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(54) **Title**: IMMUNOMODULATING PEPTIDOMIMETIC DERIVATIVES

(57) **Abstract**: The present invention relates to immunomodulating peptidomimetic derivatives as therapeutic agents capable of inhibiting the programmed cell death 1 (PD1) signalling pathway. The invention also refers to derivatives of the therapeutic agents. The invention also encompasses the use of the said therapeutic agents and derivatives for treatment of disorders via immunopotentiation comprising inhibition of immunosuppressive signal induced due to PD-1, PD-L1, or PD-L2 and therapies using them.

IMMUNOMODULATING PEPTIDOMIMETIC DERIVATIVES

This application claims the benefit of Indian provisional application number 4044/CHE/2013, filed on September 10, 2013 and Indian provisional application number 4045/CHE/2013, filed on September 10, 2013; which hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to immunomodulating peptidomimetic derivatives. The invention also relates to pharmaceutical compositions comprising the said peptidomimetic compounds and their derivatives as therapeutic agents.

BACKGROUND OF THE INVENTION

Programmed cell death-1 (PD-1) is a member of the CD28 superfamily that delivers negative signals upon interaction with its two ligands, PD-L1 or PD-L2. PD-1 and its ligands are broadly expressed and exert a wider range of immunoregulatory roles in T cells activation and tolerance compared with other CD28 members. PD-1 and its ligands are involved in attenuating infectious immunity and tumor immunity, and facilitating chronic infection and tumor progression. The biological significance of PD-1 and its ligand suggests the therapeutic potential of manipulation of PD-1 pathway against various human diseases (Hyun-Tak Jin, et al., Curr Top Microbiol Immunol. (2011); 350:17-37).

T-cell activation and dysfunction relies on direct and modulated receptors. Based on their functional outcome, co-signaling molecules can be divided as co-stimulators and co-inhibitors, which positively and negatively control the priming, growth, differentiation and functional maturation of a T-cell response (Li Shi, et al., Journal of Hematology & Oncology 2013, 6:74).

Therapeutic antibodies that block the programmed cell death protein-1 (PD-1) immune checkpoint pathway prevent T-cell down regulation and promote immune responses against cancer. Several PD-1 pathway inhibitors have shown robust activity in various phases of clinical trials (RD Harvey, Clinical Pharmacology & Therapeutics (2014); 96 2, 214–223).

Programmed death-1 (PD-1) is a co-receptor that is expressed predominantly by T cells. The binding of PD-1 to its ligands, PD-L1 or PD-L2, is vital for the physiological regulation of the immune system. A major functional role of the PD-1 signaling pathway is the inhibition of self-reactive T cells, which serve to protect against autoimmune diseases. Elimination of the PD-1 pathway can therefore result in the

breakdown of immune tolerance that can ultimately lead to the development of pathogenic autoimmunity. Conversely, tumor cells can at times co-opt the PD-1 pathway to escape from immunosurveillance mechanisms. Therefore, blockade of the PD-1 pathway has become an attractive target in cancer therapy. Current approaches include six agents that are either PD-1 and PD-L1 targeted neutralizing antibodies or fusion proteins. More than forty clinical trials are underway to better define the role of PD-1 blockade in variety of tumor types. (Ariel Pedoeem et al., Clinical Immunology (2014), 153(1), 145-152).

International applications WO 01/14557, WO 02/079499, WO 2002/086083, WO 03/042402, WO 2004/004771, WO 2004/056875, WO2006121168, WO2008156712, WO2010077634, WO2011066389, WO2014055897, WO2014059173, WO2014100079 and US patent US08735553 report PD-1 or PD-L1 inhibitory antibodies or fusion proteins.

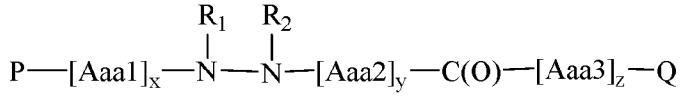
Further, International applications, WO2011161699, WO2012/168944, WO2013144704 and WO2013132317report peptides or peptidomimetic compounds which are capable of suppressing and/or inhibiting the programmed cell death 1 (PD1) signaling pathway.

Still there is a need for more potent, better and/or selective immune modulators of PD-1 pathway. The present invention provides peptidomimetic compounds which are capable of suppressing and/or inhibiting the programmed cell death 1 (PD1) signalling pathway.

SUMMARY OF INVENTION

In accordance with the present invention, provided are peptidomimetic compounds or a pharmaceutically acceptable salt or a stereoisomer thereof, which are capable of suppressing and/or inhibiting the programmed cell death 1 (PD1) signalling pathway.

In one aspect, the present invention provides a peptidomimetic compounds of formula (I):



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

x, y and z are integers, each independently selected from 1 to 2;

each of [Aaa1], [Aaa2] and [Aaa3] represents x, y and z independently selected amino acid residues, with a proviso that [Aaa1] is not selected from Ser, Thr, Ala or Leu if

(i) [Aaa2] is selected from Asp, Asn, Glu or Gln;

(ii) [Aaa3] is selected from Ser, Asp, Ala, Ile, Phe, Trp, Glu or Thr; and

(iii) each of x, y and z is 1;

wherein, [Aaa1], [Aaa2] and [Aaa3] are optionally substituted by hydroxyl;

R_1 and R_2 are independently hydrogen or alkyl;

P represents free N-terminus, alkylated N-terminus or acylated N-terminus of [Aaa1];

Q represents free C-terminus, amidated C-terminus or esterified C-terminus of [Aaa3]; and

the bond between [Aaa1] and $-NR_1-$ and/or between [Aaa2] and $-NR_2-$ is a peptide bond or a reduced peptide bond.

In a further aspect of the present invention, it relates to the pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer and processes for preparing thereof.

In yet another aspect of the present invention, it provides use of peptidomimetic compounds of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof, which are capable of suppressing and/or inhibiting the programmed cell death 1 (PD1) signaling pathway.

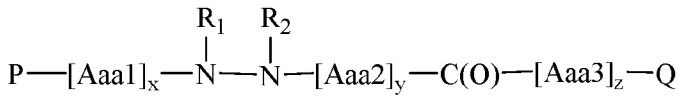
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides peptidomimetic compounds as therapeutic agents useful for treatment of disorders via immunopotentiation comprising inhibition of immunosuppressive signal induced due to PD-1, PD-L1, or PD-L2 and therapies using them.

Each embodiment is provided by way of explanation of the invention, and not by way of limitation of the invention. In fact, it will be apparent to those skilled in the art that various modification and variations can be made in the present invention without departing from the scope or spirit of the invention. For instance, features illustrated or described as part of one embodiment can be used on another embodiment to yield a still further embodiment. Thus it is intended that the present invention cover such modifications and variations as come within the scope of the appended claims and their

equivalents. Other objects, features, and aspects of the present invention are disclosed in, or are obvious from, the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only, and is not to be construed as limiting the broader aspects of the present invention.

In one embodiment, the present invention relates to compounds of formula (I)



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

x, y and z are integers, each independently selected from 1 to 2;

each of [Aaa1], [Aaa2] and [Aaa3] represents x, y and z independently selected amino acid residues, with a proviso that [Aaa1] is not selected from Ser, Thr, Ala or Leu if

(i) [Aaa2] is selected from Asp, Asn, Glu or Gln;

(ii) [Aaa3] is selected from Ser, Asp, Ala, Ile, Phe, Trp, Glu or Thr; and

(iii) each of x, y and z is 1;

wherein, [Aaa1], [Aaa2] and [Aaa3] are optionally substituted by hydroxyl;

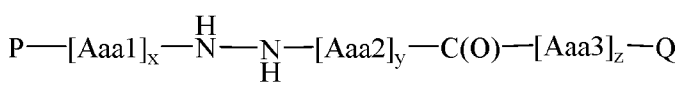
R_1 and R_2 are independently hydrogen or alkyl;

P represents free N-terminus, alkylated N-terminus or acylated N-terminus of [Aaa1];

Q represents free C-terminus, amidated C-terminus or esterified C-terminus of [Aaa3]; and

the bond between [Aaa1] and $-NR_1-$ and/or between [Aaa2] and $-NR_2-$ is a peptide bond or a reduced peptide bond.

In yet another embodiment, the present invention provides compounds of formula (IA)

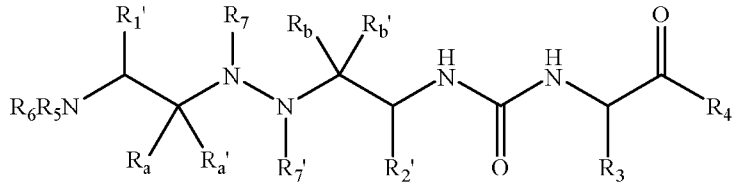


(IA)

or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

x, y, z, [Aaa1], [Aaa2], [Aaa3], P and Q are same as defined in compound of formula (I).

In yet another embodiment, the present invention provides peptidomimetic compounds of formula (IB):



(IB)

or a stereoisomer or a pharmaceutically acceptable salt thereof;

wherein;

each of R_1', R_2' and R_3 independently represents side chain of an amino acid with the proviso that R_1' is not a side chain of Ser, Thr, Ala or Leu if R_2' is a side chain of Asp, Asn, Glu or Gln and R_3 is a side chain of Ser, Asp, Ala, Ile, Phe, Trp, Glu or Thr;

R_4 is –OR or -NH_2;

R is hydrogen, alkyl or arylalkyl;

R_5 and R_6 are independently selected from hydrogen, alkyl or acyl;

each of R_7 and R_7' independently represents hydrogen or alkyl;

both R_a and R_a' represent hydrogen; or together represent an oxo (=O) group;

both R_b and R_b' represent hydrogen; or together represent an oxo (=O) group.

In yet another embodiment, the present invention provides compounds of the formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein, [Aaa1] is selected from the group consisting of: Ser, Ala, Cys, Asp, Phe, Pro, Asn and Lys.

In yet another embodiment, the present invention provides compounds of the formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein, [Aaa2] is selected from the group consisting of: Ala, Asn, Phe, Lys, Thr and Phe;

In yet another embodiment, the present invention provides compounds of the formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein, [Aaa3] is selected from the group consisting of: Thr, Ala, Phe, Ser, Lys, Gly, val and Asn.

The embodiment below are illustrative of the present invention and are not intended to limit the claims to the specific embodiments exemplified.

According to one embodiment, specifically provided are compounds of the formula (I), in which R_1 is hydrogen.

According to another embodiment, specifically provided are compounds of the formula (I), in which R_2 is hydrogen.

According to yet another embodiment, specifically provided are compounds of the formula (I) and (IA), in which P is free N-terminus.

According to yet another embodiment, specifically provided are compounds of the formula (I) and (IA), in which Q is free C-terminus.

According to yet another embodiment, specifically provided are compounds of the formula (I), in which x, y and z are independently are 1.

According to yet another embodiment, specifically provided are compounds of the formula (I), in which x, y and z do not simultaneously have a value of 1.

According to yet another embodiment, specifically provided are compounds of the formula (I) and (IA), in which x is 2, y is 1 and z is 1.

According to yet another embodiment, specifically provided are compounds of the formula (I) and (IA), in which x is 1, y is 1 and z is 2.

According to yet another embodiment, specifically provided are compounds of the formula (I) and (IA), in which [Aaa1] is selected from the group of: Ser, Ala, Asp, Phe and Lys.

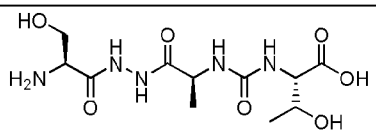
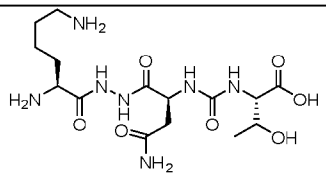
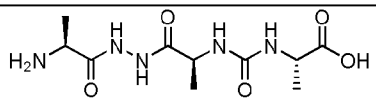
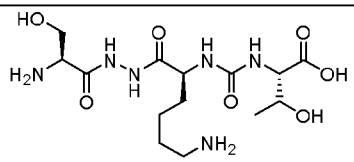
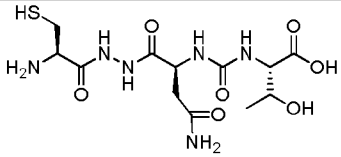
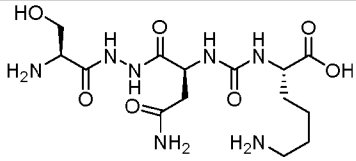
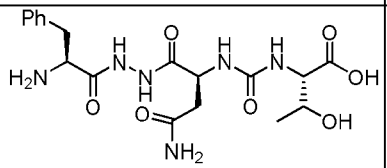
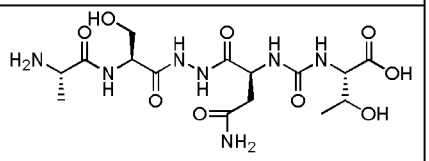
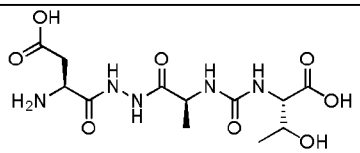
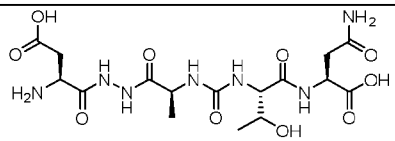
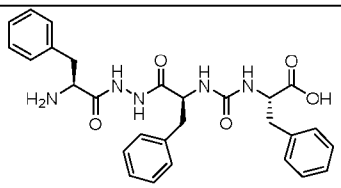
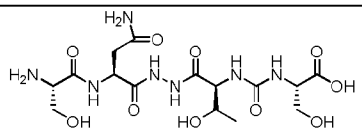
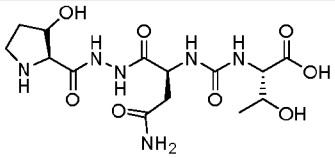
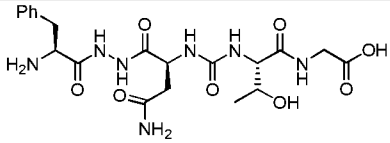
According to yet another embodiment, specifically provided are compounds of the formula (I) and (IA), in which [Aaa2] is selected from the group of: Ala and Asn.

According to yet another embodiment, specifically provided are compounds of the formula (I) and (IA), in which [Aaa3] selected from the group of: Thr, Ala, Lys and Gly.

According to yet another embodiment, specifically provided are compounds of the formula (I) and (IA) in which one, more or all amino acid/s is/are D amino acid/s.

In an embodiment, specific compounds of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof; without any limitation are enumerated in table 1.

Table 1

Compound No.	Structure	Compound No.	Structure
1		8	
2		9	
3		10	
4		11	
5		12	
6		13	 and
7		14	

The compounds as disclosed in the present invention are formulated for pharmaceutical administration.

In one embodiment, the present invention provides a pharmaceutical composition comprising the compound as disclosed, and a pharmaceutically acceptable carrier or a diluent.

In another embodiment, the said pharmaceutical composition further comprising at least one of an anticancer agent, chemotherapy agent, or antiproliferative compound.

In one embodiment, use of compounds as disclosed in the present invention for use as a medicament.

In another embodiment, use of compounds as disclosed in the present invention in the manufacture of a medicament for the treatment of cancer or infectious disease.

In another embodiment, use of the compounds as disclosed in the present invention in the manufacture of a medicament for the treatment bone cancer, cancer of the head or neck, pancreatic cancer, skin cancer, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumours of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumour angiogenesis, spinal axis tumour, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers.

In another embodiment, the present invention provides the compounds as disclosed in the present invention for use in the treatment of cancer.

In another embodiment, the present invention provides the compounds as disclosed in the present invention for use in the treatment of infectious disease.

In one embodiment, the present invention provides the compounds as disclosed in the present invention for use as a medicament for the treatment of bacterial infectious disease, a viral infectious disease or a fungal infectious disease.

In one embodiment, the present invention provides a method of treatment of cancer, wherein the method comprises administration of an effective amount of the compound of the present invention to the subject in need thereof.

In another embodiment the present invention provides a method of modulating an immune response mediated by PD-1 signaling pathway in a subject, comprising administering to the subject therapeutically effective amount of the compound of the present invention such that the immune response in the subject is modulated.

In yet another embodiment the present invention provides a method of inhibiting growth of tumour cells and/or metastasis in a subject, comprising administering to the subject a therapeutically effective amount of compound of the present invention capable of inhibiting the programmed cell death 1 (PD1) signaling pathway.

The said tumour cells include cancer such as but not limited to bone cancer, cancer of the head or neck, pancreatic cancer, skin cancer, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumours of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumour angiogenesis, spinal axis tumour, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers.

In yet another further embodiment the present invention provides a method of treating an infectious disease in a subject comprising administering to the subject a therapeutically effective amount of the compound of the present inventioncapable of inhibiting the programmed cell death 1 (PD1) signaling pathway such that the subject is treated for the infectious disease.

Still yet another embodiment of the present invention provides a method of treating bacterial, viral and fungal infections in a subject comprising administering to the subject a therapeutically effective amount of the compound of the present invention capable of inhibiting the programmed cell death 1 (PD1) signalling pathway such that the subject is treated for the bacterial, viral and fungal infections.

The infectious disease includes but not limited to HIV, Influenza, Herpes, Giardia, Malaria, Leishmania, the pathogenic infection by the virus Hepatitis (A, B, & C), herpes virus (e.g., VZV, HSV-I, HAV-6, HSV-II, and CMV, Epstein Barr virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, cornovirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus, pathogenic infection by the bacteria chlamydia, rickettsial bacteria, mycobacteria, staphylococci, streptococci, pneumonococci, meningococci and conococci, klebsiella, proteus, serratia, pseudomonas, E. coli, legionella, diphtheria, salmonella, bacilli, cholera, tetanus, botulism, anthrax, plague, leptospirosis, and Lyme's disease bacteria, pathogenic infection by the fungi Candida (albicans, krusei, glabrata, tropicalis, etc.), Cryptococcus neoformans, Aspergillus (fumigatus, niger, etc.), Genus Mucorales (mucor, absidia, rhizophus), Sporothrix schenkii, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Coccidioides immitis and Histoplasma capsulatum, and pathogenic infection by the parasites Entamoeba histolytica, Balantidium coli, Naegleriafowleri, Acanthamoeba sp., Giardia lambia, Cryptosporidium sp., Pneumocystis carinii, Plasmodium vivax, Babesia microti, Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondi, Nippostrongylus brasiliensis.

The compounds of the present invention may be used as single drugs or as a pharmaceutical composition in which the compound is mixed with various pharmacologically acceptable materials.

The pharmaceutical composition is usually administered by oral or inhalation routes, but can be administered by parenteral administration route. In the practice of this invention, compositions can be administered, for example, by orally, intravenous infusion, topically, intraperitoneally, intravesically or intrathecally. Examples of the parenteral administration includes but not limited to intraarticular (in the joints), intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes,

include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Oral administration, parenteral administration, subcutaneous administration and intravenous administration are the preferred methods of administration.

The dosage of the compounds of the present invention varies depending on age, weight, symptom, therapeutic efficacy, dosing regimen and/or treatment time. Generally, they may be administered by oral or inhalation routes, in an amount of 1 mg to 100 mg per time, from once a couple of days, once 3 days, once 2 days, once a day to a couple of times a day, in the case of an adult, or continuously administered by oral or inhalation routes from 1 to 24 hours a day. Since the dosage is affected by various conditions, an amount less than the above dosage may sometimes work well enough, or higher dosage may be required in some cases.

The compounds of the present invention may be administered in combination with other drugs for (1) complementation and/or enhancement of prevention and/or therapeutic efficacy of the preventive and/or therapeutic drug of the present invention, (2) dynamics, absorption improvement, dosage reduction of the preventive and/or therapeutic drug of the present invention, and/or (3) reduction of the side effects of the preventive and/or therapeutic drug of the present invention.

A concomitant medicine comprising the compounds of the present invention and other drug may be administered as a combination preparation in which both components are contained in a single formulation, or administered as separate formulations. The administration by separate formulations includes simultaneous administration and administration with some time intervals. In the case of the administration with some time intervals, the compound of the present invention can be administered first, followed by another drug or another drug can be administered first, followed by the compound of the present invention. The administration method of the respective drugs may be the same or different.

The dosage of the other drug can be properly selected, based on a dosage that has been clinically used. The compounding ratio of the compound of the present invention and the other drug can be properly selected according to age and weight of a subject to

be administered, administration method, administration time, disorder to be treated, symptom and combination thereof. For example, the other drug may be used in an amount of 0.01 to 100 parts by mass, based on 1 part by mass of the compound of the present invention. The other drug may be a combination of two or more kind of arbitrary drugs in a proper proportion. The other drug that complements and/or enhances the preventive and/or therapeutic efficacy of the compound of the present invention includes not only those that have already been discovered, but those that will be discovered in future, based on the above mechanism.

Diseases on which this concomitant use exerts a preventive and/or therapeutic effect are not particularly limited. The concomitant medicine can be used for any diseases, as long as it complements and/or enhances the preventive and/or therapeutic efficacy of the compound of the present invention.

The compound(s) of the present invention can be used with an existing chemotherapeutic concomitantly or in a mixture form. Examples of the chemotherapeutic include an alkylation agent, nitrosourea agent, antimetabolite, anticancer antibiotics, vegetable-origin alkaloid, topoisomerase inhibitor, hormone drug, hormone antagonist, aromatase inhibitor, P-glycoprotein inhibitor, platinum complex derivative, other immunotherapeutic drugs and other anticancer drugs. Further, it can be used with a cancer treatment adjunct, such as a leucopenia (neutropenia) treatment drug, thrombocytopenia treatment drug, antiemetic and cancer pain intervention drug, concomitantly or in a mixture form.

In one embodiment, the compound(s) of the present invention can be used with other immunomodulators and/or a potentiating agent concomitantly or in a mixture form. Examples of the immunomodulator include various cytokines, vaccines and adjuvants. Examples of these cytokines, vaccines and adjuvants that stimulates immune responses include but not limited to GM-CSF, M-CSF, G-CSF, interferon-α, β, or γ, IL-1, IL-2, IL-3 , IL-12, Poly (I:C) and C_pG.

In another embodiment, the potentiating agents includes cyclophosphamide and analogs of cyclophosphamide, anti-TGFβ and Imatinib (Gleevac), a mitosis inhibitor, such as paclitaxel, Sunitinib (Sutent) or other antiangiogenic agents, an aromatase inhibitor, such as letrozole, an A2a adenosine receptor (A2AR) antagonist, an angiogenesis inhibitor, anthracyclines, oxaliplatin, doxorubicin, TLR4 antagonists, and IL-18 antagonists.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in art to which the subject matter herein belongs. As used herein, the following definitions are supplied in order to facilitate the understanding of the present invention.

As used herein, the term "acyl" refers to RC(O)-, wherein R is alkyl as defined below. Examples of acyl group include, but are not limited to -C(O)CH_3, -C(O)CH_2CH_3, -C(O)$(CH_2)_2CH_3$, -C(O)$(CH_2)_3CH_3$, -C(O)$(CH_2)_4CH_3$ or -C(O)$(CH_2)_5CH_3$.

As used herein the term "alkyl" refers to a hydrocarbon chain radical that includes solely carbon and hydrogen atoms in the backbone, containing no unsaturation, having from one to twenty carbon atoms (i.e., C_{1-20} alkyl) or one to ten carbon atoms (i.e., C_{1-10} alkyl) or one to five carbon atoms (i.e., C_{1-5} alkyl) and which is attached to the rest of the molecule by a single bond, e.g., including but not limited to methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, tert-butyl, isopentyl or neopentyl. Unless set forth or recited to the contrary, all alkyl groups described or claimed herein may be straight chain or branched, substituted or unsubstituted.

As used herein, the term "amidated C-terminus" refers to that the C-terminal of the amino acid in amide form.

As used herein, the term "amide form" refers to primary, secondary and/or tertiary amides and may be represented by the formula -C(O)NR_xR_y, wherein each of R_x and R_y independently represents hydrogen or alkyl.

As used herein, the term "amino" refers to -NH_2 group. Unless set forth or recited to the contrary, all amino groups described or claimed herein may be substituted or unsubstituted.

As used herein, the term "amino acid" refers to amino acids having L or D stereochemistry at the alpha carbon.

As used herein, the term 'compound(s)' refers to the compounds disclosed in the present invention.

As used herein, the term "comprise" or "comprising" is generally used in the sense of include, that is to say permitting the presence of one or more features or components.

As used herein the term "ester" refers to (C_1-C_6) linear or branched alkyl, (C_4-C_{10})aryl, (C_4-C_{10})heteroaryl or arylalkyl esters.

As used herein the term “esterified C-terminus” refers to that the C-terminal of the amino acid in ester form.

As used herein the term “free C-terminus’ refers to that the C-terminal of the amino acid in -CO_2H form.

As used herein, the term “hydroxyl” refers to –OH group.

As used herein, the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting.

As used herein, the term "optionally substituted" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: alkyl, alkoxy, acyl, halo, and hydroxyl. It is understood that the substituent may be further substituted.

“Pharmaceutically acceptable salt” is taken to mean an active ingredient, which comprises a compound of the formula (I) in the form of one of its salts, in particular if this salt form imparts improved pharmacokinetic properties on the active ingredient compared with the free form of the active ingredient or any other salt form of the active ingredient used earlier. The pharmaceutically acceptable salt form of the active ingredient can also provide this active ingredient for the first time with a desired pharmacokinetic property which it did not have earlier and can even have a positive influence on the pharmacodynamics of this active ingredient with respect to its therapeutic efficacy in the body.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary as well as human pharmaceutical use.

The term “stereoisomer” refers to any enantiomers, diastereoisomers, or geometrical isomers of the compounds of formula (I), wherever they are chiral or when they bear one or more double bond. When the compounds of the formula (I) and related formulae are chiral, they can exist in racemic or in optically active form. Since the pharmaceutical activity of the racemates or stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product or even the intermediates can be separated into enantiomeric compounds by chemical or physical measures known to the person skilled in the art or even employed as such in the synthesis. In the case of racemic amines, diastereomers are formed from

the mixture by reaction with an optically active resolving agent. Examples of suitable resolving agents are optically active acids such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitable N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline), or the various optically active camphorsulfonic acids. Also advantageous is chromatographic enantiomer resolution with the aid of an optically active resolving agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other derivatives of carbohydrates or chirally derivatised methacrylate polymers immobilised on silica gel).

The term "subject" includes mammals (especially humans) and other animals, such as domestic animals (e.g., household pets including cats and dogs) and non-domestic animals (such as wildlife).

“Therapeutically effective amount” or “efficient amount” means sufficient amount of the compound(s) of the present invention that (i) treats or prevents the particular disease, disorder or syndrome (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, disorder or syndrome or (iii) prevents or delays the onset of one or more symptoms of the particular disease, disorder or syndrome described herein. In the case of cancer, the therapeutically effective amount of the drug may decrease the number of cancer cells; decrease the cancer size; inhibit (i.e., slow to some extent and alternatively stop) cancer cell infiltration into peripheral organs; suppress (i.e., slow to some extent and alternatively stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. In the case of infectious disease states, the therapeutic effective amount is an amount sufficient to decrease or alleviate an infectious diseases, the symptoms of an infections caused by bacterial, viral and fungal.

Naturally-occurring amino acids are identified throughout the specification by the conventional three-letter abbreviations indicated in the below table 2.

Table 2 (Amino acid codes)

Name	3-letter code	Name	3-letter code
Alanine	Ala	Hydroxyproline	Hyp
Asparagine	Asn	Lysine	Lys
Aspartic acid	Asp	Phenylalanine	Phe
Cysteine	Cys	Proline	Pro

Glutamic acid	Glu	Serine	Ser
Glutamine	Gln	Threonine	Thr
Glycine	Gly	Valine	Val

The abbreviations used in the entire specification may be summarized hereinbelow with their particular meaning.

°C (degree Celsius); δ (delta); % (percentage); brine (NaCl solution); CH_2Cl_2/DCM (Dichloromethane); BnBr (Benzyl bromide); br s (Broad singlet); Boc (Tert-butyloxycarbonyl); Bzl (Benzyloxy-carbonyl); Cs_2CO_3 (Caesium carbonate); d (Doublet); DIPEA (N,N-Diisopropylethylamine); DMF (Dimethyl formamide); DMSO (Dimethyl sulphoxide); DMSO-d_6 (Deuterated DMSO); EDC.HCl/EDCI (1-(3-Dimethyl aminopropyl)-3-carbodiimide hydrochloride); Et_2NH (Diethylamine); Fmoc (9-Fluorenylmethyloxycarbonyl); g or gr (gram); H or H_2 (Hydrogen); H_2O (Water); HOBt/HOBT (1-Hydroxy benzotriazole); HCl (Hydrochloric acid); h or hr (Hours); Hz (Hertz); HPLC (High-performance liquid chromatography); K_2CO_3 (Potassium carbonate); LCMS (Liquid chromatography mass spectroscopy); MeOH (Methanol); mmol (Millimoles); M (Molar); µl (Microlitre); mL (Millilitre); mg (Milligram); m (Multiplet); MHz (Megahertz); MS (ES) (Mass spectroscopy-electro spray); min./min (Minutes); Na (Sodium); $NaHCO_3$ (Sodium bicarbonate); $NH_2NH_2.H_2O$ (Hydrazine hydrate); NMM (N-methyl morpholine); Na_2SO_4 (Sodium sulphate); N_2 (Nitrogen); NMR (Nuclear magnetic resonance spectroscopy); Pd/C (Palladium on carbon); PD-L1 (Programmed death-ligand 1); PD-L2 (Programmed cell death 1 ligand 2); prep-HPLC/preparative HPLC (Preparative High-performance liquid chromatography); S (Singlet); ^{t}Bu/tBu (Tertiary butyl); TEA/Et_3N (Triethylamine); TLC (Thin Layer Chromatography); THF (Tetrahydrofuran); TIPS (Triisopropylsilane); TFA/CF_3COOH (Trifluoroacetic acid); t (Triplet); t_{R} = (Retention time); TPP (Triphenylphosphine); Trt (Trityl or Triphenylmethyl), etc.

EXPERIMENTAL

An embodiment of the present invention provides the preparation of compounds of formula (I) according to the procedures of the following examples, using appropriate materials. Those skilled in the art will understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. Moreover, by utilizing the procedures described in detail, one of ordinary skill in the art can prepare additional compounds of the present invention.

The starting materials are generally available from commercial sources such as Sigma-Aldrich, USA or Germany; Chem-Impex USA; G.L. Biochem, China and Spectrochem, India.

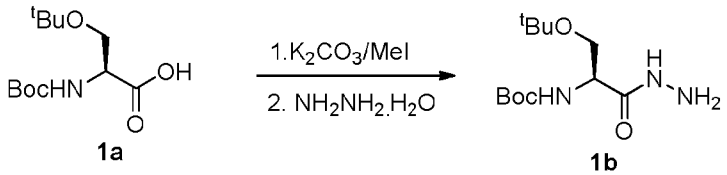
Purification and characterization of compounds

Analytical HPLC method: Analytical HPLC was performed using on ZIC HILIC 200A° column (4.6 mm × 250 mm, 5 µm), Flow rate: 1.0 mL / min. The elution conditions used are: Buffer A: 5 mmol ammonium acetate, Buffer B: Acetonitrile, Equilibration of the column with 90 % buffer B and elution by a gradient of 90 % to 40 % buffer B during 30 min.

Preparative HPLC Method: The crude material was purified by preparative HPLC using ZIC HILIC 200A° column (21.2 mm × 150 mm, 5 µm). The elution conditions used are Eluent: A: 5 mmol ammonium acetate B: Acetonitrile, Flow rate: 20 mL / min. The compound was eluted by gradient elution 0-2 min = 90 % buffer B, 2-20 min = 90-40 % buffer B with a flow rate of 20 mL/min.

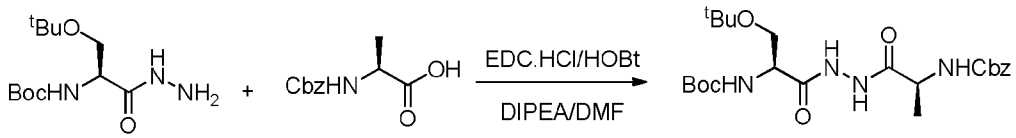
Example 1: Synthesis of compound 1

Step 1a:



Potassium carbonate (3.9 g, 28 mmol) and methyl iodide (3.26 g, 22mmol) were added to a solution of **1a** (5.0 g, 19.15 mmol) in DMF (50 mL) and stirred at room temperature for 3 h. The completeness of the reaction was confirmed by TLC analysis. DMF was evaporated from the reaction mass and partitioned between water and ethyl acetate. Organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure to yield crude compound. The resulting crude compound was dissolved in methanol (50 mL), 99% hydrazine hydrate (12.5 mL) was added to the crude compound solution and stirred at room temperature for 6 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was evaporated under reduced pressure to yield 5 g of compound **1b** (Yield: 96.15%), LCMS: 276.3 $(M+H)^+$.

Step 1b:



1b 1c 1d

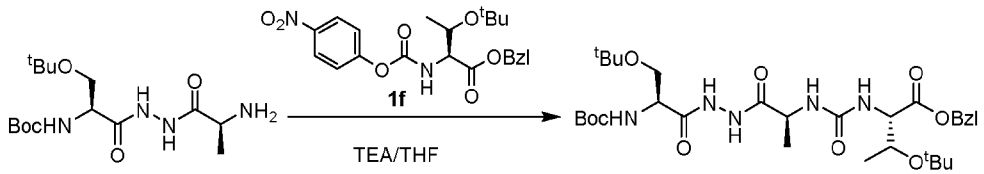
DIPEA (4.3 g, 33.5 mmol) was added slowly to a stirred solution of **1c** (3 g, 13.4 mmol), HOBt (2.2 g, 16.1 mmol) and EDC.HCl (3.1 g, 16.1 mmol) in DCM (50 mL) at room temperature. To the above reaction mixture **1b** (3.7 g, 13.4 mmol) was added slowly and stirred at room temperature for 12 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was then quenched with ice, precipitate was filtered and the solid re-crystallized with CH_2Cl_2 to yield 6 g of **1d,** (Yield: 93%), LCMS: 481.4 $(M+H)^+$.

Step 1c:

1d 1e

To a solution of **1d** (1.5 g) in methanol (20 mL) under inert atmosphere 10% Pd/C (0.5 g) was added and stirred for 1 h under H_2 atmosphere. The completion of the reaction was confirmed by TLC analysis. The Pd/C catalyst was removed by filtration through a Celite® pad, and washed with 50 mL of methanol. The combined organic filtrate on evaporation under reduced pressure to yield 1 g of **1e** (Yield: 93%), LCMS: 347.2 $(M+H)^+$.

Step 1d:

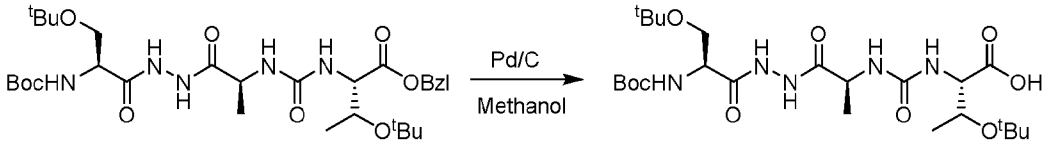


1e 1g

The urea linkage was carried out using coupling of **1e** (1 g, 2.8 mmol) in THF (20 mL) at room temperature, with **1f** (1.24 g, 2.8 mmol). The coupling was initiated by the addition of TEA (0.42 g, 4.2 mmol) and the resultant mixture was stirred at room temperature. After the completion of 20 h, THF was evaporated from the reaction mass, and partitioned between water and ethyl acetate. Organic layer was washed with water, brine,

dried over Na_2SO_4 and evaporated under reduced pressure to yield crude compound which was further washed with diethyl ether to yield 1.4 g of **1g**. LCMS: 638.2 $(M+H)^+$.

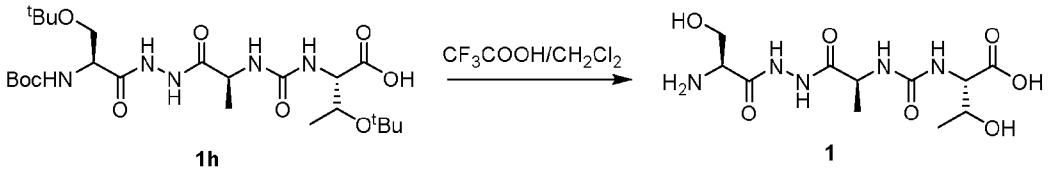
Step 1e:



1g **1h**

To a solution of **1g** (1.4 g) in methanol (10 mL) under inert atmosphere, 10% Pd-C (0.4 g) was added and stirred at room temperature for 1 h under H_2 atmosphere. The completion of the reaction was confirmed by TLC analysis. The Pd-C catalyst was then removed by filtration through a Celite® pad, which was then washed with 40 mL of methanol. The combined organic filtrate was evaporated under reduced pressure to obtain the desired 1.1 g of **1h**. LCMS: 548.1 $(M+H)^+$.

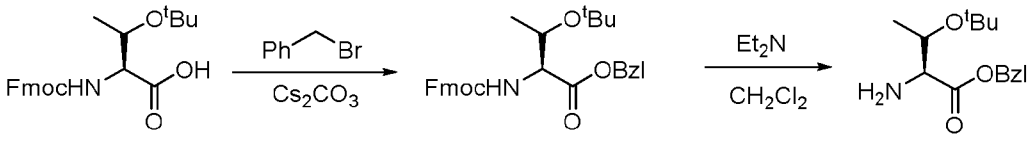
Step 1f:



1h **1**

To a solution of **1h** (1 g) in CH_2Cl_2 (10 mL), trifluoroacetic acid (10 mL) and catalytic amount of triisopropylsilane were added and stirred for 3 h at room temperature. The resulting solution was concentrated in vacuum to yield 0.2 g of compound **1** (Yield: 32.6%), LCMS: 336.2 $(M+H)^+$. The crude solid material was purified as preparative HPLC method described under experimental conditions (yield: 30 mg, HPLC: t_R= 13.9 min).

Synthesis of 1f, (NO_2-C_6H_4-OCO-Thr(tBu)-OBzl):

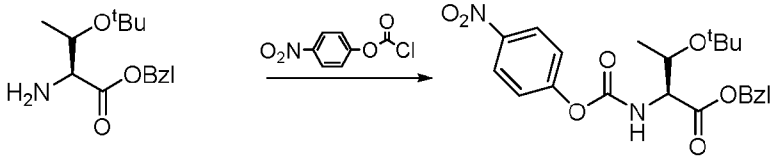


Fmoc-Thr(tBu)-OH **1i** **1j**

To a solution of Fmoc-Thr(tBu)-OH (15.0 g, 37.7 mmol) in 100.0 mL of DMF, Cs_2CO_3 (14.8 g, 45.2 mmol) was added and the resutling mixture was cooled to 0 °C. To the reaction mixture benzyl bromide (7.74 g, 345.2 mmol) was added and the solution was stirred for 30 min at ice cold temperature followed by at room temperature for 12 h. The

reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate (150 mL). The organic layer was washed with water (2 × 100 mL), brine (1 × 100 mL) and dried over Na_2SO_4. The filtered solution was concentrated and purified by silica gel column chromatogrophy (Eluent: 0-30% ethyl acetate in Hexane) to yeild 18.5 g of **1i** as a white solid. LCMS: 433.1 $(M\text{-}O^tBu+H)^+$, 397.2 $(M\text{-}OBzl)^+$.

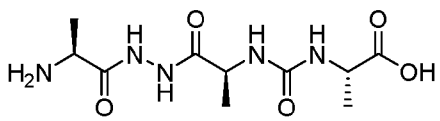
Fmoc group on **1i** was deprotected by adding diethylamine (40.0 mL) to **1i** (10.0 g, 20.5 mmol) in CH_2Cl_2 (40.0 mL). After an hour the resulting solution was concentrated in vacuum and the thick-residue was purified by column chromatography over neutral alumina (Eluent: 0-50% ethyl acetate in hexane then 0-5% methanol in chloroform) to yield 3.9 g of **1j** (Yield: 72%), LCMS: 266.5 $(M+H)^+$.



1j **1f**

To a stirred solution of **1j** (1.6 g, 6.0 mmol) in CH_2Cl_2 (30 mL), TEA (1.2 g, 12.0 mmol) was added followed by the addition of 4-nitrophenyl chloroformate (1.3 g, 6.6 mmol) in CH_2Cl_2 (10 mL). The resultant mixture was stirred at room temperature for 12 h. The completion of the reaction was confirmed by TLC analysis. After completion of reaction, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1.0 M of sodium bisulphate (50 mL × 2) and 1.0 M sodium carbonate (50 mL × 2), dried over Na_2SO_4 and evaporated under reduced pressure to yield crude compound **1f**, which was further purified by silica gel column chromatography (eluent: 0-20% ethyl acetate in Hexane) to yield 0.8 g of **1f**. ^1H NMR (DMSO-d_6, 300 MHz): δ 8.23-8.27 (m, 2H), 7.27-7.39 (d, 7H), 5.99-6.01 (m, 1H), 5.10-5.25 (m, 2H), 4.28-4.31 (m, 2H), 1.28-1.30 (d, 3H), 1.12 (s, 9H).

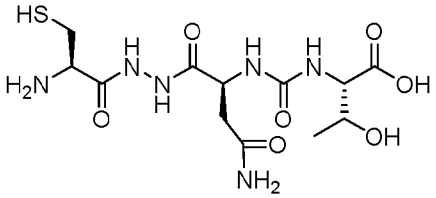
Example 2: Synthesis of compound 2



The compound **2** was synthesised by similar procedure as depicted in Example **1** using Boc-L-Ala-OH instead of Boc-L-Ser(tBu)-OH (compound 1a) and L-Ala-OtBu instead of L-Thr(tBu)-OBzl (compound 1j) to yield 1.5 g of crude compound 2. The crude solid

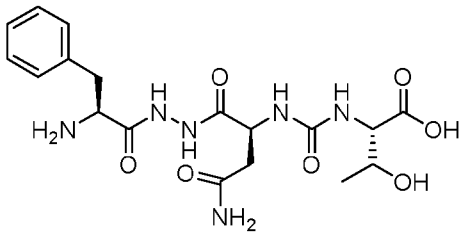
material (0.5 g) was purified as preparative HPLC method described under experimental conditions (yield: 0.17 g, analytical HPLC: t_R = 15.2 min), LCMS: 290.5 $(M+H)^+$.

Example 3: Synthesis of compound 3



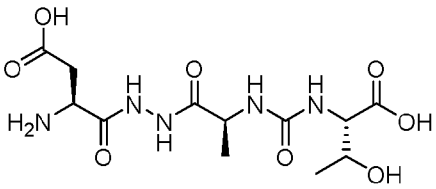
The compound **3** was synthesised by similar procedure as depicted in Example **1** using Boc-L-Cys(tBu)-OH instead of Boc-L-Ser(tBu)-OH (compound 1a) and Cbz-Asn-OH instead of Cbz-Ala-OH (compound 1c). Yield: 2 g (crude); LCMS: 434.4 $(M+H_2O)^+$.

Example 4: Synthesis of compound 4



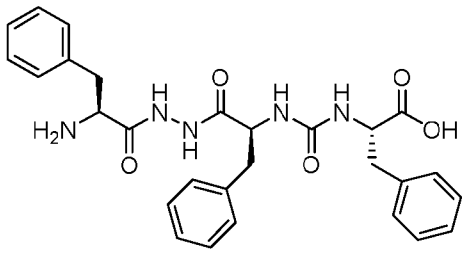
The compound **4** was synthesised by similar procedure as depicted in Example **1** using Boc-L-Phe-OH instead of Boc-L-Ser(tBu)-OH (compound 1a) and Cbz-Asn-OH instead of Cbz-Ala-OH (compound 1c). The crude solid material (0.06 g) was purified as preparative HPLC method described under experimental conditions. LCMS: 439.2 $(M+H)^+$, HPLC: t_R = 8.63 min.

Example 5: Synthesis of compound 5



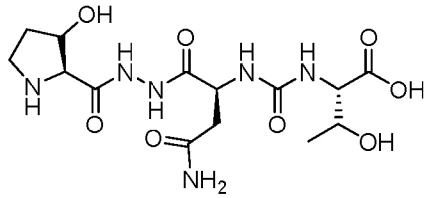
The compound **5** was synthesised by similar procedure as depicted in Example **1** using Boc-L-Asp(OtBu)-OH instead of Boc-L-Ser(tBu)-OH (compound 1a). The crude solid material (0.35 g) was purified as preparative HPLC method described under experimental conditions. LCMS: 364.1 $(M+H)^+$, HPLC: t_R = 12.19 min.

Example 6: Synthesis of compound 6



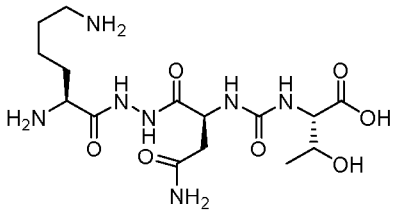
The compound **6** was synthesised by similar procedure as depicted in Example **1** using Boc-L-Phe-OH instead of Boc-L-Ser(tBu)-OH (compound 1a), Cbz-Phe-OH instead of Cbz-Ala-OH (compound 1c) and H-Phe-OtBu instead of L-Thr(tBu)-OBzl (compound 1j). The crude solid material (0.18 g) was purified as preparative HPLC method described under experimental conditions. LCMS: 518.5 $(M+H)^+$, HPLC: t_R = 4.8 min.

Example 7: Synthesis of compound 7



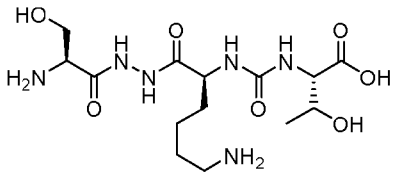
The compound **7** was synthesised by similar procedure as depicted in Example **1** using Boc-L-Hyp-OMe instead of Boc-L-Ser(tBu)-OH and Fmoc-Asn-OH instead of Cbz-Ala-OH (compound 1c). The crude solid material (0.6 g) was purified as preparative HPLC method described under experimental conditions. LCMS: 405.2 $(M+H)^+$, HPLC: t_R = 15.15 min.

Example 8: Synthesis of compound 8



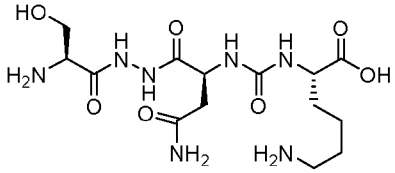
The compound **8** was synthesised by similar procedure as depicted in Example **1** using Boc-Lys(Boc)-OH instead of Boc-L-Ser(tBu)-OH (compound 1a) and Fmoc-Asn-OH instead of Cbz-Ala-OH (compound 1c). The crude solid material (0.15 g) was purified as preparative HPLC method described under experimental conditions. LCMS: 420.5 $(M+H)^+$, HPLC: t_R = 20.15 min.

Example 9: Synthesis of compound 9



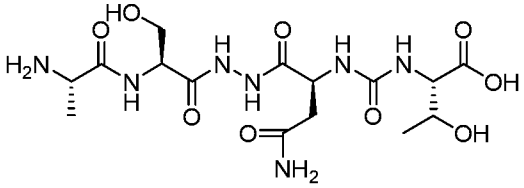
The compound **9** was synthesised using by procedure as depicted in Example **1** using Fmoc-Lys(Boc)-OH instead of Cbz-L-Ala-OH (compound 1c). The crude solid material (1 g) was purified as preparative HPLC method described under experimental conditions LCMS: 393.2 $(M+H)^+$, HPLC: t_R = 9.95 min.

Example 10: Synthesis of compound 10

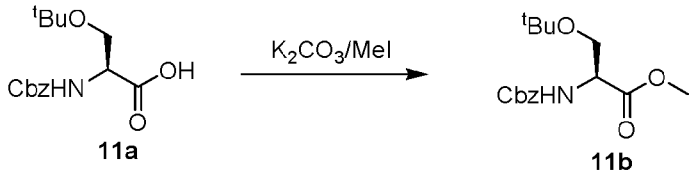


The compound **10** was synthesised using similar procedure as depicted in Example **1** using Fmoc-Asn(Trt)-OH instead of Cbz-L-Ala-OH (compound 1c) and H-Lys(Boc)-OtBu instead of L-Thr(tBu)-OBzl (compound 1j). The crude solid material (1 g) was purified as preparative HPLC method described under experimental conditions. LCMS: 406.2 $(M+H)^+$, HPLC: t_R = 16.91 min.

Example 11: Synthesis of compound 11



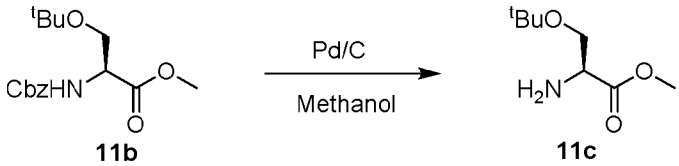
Step 11a:



Potassium carbonate (7.0 g, 50.8 mmol) and methyl iodide (2.5 g, 18.6 mmol) were added to a solution of compound **11a** (5.0 g, 16.9 mmol) in DMF (35 mL) and stirred at room temperature for 3 h. The completeness of the reaction was confirmed by TLC analysis. DMF was evaporated from the reaction mass, and partitioned between water and ethyl acetate. Organic layer was washed with water, brine, dried over Na_2SO_4 and

evaporated under reduced pressure get the desired 4.4 g of compound **11b** (Yield: 84.6%). LCMS: 310.1 $(M+H)^+$.

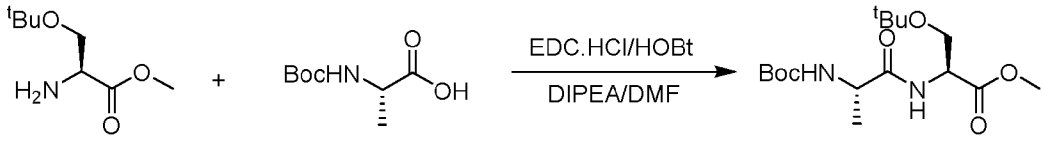
Step 11b:



11b **11c**

To a solution of compound **11b** (4.4 g) in methanol (25 mL) under inert atmosphere 10% Pd/C (0.8 g) was added and stirred for 10 h under H_2 atmosphere. The completion of the reaction was confirmed by TLC analysis. The Pd/C catalyst was then removed by filtration through a Celite® bed and washed with 50 mL of methanol. The combined organic filtrate on evaporation under reduced pressure to yield 2.0 g of compound **11c** (Yield: 80%). LCMS: 176.1 $(M+H)^+$.

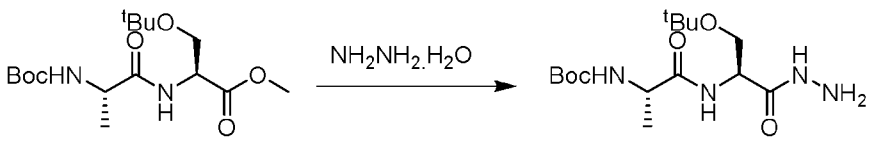
Step 11c:



11c **11d** **11e**

DIPEA (2.2 g, 17.1 mmol) was added slowly to a stirred solution of **11c** (1.1 g, 5.7 mmol), HOBt (0.9 g, 6.8 mmol) and EDC.HCl (1.3 g, 6.8 mmol) in DMF (10 mL). The reaction mixture was stirred at room temperature for 5 min. To the above reaction mixture compound **11d** (1.0 g, 5.7 mmol) was added slowly and stirred at room temperature for 12 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was then quenched with ice and the precipitate was filtered. The solid re-crystallized with CH_2Cl_2 to yield 1.1 g of compound **11e**, (Yield: 57.8%). LCMS: 347.4 $(M+H)^+$.

Step 11d:



11e **11f**

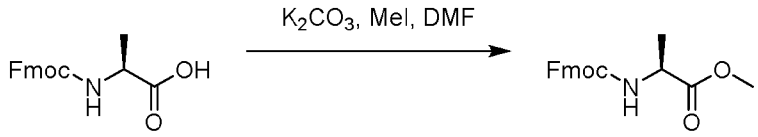
To a solution of compound **11e** (1.1 g, 3.17 mmol) in methanol (10 mL), 99% hydrazine hydrate (1.2 mL) was added and stirred at room temperature for 6 h. The completeness of

the reaction was confirmed by TLC analysis. The reaction mixture was evaporated under reduced pressure to yield 1g of compound **11f** (Yield: 91.15%), LCMS: 347.4 $(M+H)^+$.

The compound **11** was synthesised by similar procedure as depicted in Example **1** using compound **11f** in place compound **1b** (Example 1, step 1a) and Cbz-Asn-OH in place of Cbz-Ala-OH to yield 0.25 g crude material of the title compound **11**, LCMS: 450.2 $(M+H)^+$.

Example 12: Synthesis of compound 12

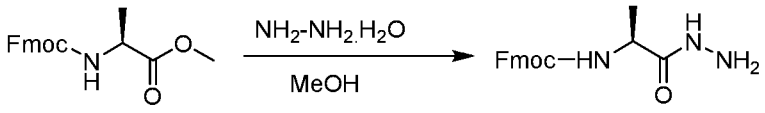
Step 12a:



12a **12b**

Potassium carbonate (4.4 g, 32.2 mmol) and methyl iodide (2.5 g, 17.7 mmol) were added to a solution of compound **12a** (5.0 g, 16.1 mmol) in DMF and stirred at room temperature for 2 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was partitioned between water and ethyl acetate. Organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure to get 5.0 g of compound **12b**, LCMS: 326.5 $(M+H)^+$.

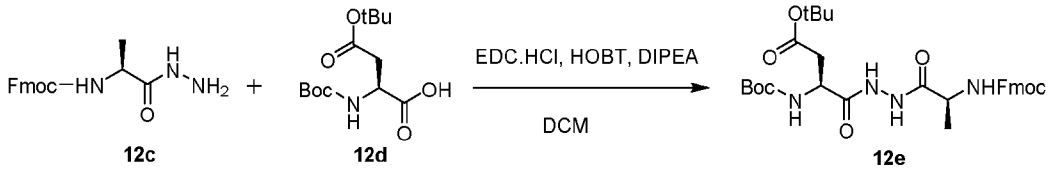
Step 12b:



12b **12c**

Hydrazine hydrate (6.9 g, 138 mmol) was added to a solution of compound **12b** (4.5 g, 13.8 mmol) in methanol and stirred at room temperature for 2 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was evaporated under reduced pressure; the residue obtained was partitioned between water and ethyl acetate. Organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure yielded 3.2 g of compound **12c**. LCMS: 326.2 $(M+H)^+$.

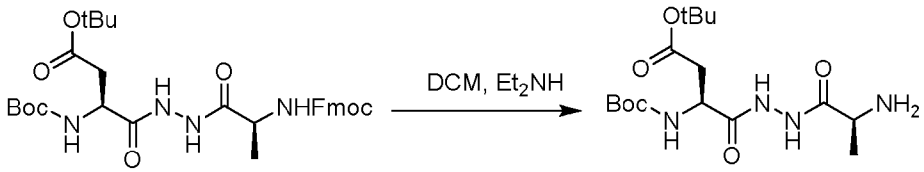
Step 12c:



12c **12d** **12e**

DIPEA (3.2 g, 25.3 mmol) was added slowly to a stirred solution of **12d** (2.7 g, 9.2 mmol), HOBt (1.36 g, 10.1 mmol) and EDC.HCl (1.93 g, 10.1 mmol) in DCM and stirred at room temperature. To the above reaction mixture **12c** (3.0 g, 9.2 mmol) was added slowly and stirred at room temperature for 1 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mass was partitioned between ethyl acetate and water. Organic layer was washed with citric acid, $NaHCO_3$, brine, and dried over Na_2SO_4 and evaporated under reduced pressure to give crude compound. The crude was washed with diethyl ether and dried to yield 4.52 g of compound **12e**; LCMS: 619.4$(M+Na)^+$.

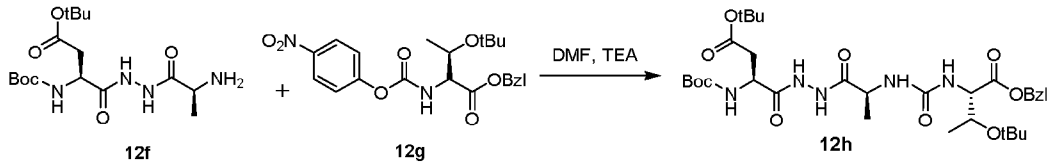
Step 12d:



12e **12f**

Fmoc group was deprotected by the addition of diethylamine (13.5 mL) to a solution of compound **12e** (4.5 g, 7.54 mmol) in CH_2Cl_2 at -10 °C. The reaction was stirred at room temperature for 3 h. Progress of reaction was monitored by TLC. After completion, the resulting solution was concentrated in vacuum to get a thick gummy residue. The crude compound was purified by silica gel (60-120mesh) column chromatography (eluent: 5% methanol in DCM) to afford 2.2 g of compound **12f**, LCMS: 375.5 $(M+H)^+$, 397.4 $(M+Na)^+$.

Step 12e:

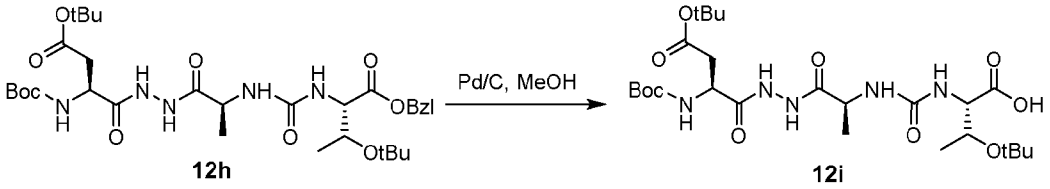


12f **12g** **12h**

The urea linkage was carried out using coupling of **12f** (1.5 g, 4.0 mmol) in DMF at room temperature, with **12g** (1.72 g, 4.0 mmol). The coupling was initiated by the addition of TEA (0.81 g, 8.0 mmol) and the resultant mixture was stirred at room temperature for 30 min. Progress of reaction was monitored by TLC. After completion, the reaction mass was partitioned between ethyl acetate and water. Organic layer was washed with citric acid, brine, dried over Na_2SO_4 and evaporated under reduced pressure

to give crude compound. The resulting solid was washed with ether and dried to afford 1.1 g of Compound **12h**.

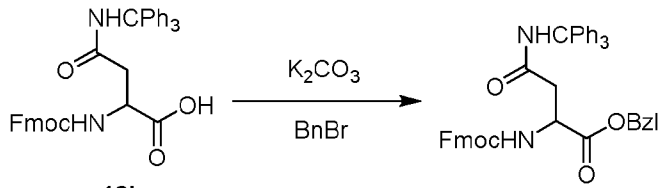
Step 12f:



12h **12i**

To a solution of compound **12h** (1.1 g, 1.65 mmol) in methanol, was added 10% Pd-C (0.15 g) under inert atmosphere. The mixture was stirred for 1 h under H_2 atmosphere at room temperature. The completion of the reaction was confirmed by TLC analysis. The Pd-C catalyst was then removed by filtration through a Celite® pad and washed with methanol (2 × 50 mL). The combined organic filtrate on evaporation under reduced pressure resulted in the isolation of 0.7 g compound **12i**, LCMS: 576.3 $(M+H)^+$, 598.4 $(M+H)^+$.

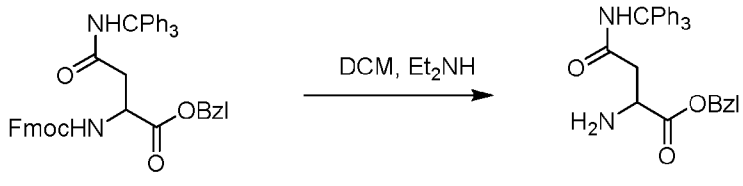
Step 12g:



12j **12k**

To a stirred solution of **12j** (10 g, 16.7 mmol) in DMF, potassium carbonate (4.62 g, 33.6 mmol) and BnBr (3.2 g, 18.5 mmol) were added and continued reaction at room temperature for 2 h. The progress of reaction was monitored by TLC. After completion, the reaction mass was partitioned between ethyl acetate and water. Organic layer was washed with water, brine, and dried over Na_2SO_4 and evaporated under reduced pressure. The resulting solid was washed with n-hexane and dried to yield 10.0 g of compound **12k**.

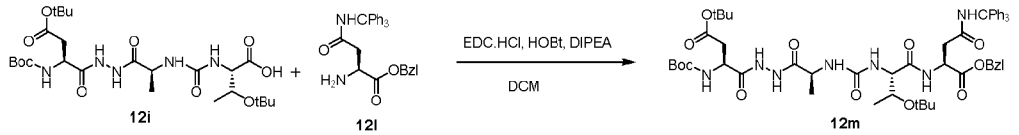
Step 12h:



12k **12l**

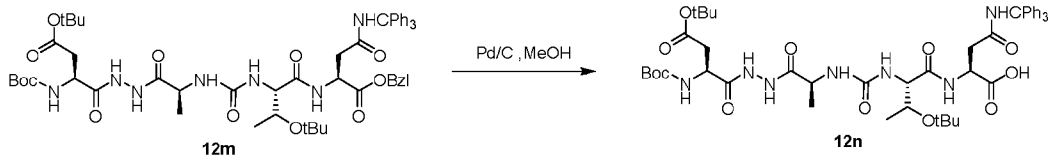
Fmoc group was deprotected by the addition of diethylamine (30 mL) to a solution of compound **12k** (10 g, 14.5 mmol) in CH_2Cl_2 at -10 °C. The reaction was stirred at room temperature for 3 h. Progress of reaction was monitored by TLC. After completion, the resulting solution was concentrated in vacuum to get a thick gummy residue. The crude compound was purified by silica gel (60-120mesh) column chromatography (eluent: 5% methanol in DCM) to afford 6.0 g of compound **12l**.

Step 12i:



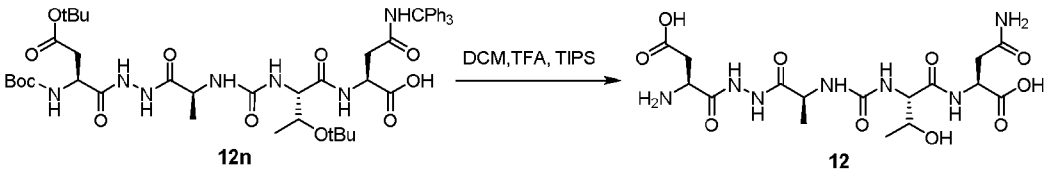
DIPEA (4.8 g, 3.8 mmol) was added slowly to a stirred solution of **12i** (0.83 g, 1.5 mmol), HOBt (0.22 g, 1.65 mmol) and EDC.HCl (0.32 g, 1.65 mmol) in DCM and stirred at room temperature. To the above reaction mixture **12l** (0.47 g, 1.5 mmol) was added slowly and stirred at room temperature for 1 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mass was partitioned between ethyl acetate and water. Organic layer was washed with citric acid, $NaHCO_3$, brine, and dried over Na_2SO_4 and evaporated under reduced pressure to give crude compound. The crude was washed with diethyl ether and dried to yield 1.0 g of compound **12m**.

Step 12j:



To a solution of compound **12m** (1.0 g, 0.98 mmol) in methanol, was added 10% Pd-C (0.1 g) under inert atmosphere. The mixture was stirred for 1 h under H_2 atmosphere at room temperature. The completion of the reaction was confirmed by TLC analysis. The Pd-C catalyst was then removed by filtration through a Celite® pad and washed with methanol (2 × 50 mL). The combined organic filtrate on evaporation under reduced pressure resulted in the isolation of 0.77 g compound **12n**, LCMS: 932.7 $(M+H)^+$, 954.8 $(M+Na)^+$.

Step 12k:

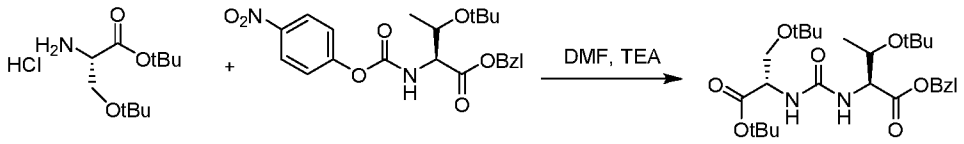


12n 12

To a solution of compound **12n** (0.77 g, 0.77 mmol) in CH_2Cl_2, trifluoroacetic acid (2.5 mL) and catalytic amount of triisopropylsilane were added and stirred at room temperature for 2 h. The resulting solution was concentrated under nitrogen and the solid material was further washed with diethyl ether, dried under vacuum to afford 0.5 g of crude compound. Crude compound was further purified by preparative HPLC method described under experimental conditions to yield pure compound **12**, LCMS: 478.2. $(M+H)^+$.

Example 13: Synthesis of compound 13

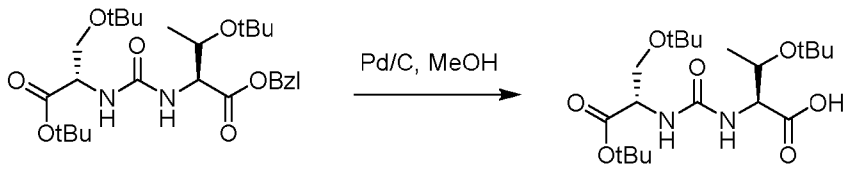
Step 13a:



13a 13b 13c

Compound **13b** (2.5 g, 5.9 mmol), TEA (1.2 g, 11.8 mmol) dissolved in DMF were added drop wise to a solution of **13a** (1.5 g, 5.9 mmol) at 0 °C for urea bond formation and the mixture was stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC analysis. After completion, the reaction mass was partitioned between ethyl acetate and water. Organic layer was washed with water, brine, and dried over Na_2SO_4 and evaporated under reduced pressure to give crude compound. The crude was further crystallized from hexane to yield 1.2 g of compound **13c**.

Step 13b:

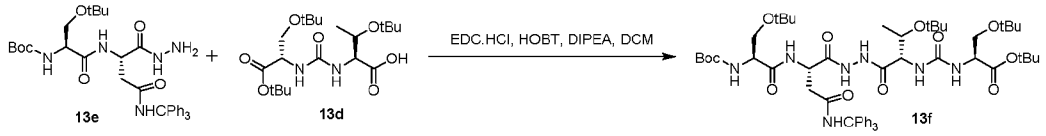


13c 13d

To a solution of compound **13c** (1.2 g, 2.35 mmol) in methanol (20 mL), was added 10% Pd-C (0.15 g) under inert atmosphere. The mixture was stirred for 1 h under H_2 atmosphere at room temperature. The completion of the reaction was confirmed by TLC analysis. The Pd-C catalyst was then removed by filtration through a Celite® pad and

washed with methanol (2 × 75 mL). The combined organic filtrate on evaporation under reduced pressure resulted in the isolation of 0.7 g compound **13d**, LCMS: 419.4 $(M+H)^+$.

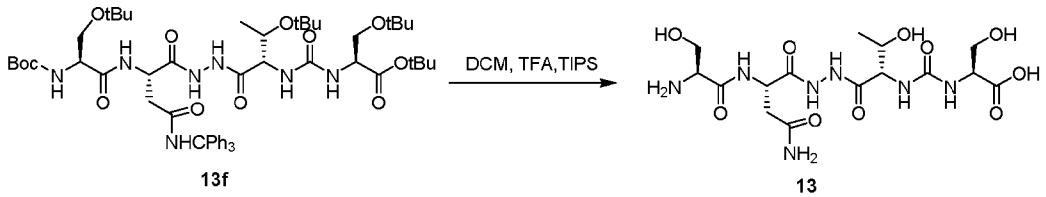
Step 13c:



Compound 13e was synthesised by similar procedure as depicted for compound 11f in step 11d of Example 11 using Boc-Ser(OtBu)-OH instead of Boc-Ala-OH (compound 11d) and Fmoc-Asn(Trt)-OH instead of Cbz-Ser(OtBu)-OH (compound 11a). Yield: 2.5 g; LCMS: 654.3 $(M+Na)^+$.

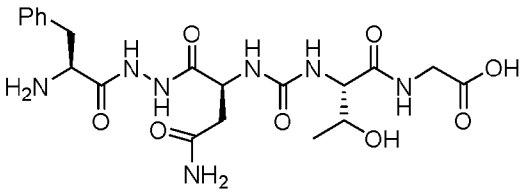
DIPEA (0.35 g, 2.8 mmol) was slowly added to a stirred solution of compound **13d** (0.46 g, 1.1 mmol), compound **13e** (0.7 g, 1.1 mmol), HOBt (0.16 g, 1.2 mmol) and EDC.HCl (0.23 g, 1.2 mmol) in DCM at 0°C. The reaction mixture was stirred at room temperature for 1 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mass was partitioned between ethyl acetate and water. Organic layer was washed with citric acid, $NaHCO_3$, brine, and dried over Na_2SO_4 and evaporated under reduced pressure to give crude compound. The crude was washed with diethyl ether and dried to afford 0.82 g of compound **13f**. LCMS: 1032.9 $(M+H)^+$.

Step 13d:



To a solution of compound **13f** (0.8 g, 0.77 mmol) in CH_2Cl_2, trifluoroacetic acid (1 mL) and catalytic amount of triisopropylsilane were added and stirred at room temperature for 2 h. The resulting solution was concentrated under nitrogen and the solid material was further washed with diethyl ether, dried under vacuum to afford 0.5 g of crude compound. Crude compound was further purified by preparative HPLC method described under experimental conditions to yield pure compound **13**, LCMS: 466.3 $(M+H)^+$, HPLC: t_R = 16.41 min.

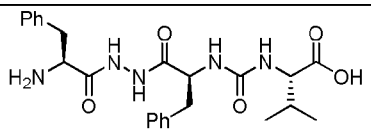
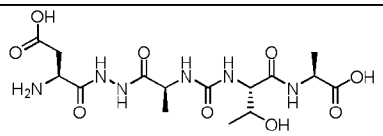
Example 14: Synthesis of compound 14



The compound **14** was synthesised by similar procedure as depicted in Example 12 using Boc-Phe-OH instead of Boc-Asp(OtBu)-OH (compound 12d); Fmoc-Asn-OH instead of Fmoc-Ala-OH (compound 12a) and H-Gly-OtBu instead of H-Asn(Trt)-OBzl (compound 12 l). The crude solid material was purified as preparative HPLC method described under experimental conditions. LCMS: 496.4 $(M+H)^+$, HPLC: t_R = 11.6 min.

The compounds shown in below table 3, which can be prepared by following similar procedure as described above with suitable modification known to the one ordinary skilled in the art are also included in the scope of the present application.

Table 3

Compound No.	Structure	Compound No.	Structure
15		16	

Rescue of mouse splenocyte proliferation in the presence of recombinant PD-L1/PD-L2:

Recombinant mouse PD-L1 (rm-PDL-1, cat no: 1019-B7-100; R&D Systems) were used as the source of PD-L1.

Requirement:

Mouse splenocytes harvested from 6-8 weeks old C57 BL6 mice; RPMI 1640 (GIBCO, Cat # 11875); DMEM with high glucose (GIBCO, Cat # D6429); Fetal Bovine Serum [Hyclone, Cat # SH30071.03]; Penicillin (10000unit/ml)-Streptomycin(10,000µg/ml) Liquid (GIBCO, Cat # 15140-122); MEM Sodium Pyruvate solution 100mM (100x), Liquid (GIBCO, Cat # 11360); Nonessential amino acid (GIBCO, Cat # 11140); L-Glutamine (GIBCO, Cat # 25030); Anti-CD3 antibody (eBiosciences – 16-0032); Anti-CD28 antibody (eBiosciences – 16-0281); ACK lysis buffer (1mL) (GIBCO, Cat # -

A10492); Histopaque (density-1.083 gm/mL) (SIGMA 10831); Trypan blue solution (SIGMA-T8154); 2 mL Norm Ject Luer Lock syringe- (Sigma 2014-12); 40 µM nylon cell strainer (BD FALCON 35230); Hemacytometer (Bright line-SIGMA Z359629); FACS Buffer (PBS/0.1% BSA): Phosphate Buffered Saline (PBS) pH 7.2 (HiMedia TS1006) with 0.1% Bovine Serum Albumin (BSA) (SIGMA A7050) and sodium azide (SIGMA 08591); 5 mM stock solution of CFSE: CFSE stock solution was prepared by diluting lyophilized CFSE with 180 µL of Dimethyl sulfoxide (DMSO C_2H_6SO, SIGMA-D-5879) and aliquoted in to tubes for further use. Working concentrations were titrated from 10 µM to 1 µM. (eBioscience-650850-85); 0.05% Trypsin and 0.02% EDTA (SIGMA 59417C); 96-well format ELISA plates (Corning CLS3390); BD FACS caliber (E6016); Recombinant mouse B7-H1/PDL1 Fc Chimera, (rm-PD-L1 cat no: 1019-B7-100).

Protocol

Splenocyte preparation and culturing:

Splenocytes harvested in a 50 mL falcon tube by mashing mouse spleen in a 40 µm cell strainer were further treated with 1 mL ACK lysis buffer for 5 min at room temperature. After washing with 9 mL of RPMI complete media, cells were re-suspended in 3 mL of 1xPBS in a 15 mL tube. 3 mL of Histopaque was added carefully to the bottom of the tube without disturbing overlaying splenocyte suspension. After centrifuging at 800xg for 20 min at room temperature, the opaque layer of splenocytes was collected carefully without disturbing / mixing the layers. Splenocytes were washed twice with cold 1xPBS followed by total cell counting using Trypan Blue exclusion method and used further for cell based assays.

Splenocytes were cultured in RPMI complete media (RPMI + 10% fetal bovine serum + 1 mM sodium pyruvate + 10,000units/ml penicillin and 10,000µg/ml streptomycin) and maintained in a CO_2 incubator with 5% CO_2 at 37°C.

CFSE Proliferation assay:

CFSE is a dye that passively diffuses into cells and binds to intracellular proteins. $1x10^6$ cells/mL of harvested splenocytes were treated with 5 µM of CFSE in pre-warmed 1xPBS/0.1% BSA solution for 10 min at 37°C. Excess CFSE was quenched using 5 volumes of ice-cold culture media to the cells and incubated on ice for 5 min. CFSE labelled splenocytes were further given three washes with ice cold complete RPMI media. CFSE labelled $1x10^5$ splenocytes added to wells containing either MDA-MB231

cells ($1x10^5$ cells cultured in high glucose DMEM medium) or recombinant human PDL-1 (100 ng/mL) and test compounds. Splenocytes were stimulated with anti-mouse CD3 and anti- mouse CD28 antibody (1 µg/mL each), and the culture was further incubated for 72 h at 37°C with 5% CO_2. Cells were harvested and washed thrice with ice cold FACS buffer and % proliferation was analyzed by flow cytometry with 488 nm excitation and 521 nm emission filters.

Data compilation, processing and inference:

Percent splenocyte proliferation was analyzed using cell quest FACS program and percent rescue of splenocyte proliferation by compound was estimated after deduction of % background proliferation value and normalising to % stimulated splenocyte proliferation (positive control) as 100%.

Stimulated splenocytes: Splenocytes + anti-CD3/CD28 stimulation

Background proliferation: Splenocytes + anti-CD3/CD28 + PD-L1

Compound proliferation: Splenocytes + anti-CD3/CD28 + PD-L1 + Compound

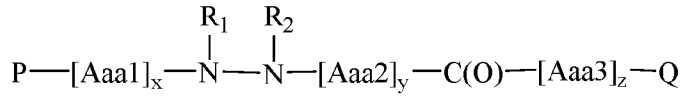
Compound effect is examined by adding required concentration of compound to anti-CD3/CD28 stimulated splenocytes in presence of ligand (PDL-1)

Table 4

Compound No.	Percent rescue of splenocyte proliferation (@100 nM compound concentration)	Compound No.	Percent rescue of splenocyte proliferation (@100 nM compound concentration)
1	72.6	9	71
2	81.2	10	87
4	62	11	58
5	82	12	81
6	51	13	32
7	62	14	84
8	81	-	-

We claim:

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

x, y and z are integers, each independently selected from 1 to 2;

each of [Aaa1], [Aaa2] and [Aaa3] represents x, y and z independently selected amino acid residues, with a proviso that [Aaa1] is not selected from Ser, Thr, Ala or Leu if

(i) [Aaa2] is selected from Asp, Asn, Glu or Gln;

(ii) [Aaa3] is selected from Ser, Asp, Ala, Ile, Phe, Trp, Glu or Thr; and

(iii) each of x, y and z is 1;

wherein, [Aaa1], [Aaa2] and [Aaa3] are optionally substituted by hydroxyl;

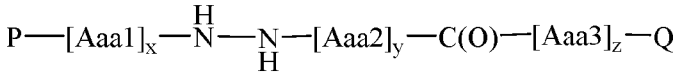
R_1 and R_2 are independently hydrogen or alkyl;

P represents free N-terminus, alkylated N-terminus or acylated N-terminus of [Aaa1];

Q represents free C-terminus, amidated C-terminus or esterified C-terminus of [Aaa3]; and

the bond between [Aaa1] and $–NR_1–$ and/or between [Aaa2] and $–NR_2–$ is a peptide bond or a reduced peptide bond.

2. The compound according to claim 1, wherein the compound of formula (I) is compound of formula (IA):



(IA)

or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

x, y, z, [Aaa1], [Aaa2], [Aaa3], P and Q are same as defined in claim1.

3. The compound according to any one of claims 1 to 2, wherein x, y and z are independently 1.

4. The compound according to any one of claims 1 to 2, wherein x, y and z simultaneously do not have a value of 1.

5. The compound according to any one of claims 1, 2 or 4, wherein x is 1 or 2, y is 1 and z is 1 or 2.

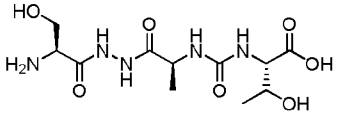
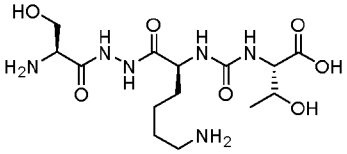
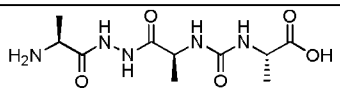
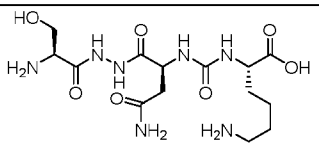
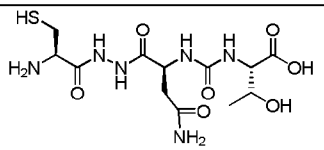
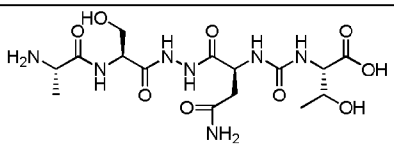
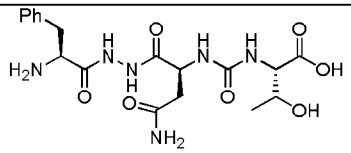
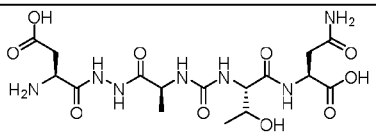
6. The compound according to claim 1, or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein [Aaa1] is selected from the group consisting of: Ser, Ala, Cys, Asp, Phe, Pro, Asn and Lys.

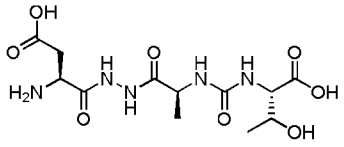
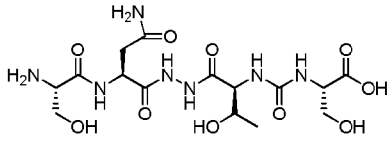
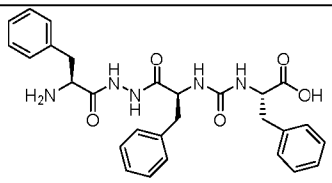
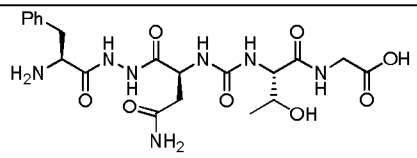
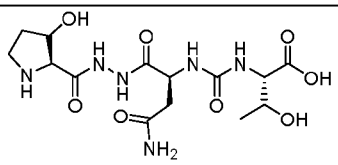
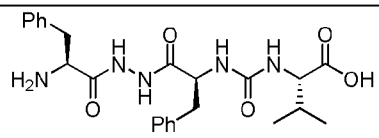
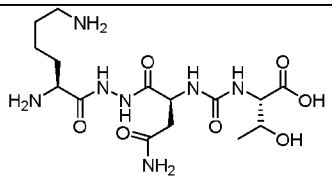
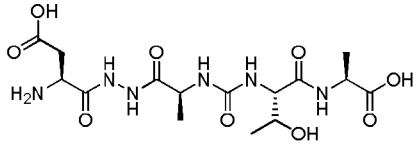
7. The compound according to claim 1, or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein [Aaa2] is selected from the group consisting of: Ala, Asn, Phe, Lys, Thr and Phe.

8. The compound according to claim 1, or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein [Aaa3] is selected from the group consisting of: Thr, Ala, Phe, Ser, Lys, Gly, val and Asn.

9. The compound according to any one of claims 1 to 8, wherein P is free N-terminus and Q is free C-terminus.

10. A compound is selected from the group consisting of

Compound No.	Structure	Compound No.	Structure
1		9	
2		10	
3		11	
4		12	

5		13	
6		14	
7		15	 and
8		16	

or a pharmaceutically acceptable salt or a stereoisomer thereof.

11. A pharmaceutical composition comprising at least one compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt or a stereoisomer thereof, and a pharmaceutically acceptable carrier or excipient.

12. The pharmaceutical composition according to claim 11, further comprising at least one of an anticancer agent, chemotherapy agent, or antiproliferative compound.

13. Use of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt or a stereoisomer thereof, as a medicament.

14. Use of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt or a stereoisomer thereof, in the manufacture of a medicament for the treatment of cancer or infectious disease.

15. The use according to claim 14, wherein the cancer is selected from bone cancer, cancer of the head or neck, pancreatic cancer, skin cancer, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the

endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumours of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumour angiogenesis, spinal axis tumour, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers.

16. The use according to claim 14, wherein the infectious disease is a bacterial infectious disease, a viral infectious disease or a fungal infectious disease.

17. A method of modulating an immune response mediated by PD-1 signaling pathway in a subject, comprising administering to the subject therapeutically effective amount of a compound according to any one of claims 1 to 10.

18. A method of inhibiting growth of tumour cells and/or metastasis in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 10.

19. The method of claim 18, wherein the tumour cells are of a cancer selected from the group consisting of breast cancer, colon cancer, lung cancer, melanoma, prostate cancer and renal cancer.

20. The method of claim 18, wherein the tumour cells are of a cancer selected from the list consisting of bone cancer, cancer of the head or neck, pancreatic cancer, skin cancer, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumours of childhood, lymphocytic

lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumour angiogenesis, spinal axis tumour, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers including those induced by asbestos, and combinations of said cancers.

21. A method of treating an infectious disease in a subject comprising administering to the subject a therapeutically effective amount of compound according to any one of claims 1 to 10.

22. A method of treating bacterial, viral and fungal infections in a subject comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1 to 10.

23. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of compound according to any one of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/064380

A. CLASSIFICATION OF SUBJECT MATTER

C07K 7/02(2006.01)i; C07K 5/02(2006.01)i; A61K 38/08(2006.01)i; A61P 37/02(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K 7/-; C07K 5/-; A61K 38/-

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

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

CNABS, VEN ,CNTXT, CNKI, CAPLUS, REGISTRY, AURIGINE, PD, PCD, PEPTIDOMIMETIC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 2013132317 A1 (AURIGENE DISCOVERY TECH LTD) 12 September 2013 (2013-09-12) claims 7-21	1-16
A	CN 103096915 A (AURIGENE DISCOVERY TECH LTD) 08 May 2013 (2013-05-08) the whole document	1-16
A	WO 2012168944 A1 (AURIGENE DISCOVERY TECH LTD) 13 December 2012 (2012-12-13) the whole document	1-16

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 December 2014	**12 January 2015**

Name and mailing address of the ISA/CN	Authorized officer
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA(ISA/CN) **6,Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088 China**	**HUANG,Minghui**
Facsimile No. **(86-10)62019451**	Telephone No. **(86-10)62086310**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/064380

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **13**, **17-23**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 13, 17-23 are directed to methods for the treatment of the human/animal body by therapy. Thus, the subject-matter of claims 13, 17-23 is not required to be searched by this Authority. (Rule 39.1(iv) PCT).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2014/064380

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2013132317 A1	12 September 2013	WO 2013132317 A8	07 November 2013
		US 2013237580 A1	12 September 2013
		WO 2013132317 A9	09 January 2014
CN 103096915 A	08 May 2013	EA 201300005 A1	31 March 2014
		MX 2012014785 A	29 April 2013
		WO 2011161699 A2	29 December 2011
		KR 20140002594 A	08 January 2014
		WO 2011161699 A3	18 May 2012
		AU 2011268484 A1	31 January 2013
		SG 186809 A1	28 February 2013
		CA 2803859 A1	29 December 2011
		JP 2013534922 A	09 September 2013
		US 2011318373 A1	29 December 2011
		EP 2585099 A2	01 May 2013
WO 2012168944 A1	13 December 2012	US 2014199334 A1	17 July 2014
		EP 2717895 A1	16 April 2014
		CN 103732238 A	16 April 2014