1827 (98.72%)
197	Aib-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-A-Cit-(αMe-2F-Phe)	
198	Aib-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Cit-(αMe-2F-Phe)	1806 (97.09%)
199	Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-MHE-Har-A-Cit-(αMe-2F-Phe)	
200	Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Cit-(αMe-2F-Phe)	1832 (98.78%)
201	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-A-Cit-(αMe-2F-Phe)	
202	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Cit-(αMe-2F-Phe)	1832 (97.12%)
203	Aib-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-A-Har-(αMe-2F-Phe)	
204	Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-ME-Har-Aib-Har-(αMe-2F-Phe)	

205	Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-MHE-Har-A-Har-(αMe-2F-Phe)	1827 (98.23%)
206	Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Har-(αMe-2F-Phe)	
207	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-A-Har-(αMe-2F-Phe)	
208	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Har-(αMe-2F-Phe)	

Table 2 (xv): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
209	Aib-V-Aib-EIK-L-Nle-H-E-Har-A-Cit-(αMe-2F-Phe)	
210	Aib-V-Aib-EIK-L-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe)	1722 (99.54%)
211	Aib-V-(AC₅C)-EIK-L-Nle-HE-Har-A-Cit-(αMe-2F-Phe)	
212	Aib-V-(AC₅C)-EIK-L-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe)	1748 (97.89%)
213	(AC₅C)-V-Aib-EIK-L-Nle-HE-Har-A-Cit-(αMe-2F-Phe)	
214	(AC₅C)-V-Aib-EIKL-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe)	1748 (98.64%)
215	Aib-V-Aib-EIKL-Nle-HE-Har-A-Har-(αMe-2F-Phe)	
216	Aib-V-Aib-EIKL-Nle-HE-Har-Aib-Har-(αMe-2F-Phe)	
217	Aib-V-(AC₅C)-EIKL-Nle-HE-Har-A-Har-(αMe-2F-Phe)	1735 (96.89%)
218	Aib-V-(AC₅C)-EIKL-Nle-HE-Har-Aib-Har-(αMe-2F-Phe)	
219	(AC₅C)-V-Aib-EIKL-Nle-HE-Har-A-Har-(αMe-2F-Phe)	
220	(AC₅C)-V-Aib-EIKL-Nle-HE-Har-Aib-Har-(αMe-2F-Phe)	1735 (98.67%)
221	Aib-V-Aib-EIKLMHE-Har-A-Cit-(αMe-2F-Phe)	

222	Aib-V-Aib-EIKLMHE-Har-Aib-Cit-(αMe-2F-Phe)	1740 (95.75%)
223	Aib-V-(AC5C)-EIKLMHE-Har-A-Cit-(αMe-2F-Phe)	
224	Aib-V-(AC5C)-EIKLMHE-Har-Aib-Cit-(αMe-2F-Phe)	1756 (97.88%)
225	(AC5C)-V-Aib-EIKLMHE-Har-A-Cit-(αMe-2F-Phe)	
226	(AC5C)-V-Aib-EIKLMHE-Har-Aib-Cit-(αMe-2F-Phe)	1756 (99.11%)
227	Aib-V-Aib-EIKLMHE-Har-A-Har-(αMe-2F-Phe)	
228	Aib-V-Aib-EIKLMHE-Har-Aib-Har-(αMe-2F-Phe)	
229	Aib-V-(AC5C)-EIKLMHE-Har-A-Har-(αMe-2F-Phe)	
230	Aib-V-(AC5C)-EIKLMHE-Har-Aib-Har-(αMe-2F-Phe)	1779 (97.71%)
231	(AC5C)-V-Aib-EIKLMHE-Har-A-Har-(αMe-2F-Phe)	
232	(AC5C)-V-Aib-EIKLMHE-Har-Aib-Har-(αMe-2F-Phe)	1779 (98.76%)

Table 2 (xvi): List of cyclic short chain peptides prepared including mass & % purity for several of the peptides prepared.

Seq. ID No.	Sequence of cyclic peptide	Mass (%Purity)
233	Aib-V-Aib-EIKL-Nle-HD-Har-A-Cit-(αMe-2F-Phe)	
234	Aib-V-Aib-EIKL-Nle-HD-Har-Aib-Cit-(αMe-2F-Phe)	1708 (98.86%)
235	Aib-V-(AC5C)-EIKL-Nle-HD-Har-A-Cit-(αMe-2F-Phe)	
236	Aib-V-(AC5C)-EIKL-Nle-HD-Har-Aib-Cit-(αMe-2F-Phe)	
237	(AC5C)-V-Aib-EIKL-Nle-HD-Har-A-Cit-(αMe-2F-Phe)	1734 (97.57%)
238	(AC5C)-V-Aib-EIKL-Nle-HD-Har-Aib-Cit-(αMe-2F-Phe)	

239	Aib-V-Aib-EIKL-Nle-HD-Har-A-Har-(αMe-2F-Phe)	
240	Aib-V-Aib-EIK-L-Nle-HD-Har-Aib-Har-(αMe-2F-Phe)	1721 (99.69%)
241	Aib-V-(AC₅C)-EIKL-Nle-HD-Har-A-Har-(αMe-2F-Phe)	
242	Aib-V-(AC₅C)-EIKL-Nle-HD-Har-Aib-Har-(αMe-2F-Phe)	1747 (96.69%)
243	(AC₅C)-V-Aib-EIKL-Nle-HD-Har-A-Har-(αMe-2F-Phe)	
244	(AC₅C)-V-Aib-EIKL-Nle-HD-Har-Aib-Har-(αMe-2F-Phe)	1747 (98.89%)
245	Aib-V-Aib-EIKLMHD-Har-A-Cit-(αMe-2F-Phe)	
246	Aib-V-Aib-EIKLMHD-Har-Aib-Cit-(αMe-2F-Phe)	1726 (99.43%)
247	Aib-V-(AC₅C)-EIKLMHD-Har-A-Cit-(αMe-2F-Phe)	
248	Aib-V-(AC₅C)-EIKLMHD-Har-Aib-Cit-(αMe-2F-Phe)	1752 (99.78%)
249	(AC₅C)-V-Aib-EIKLMHD-Har-A-Cit-(αMe-2F-Phe)	
250	(AC₅C)-V-Aib-EIKLMHD-Har-Aib-Cit-(αMe-2F-Phe)	1752 (95.56%)
251	Aib-V-Aib-EIKLMHD-Har-A-Har-(αMe-2F-Phe)	
252	Aib-V-Aib-EIKLMHD-Har-Aib-Har-(αMe-2F-Phe)	
253	Aib-V-(AC₅C)-EIKLMHD-Har-A-Har-(αMe-2F-Phe)	
254	Aib-V-(AC₅C)-EIKLMHD-Har-Aib-Har-(αMe-2F-Phe)	
255	(AC₅C)-V-Aib-EIKLMHD-Har-A-Har-(αMe-2F-Phe)	
256	(AC₅C)-V-Aib-EIKLMHD-Har-Aib-Har-(αMe-2F-Phe)	1765 (98.80%)
257	Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har	
258	Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har	1622 (97.78%)
259	(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har	

260	(AC$_5$C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har	1648 (98.76%)

***In vitro* and *in vivo* studies of novel cyclic short-chain peptides:**

The cyclic short-chain peptides prepared as described above were tested for

a) *In vitro* Rat PTH-1 R agonistic activity (Cyclic AMP determination, in UMR-106

5   cells);

b) Stability of peptides in human plasma, simulated gastric fluid, intestinal fluid and liver microsomes (ex-vivo); and

c) *In vivo* anti-osteoporosis activity testing in OVX rat model.

a) *In vitro* Rat PTH-1 R agonist activity (Cyclic AMP determination, in UMR-106

10 **cells):**

The PTHR is a GPCR and the PTHR agonist binds to it and through signal transduction causes activation of adenylate cyclase and raises intracellular cAMP levels. To monitor agonistic activity of new compounds, UMR-106 rat osteosarcoma cells (Source ATCC) endogenously expresses rat PTHR, especially, PTH-1R was

15 treated with various concentration of test compounds and amount of cAMP released were determined.

UMR-106 cells were cultured in DMEM nutrition media (Sigma) containing 10% Fetal Bovine Serum (FBS) and 1X Penstrep. Cultured cells were plated at a density of 5 x 10^4 cells per well in DMEM media supplemented with 10% FBS, in 96-

20 well tissue culture plates and grown for 2 days before the efficacy assays. On the day of assay, the growth medium was carefully removed by suction and cells were washed once with 200 µl of PBS, incubated in 90 µl reaction media (plain DMEM media, low glucose, 0.1% BSA (Sigma) and 1 mM 3-isobutyl-1-methylxanthine (Sigma), at 37 °C for 30 min and then treated with 10 µl of test compounds (concentrations 1, 10 and 100

25 nM) in 90 µl of reaction media and incubated at room temperature for 30 min. The medium was aspirated, 60 µl of lysis buffer, enzyme donor (ED) substrate reagent and cAMP-antibody reagent was added and plates were incubated at room temperature for 1h. Further, enzyme acceptor (EA) reagent (40 µl) was added and luminescence was read after incubation for 2 h at room temperature in Top Count L-Max Luminometer

30 (each well reading for 20 sec). From cAMP standard curve, the amount of released cAMP was determined. Data is calculated as percent of control (Vehicle: water) and

expressed as Mean ± SD. The *in-vitro* PTH-1 receptor agonistic activities of representative peptides are listed in **Table 3**. The data was analysed by non-linear regression curve fit (Sigmoidal dose) to determine the EC_{50} of the selected test compounds (Carter P. H., et al., PNAS, 2007, 104(16), 6846-6851; Merritt B. S., J.
5   Cellular Physiology, 2005, 152(3), 520-528; Reid I. R., Am. J. Physiol. Endocrinol. Metab., 253, 1987, E45-E50).

Table 3: *In vitro* PTH-1 R agonistic activity of selected test compd, amount of cAMP released with respect to control

Compounds	1nM	10 nM	100 nM
PTH (1-34)	41±0.12	96±0.09	101±0.08
Seq. ID. 8	16±0.06	56±0.21	73±0.05
Seq. ID. 10	18±0.01	65±0.01	84±0.23
Seq. ID. 14	28±0.11	52±0.17	69±0.21
Seq. ID. 22	40±0.14	101±0.22	121±0.10
Seq. ID. 29	26±0.02	68±0.46	81±0.38
Seq. ID. 35	57±0.19	101±0.07	126±0.14
Seq. ID. 51	35±0.09	88±0.23	116±0.04
Seq. ID. 60	46±0.11	99±0.20	112±0.03
Seq. ID. 77	15±0.31	48±0.16	66±0.15
Seq. ID. 85	33±0.11	74±0.14	99±0.01
Seq. ID. 98	24±0.12	51±0.15	70±0.28
Seq. ID. 105	18±0.11	42±0.09	60±0.06
Seq. ID. 117	31±0.020	72±0.17	100±0.11
Seq. ID. 132	38±0.14	92±0.14	119±0.11
Seq. ID. 144	39±0.11	104±0.29	120±0.16
Seq. ID. 161	46±0.02	97±0.01	115±0.11
Seq. ID. 177	34±0.04	83±0.16	104±0.12
Seq. ID. 185	21±0.03	73±0.01	94±0.3
Seq. ID. 189	42±0.01	101±0.21	109±0.03
Seq. ID. 202	13±0.04	39±0.16	72±0.02

Seq. ID. 210	28±0.05	82±0.27	100±0.01
Seq. ID. 222	31±0.23	88±0.03	106±0.04
Seq. ID. 240	33±0.02	72±0.09	100±0.11
Seq. ID. 248	38±0.39	97±0.03	116±0.01
Seq. ID. 255	19±0.12	50±0.15	72±0.18
Seq. ID. 258	22±0.02	49±0.12	69±0.17

b) Stability of peptides in human plasma, simulated gastric fluid, intestinal fluid and liver microsomes (ex-vivo):

Different cyclic short-chain peptides (final concentration 2 µM) were incubated with either pooled human plasma (7.5 µL) or simulated gastric fluid (pH 1.5; composition HCl, NaCl and Pepsin) or simulated intestinal fluid (pH 7.5) or human liver microsomes, for 0, 2, 4, 6, 12 and 24 h (37 °C; 50 mM triethanolamine-HCl buffer; pH 7.8). Concentrations of human plasma/ simulated gastric fluid/ simulated intestinal fluid/ human liver microsomes were selected in preliminary experiments to provide degradation of approximately 50% of PTH(1-34) within 1 h, therefore allowing time-dependent degradation to be viewed over 24 h. Reactions were terminated by the addition of TFA/H$_2$O (15 mL, 10% (v/v)). The reaction products were then applied to a Vydac C$_{18}$ analytical column (4.6 x 250-mm) and the major degradation fragment separated from intact short-chain peptides. The column was equilibrated with TFA/H$_2$0, at a flow rate of 1 mL/min. Using 0.1% (v/v) TFA in 70% acetonitrile/H$_2$O, the concentration of acetonitrile in the eluting solvent was raised from 0% to 28% over 10 min and from 28% to 42% over 30 min. The absorbance was monitored at 206 nm using UV detector and peaks were collected manually prior to ESI-MS analysis. Area under the curve was measured for test peptides and their metabolites and percentage degradation were calculated at each time point over a period of 24 h. Stability study results of selected peptides, in human plasma, simulated gastric fluid, intestinal fluid and liver microsomes (*in vitro*) are listed in **Table 4**.

Table 4: Stability study results of selected cyclic short-chain peptides in human plasma, simulated gastric fluid, intestinal fluid and liver microsomes (*in vitro*)			
Seq. ID. No.	**Human plasma[a]**	**Simulated**	**Simulated intestinal**	**liver**

		gastric fluid[b]	fluid[c]	microsomes[d]
PTH(1-34)	97 (0.5)	100 (0.1)	100 (0.2)	100 (0.1)
Seq. ID. 34	73(6)	17 (8)	41 (7)	77 (2)
Seq. ID. 6	00 (>24)	00 (>24)	00 (>24)	33 (5)
Seq. ID. 9	68(8)	14 (6)	42 (6)	72 (1)
Seq. ID. 17	70(7)	17 (7)	41 (4)	73 (1)
Seq. ID. 25	60(8)	13 (8)	41 (6)	76 (1)
Seq. ID. 39	00 (>24)	00 (>24)	00 (>24)	33 (4)
Seq. ID. 49	10 (>20)	48 (4)	00 (>24)	82 (2)
Seq. ID. 66	05 (>20)	55 (5)	00 (>24)	78 (2)
Seq. ID. 75	07 (>22)	42 (4)	00 (>24)	81 (2)
Seq. ID. 95	00 (>24)	43 (5)	00 (>24)	86 (2)
Seq. ID. 110	00 (>24)	00 (>24)	00 (>24)	29 (5)
Seq. ID. 121	00 (>24)	00 (>24)	00 (>24)	32 (5)
Seq. ID. 150	00 (>24)	00 (>24)	00 (>24)	34 (5)
Seq. ID. 165	79(8)	100 (0.5)	100 (0.5)	100 (0.5)
Seq. ID. 178	77(7)	100 (0.5)	100 (0.5)	100 (0.5)
Seq. ID. 190	80(6)	100 (0.5)	100 (0.5)	100 (0.5)
Seq. ID. 205	00 (>24)	49 (3)	00 (>24)	78 (2)
Seq. ID. 215	76(8)	14 (7)	52 (6)	78 (1)
Seq. ID. 230	80(7)	13 (7)	50 (6)	82 (2)
Seq. ID. 250	78(8)	14 (8)	43 (6)	80 (1)
Seq. ID. 258	73(9)	100 (1)	100 (1)	100 (0.5)

a: % degradation of peptides in 24h when incubated with human plasma and values in bracket represent half-life ($t_{1/2}$), in h;

b: % degradation of peptides in 24h when incubated with simulated gastric fluid and values in bracket represent half-life ($t_{1/2}$), in h;

c: % degradation of peptides in 24h when incubated with simulated intestinal fluid and values in bracket represent half-life ($t_{1/2}$), in h;

d: % degradation of peptides in 24h when incubated with liver microsomes and values in bracket represent half-life ($t_{1/2}$), in h.

c) In vivo **anti-osteoporosis activity testing in OVX rat model:**

The ovariectomiced (OVX) rats were used to study anti-osteoporosis activity of test compounds (cyclic short-chain peptides) *in vivo*. The OVX rats develop osteopenia

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due to ovarian hormone deficiency. Osteopenia can be detected as early as 14 days post OVX, increase for the next 100 days and then stabilised (Wronski T. J., et al., Calcif. Tissue Int., 43(3), 1988, 179-183).

Detailed study protocol to evaluate the effects of anabolic therapy on bone markers and
5   *histomorphometry in OVX animals:*

10 to 11 weeks old Female Wistar Rats (150-200 g) were used. The animals were marked with picric acid for identification and acclimatized to experimental room conditions for 2 days prior to initiation of the study. For the induction of osteoporosis, rats were bilaterally ovariectomised under anesthesia. For Ovariectomy, Incision was
10   made on dorsa-lateral side near lumbar region of animal. After that, ovary was excised and the veins were tied with ligature before removing ovary to prevent blood loss. Then incision was sutured back with ligature.

After Bilateral ovariectomy, animals were allowed to rest for 4 weeks. . They were then divided into different groups (n=9) based on their body weight. The treatment was
15   given for the duration of 6 weeks. At the last day of treatment animals were kept overnight in metabolic cages under fasting for the collection of Urine. Next day, blood was collected after 24 hours of last dosing and animals were sacrificed. Changes in biochemical parameters and bone turnover parameters (Increase in serum Calcium and decrease in Phosphate levels, Acid Phosphatase and TRAP) were evaluated in the urine
20   and serum. After sacrificing, intact femur and tibial bones are removed and cleaned from adherent tissues, muscles and tendons; weighed and collected in formal saline (10% formaldehyde solution). Lumbar vertebra (L5) was excised, carefully cleaned and collected in formal saline. Femur, tibia and Lumbar vertebra-5 (L5) were later processed for histomorphometric evaluation (Zhang L., et al., Tohoku J Exp Med.,
25   1998, 186(2), 131-41; Tanizawa T., et al., Toxicol Lett., 1998,102, 399-403). Increase in serum Calcium and decrease in Phosphate levels (% change vs PTH) of selected peptides are listed in **Table 5.**

Table 5: Increase in serum Calcium and decrease in Phosphate levels (% change vs PTH/ Control) in OVX Rats			
Seq. ID NO.	Dose	% increase in serum Ca^{2+} Levels (mg/dl) vs control	% decrease in serum PO_4 Levels (mg/dl) vs control
PTH(1-34)	20 µg/kg, sc	100	100

Seq. ID. 5	5 mg/kg, po	85	83
Seq. ID. 11	3 mg/kg, po	60	66
Seq. ID. 16	0.02 mg/kg, po	97	98
Seq. ID. 20	0.05 mg/kg, po	88	76
Seq. ID. 28	0.5 mg/kg, po	77	80
Seq. ID. 55	0.3 mg/kg, po	106	90
Seq. ID. 64	0.8 mg/kg, po	110	96
Seq. ID. 79	1 mg/kg, po	92	88
Seq. ID. 94	5 mg/kg, po	118	103
Seq. ID. 109	1 mg/kg, po	97	99
Seq. ID. 120	0.1 mg/kg, po	88	91
Seq. ID. 135	1 mg/kg, po	69	54
Seq. ID. 146	10 mg/kg, po	118	97
Seq. ID. 151	2 mg/kg, po	121	92
Seq. ID. 175	0.9 mg/kg, po	98	94
Seq. ID. 188	5 mg/kg, po	68	76
Seq. ID. 195	3 mg/kg, po	102	94
Seq. ID. 200	0.1 mg/kg, po	80	59
Seq. ID. 209	0.03 mg/kg, po	78	81
Seq. ID. 220	0.01 mg/kg, po	45	66
Seq. ID. 235	1 mg/kg, po	85	88
Seq. ID. 254	5 mg/kg, po	76	84
Seq. ID. 260	0.03 mg/kg, po	110	91

The *In vitro* DRC study (in Rat PTH-1 R assay) data (EC_{50}) of PTH(1-34) (Figure A) and Seq. ID No. 247 (Figure B), as representative figure is shown in **Figure 2**. The *In vivo* DRC study data, after 6-weeks treatment with Seq. ID. No. 247

Aib-V-(AC$_5$C)-EIKLMHD-Har-A-Cit-(αMe-2F-Phe) at different doses (0.1/0.2/0.3/0.5 mg/kg, po), in OVX Female Wister rats, via oral route of administration, as representative figure is shown as **Figure 3** (Figure A: % increase in serum Ca^{2+} levels; Figure B: % decrease in serum PO_4 levels). The **Figure 4** represents the Changes in biochemical parameters and femur weight, in OVX Rat after 6 weeks treatment with Seq. ID No. 247 and PTH(1-34).

Utilities:

In a preferred embodiment, the present invention provides a method of making cyclic short chain peptides that function as an agonist of the PTH-1 receptor having different degree of affinity (1-1000 nM concentration) in UMR-106 cells. The PTH-1 receptor agonistic activity was assessed by estimation of amount of cAMP released by the test compounds (in vitro). In OVX mice/ rat models (in vivo), some of the cyclic short-chain peptides showed improvement in bone growth parameters thus making them ideal therapeutic candidates for the treatment and prevention of osteoporosis.

Novel cyclic short chain peptides of present invention showed increased stability against various proteolytic enzymes and due to increased stability and short chain length, such cyclic short chain peptides can also be delivered by oral route of administration, along with other invensive and non-invensive routes of administration.

The cyclic short chain peptides of the present invention can be used either alone or in combination with other anti-osteophoratic agents such as growth harmone secretagogues, Insulin-like growth factor (IGF-1), Vitamine-D analogues, estrogen, raloxifene (oestrogen receptor modulators), calcitonin, PTH-1r agonist and the bisphosphonates (etidronate, alendronate and risedronate) for the treatment and prevention of osteoporosis.

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

The pharmaceutical composition containg the short 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 cyclic short-chain peptides of formula (I) either alone or combination, according to this invention. The pharmaceutical composition can be prepared by known processes by combining the compound of formula (I) with suitable excipients comprising suitable excipients selected from suitable diluents, stabilizers, buffers and the like as is known in the art.
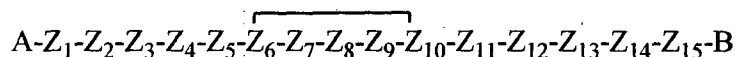
The quantity of active component, that is, the cyclic short chain peptides of formula (I) according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular short chain peptides and the desired concentration. Generally, the quantity of active component will range between 0.5 % to 90 % by weight of the composition.

Accordingly, the cyclic short chain peptides 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 preventing osteoporosis, such as primary osteoporosis, endocrine osteoporosis (hyperthyroidism,

5   hyperparathyroidism, Cushing's syndrome, acromegaly, type 1 diabetes mellitus, adrenal insufficiency), hereditary and congenital forms of osteoporosis (osteogenesis imperfecta, homocystinuria, Menkes' syndrome and Riley-Day syndrome), nutritional and gastrointestinal disorders, haematological disorders/malignancy (multiple myeloma, lymphoma and leukaemia, hemophilia, thalassemia), osteoporosis due to

10   immobilization, chronic obstructive pulmonary disease or rheumatologic disorders (rheumatoid arthritis, spondylitis), Osteomyelitis or an infectious lesion in bone, leading to bone loss.

Hypercalcemia resulting from solid tumours and hematologic malignancies, idiopathic hypercalcemia and hypercalcemia associated with hyperthyroidism and renal function

15   disorders. Osteopenia following surgery induced by steroid administration and associated with disorders of the small and large intestine and with chronic hepatic and renal diseases. Osteonecrosis or bone cell death, associated with traumatic injury or nontraumatic necrosis associated with Gaucher's disease, sickle cell anaemia, systemic lupus erythematosus and other conditions. Periodontal bone loss, Osteolytic metastasis,

20   bone fracture healing and hyperproliferative skin disorders such as psoriasis.

We claim:

1.   Cyclic short-chain peptides having a sequence of Formula (I), including their tautomers, solvates

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$$A\text{-}Z_1\text{-}Z_2\text{-}Z_3\text{-}Z_4\text{-}Z_5\text{-}\overline{Z_6\text{-}Z_7\text{-}Z_8\text{-}Z_9\text{-}Z_{10}}\text{-}Z_{11}\text{-}Z_{12}\text{-}Z_{13}\text{-}Z_{14}\text{-}Z_{15}\text{-}B$$

(I)

wherein,

A' represents the groups $-NH\text{-}R_1$ or $R_3\text{-}CO\text{-}NH\text{-}$, wherein R_1 represents hydrogen or optionally substituted linear ($C_{1\text{-}18}$) alkyl chain, or suitable amino
10   acids preferably selected from pyroglutamic acid (Pyr), Pro (P), alpha-methyl-Proline (αMe-P), Val (V), alpha-methyl-Valine (αMe-V); R_3 is selected from optionally substituted linear ($C_{1\text{-}18}$) alkyl chain, ($C_{1\text{-}6}$)alkoxy, ($C_3\text{-}C_6$) cycloalkyl, aryl, heteroaryl or arylalkyl groups; 'B' represents $-COOR_2$, -$CONHR_2$ or CH_2OR_2, wherein R_2 represents H or suitable amino acids; Each of
15   Z_1, Z_3 & Z_{12} may be same or different and independently represents a naturally or unnaturally occurring amino acids selected from the group comprising of Ser (S), Val (V), Pro (P), alpha-methyl-Proline (αMe-P), Gly (G), Ala (A), α-amino-isobutyric acid (Aib), 1-amino cyclopropane carboxylic acid (AC_3C), 1-amino-cyclopentanecarboxylic acid (AC_5C), 1-amino-cyclohexanecarboxylic
20   acid (AC_6C); Z_2 represents either a Val (V) or alpha-methyl-valine (αMe-V); Z_4 represents a naturally or unnaturally occurring amino acids selected from the group comprising of Glu(E), Asp(D); each of Z_6 & Z_{10}, may be same or different and independently represents a naturally or unnaturally occurring amino acid selected from the group comprising of Ser (S), Homoserine (HoSer),
25   Lys (K), Orn (Ornithine), Glu (E), Homoglutamic acid (HoGlu), Asp (D), wherein, when the side chains of Z_6 and Z_{10} have acidic or basic group they together form a lactam bridge or when the side chain of Z_6 and Z_{10} have alcoholic group, they are cross-linked as a diester bridge, with dicarboxylic acids; Each of Z_5, Z_7 & Z_9 may be same or different and independently
30   represents a naturally or unnaturally occurring amino acid selected from the group comprising of Leu (L), Ile (I), Nle (Norleucine), HoLeu (Homoleucine), His (H), Phe (F), alpha-methyl-phenylalanine (αMe-Phe-), alpha-methyl-2-

fluorophenylalanine (αMe-2F-Phe-), alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-) or 2-fluorophenylalanine (2F-Phe-); Z_8 represents a naturally or unnaturally occurring amino acid selected from the group comprising of Met, alpha-methyl-Valine (αMe-V), Leu, Nle, HoLeu, Val; Z_{11} & Z_{13} may be same or different and independently represents a naturally or unnaturally occurring amino acid selected from the group comprising of Lysine (K), Arginine (R), Homoarginine (Har), Ornithine (Orn), Citrulline (Cit), Phenyl alanine (F), alpha-methyl-phenylalanine (αMe-Phe-), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-) or alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-) or 2-fluorophenylalanine (2F-Phe-); Z_{14} when present represents a naturally or unnaturally occurring amino acid selected from the group comprising of 2'-ethyl-4'-methoxy-biphenylalanine (Bip(OMe)), α-methylated Bip(OMe) [αMe-Bip(OMe)], alpha-methyl-tryptophan (αMe-Trp), alpha-methyl-tyrosine (αMe-Tyr), Tryptophan (W), Tyrosine (Y), D-Tryptophan (*d*W), D-Tyrosine (*d*Y), alpha-methyl-phenylalanine (αMe-Phe-), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-), alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-) or 2-fluorophenylalanine (2F-Phe-); Z_{15} when present represents a naturally or unnaturally occurring amino acid selected from the group comprising of 2-amino-5-phenylpentanoic acid (APPA) or 2-amino-2-methyl-5-phenylpentanoic acid (αMe-APPA);

2.   The compound as claimed in claim 1 wherein R_2 reprsents suitable amino acids selected from the group comprising of Val (V), alpha-methyl-Valine (αMe-V).

3.   The compound as claimed in claim 1 wherein each of Z_1, Z_3 & Z_{12} represents amino acid selected from Ala (A), α-amino-isobutyric acid (Aib), 1-amino cyclopropane carboxylic acid (AC₃C) or 1-amino-cyclopentanecarboxylic acid (AC₅C).

4.   The compound as claimed in claim 1 wherein when the side chain of Z_6 and Z_{10} are cross-linked as a diester bridge, with dicarboxylic acids, the dicarboxylic acids are selected from succinic acid, glutaric acid, adipic acid, pimelic acid, suberic acid, azelaic acid or sebacic acid.

5.   The compound as claimed in claims 1 and 4 wherein each of Z_6 & Z_{10} represents amino acid selected from Ser (S), Lys (K), Glu (E) or Asp (D).

6.   The compound as claimed in claim 1 wherein each of Z_5, Z_7 & Z_9 represents amino acid selected from Ile (I), Nle (Norleucine), His (H), Phe(F), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-) or alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-).

7.   The compound as claimed in claim 1 wherein Z_8 represents amino acid selected from Met, Leu or Val.

8.   The compound as claimed in claim 1 wherein each of Z_{11} & Z_{13} represents amino acid selected from Lysine (K), Arginine (R), Homoarginine (Har) or Citrulline (Cit).

9.   The compound as claimed in claim 1 wherein Z_{14} when present represents amino acid selected from Tryptophan (W), Tyrosine (Y), D-Tryptophan (dW), D-Tyrosine (dY), alpha-methyl-2-fluorophenylalanine (αMe-2F-Phe-), or alpha-methyl-2,6-diflurophenylalanine (αMe-2,6-F-Phe-).

10. The compound as claimed in preceding claims wherein the aryl group is selected from phenyl, napthyl, indanyl or biphenyl, groups.

11. The compound as claimed in preceding claims wherein the heteroaryl group is selected from pyridyl, thienyl, furyl, imidazolyl, benzofuranyl groups

12. The compound of formula (I) selected from

Aib-V-Aib-EISLMHS-Har-AK-(αMe-Phe);

Aib-V-Aib-EISL-Nle-HS-Har-AK-(αMe-Phe);

Aib-V-Aib-EISLMHS-Har-Aib-K-(αMe-Phe);

Aib-V-Aib-EISL-Nle-HS-Har-Aib-K-(αMe-Phe);

Aib-V-(AC$_5$C)-EISLMHS-Har-Aib-K-(αMe-Phe);

Aib-V-(AC$_5$C)-EISL-Nle-HS-Har-Aib-K-(αMe-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe);

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe);

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-AK-(αMe-2,6-F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-K-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe);

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(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Aib-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Aib-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe);

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe);

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Aib-(αMe-2,6-F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Aib-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)-(APPA);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)-(APPA);

Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)-(APPA);

Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)-(APPA);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Cit-(αMe-2F-Phe)-(APPA);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2F-Phe)-(APPA);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)-(APPA);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)-(APPA);

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)-(APPA);

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Cit-(αMe-2,6-F-Phe)-(APPA);

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)-(APPA);

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Cit-(αMe-2,6-F-Phe)-(APPA);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2,6-F-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe);

(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-H-S-Har-A-Har-(αMe-2,6-F-Phe);

(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-dY;

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-dY;

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-dY;

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-dY;

(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-dY;

(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-dY;

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-dY;

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-dY;

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-dY;

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-dY;

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-dY;

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-dY;

(AC₅C)-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-dY;

(AC₅C)-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-dY;

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-dY;

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-dY;

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-W;

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-W;

Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-W;

Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-W;

(AC₅C)-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-W;

(AC₅C)-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-W;

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-W;

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-W;

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-W;

Aib-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-W;

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-W;

Aib-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-W;

(AC₅C)-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HSHar-A-Har-W;

(AC₅C)-V-(AC₅C)-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-W;

(AC₅C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-A-Har-W;

(AC$_5$C)-V-Aib-EIS-(αMe-2,6-F-Phe)-Nle-HS-Har-Aib-Har-W;

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AR-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-R-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-AR-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-R-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-AR-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-R-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-dK-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-dK-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-dK-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-dK-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-dK-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-dK-(αMe-2F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Trp);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp);

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Trp);

Aib-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp);

(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Trp);

(AC$_5$C)-V-(AC$_5$C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Trp);

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Tyr);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Tyr);

Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Tyr);

Aib-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Tyr);

(AC₅C)-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Tyr);

(AC₅C)-V-(AC₅C)-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Tyr);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har-(αMe-Tyr);

(AC₅C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Tyr);

Aib-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer( )-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe);

Aib-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe);

(AC₅C)-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe);

(AC₅C)-V-Aib-EI-HoSer-(αMe-2F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe);

Aib-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe);

Aib-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe);

Aib-V-(AC₅C)-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe);

Aib-V-(AC₅C)-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-A-Cit-(αMe-2,6-F-Phe);

(AC$_5$C)-V-Aib-EI-HoSer-(αMe-2,6-F-Phe)-Nle-H-HoSer-Har-Aib-Cit-(αMe-2,6-F-Phe);

Aib-V-Aib-EIS-(αMe-2F-Phe)-MHS-Har-Aib-Har-(αMe-Bip(OMe))-(APPA);

Aib-V-Aib-EIS-(αMe-2F-phe)-Nle-HS-Har-Aib-Har-(αMe-Bip(OMe))-(APPA);

Aib-V-Aib-EIS-(αMe-2F-Phe)-MHS-Har-Aib-Har-(Bip(OMe))-(αMe-APPA);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(Bip(OMe))-(αMe-APPA);

Aib-V-Aib-EIS-(αMe-2F-Phe)-MHS-Har-Aib-Har-(αMe-Trp)-(APPA);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har-(αMe-Trp)-(APPA);

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har;

Aib-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har;

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-A-Har;

(AC$_5$C)-V-Aib-EIS-(αMe-2F-Phe)-Nle-HS-Har-Aib-Har;

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Cit-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har-(αMe-2F-Phe);

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har-(αMe-2F-Phe);

Aib-V-(AC$_5$C)-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har-(αMe-2F-Phe);

(AC$_5$C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-MHE-Har-A-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-A-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-A-Har-(αMe-2F-Phe);

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-ME-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-MHE-Har-A-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-A-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-MHE-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-Aib-EIK-L-Nle-H-E-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIK-L-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIK-L-Nle-HE-Har-A-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIK-L-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIK-L-Nle-HE-Har-A-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKL-Nle-HE-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIKL-Nle-HE-Har-A-Har-(αMe-2F-Phe);

Aib-V-Aib-EIKL-Nle-HE-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKL-Nle-HE-Har-A-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKL-Nle-HE-Har-Aib-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKL-Nle-HE-Har-A-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKL-Nle-HE-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-Aib-EIKLMHE-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIKLMHE-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKLMHE-Har-A-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKLMHE-Har-Aib-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKLMHE-Har-A-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKLMHE-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIKLMHE-Har-A-Har-(αMe-2F-Phe);

Aib-V-Aib-EIKLMHE-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKLMHE-Har-A-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKLMHE-Har-Aib-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKLMHE-Har-A-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKLMHE-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-Aib-EIKL-Nle-HD-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIKL-Nle-HD-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKL-Nle-HD-Har-A-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKL-Nle-HD-Har-Aib-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKL-Nle-HD-Har-A-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKL-Nle-HD-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIKL-Nle-HD-Har-A-Har-(αMe-2F-Phe);

Aib-V-Aib-EIK-L-Nle-HD-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKL-Nle-HD-Har-A-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKL-Nle-HD-Har-Aib-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKL-Nle-HD-Har-A-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKL-Nle-HD-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-Aib-EIKLMHD-Har-A-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIKLMHD-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKLMHD-Har-A-Cit-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKLMHD-Har-Aib-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKLMHD-Har-A-Cit-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKLMHD-Har-Aib-Cit-(αMe-2F-Phe);

Aib-V-Aib-EIKLMHD-Har-A-Har-(αMe-2F-Phe);

Aib-V-Aib-EIKLMHD-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKLMHD-Har-A-Har-(αMe-2F-Phe);

Aib-V-(AC₅C)-EIKLMHD-Har-Aib-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKLMHD-Har-A-Har-(αMe-2F-Phe);

(AC₅C)-V-Aib-EIKLMHD-Har-Aib-Har-(αMe-2F-Phe);

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har;

Aib-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har;

(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-A-Har;

(AC₅C)-V-Aib-EIK-(αMe-2F-Phe)-Nle-HE-Har-Aib-Har;

13. A pharmaceutical composition comprising compounds of formula (I) as claimed in any preceding claims, and suitable pharmaceutically acceptable excipient(s).

14. The compounds of formula (I) or their pharmaceutical compositions as claimed in any preceding claims which act as an agonist of PTH-1 receptor. The compounds or their pharmaceutical compositions as claimed in any preceding claims, useful for treating or delaying the progression or onset of osteoporosis, especially primary osteoporosis, endocrine osteoporosis, postmenopausal osteoporosis, hereditary and congentinal forms of osteoporosis.

15. A method of preventing or treating diseases caused by primary osteoporosis, endocrine osteoporosis, hereditary and congenital forms of osteoporosis, osteoporosis due to immobilization, chronic obstructive pulmonary disease or rheumatologic disorders (rheumatoid arthritis, spondylitis). Osteomyelitis or an infectious lesion in bone, leading to bone loss complications comprising

administering an effective, non-toxic amount of compound of formula (I) as defined in any preceding claims to a patient in need thereof.

16. A medicine for treating/reducing any of the disease conditions described in any preceding claims which comprises administering a compound of formula (I), as claimed in any preceding claims and a pharmaceutically acceptable carrier, diluent, excipients or solvate to a patient in need thereof.

17. Use of compounds of formula (I) as claimed in any preceding claims, their pharmaceutical compositions and medicines containing them, as a medicament suitable for the treatment of diseases mentioned in any of the aforesaid claims.

18. The cyclic short chain peptides of the present invention in combination with suitable anti-osteophoratic agents selected from growth harmone secretagogues, insulin-like growth factor (IGF-1), Vitamin-D analogues, estrogens, oestrogen receptor modulators, calcitonin, PTH-1r agonist and bisphosphonates for the treatment and prevention of osteoporosis.
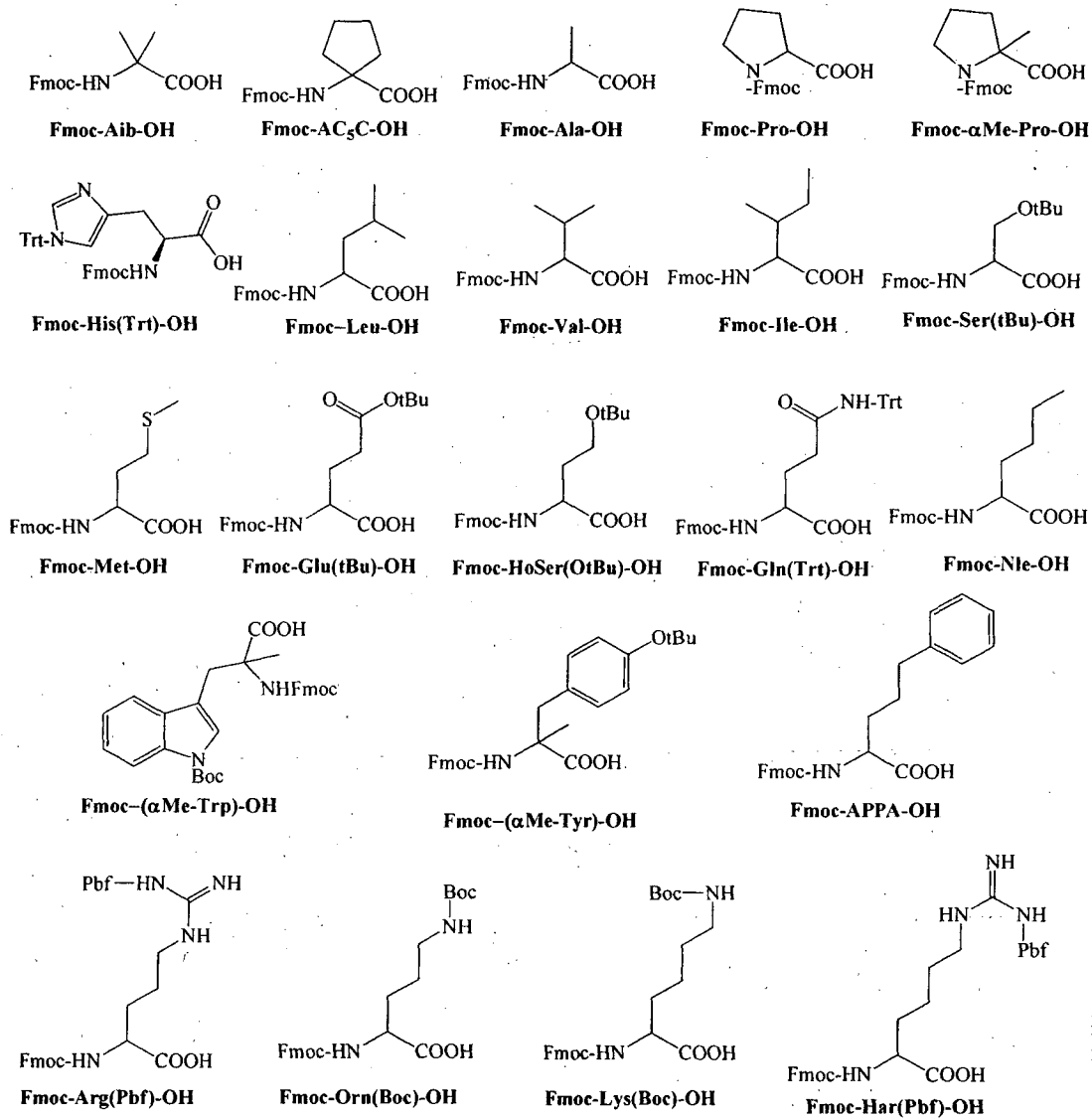
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Figure 1: Examples of some of the protected amino acids used in Fmoc based-solid phase peptide synthesis (SPPS) of short-chain peptides.
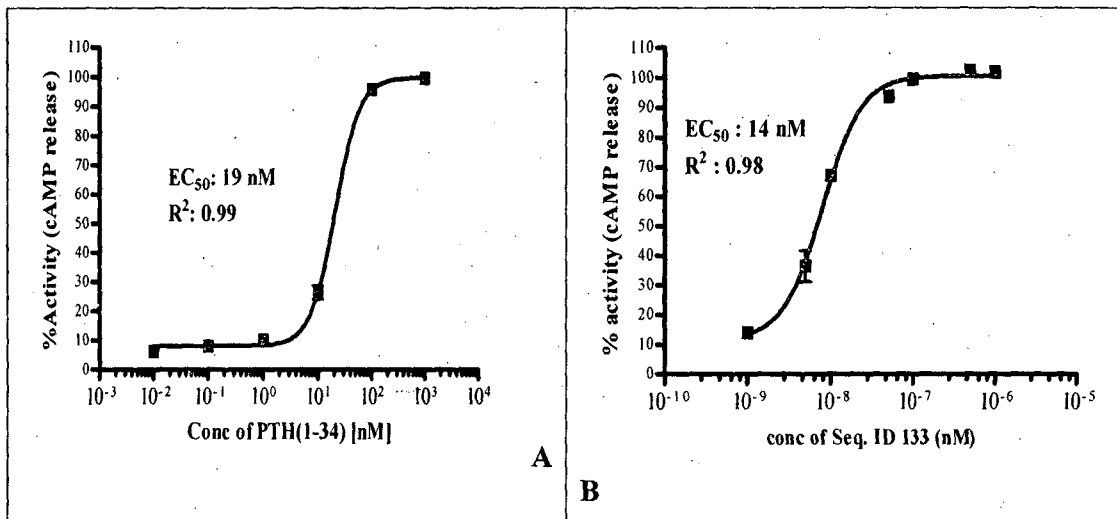
Figure 2: *In vitro* DRC and EC_{50} determination of PTH(1-34) (**Figure A**) and **Seq. ID No. 133** (**Figure B**), in Rat PTH-1 R assay (agonistic activity, measured by amount of cAMP released).

Figure 3: *In vivo* DRC study with **Seq. ID No. 168** (**Figure A:** % increase in serum Ca^{2+} levels; **Figure B:** % decrease in serum PO_4 levels), in OVX Female Rat.

Figure 4: Changes in biochemical parameters and femur weight, in OVX Rat after 6 weeks treatment with Seq. ID No. 247 and PTH(1-34).