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(71) Applicant: **AURIGENE DISCOVERY TECHNOLOGIES LIMITED** [IN/IN]; 39-40, KIADB Industrial Area, Electronic City Phase II, Hosur Road, Bangalore 560100 (IN).

(72) Inventors: **SASIKUMAR, Pottayil Govindan Nair**; # 5, Deccan Palms, Ananth Nagar Phase, II, Electronic city post, Bangalore 560100 (IN). **RAMACHANDRA, Muralidhara**; V173, Adarsh Palm Retreat, Outer Ring, Road, Bellandur Post, Bangalore 560103 (IN). **NAREMADDEPALLI, Seetharamaiah Setty Sudarshan**; 33/A, Shenimahathama temple compound, R., K. Layout, K. G. Nagar, Bangalore 560019 (IN).

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(54) Title: THERAPEUTIC CYCLIC COMPOUNDS AS IMMUNOMODULATORS

(57) Abstract: The present invention relates to cyclic compounds of formula (I) and their use to inhibit the programmed cell death 1 (PD-1) signaling pathway and/or for treatment of disorders by inhibiting an immunosuppressive signal induced by PD-1, PD-L1 or PD-L2.

THERAPEUTIC CYCLIC COMPOUNDS AS IMMUNOMODULATORS

This application claims the benefit of Indian provisional application number 1183/CHE/2015, filed on March 10, 2015; the specifications of which are hereby incorporated by reference in their entirety.

TECHNICAL FIELD

The present invention relates to cyclic compounds and their derivatives therapeutically useful as immune modulators. The invention also relates to pharmaceutical compositions comprising the said cyclic compounds 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 cell 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 WO2002086083, WO2004004771, WO2004056875, WO2006121168, WO2008156712, WO2010077634, WO2011066389, WO2014055897 and WO2014100079 report PD-1, PD-L1 inhibitory antibodies and/or methods of identifying such antibodies. Further, US patents such as US8735553 and US8168757 report PD-1 or PD-L1 inhibitory antibodies and/or fusion proteins.

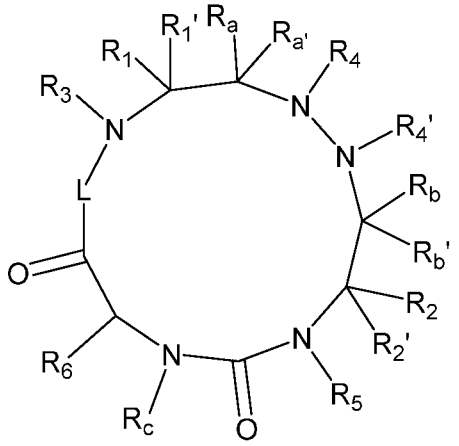
Furthermore, International applications, WO2011161699, WO2012168944, WO2013144704 and WO2013132317 report peptides or peptidomimetic compounds which are capable of suppressing and/or inhibiting the programmed cell death 1 (PD1) signaling pathway.

Still there is a need for more potent, better and/or selective immune modulators of PD-1 pathway.

SUMMARY OF INVENTION

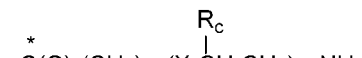
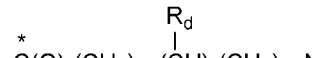
The present invention provides cyclic compounds of formula (I) and their pharmaceutically acceptable salts or stereoisomers, which are capable of suppressing and/or inhibiting the programmed cell death 1 (PD-1) signaling pathway.

In one aspect, the present invention provides therapeutic cyclic compounds of formula (I):



(I)

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

L is  or  , wherein the -C(O)- group marked with * is connected to the nitrogen bearing R_3 in Formula (I);

X is CH_2, O, NH or S;

R_1, R_2 and R_6 independently are a side chain of an amino acid, hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl; wherein (C_1-C_6)alkyl, (C_2-C_6)alkenyl and (C_2-C_6)alkynyl are optionally substituted by one or more substituents selected from hydroxy, amino, amido, alkylamino, acylamino, -$(CH_2)_m$-COOH, -$(CH_2)_m$-COO-alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl, (heteroaryl)alkyl, -SH and -S-(alkyl); optionally wherein cycloalkyl, aryl, heterocyclyl and heteroaryl are further substituted optionally by one or more substituents such as hydroxy, alkoxy, halo, amino, nitro, cyano or alkyl; optionally wherein two or three carbon atoms of the (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl form part of a 3-7-membered carbocyclic or heterocyclic ring (such as a cyclobutyl or oxirane ring);

R_1', R_2', R_3 and R_5 independently are hydrogen or alkyl;

or R_1 and R_1', together with the carbon atom to which they are attached, may optionally form an optionally substituted cycloalkyl or heterocycloalkyl ring;

or R_1 and R_3, together with the atoms to which they are attached, may optionally form a heterocyclic ring optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy;

or R_2 and R_2', together with the carbon atom to which they are attached, may optionally form an optionally substituted cycloalkyl or heterocycloalkyl ring;

or R_2 and R_5, together with the atoms to which they are attached, may optionally form a heterocyclic ring optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy;

R_4 and R_4' independently are hydrogen or alkyl;

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

R_b and R_b' are each hydrogen; or together represent an oxo (=O) group;

R_c at each occurrence is independently hydrogen or alkyl;

R_d is amino or -NH-C(O)-$(CH_2)_r$-CH_3;

m is an integer from 0 to 3;

n, independently for each occurrence, is an integer from 2 to 20;

r, is an integer from 0-20; and

with a proviso that R_6 is not a side chain of Ser, Asp, Ala, Ile, Phe, Trp, Lys, Glu and Thr, when R_1 is a side chain of Ala, Ser, Thr or Leu, R_2 is a side chain of Asp, Asn, Glu or Gln and R_5 and R_c are hydrogen.

In one aspect, the present invention relates to the process for preparation of compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof.

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

Yet another aspect of the present invention provides methods of administering a compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer, to suppress and/or inhibit the programmed cell death 1 (PD-1) signaling pathway. For example, these compounds can be used to treat one or more diseases characterized by aberrant or undesired activity of the PD-1 signaling pathway.

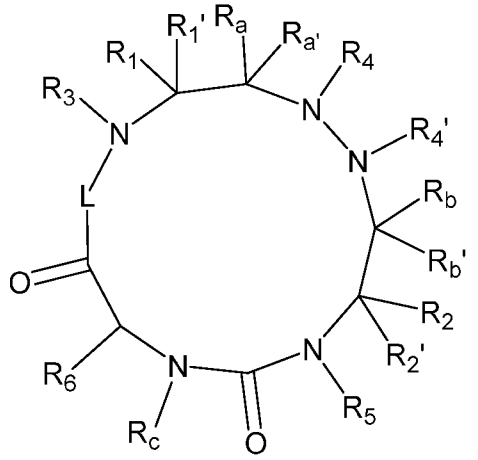
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides cyclic compounds and their derivatives 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 modifications and variations can be made to the compounds, compositions

and methods described herein without departing from the scope or spirit of the invention. For instance, features illustrated or described as part of one embodiment can be applied to another embodiment to yield a still further embodiment. Thus it is intended that the present invention include such modifications and variations 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 certain embodiments, the present invention provides compounds of formula (I):



(I)

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

L is $^{*}\text{-C(O)-(CH}_2\text{)}_m\text{-(X-}\overset{R_c}{\underset{|}{C}}\text{H-CH}_2\text{)}_n\text{-NH-}$ or $^{*}\text{-C(O)-(CH}_2\text{)}_m\text{-(}\overset{R_d}{\underset{|}{C}}\text{H)-(CH}_2\text{)}_n\text{-NH-}$, wherein the -C(O)- group marked with * is connected to the nitrogen bearing R_3 in Formula (I);

X is CH_2, O, NH or S;

R_1, R_2 and R_6 independently are a side chain of an amino acid, hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl; wherein (C_1-C_6)alkyl, (C_2-C_6)alkenyl and (C_2-C_6)alkynyl are optionally substituted by one or more substituents selected from hydroxy, amino, amido, alkylamino, acylamino, -$(CH_2)_m$-COOH, -$(CH_2)_m$-COO-alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl, (heteroaryl)alkyl, -SH and -S-(alkyl); optionally wherein cycloalkyl, aryl, heterocyclyl and heteroaryl are further substituted optionally by one or more substituents such as hydroxy, alkoxy, halo, amino, nitro, cyano or alkyl; optionally wherein two or three carbon atoms of the (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl

form part of a 3-7-membered carbocyclic or heterocyclic ring (such as a cyclobutyl or oxirane ring);

R_1', R_2', R_3 and R_5 independently are hydrogen or alkyl;

or R_1 and R_1', together with the carbon atom to which they are attached, may optionally form an optionally substituted cycloalkyl or heterocycloalkyl ring;

or R_1 and R_3, together with the atoms to which they are attached, may optionally form a heterocyclic ring optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy;

or R_2 and R_2', together with the carbon atom to which they are attached, may optionally form an optionally substituted cycloalkyl or heterocycloalkyl ring;

or R_2 and R_5, together with the atoms to which they are attached, may optionally form a heterocyclic ring optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy;

R_4 and R_4' independently are hydrogen or alkyl;

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

R_b and R_b' are each hydrogen; or together represent an oxo (=O) group;

R_c at each occurrence is independently hydrogen or alkyl;

R_d is amino or -NH-C(O)-$(CH_2)_r$-CH_3;

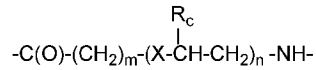
m is an integer from 0 to 3;

n, independently for each occurrence, is an integer from 2 to 20;

r, is an integer from 0-20; and

with a proviso that R_6 is not a side chain of Ser, Asp, Ala, Ile, Phe, Trp, Lys, Glu and Thr, when, R_1 is a side chain of Ala, Ser, Thr or Leu, R_2 is a side chain of Asp, Asn, Glu or Gln and R_5 and R_c are hydrogen.

In certain embodiments, the present invention provides compounds of formula (I) or a pharmaceutically acceptable salt thereof or a stereoisomer thereof; wherein,

L is  ;

X is CH_2, O or S;

R_1, R_2 and R_6 independently are a side chain of an amino acid or (C_1-C_6)alkyl, (C_1-C_6)alkenyl, or (C_1-C_6)alkynyl; wherein (C_1-C_6)alkyl, (C_1-C_6)alkenyl, and (C_1-C_6)alkynyl substituted by one or more substituents selected from amino, alkylamino, acylamino, -COO-alkyl, cycloalkyl, heterocyclyl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl, and (heteroaryl)alkyl; optionally wherein two or

three carbon atoms of the (C_1-C_6)alkyl, (C_1-C_6)alkenyl, or (C_1-C_6)alkynyl form part of a 3-7-membered carbocyclic or heterocyclic ring (such as a cyclobutyl or oxirane ring);

R_3 is hydrogen or alkyl;

or R_1 and R_3, together with the atoms to which they are attached, may form pyrrolidine or piperidine optionally substituted with one or more groups independently selected from amino, cyano, methyl, halo, and hydroxy;

R_1' and R_2' are each hydrogen;

R_4 and R_4' independently are hydrogen or alkyl;

R_5 is hydrogen or alkyl;

or R_2 and R_5, together with the atoms to which they are attached, may form pyrrolidine or piperidine optionally substituted with one or more groups independently selected from amino, cyano, methyl, halo, and hydroxy;

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

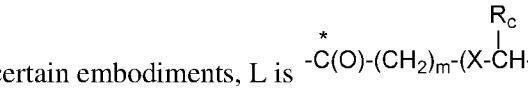
R_b and R_b' independently are hydrogen; or together represent an oxo (=O) group;

R_c is hydrogen or alkyl;

m is an integer selected from 1 to 3;

n is an integer selected from 2 to 20; and

with a proviso that R_6 is not a side chain of Ser, Asp, Ala, Ile, Phe, Trp, Lys, Glu and Thr, when, R_1 is a side chain of Ala, Ser, Thr or Leu, R_2 is a side chain of Asp, Asn, Glu or Gln and R_5 and R_c are hydrogen.

In certain embodiments, L is  ;

X is CH_2, O or S; and

R_1' and R_2' are each hydrogen.

Alternatively, R_1' may be alkyl.

In certain embodiments, R_1 is (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl; optionally substituted by one or more substituents selected from amino, alkylamino, acylamino, -COO-alkyl, cycloalkyl, heterocyclyl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl, (heteroaryl)alkyl and -S-(alkyl).

In certain embodiments, R_1 is (C_1-C_6)alkyl, optionally substituted by one or more substituents selected from amino, aryl, -COOH, heteroaryl, guanidino, hydroxyl and amido.

In certain preferred embodiments, R_1 is $(C_1\text{-}C_6)$alkyl wherein the said $(C_1\text{-}C_6)$alkyl is optionally substituted by cycloalkyl or –S-(alkyl) and the said cycloalkyl is preferably cyclopropyl or cyclohexyl.

In certain embodiments, R_1' is hydrogen. Alternatively, R_1 and R_1', together with the carbon atom to which they are attached, may optionally form an optionally substituted cycloalkyl or heterocycloalkyl ring; e.g., a substituted cycloalkyl ring.

In certain embodiments, R_2 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl; optionally substituted by one or more substituents selected from amino, alkylamino, acylamino, -COO-alkyl, cycloalkyl, heterocyclyl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl, (heteroaryl)alkyl and -S-(alkyl).

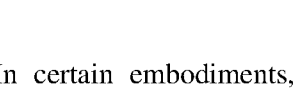
In certain embodiments, R_2 is $(C_1\text{-}C_6)$alkyl, optionally substituted by one or more substituents selected from amino, aryl, -COOH, hydroxyl and amido.

In certain embodiments, R_2' is hydrogen or alkyl, preferably hydrogen. Alternatively, R_2 and R_2', together with the carbon atom to which they are attached, may optionally form an optionally substituted cycloalkyl or heterocycloalkyl ring;

In certain embodiments, R_6 is $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$ alkynyl; optionally substituted by one or more substituents selected from amino, alkylamino, acylamino, -COO-alkyl, cycloalkyl, heterocyclyl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl, (heteroaryl)alkyl and -S-(alkyl).

In certain embodiments, R_6 is $(C_1\text{-}C_6)$alkyl, optionally substituted by one or more substituents selected from amino, aryl, -COOH, hydroxyl and amido.

In some embodiments, R_1, R_2 or R_6 may be $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl; optionally substituted by -S-(alkyl) or aryl.

In certain embodiments, L is  . In certain such embodiments, X is CH_2, O or S. Alternatively, X can be NH.

Alternatively, L can be . In certain such embodiments, R_d is amino or -NH-C(O)-$(CH_2)_n$-CH_3.

In certain embodiments, L is not , wherein X is selected from CH_2, O or S.

In certain embodiments, R_1 and R_3, together with the atoms to which they are attached, may optionally form a heterocyclic ring, optionally substituted with one or more groups independently selected from amino, cyano, methyl, halo and hydroxy.

In certain embodiments, R_1 and R_3, together with the atoms to which they are attached, may optionally form a pyrrolidine or piperidine ring, optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy.

In certain embodiments, R_1 and R_3, together with the atoms to which they are attached, may optionally form a pyrrolidine or piperidine ring, optionally substituted with one or more groups independently selected from amino, cyano, methyl, halo and hydroxy.

In some embodiments, R_1 and R_3, together with the atoms to which they are attached, form an optionally substituted heterocyclic ring, wherein that heterocyclic ring is not a pyrrolidine or piperidine ring. In certain such embodiments, the heterocyclic ring is substituted by a C_2-C_{10} alkyl group.

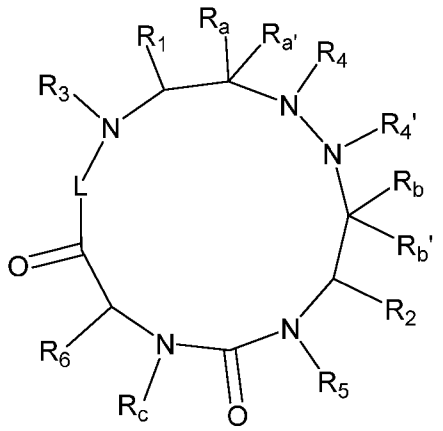
In certain embodiments, R_2 and R_5, together with the atoms to which they are attached, may optionally form a heterocyclic ring, optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy.

In certain embodiments, R_2 and R_5, together with the atoms to which they are attached, may optionally form a pyrrolidine or piperidine ring, optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy.

In certain embodiments, R_2 and R_5, together with the atoms to which they are attached, may optionally form a pyrrolidine or piperidine ring, optionally substituted with one or more groups independently selected from amino, cyano, methyl, halo and hydroxy.

In some embodiments, R_2 and R_5, together with the atoms to which they are attached, form an optionally substituted heterocyclic ring, wherein that heterocyclic ring is not a pyrrolidine or piperidine ring. In certain such embodiments, the heterocyclic ring is substituted by a C_2-C_{10} alkyl group.

In certain embodiments, the present invention provides compounds of formula (IA):

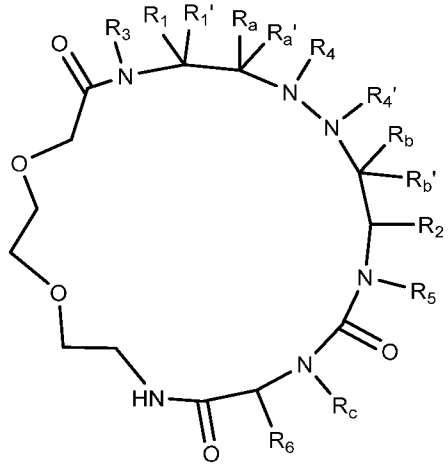


(IA)

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

L, R_1, R_2, R_3, R_4, R_4', R_5, R_6, R_a, R_a', R_b, R_b' and R_c are same as defined in formula (I).

In certain embodiments, the present invention provides compounds of formula (IB):

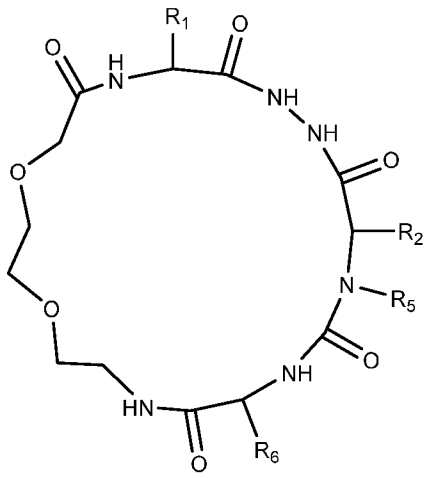


(IB)

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

R_1, R_1', R_2, R_3, R_4, R_4', R_5, R_6, R_a, R_a', R_b, R_b' and R_c are same as defined in formula (I).

In certain embodiments, the present invention provides compounds of formula (IC):



(IC)

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

R_1, R_2 and R_6 independently are side chain of an amino acid; and

R_5 is hydrogen or alkyl.

An amino acid is understood in the art to mean a carboxylic acid, substituted at the alpha, beta or gamma carbon by an amino ($-NH_2$) group.

In accordance with any of the foregoing embodiments, in certain embodiments, R_1 is a side chain of Ser, Tyr, Ile, Asp, Lys, Phe, Asn, Gln, Glu, Trp, His, Arg, Val or Thr.

In accordance with any of the foregoing embodiments, in preferred embodiments, R_1 is a side chain of Thr, Tyr, Ser, Lys and Asp.

In certain embodiments, R_1 does not represent a side chain of Ala, Ser, Thr or Leu; i.e., R_1 is not CH_3, CH_2OH, $CH(OH)CH_3$ or *iso*-butyl.

In accordance with any of the foregoing embodiments, in certain embodiments, R_2 is a side chain of Asp, Asn, Ile, Lys, Phe, Ser, Thr, Val, Pro or Glu.

In accordance with any of the foregoing embodiments, in preferred embodiments, R_2 is a side chain of Thr, Pro, Phe, Asn or Asp.

In certain embodiments, R_2 does not represent a side chain of Asp, Glu, Gln or Asn; i.e., R_2 is not $CH_2C(O)OH$, $CH_2CH_2C(O)OH$, $CH_2CH_2C(O)NH_2$ or $CH_2C(O)NH_2$.

In accordance with any of the foregoing embodiments, in certain embodiments, R_6 is a side chain of Ser, Leu, Tyr, Lys, Asp, Asn, Glu, Gln, Val or Thr.

In alternative embodiments, R_6 does not represent a side chain of Ser, Asp, Ala, Ile, Phe, Trp, Lys, Glu or Thr; i.e., R_6 is not CH_2OH, $CH_2C(O)OH$, CH_3, *sec*-butyl, CH_2Ph, CH_2(*para*-OH)Ph, $CH_2CH_2CH_2CH_2NH_2$, $CH_2CH_2C(O)OH$ or $CH(OH)CH_3$.

In accordance with any of the foregoing embodiments, in preferred embodiments, R_6 is a side chain of Thr, Tyr, Asp or Leu.

In accordance with any of the foregoing embodiments, in certain embodiments, R_1', R_3, R_4, R_4' and R_c are hydrogen.

In accordance with any of the foregoing embodiments, in certain embodiments, R_1 and R_1', together with the carbon atom to which they are attached, may optionally form an optionally substituted cycloalkyl ring; preferably the said cycloalkyl is cyclopentyl or cyclohexyl.

In accordance with any of the foregoing embodiments, in certain embodiments, R_2 and R_5, together with the atoms to which they are attached, may form pyrrolidine optionally substituted by hydroxyl.

In accordance with any of the foregoing embodiments, in certain embodiments, m is 0 to 3.

In accordance with any of the foregoing embodiments, in certain embodiments, m is 1.

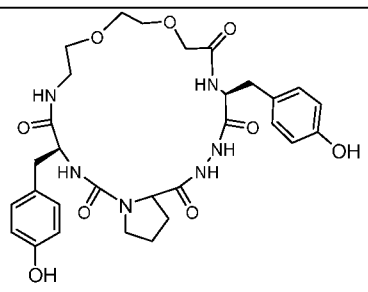
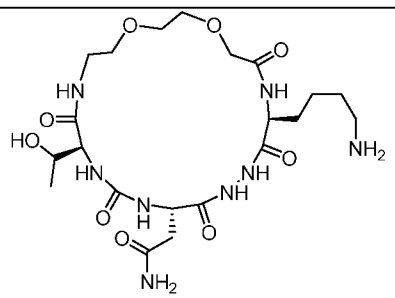
In accordance with any of the foregoing embodiments, in certain embodiments, n is 2 to 5.

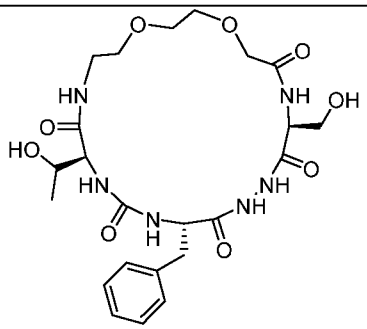
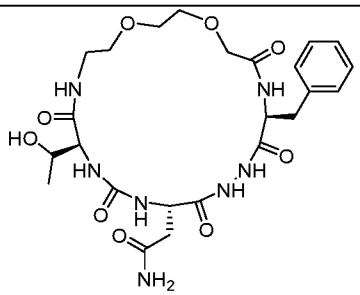
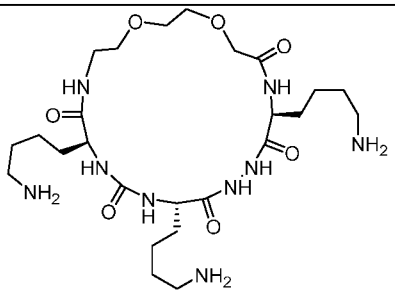
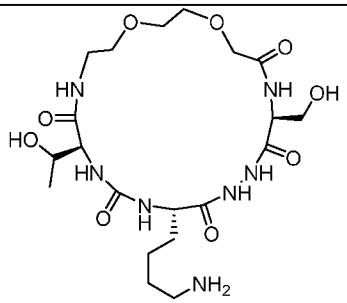
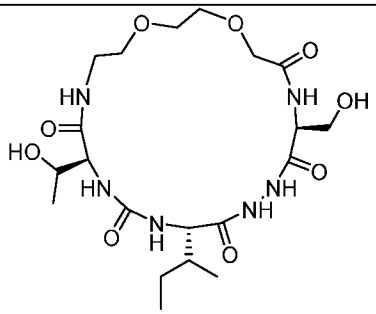
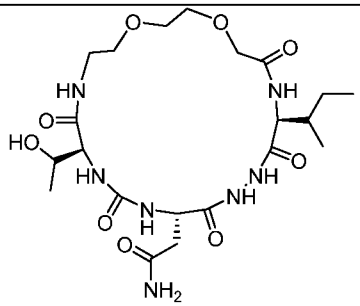
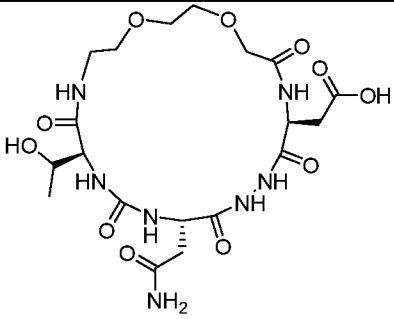
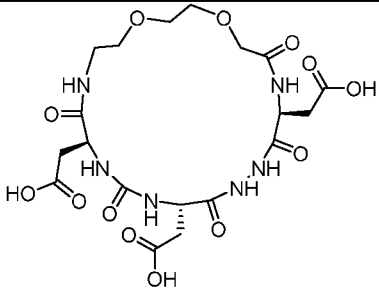
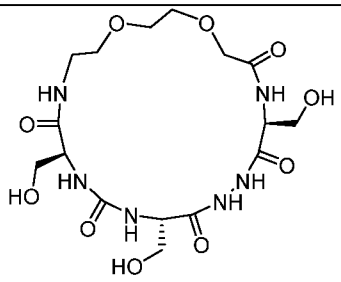
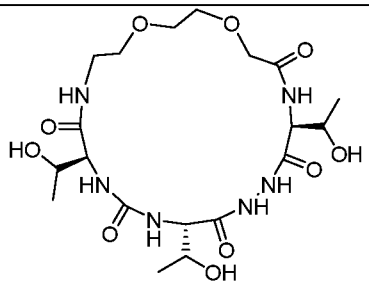
In accordance with any of the foregoing embodiments, in certain embodiments, n is 2.

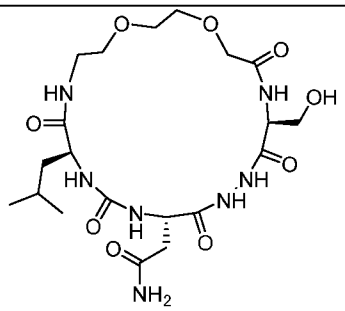
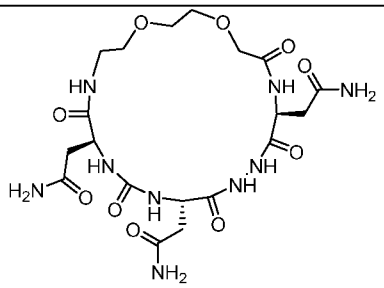
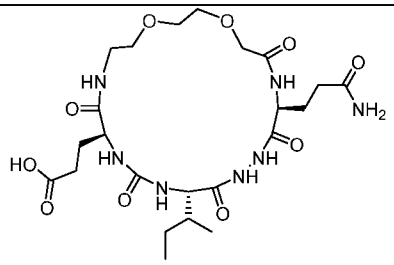
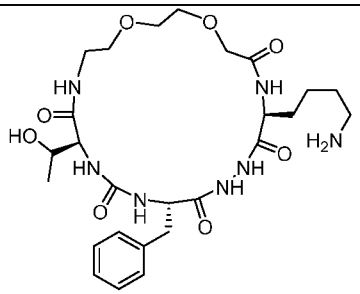
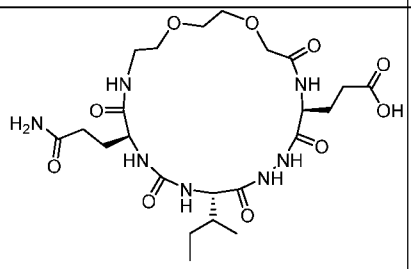
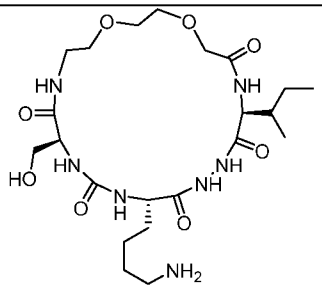
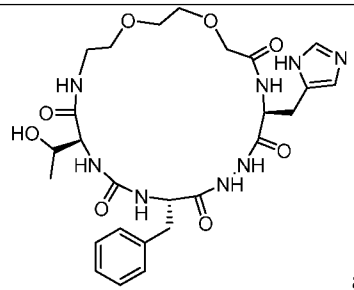
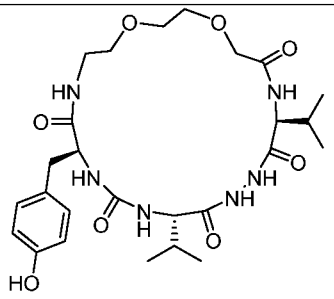
In accordance with any of the foregoing embodiments, in certain embodiments, one, more than one or all amino acids are D amino acids.

In accordance with any of the foregoing embodiments, in certain embodiments, one, more than one or all amino acids are L amino acids.

In certain embodiments, the present invention provides a compound or a pharmaceutically acceptable salt or a stereoisomer thereof, selected from:

Comp. No.	Structure	Comp. No.	Structure
1.		2.	

3.		4.	
5.		6.	
7.		8.	
9.		10.	
11.		12.	

13.		14.	
15.		16.	
17.		18.	
19.	 and	20.	

In certain embodiments, the compounds of the invention may be prodrugs of the compounds of formula (I), e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid present in the parent compound is presented as an ester. In a further embodiment, the prodrug is metabolized to the active parent compound in vivo (e.g., the ester is hydrolyzed to the corresponding hydroxyl or carboxylic acid).

In certain embodiments, the compounds of the present invention can also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such

compounds. For example, the present invention also embraces isotopically-labeled variants of the present invention which are identical to those recited herein, but for the fact that one or more atoms of the compound are replaced by an atom having the atomic mass or mass number different from the predominant atomic mass or mass number usually found in nature for the atom. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention and their uses. Exemplary isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^{2}H ("D"), ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I and ^{125}I. Isotopically labeled compounds of the present inventions can generally be prepared by following procedures analogous to those disclosed in the schemes and/or in the examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Further embodiments of the invention:

Pharmaceutical Compositions

In certain embodiments, the present invention provides a pharmaceutical composition comprising a compound as disclosed herein, optionally admixed with a pharmaceutically acceptable carrier or excipient.

The present invention also provides methods for formulating the disclosed compounds for pharmaceutical administration.

The compositions and methods of the present invention may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil or injectable organic esters. In a preferred embodiment, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed

release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation of pharmaceutical composition can be a self-emulsifying drug delivery system or a self-microemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as

cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin or as an eye drop). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules or as a solution or a suspension in an aqueous or non-aqueous liquid or as an oil-in-water or water-in-oil liquid emulsion or as an elixir or syrup or as pastilles (using an inert base, such as gelatin and glycerin or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as

lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol,

tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth and mixtures thereof.

Formulations of the pharmaceutical compositions for rectal, vaginal or urethral administration may be presented as a suppository, which may be prepared by mixing one or more active compounds with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the pharmaceutical compositions for administration to the mouth may be presented as a mouthwash or an oral spray or an oral ointment.

Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum or intestine.

Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier and with any preservatives, buffers or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide

powder or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention. Exemplary ophthalmic formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Pat. No. 6,583,124, the contents of which are incorporated herein by reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatable with such fluids. A preferred route of administration is local administration (e.g., topical administration, such as eye drops or administration via an implant).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol and the like) and suitable mixtures thereof, vegetable oils, such as olive oil and injectable organic esters, such as ethyl

oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested in vivo in recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels),

including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By "therapeutically effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher et al. (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid and the like.

Methods of Treatment

The programmed cell death protein 1 pathway (PD-1) pathway has been implicated in a number of diseases and conditions and the pathway is known to regulate various immune responses. Numerous studies have sought to activate immune response by targeting the PD-1 pathway, thereby providing a therapy for certain conditions, such as cancers. In fact, studies indicate that blockade of the PD-1 pathway, for example by inhibiting an immunosuppressive signal induced by PD-1, PD-LI or PD-L2, leads to anti-tumor activity in various cancers [1-7], including lung, breast, colon, renal, bladder, thyroid, prostate, osteosarcoma and Hodgkin's lymphoma.

Furthermore, PD-1 activity has also been associated with autoimmune conditions, such as lupus erythematosus [8], juvenile idiopathic arthritis and allergic encephalomyelitis.

In certain embodiments, the present invention provides uses of a compound of the present invention for the preparation of a medicament, e.g., for the treatment of cancer.

In certain embodiments, the present invention provides methods for treating cancer, wherein the method comprises administration of a therapeutically effective amount of a compound of the present invention to the subject in need thereof.

In certain embodiments, the present invention provides methods for inhibiting growth of tumour cells and/or metastasis by administering a therapeutically effective amount of a compound of the present invention to the subject in need thereof.

Representative tumour cells include cells of a cancer such as but not limited to melanoma, renal cancer, prostate cancer, breast cancer, colon cancer and lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular 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), non-small cell lung cancer (NSCLC), 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 certain embodiments, the present invention provides uses of a compound of the present invention for the preparation of a medicament for the treatment of bacterial, viral and fungal infection, as well as methods of administering a therapeutically effective amount of a compound of the present invention for the treatment of a bacterial, viral or fungal infection.

Still yet other embodiments of the present invention provides a method of treatment of infection by blockade of the PD-1 pathway, for example inhibiting an immunosuppressive signal induced by PD-1, PD-L1 or PD-L2, wherein the method

comprises administration of a therapeutically effective amount of a compound of the present invention to the subject in need thereof.

In certain embodiments, the invention provides uses of a compound of the present invention in inhibiting the PD-1 pathway (e.g., PD-1, PD-L1 or PD-L2).

In certain embodiments, the invention provides method of inhibiting the PD-1 pathway (e.g., PD-1, PD-L1 or PD-L2) in a subject, comprising administering to the subject a compound of the present invention.

In certain embodiments, the present invention provides methods for treating cancer in a subject comprising administering a therapeutically effective amount of a compound of the present invention.

In certain embodiments, the present invention provides methods for treating cancers selected from lung cancer, breast cancer, colon cancer, renal cancer, bladder cancer, thyroid cancer, prostate cancer, osteosarcoma and Hodgkin's lymphoma.

In certain embodiments, the present invention provides methods for treating cancer or an infectious disease comprising an additional step of administering to the subject in need thereof one or more additional chemotherapeutic agents independently selected from anti-proliferative agents, anti-cancer agents, immunosuppressant agents and pain-relieving agents.

In certain embodiments, the present invention provides methods for treating infectious disease in a subject comprising administering a therapeutically effective amount of a compound of the present invention for the treatment of the infectious disease.

Representative infectious disease include but are 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 (monotherapy) or conjointly with one or more other agents (conjoint therapy). The compounds may be used by themselves or, preferably, in a pharmaceutical composition in which the compound is mixed with one or more pharmaceutically acceptable materials.

The pharmaceutical composition may be administered by oral or inhalation routes or by parenteral administration route. For example, compositions can be administered orally, by intravenous infusion, topically, intraperitoneally, intravesically or intrathecally. Examples of parenteral administration includes but not limited to intraarticular (in the joints), intravenous, intramuscular, intradermal, intraperitoneal and subcutaneous routes. Suitable liquid compositions may be aqueous or non-aqueous, isotonic sterile injection solutions, and may 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 preferred methods of administration.

The dosage of the compounds of the present invention varies depending on a patient's age, weight or symptoms, as well as the compound's potency or therapeutic efficacy, the dosing regimen and/or treatment time. Generally, suitable routes of administration may, for example, include oral, eyedrop, rectal, transmucosal, topical or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal or intraocular injections. The compounds of the invention may be administered in an amount of 0.5 mg or 1 mg up to 500 mg, 1 g or 2 g per dosage regimen. The dosage may be administered once per week, once per three days, once per two days, once per day, twice per day, three times per day or more often. In alternative

embodiments, in certain adults the compound can be continuously administered by intravenous administration for a period of time designated by a physician. Since the dosage is affected by various conditions, an amount less than or greater than the dosage ranges contemplated about may be implemented in certain cases. A physician can readily determine the appropriate dosage for a patient undergoing therapeutic treatment.

The compounds of the present invention may be administered in combination with one or more other drugs (1) to complement and/or enhance effect of the compound of the present invention, (2) to modulate pharmacodynamics, improve absorption or reduce dosage of the compound of the present invention and/or (3) to reduce or ameliorate the side effects of the compound of the present invention. As used herein, the phrase "conjoint administration" refers to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still effective in the body (e.g., the two compounds are simultaneously effective in the patient, which may include synergistic effects of the two compounds). For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. In certain embodiments, the different therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours or a week of one another. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic compounds. The respective compounds may be administered by the same or different route and the same or different method.

The dosage of the other drug can be a dosage that has been clinically used or may be a reduced dosage that is effective when administered in combination with a compound of the present invention. The ratio of the compound of the present invention and the other drug can vary 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.

Conjoint therapy can be employed to treat any diseases discussed herein. For example, in the methods of the invention directed to the treatment of cancer, the compound of the present invention can be used with an existing chemotherapeutic conjointly using a single pharmaceutical composition or a combination of different pharmaceutical compositions. 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, a compound of the invention can be administered conjointly 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. Chemotherapeutic agents that may be conjointly administered with compounds of the invention include: aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carboplatin, carfilzomib, carmustine, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dexamethasone, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, lenalidomide, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, perifosine, plicamycin, pomalidomide, porfimer, procarbazine, raltitrexed, rituximab, sorafenib, streptozocin, sunitinib, suramin, tamoxifen, temozolomide, temsirolimus, teniposide, testosterone, thalidomide, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine and vinorelbine.

In certain embodiments, a compound of the invention may be conjointly administered with non-chemical methods of cancer treatment. In a further embodiment, a compound of the invention may be conjointly administered with radiation therapy. In a further embodiment, a compound of the invention may be conjointly administered with surgery, with thermoablation, with focused ultrasound therapy, with cryotherapy or with any combination of these.

In certain embodiments, different compounds of the invention may be conjointly administered with one or more other compounds of the invention. Moreover, such combinations may be conjointly administered with other therapeutic agents, such as other agents suitable for the treatment of cancer, immunological or neurological diseases,

such as the agents identified above. In certain embodiments, conjointly administering one or more additional chemotherapeutic agents with a compound of the invention provides a synergistic effect. In certain embodiments, conjointly administering one or more additional chemotherapeutics agents provides an additive effect.

The compound of the present invention can be used with one or more other immunomodulators and/or potentiating agents conjointly using a single pharmaceutical composition or a combination of different pharmaceutical compositions. Suitable immunomodulators include various cytokines, vaccines and adjuvants. Examples of cytokines, vaccines and adjuvants that stimulate immune responses include 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 certain embodiments, the potentiating agents includes cyclophosphamide and analogs of cyclophosphamide, anti-TGFβ and Imatinib (Gleevec), 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.

The compound of the present invention refers to a compound of formula (I) of this patent application.

An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C_1-C_6 straight chained or branched alkyl group is also referred to as a "lower alkyl" group. An alkyl group may be optionally substituted at one or more positions as permitted by valence. Such optional substituents include, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, —CF_3, —CN and the like.

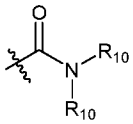
The term "alkoxy" refers to an alkyl group, preferably a lower alkyl group, having oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl or heteroaryl groups is contemplated.

The term "alkylthio", as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula (alkyl)-S—.

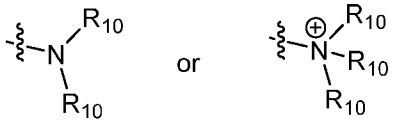
The term "alkynyl", as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl or heteroaryl groups is contemplated.

The term "amide" or "amido" as used herein, refers to a group



wherein each R^{10} independently represent a hydrogen or hydrocarbyl group or two R^{10} are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



wherein each R^{10} independently represents a hydrogen or a hydrocarbyl group or two R^{10} are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term "aminoalkyl", as used herein, refers to an alkyl group substituted with an amino group.

The term "alkylamino", as used herein, refers to an amino group substituted with at least one alkyl group.

The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)—, preferably alkylC(O)—.

The term "acylamino", as used herein, refers to an amino group substituted with acyl group.

The term "aryl" as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline and the like.

A "cycloalkyl" group is a cyclic hydrocarbon which is completely saturated. "Cycloalkyl" includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused cycloalkyl" refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. A "cycloalkenyl" group is a cyclic hydrocarbon containing one or more double bonds. A cycloalkyl group may be substituted at one or more positions, as permitted by valence, with any optional substituents described herein.

The term "carboxy" or "carboxylic acid", as used herein, refers to a group represented by the formula —CO_2H. The term "carboxylate" refers to a group represented by the formula -$(CO_2)^-$.

The term "ester", as used herein, refers to a group -$C(O)OR^{10}$ wherein R^{10} represents a hydrocarbyl group.

The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo and iodo.

The term "heteroalkyl", as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine and the like. A heteroaryl group may be substituted at one or more positions, as permitted by valence, with any optional substituents described herein.

The terms "carbocycle", "carbocyclic" or "carbocyclyl" as used herein, refers to any stable 3-, 4-, 5-, 6- or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12- or 13-membered bicyclic or tricyclic hydrocarbon ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and indanyl. When the term "carbocycle" or "carbocyclyl" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link

two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The terms "(heteroaryl)alkyl" or "hetaralkyl" or "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen and sulfur.

The terms "heterocyclyl", "heterocycle" "heterocycloalkyl" and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams and the like. Heterocyclyl groups may be optionally substituted as permitted by valence.

The term "(heterocyclyl)alkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

The term "thioester", as used herein, refers to a group —C(O)SR^{10} or —SC(O)R^{10} wherein R^{10} represents a hydrocarbyl.

The term "thiocarboxy" or "thiocarboxylic acid", as used herein, refers to a group represented by the formula -C(O)SH. The term "thiocarboxylate" refers to a group represented by the formula -(C(O)S)$^{-}$.

As used herein, the term "guanidino" refers to –NH-C(=NH)-NH$_2$ group.

As used herein, the term "cyano" refers to -CN group.

As used herein, the term "hydroxyl" refers to -OH group.

As used herein, the term "nitro" refers to -NO$_2$ group.

As used herein, the term "oxo" refers to (=O) group.

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl or alkoxy is meant to include groups where there

are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl or an acyl), a thiocarbonyl (such as a thioester, a thioacetate or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as "unsubstituted," references to chemical moieties herein are understood to include substituted variants. For example, reference to an "aryl" group or moiety implicitly includes both substituted and unsubstituted variants.

As used herein, a therapeutic that "prevents" a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or

condition in the treated sample relative to an untreated control sample or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample.

The term "treating" includes prophylactic and/or therapeutic treatments. The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate or stabilize the existing unwanted condition or side effects thereof).

The term "prodrug" is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present invention (e.g., a compound of formula (I)). A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids) are preferred prodrugs of the present invention. In certain embodiments, some or all of the compounds of formula (I) in a formulation represented above can be replaced with the corresponding suitable prodrug, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid present in the parent compound is presented as an ester.

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 additional (unspecified) features or components.

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 "amino acid" means a molecule containing both an amino group and a carboxyl group and includes its salts, esters, combinations of its various salts, as well as tautomeric forms. In solution, at neutral pH, amino and acid groups of an amino acid can exchange a proton to form a doubly ionized, through overall neutral, entity identified as a zwitterion. In some embodiments, the amino acids are α-, β-, γ- or δ-amino acids, including their stereoisomers and racemates. As used herein, the term "L-amino acid" denotes an α-amino acid having the levorotatory configuration

around the α-carbon, that is, a carboxylic acid of general formula $CH(COOH)(NH_2)$-(side chain), having the L-configuration. The term "D-amino acid" similarly denotes a carboxylic acid of general formula $CH(COOH)(NH_2)$-(side chain), having the dextrorotatory-configuration around the α-carbon. Side chains of L-amino acids can include naturally occurring and non-naturally occurring moieties. Non-naturally occurring (i.e., unnatural) amino acid side chains are moieties that are used in place of naturally occurring amino acid side chains in, for example, amino acid analogs.

An "amino acid residue" as used herein, means a moiety sharing structural similarity to the parent amino acid. An amino acid residue may be covalently bonded to another chemical moiety via the amino group of the residue or the carboxylate group of the residue (i.e., a hydrogen atom of $-NH_2$ or -OH is replaced by a bond to another chemical moiety).

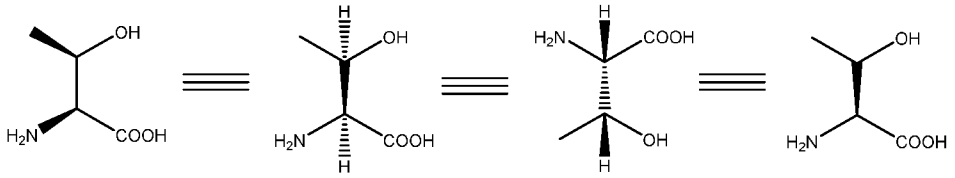
As used herein, the phrase "side chain of an amino acid" means a moiety that is covalently attached to D or L-amino acid structure and can be represented as $CH(COOH)(NH_2)$-R. For example, in case of alanine $CH(COOH)(NH_2)(CH_3)$, side chain of amino acid (R) is $–CH_3$. Examples of "side chain of amino acid" include, but are not limited to, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl. The side chain of amino acid may be substituted by one or more, same or different substituents selected from, but are not limited to, amino, amido, alkylamino, acylamino, carboxylic acid, carboxylate, thiocarboxylate, thioacid, - hydroxy, cycloalkyl, (cycloalkyl)alkyl, aryl, heterocyclyl, heteroaryl, guanidino, -SH, -S(alkyl); optionally wherein cycloalkyl, aryl, heterocyclyl and heteroaryl are further substituted optionally by one or more substituents such as hydroxy, alkoxy, halo, amino, nitro, cyano or alkyl.

Amino acids include the twenty standard amino acids used by most biological organisms in protein synthesis. Unnatural amino acids may be selected from, but are not limited to, alpha and alpha-disubstituted amino acids, N-alkyl amino acids and natural amino acids substituted with lower alkyl, aralkyl, hydroxyl, aryl, aryloxy, haloalkyl or acyl.

For example, lysine can be substituted to form an unnatural amino acid, e.g., at a carbon atom of its side chain or alternatively by mono- or dialkylation of its terminal NH_2 group (e.g., wherein the amino group of the lysine sidechain is taken together with its substituents to form a heterocyclic ring such as piperidine or pyrrolidine). In another example, the terminal amino group of the lysine sidechain can form a ring with the amino acid backbone, as in capreomycidine. Further unnatural derivatives of lysine

include homolysine and norlysine. The sidechain of lysine can alternatively be substituted by a second amino group. In another example, the alkyl portion of the lysine side chain can be incorporated into a carbocyclic ring structure to form a semirigid analog, such as, e.g., cyclohexyl or cyclopentyl.

Throughout this specification and claims, the 'L-threonine residue' and/or 'side chain of L-threonine' mentioned in compound of formula (I) and/or preparation thereof can be represented by any one of the following formulae.



L-threonine *L*-threonine *L*-threonine *L*-threonine

In certain embodiments, the unnatural amino acid can be a derivative of a natural amino acid having one or more double bonds.

In other example embodiments, in threonine, the beta-methyl group can be replaced with an ethyl, phenyl or other higher alkyl group. In histidine, the imidazole moiety can be substituted or alternatively, the alkylene backbone of the side chain can be substituted.

Further examples of unnatural amino acids include homoserine and homologs of natural amino acids.

In further example embodiments, an unnatural amino acid can be alkylated (e.g., methylated) at the alpha position.

Further examples of unnatural amino acids include alpha,beta- and beta,gamma-dehydroamino amino acid analogs.

Further exemplary amino acids include penicillamine and betamethoxyvaline.

This invention includes pharmaceutically acceptable salts of compounds of the invention and their use in the compositions and methods of the present invention. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-

hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization or adventitious to such solvent.

"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 "stereoisomers" refers to any enantiomers, diastereoisomers or geometrical isomers, such as of the compounds of the invention. When compounds of the invention 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 compounds that are enriched in one of 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).

In certain embodiments, compounds of the invention may be racemic. In certain embodiments, compounds of the invention may be enriched in one enantiomer. For example, a compound of the invention may have greater than 30% ee, 40% ee, 50% ee, 60% ee, 70% ee, 80% ee, 90% ee or even 95% or greater ee. In certain embodiments,

compounds of the invention may have more than one stereocenter. In certain such embodiments, compounds of the invention may be enriched in one or more diastereomer. For example, a compound of the invention may have greater than 30% de, 40% de, 50% de, 60% de, 70% de, 80% de, 90% de or even 95% or greater de.

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).

Naturally-occurring amino acids are identified throughout the description and claims by the conventional three-letter abbreviations indicated in the below table.

Table (Amino acid codes)

Name	3-letter code	Name	3-letter code
Alanine	Ala	Lysine	Lys
Asparagine	Asn	Phenylalanine	Phe
Aspartic acid	Asp	Proline	Pro
Glutamic acid	Glu	Serine	Ser
Glutamine	Gln	Threonine	Thr
Isoleucine	Ile	Tryptophan	Trp
Leucine	Leu	Tyrosine	Tyr
Histidine	His	Arginine	Arg
Valine	Val	-	-

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

^{o}C (degree Celsius); % (percentage); brine (NaCl solution); CH_2Cl_2/DCM (Dichloromethane); Boc (Tert-butyloxycarbonyl); Bzl (Benzyloxy-carbonyl); Cbz; Carboxybenzy; $CDCl_3$ (Deuterated chloroform); Cs_2CO_3 (Caesium carbonate); d (Doublet); DIC (N,N′-Diisopropylcarbodiimide); DIPEA (N,N-Diisopropylethylamine); DMF (Dimethyl formamide); EtOH: Ethanol; Et_2NH (Diethylamine); Fmoc: (9-Fluorenylmethyloxycarbonyl); g or gr (gram); HOBt: (1-Hydroxy benzotriazole); h or hr (Hours); Hz (Hertz); HPLC (High-performance liquid chromatography); K_2CO_3 (Potassium carbonate); LCMS (Liquid chromatography mass spectroscopy); Liq.NH_3: Liquid ammonia; mmol (Millimoles); m (Multiplet); M (Molar); µl (Microlitre); mL (Millilitre); mg (Milligram); MHz (Megahertz); MS (ES) (Mass spectroscopy-electro spray); min (Minutes); Na (Sodium); $NaHCO_3$ (Sodium bicarbonate); $NH_2NH_2.H_2O$

(Hydrazine hydrate); NMM (N-Methylmorpholine); Na_2SO_4 (Sodium sulphate); NMR (Nuclear magnetic resonance spectroscopy); $NH_2OH.HCl$ (Hydroxylamine hydrochloride); PD1/PD-1 (Programmed cell death 1); PD-L1 (Programmed death-ligand 1); PD-L2 (Programmed cell death 1 ligand 2); prep-HPLC/preparative HPLC (Preparative High-performance liquid chromatography); PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate); s (Singlet); TEA/Et_3N (Triethylamine); TFAA (Tifluoroacetic anhydride); t-Bu/^{t}Bu (Tert-butyl); TLC (Thin Layer Chromatography); THF (Tetrahydrofuran); TIPS (Triisopropylsilane); TFA (Trifluoroacetic acid); t_R = (Retention time); Trt (Trityl or Triphenylmethyl), etc.

EXPERIMENTAL

The present invention provides methods for the preparation of compounds of formula (I) according to the procedures of the following examples, using appropriate materials and/or reagents. 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 intermediates or starting materials required for the synthesis are commercially available (commercial sources such as Sigma-Aldrich, USA or Germany; Chem-Impex USA; G.L. Biochem, China and Spectrochem, India) or alternatively, these intermediates or starting materials can be prepared using known literature methods. The invention is described in greater detail by way of specific examples.

Purification and characterization of compounds

Analytical HPLC method:

Analytical HPLC was performed on ZIC HILIC 200 A° 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:

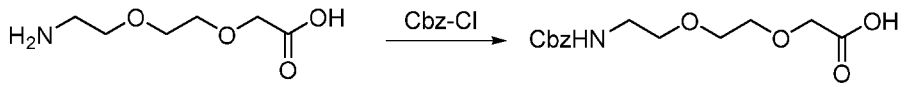
Preparative HPLC was performed on SeQuant ZIC HILIC 200 A° column (10 mm × 250 mm, 5 µm), Flow rate: 5.0 mL/min. The elution conditions used are: Buffer A: 5 mmol ammonium acetate (adjust to pH-4 with Acetic Acid), Buffer B: Acetonitrile,

Equilibration of the column with 90 % buffer B and elution by a gradient of 90 % to 40 % buffer B during 20 min.

LCMS was performed on AP1 2000 LC/MS/MS triple quad (Applied biosystems) with Agilent 1100 series HPLC with G1315 B DAD, using Mercury MS column or using Agilent LC/MSD VL single quad with Agilent 1100 series HPLC with G1315 B DAD, using Mercury MS column or using Shimadzu LCMS 2020 single quad with Prominence UFLC system with SPD-20 A DAD.

Example 1: Synthesis of compound 1

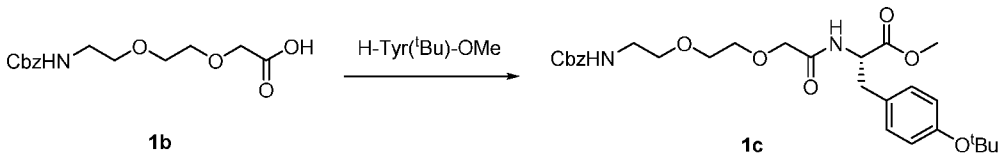
Step 1a:



1a 1b

Sodium Carbonate (78 g, 736 mmol) and Cbz-Cl (68.6 g, 405 mmol) were added to a solution of starting material 1a (60.0 g, 368 mmol) in water (250 mL) and 1,4-dioxane (250 mL) and stirred at room temperature for 8 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was diluted with water and washed with dichloromethane and the aqueous layer was acidified to pH 2-3 and extracted with dichloromethane. The organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure to yield 80 g of compound 1b. LCMS: 298.0 $(M+H)^+$.

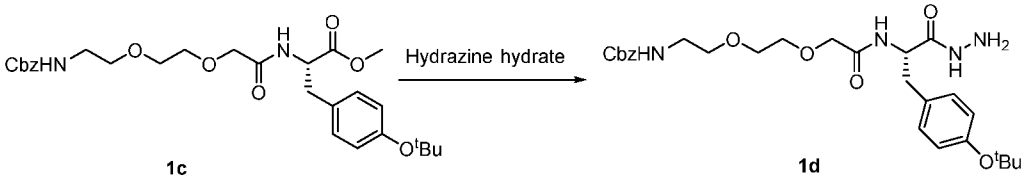
Step 1b:



1b 1c

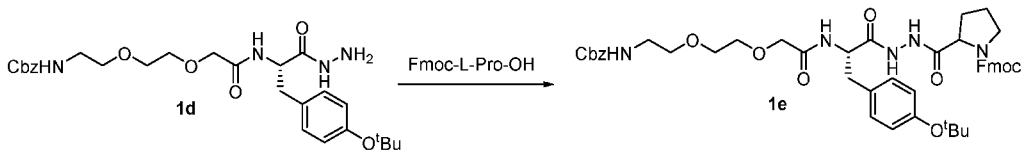
DIPEA (5.6 mL, 31.0 mmol) was added slowly to a stirred solution of compound 1b (5.0 g, 17.1 mmol) and HATU (8.85 g, 23.3 mmol) in DMF (50 mL) and was allowed to stir at room temperature for 5 more min. L-Tyr(^{t}Bu)-OMe (3.9 g, 15.5 mmol) was further added slowly and stirred at room temperature for 12 h. The completion of the reaction was confirmed by TLC analysis. The reaction mixture was quenched with ice, precipitated solid was filtered and re-crystallized with CH_2Cl_2 to yield 7.1 g of compound 1c. LCMS: 531.5 $(M+H)^+$.

Step 1c:



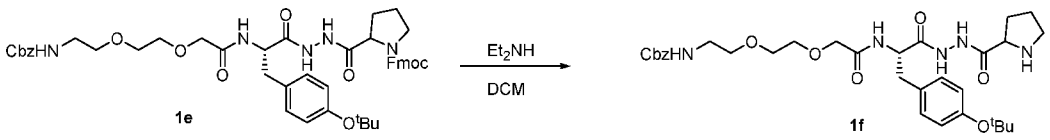
99% hydrazine hydrate solution (5.2 mL) was added slowly to a stirred solution of compound 1c (7.0 g) in methanol (50 mL) and stirred at room temperature for 2 h. The completion of the reaction was confirmed by TLC. The volatiles were evaporated and the obtained residue was partitioned between water and ethyl acetate. The organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure to get 6.8 g of compound 1d.

Step 1d:



DIPEA (3.4 mL, 18.89 mmol) was added slowly to a stirred solution of compound 1d (5 g, 9.4 mmol) and HATU (5.4 g, 14.2 mmol) in DMF (50 mL) and the mixture was allowed to stir at room temperature for 5 min. Fmoc-L-Pro-OH (3.2 g, 9.4 mmol) was further added to this mixture 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, precipitated solid was filtered and re-crystallized with diethyl ether and n-pentane to yield 10.1 g of compound 1e. LCMS: 850.6 $(M+H)^+$.

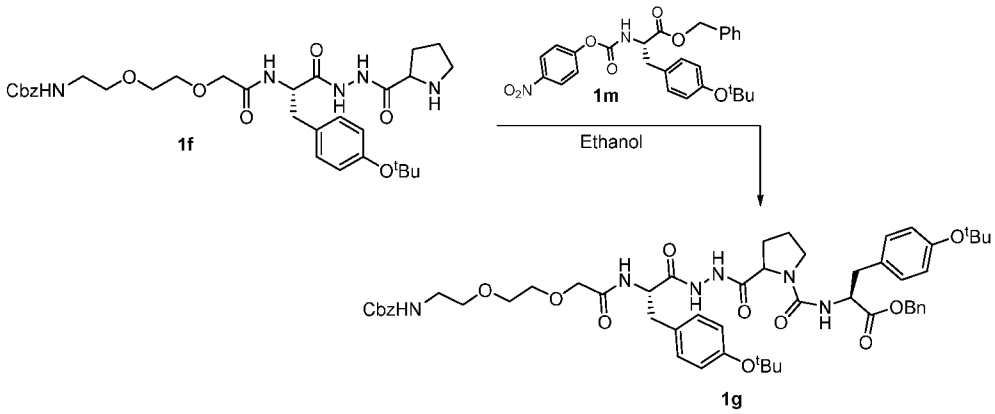
Step 1e:



A solution of compound 1e (10 g, 11.9 mmol) and diethylamine (100 mL) in DCM (100 mL) was allowed to stir at 0 °C to RT for 1 h. The completeness of the reaction was confirmed by TLC analysis. Evaporation of the volaties under reduced pressure yielded crude product, which was washed with n-hexane to remove Fmoc impurity. Then solid was partition between water and DCM (2 × 100 mL). The organic layer was washed with $NaHCO_3$ solution followed by brine solution. The organic layer was dried, filtered concentrated under reduced pressure to yield solid crude compound.

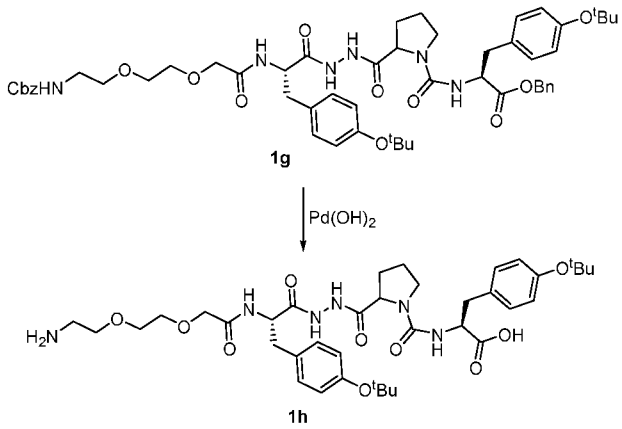
Finally, the solid was washed with n-hexane and dried under high vacuum to yield 4.5 g of compound 1f. LCMS: 628.8 $(M+H)^+$.

Step 1f:



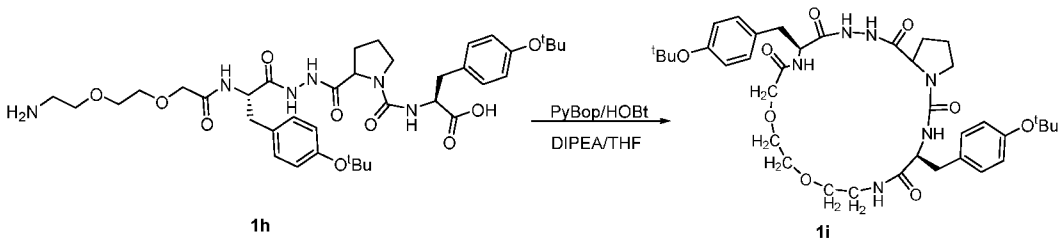
Compound 1m (3.0 g, 6.14 mmol) and compound 1f (3.5 g, 5.6 mmol) were dissolved in ethanol (100 mL) and stirred at 85 °C for 4 h. The completeness of the reaction was confirmed by TLC analysis. The solvent was removed under reduced pressure and the crude obtained was washed with ether to yield 2.9 g of compound 1g. LCMS: 981.0 $(M+H)^+$.

Step 1g:



A solution of compound 1g (2.0 g, 2.0 mmol) in methanol (25 mL) was treated with palladium hydroxide (0.5 g) at room temperature for 2 h. The completeness of the reaction was confirmed by TLC analysis. The palladium hydroxide was removed by celite bed filtration and the filtrate was evaporated under reduced pressure to yield 1.7 g of compound 1h. LCMS: 757.0 $(M+H)^+$.

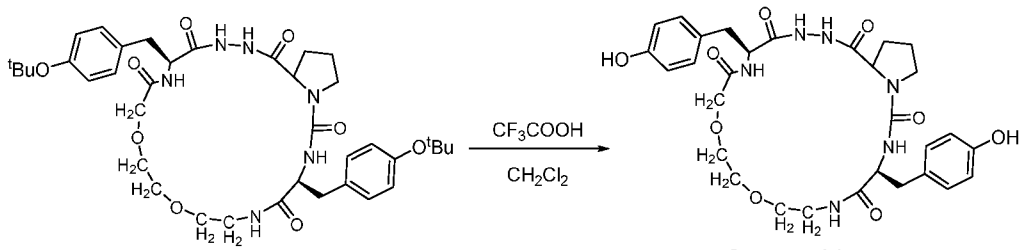
Step 1h:



1h 1i

Cyclization of compound 1h (1.7 g, 2.248 mmol) was carried out using HOBt (0.49 g, 3.4 mmol) and PyBOP (2.9 g, 5.6 mmol) in THF (500 mL). The reaction was initiated by slow addition of DIPEA (0.73 g, 5.6 mmol) and further stirred at room temperature for 12 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was diluted with CH_2Cl_2, washed with water followed by 10 % $NaHCO_3$ solution and brine solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the residue which on washing with diethyl ether yielded 1.5 g of compound 1i. LCMS: 739.2 $(M+H)^+$.

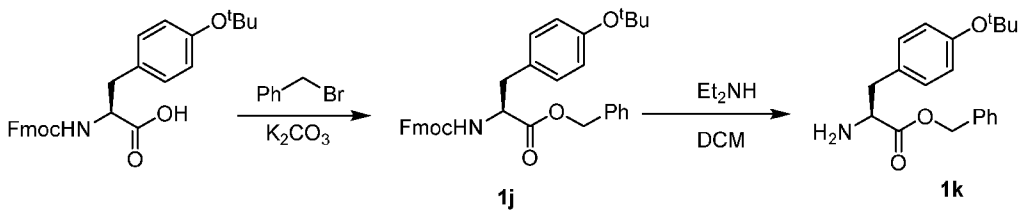
Step 1i:



1i Compound 1

TFA (10 mL) and TIPS (0.1 mL) were added slowly to a stirred solution of compound 1i (1.5, 2.0 mmol) in CH_2Cl_2 (10 mL) and reaction mixture was stirred at room temperature for 2h. After completeness of the reaction, mixture was evaporated under N_2 atmosphere and washed with Et_2O yielded 1.2 g crude compound 1. The crude solid material was purified using preparative HPLC method described under experimental conditions. LCMS: 627.3 $(M+H)^+$, HPLC: t_R = 12.3 min.

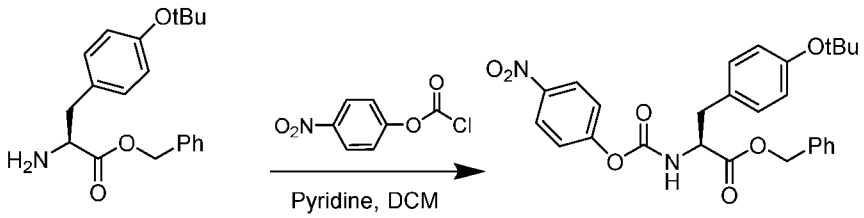
Synthesis of compound 1m



1j 1k

K_2CO_3 (6.0 g, 43.6 mmol) was added to a solution of Fmoc-L-Tyr-OH (10.0 g, 21.74 mmol) in DMF (100 mL) and the resutling mixture was cooled to 0 °C. To the cooled mixture benzyl bromide (2.84 mL, 23.913 mmol) was added and the mixture was stirred for 30 min at ice cold temperature followed by room temperature for 2 h. The reaction mixture was concentrated and the residue was diluted with ethyl acetate (150 mL). The organic layer was washed with water (2 × 100 mL) followed by brine solution (1 × 100 mL). The separated organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure to yield 12.0 g of compound 1j. LCMS: 550.2 $(M+H)^+$.

Fmoc group on compound 1j (12.0 g, 21.857 mmol) was de-protected by treating it with diethylamine (50.0 mL) in CH_2Cl_2 (50.0 mL) at room temperature for 1 h. 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 6.8 g of intermediate 1k. LCMS: 328.4 $(M+H)^+$.

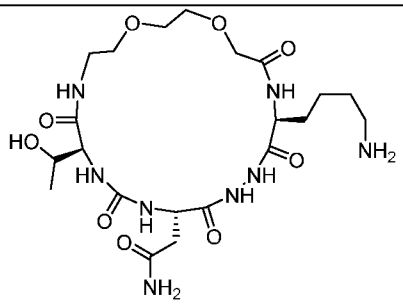
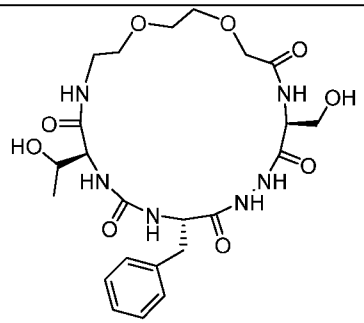
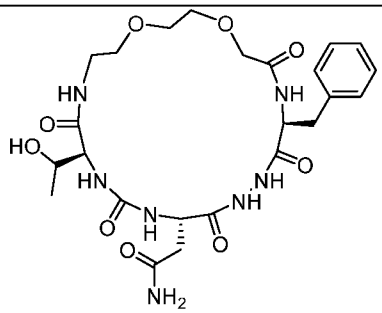
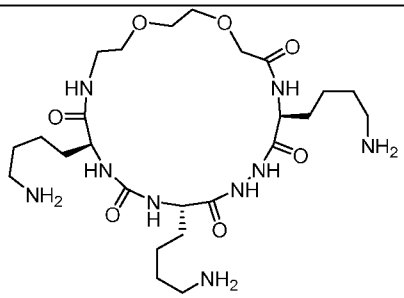


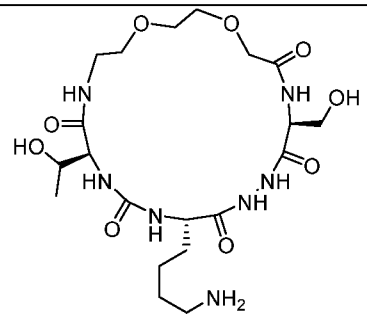
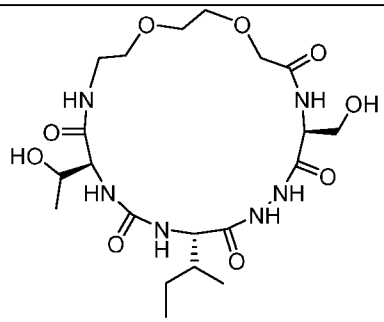
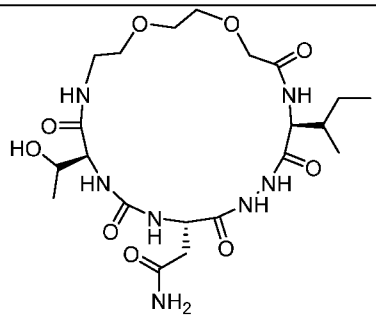
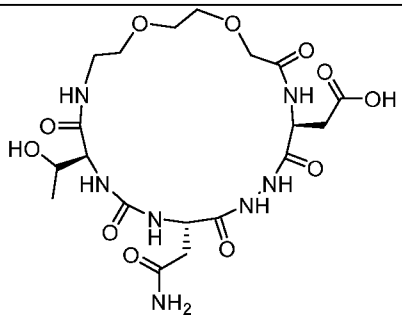
1k 1m

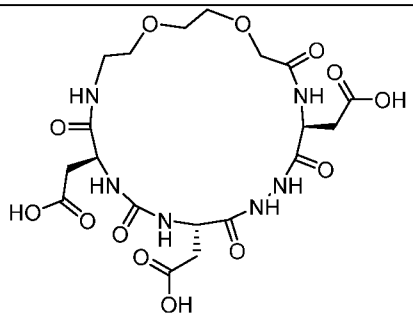
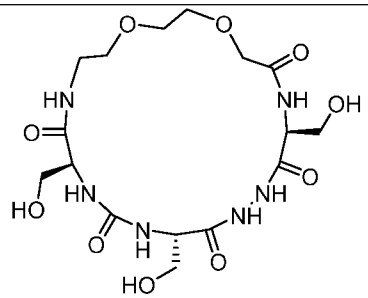
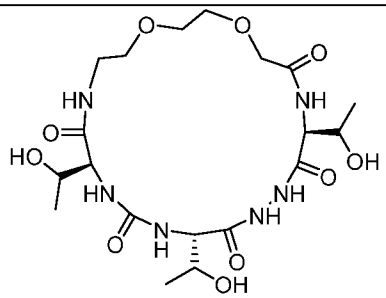
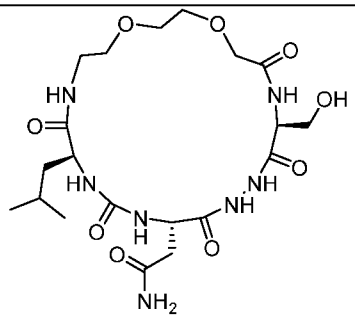
Pyridine (3.0 g, 30.48 mmol) was added to a stirred solution of intermediate 1k (5.0 g, 15.24 mmol) in CH_2Cl_2 (30 mL). To this reaction mixture 4-nitrophenyl chloroformate (3.4 g, 16.76 mmol) in CH_2Cl_2 (10 mL) was added and the reaction was continued at room temperature for 1 h. The completion of 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 aq. citric acid solution (2 x 100 mL), dried over Na_2SO_4 and evaporated under reduced pressure to yield crude compound 1m, which was further purified by silica gel column chromatography (eluent: 0-20% ethyl acetate in hexane) to yield 7.0 g of compound 1m. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 9H), 3.13 (m, 2H), 4.10 (m, 1H), 5.18 (s, 2H), 6.87 (d, 2H), 6.95 (d, 2H), 7.35 (m, 5H), 7.49 (d, 1H), 8.21 (d, 2H), 8.33 (d, 2H).

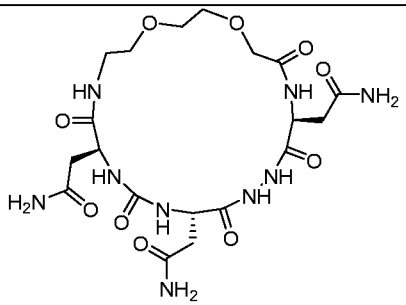
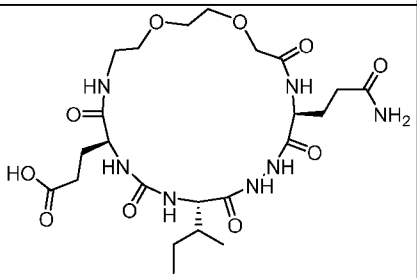
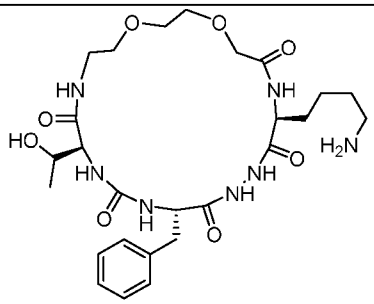
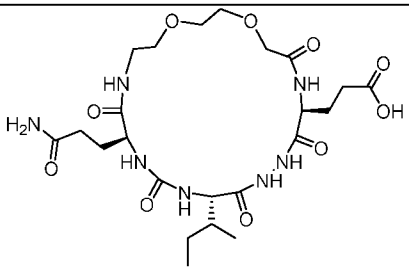
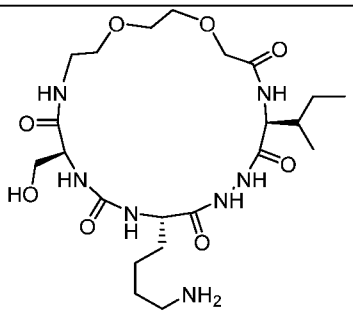
The below compounds were prepared by procedure similar to the one described in Example 1 (compound 1) with appropriate variations in reactants or amino acids,

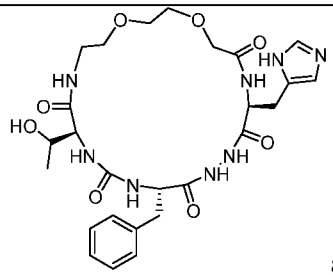
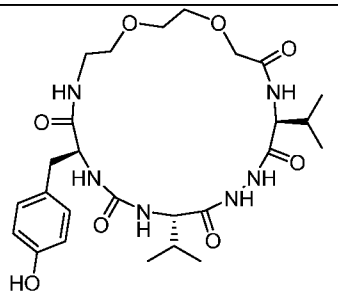
solvents, quantities of reagents and reaction conditions. The analytical data of the compounds are summarized herein below table.

Compound No.	Structure	LCMS $(M+H)^+$	HPLC (t_R in min)
2		547.4	17.2
3		538.3	12.5
4		566.1	11.9
5		588.2	9.0

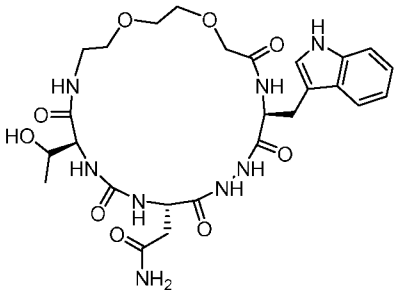
Compound No.	Structure	LCMS $(M+H)^+$	HPLC (t_R in min)
6		520.3	11.4
7		505.2	10.8
8		532.2	11.41
9		533.9	9.23

Compound No.	Structure	LCMS $(M+H)^+$	HPLC (t_R in min)
10		549	9.38
11		465.1	12.86
12		507.1	9.47
13		518.2	9.69

Compound No.	Structure	LCMS $(M+H)^+$	HPLC (t_R in min)
14		546.3	11.98
15		574.0	9.05
16		580.2	14.20
17		574.6	10.8
18		531.8	11.30

Compound No.	Structure	LCMS $(M+H)^+$	HPLC (t_R in min)
19	 and	589.8	12.1
20		565.3	-

Although the present application has been illustrated by certain preceding examples, it is not to be construed as being limited thereby; but rather, the present application encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments can be made without departing from the spirit and scope thereof. For example, the following compounds 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.



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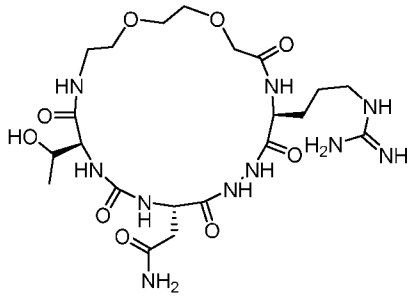

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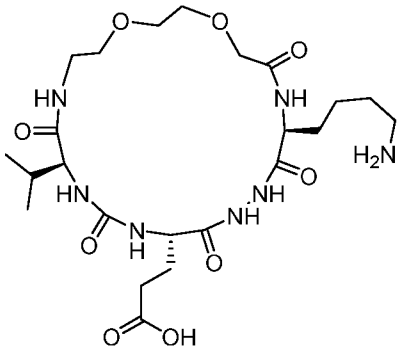

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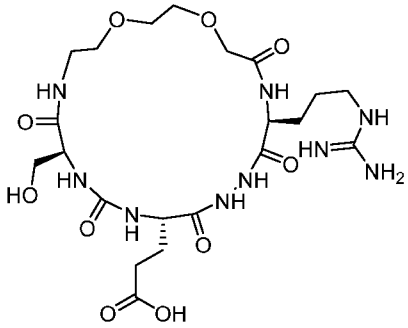

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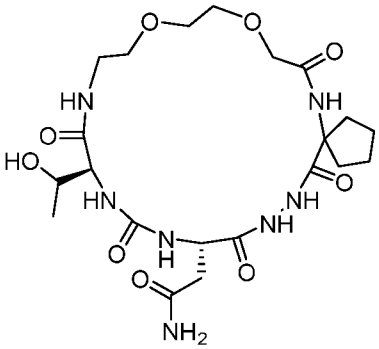

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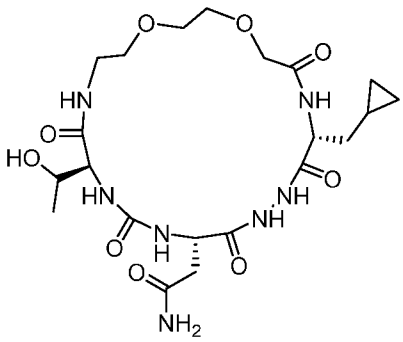

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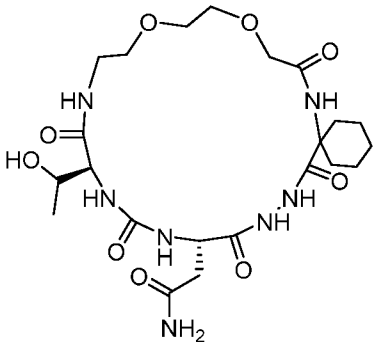

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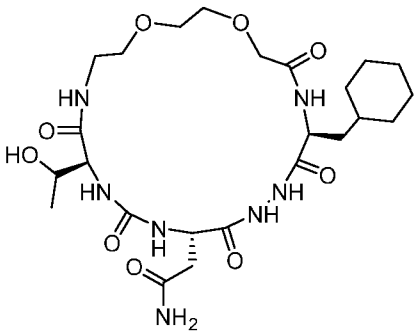

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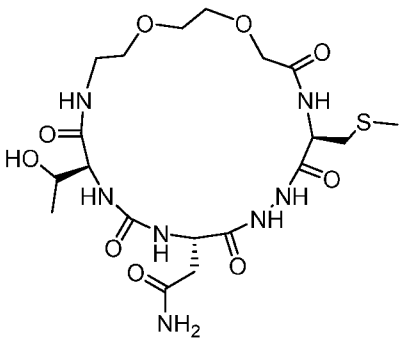

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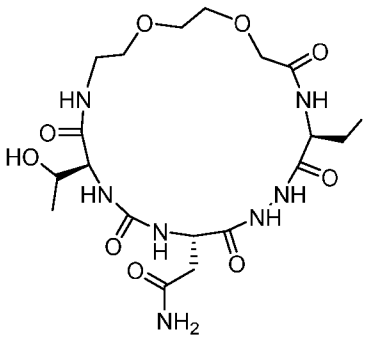

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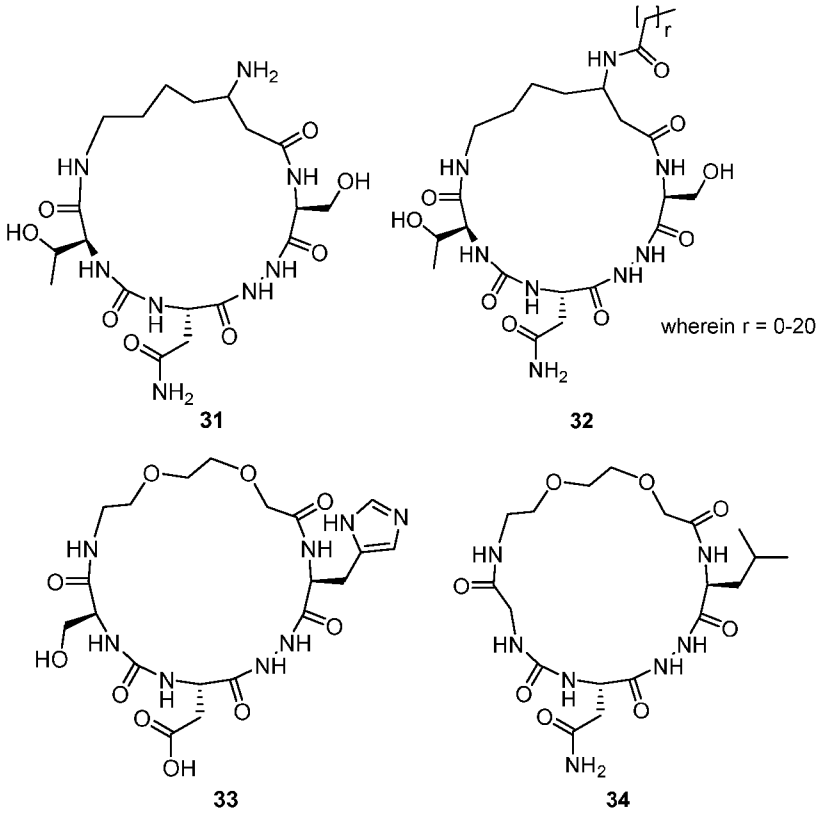

31 32 33 34

Example 2: Rescue of mouse splenocyte proliferation in the presence of recombinant PD-L1

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); 40µm 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 + 1mM 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 (1µg/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 analysed by flow cytometry with 488 nm excitation and 521 nm emission filters.

Data compilation, processing and inference:

Percent splenocyte proliferation was analysed 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 conc. of compound to anti-CD3/CD28 stimulated splenocytes in presence of ligand (PDL-1).

Compound No.	Percent rescue of proliferation (@100 nM compound concentration)	Compound No.	Percent rescue of proliferation (@100 nM compound concentration)
1	76	2	57
3	66	5	24
6	40	7	23
9	46	10	53
11	17	12	91
13	53	15	40
16	30	17	38

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4. Bishop, J. L. PD-L1 is highly expressed in non-AR driven Enzalutamide resistant prostate cancer. Abstracts; Prostate Cancer Foundation 2014.

5. Carneiro, B.A. Cancer Treatment Reviews 41 (2015) 170–178.

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7. Shen, J. K. Programmed Cell Death Ligand 1 Expression in Osteosarcoma. Cancer Immunol. Res. 2(7), 690-698 (2014).

8. Stevens, A. M. PD-L1 Expression on Monocytes Marks Active Systemic Lupus Erythematosus in Patients without Nephritis.

INCORPORATION BY REFERENCE

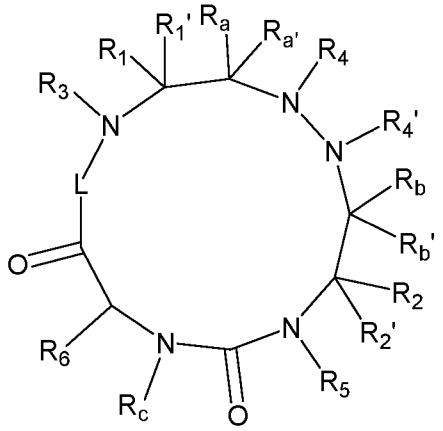
All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents and the specification, along with such variations.

We claim:

1. A compound of formula (I):



(I)

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

L is $^{*}\text{-C(O)-(CH}_2\text{)}_m\text{-(X-}\overset{R_c}{\overset{|}{C}}\text{H-CH}_2\text{)}_n\text{-NH-}$ or $^{*}\text{-C(O)-(CH}_2\text{)}_m\text{-(}\overset{R_d}{\overset{|}{C}}\text{H)-(CH}_2\text{)}_n\text{-NH-}$, wherein the -C(O)- group marked with * is connected to the nitrogen bearing R_3 in Formula (I);

X is CH_2, O, NH or S;

R_1, R_2 and R_6 independently are a side chain of an amino acid, hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl; wherein $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl and $(C_2\text{-}C_6)$alkynyl are optionally substituted by one or more substituents selected from hydroxy, amino, amido, alkylamino, acylamino, $\text{-(CH}_2\text{)}_m\text{-COOH}$, $\text{-(CH}_2\text{)}_m\text{-COO-alkyl}$, cycloalkyl, heterocyclyl, aryl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl, (heteroaryl)alkyl, -SH and -S-(alkyl); optionally wherein cycloalkyl, aryl, heterocyclyl and heteroaryl are further substituted by one or more substituents such as hydroxy, alkoxy, halo, amino, nitro, cyano or alkyl; optionally wherein two or three carbon atoms of the $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or $(C_2\text{-}C_6)$alkynyl form part of a 3-7-membered carbocyclic or heterocyclic ring (such as a cyclobutyl or oxirane ring);

R_1', R_2', R_3 and R_5 independently are hydrogen or alkyl;

or R_1 and R_1', together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl or heterocycloalkyl ring;

or R_1 and R_3, together with the atoms to which they are attached, form a heterocyclic ring optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy;

or R_2 and R_2', together with the carbon atom to which they are attached form an optionally substituted cycloalkyl or heterocycloalkyl ring;

or R_2 and R_5, together with the atoms to which they are attached form a heterocyclic ring optionally substituted with one or more groups independently selected from amino, cyano, alkyl, halo and hydroxy;

R_4 and R_4' independently are hydrogen or alkyl;

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

R_b and R_b' are each hydrogen; or together represent an oxo (=O) group;

R_c at each occurrence is independently hydrogen or alkyl;

R_d is amino or -NH-C(O)-$(CH_2)_r$-CH_3;

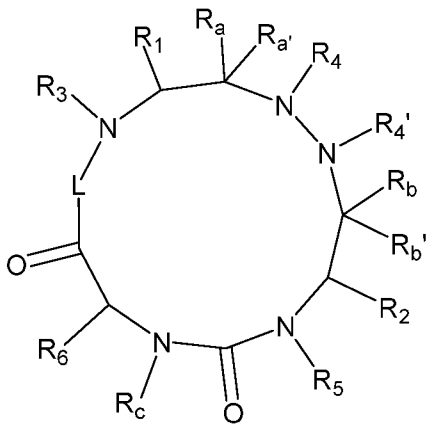
m is an integer from 0 to 3;

n, independently for each occurrence, is an integer from 2 to 20;

r is an integer from 0 to 20; and

with a proviso that R_6 is not a side chain of Ser, Asp, Ala, Ile, Phe, Trp, Lys, Glu and Thr, when, R_1 is a side chain of Ala, Ser, Thr or Leu, R_2 is a side chain of Asp, Asn, Glu or Gln and R_5 and R_c are hydrogen.

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

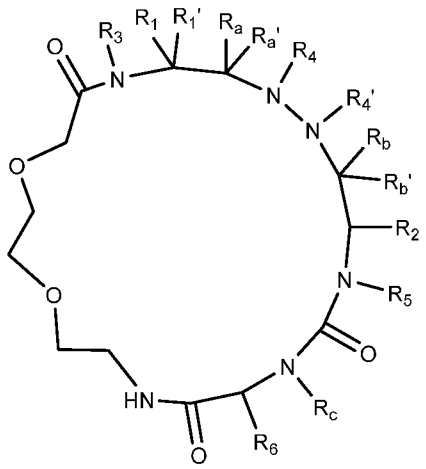


(IA)

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

L, R_1, R_2, R_3, R_4, R_4', R_5, R_6, R_a, R_a', R_b, R_b' and R_c are same as defined in claim 1.

3. The compound according to claim 1, wherein the compound of formula (I) is a compound of formula (IB):

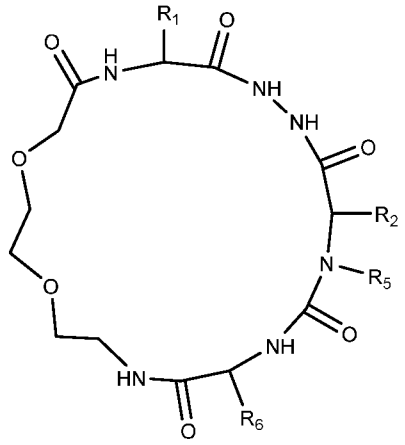


(IB)

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

R_1, R_1', R_2, R_3, R_4, R_4', R_5, R_6, R_a, R_a', R_b, R_b' and R_c are same as defined in claim 1.

4. The compound according to any one of claims 1 to 3, wherein the compound of formula (I)), (IA) or (IB) is a compound of formula (IC):



(IC)

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

R_1, R_2 and R_6 independently are side chain of an amino acid or hydrogen; and

R_5 is hydrogen or alkyl.

5. The compound according to claim 1, wherein,

R_1 is side chain of Ser, Tyr, Ile, Asp, Lys, Phe, Asn, Gln, Glu, Trp, His, Arg, Val or Thr;

R_2 is side chain of Asp, Asn, Ile, Lys, Phe, Ser, Thr, Val or Glu;

R_1' and R_2' are each hydrogen;

R_3, R_4, R_4' and R_5 independently are hydrogen;

R_6 is side chain of Ser, Leu, Tyr, Lys, Asp, Asn, Glu, Gln, Val or Thr;

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

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

L is $-C(O)-(CH_2)_m-(X-CH_2-CH_2)_n-NH-$;

X is O;

m is an integer from 0 to 3;

n, independently for each occurrence, is an integer from 2 to 20;

or a pharmaceutically acceptable salt or a stereoisomer thereof.

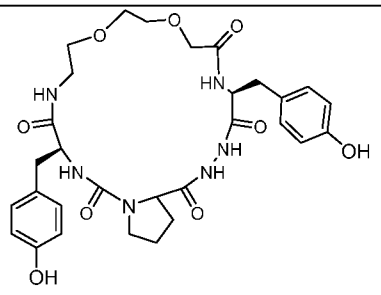
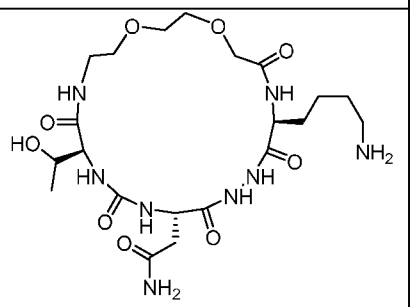
6. The compound according to any one of claims 1 to 4, wherein R_1 is (C_1-C_6)alkyl, (C_2-C_6)alkenyl or (C_2-C_6)alkynyl; wherein (C_1-C_6)alkyl, (C_2-C_6)alkenyl and (C_2-C_6)alkynyl are optionally substituted by one or more substituents selected from hydroxy, amino, amido, alkylamino, acylamino, $-(CH_2)_m-COOH$, $-(CH_2)_m-COO$-alkyl, cycloalkyl, heterocyclyl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl, (heteroaryl)alkyl and (alkyl)-S-.

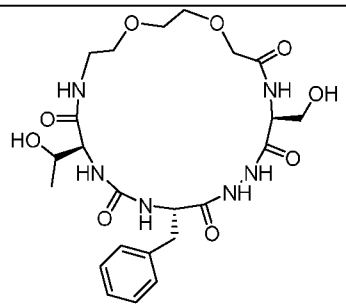
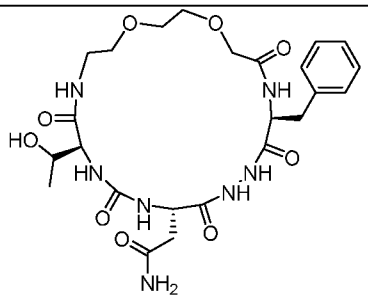
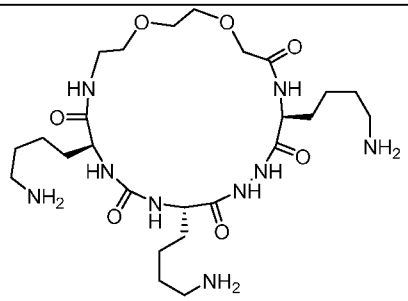
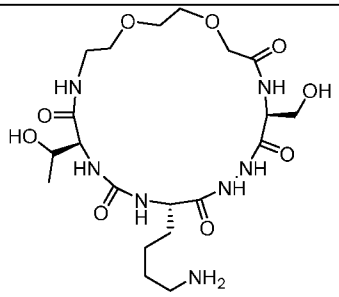
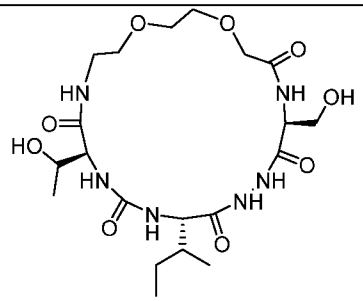
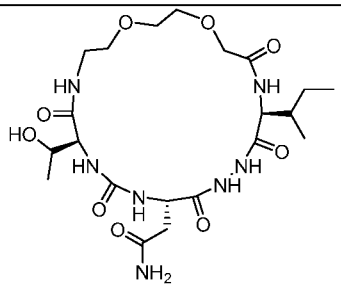
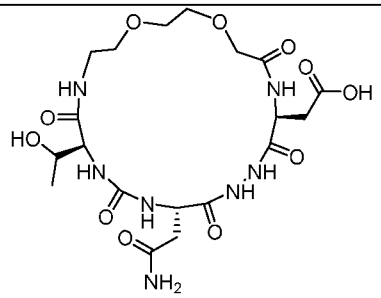
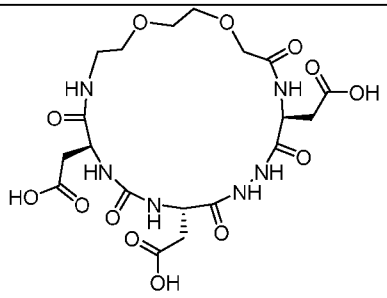
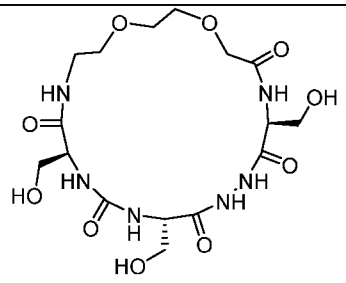
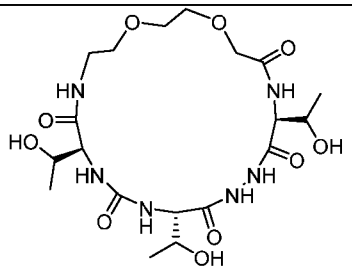
7. The compound according to the claim 6, wherein R_1 is (C_1-C_6)alkyl wherein the said (C_1-C_6)alkyl is optionally substituted by cycloalkyl or –S-(alkyl).

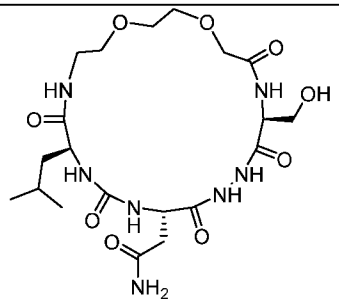
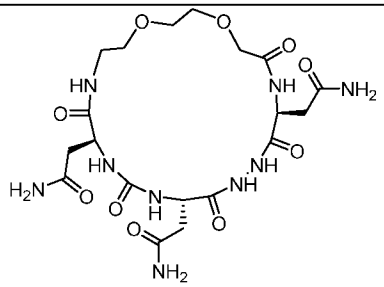
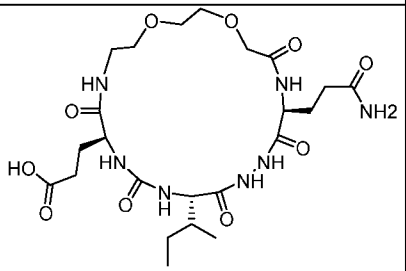
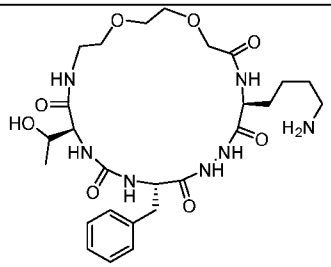
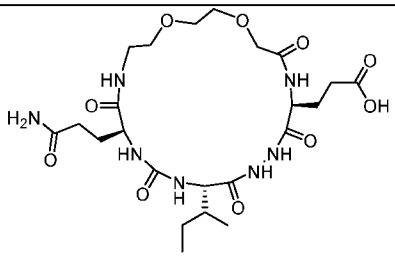
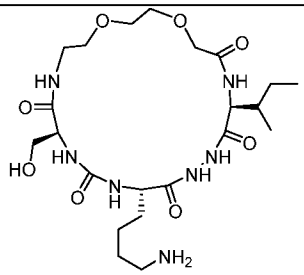
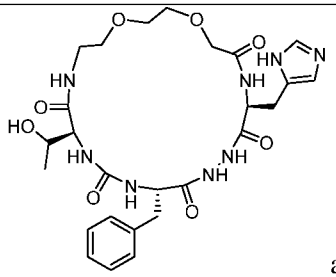
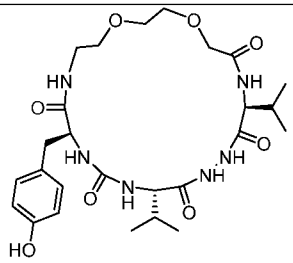
8. The compound according to any one of claims 1 and 3, wherein R_1 and R_1' together with the carbon atom to which they are attached form cycloalkyl ring; the said cycloalkyl is cyclopentyl or cyclohexyl.

9. The compound according to any of the claims 1 to 4, wherein R_2 and R_5 together with the atoms to which they are attached, form a heterocyclic ring; wherein the said heterocyclic ring is pyrrolidine.

10. A compound is selected from the group consisting of:

Comp. No.	Structure	Comp. No.	Structure
1.		2.	

3.		4.	
5.		6.	
7.		8.	
9.		10.	
11.		12.	

13.		14.	
15.		16.	
17.		18.	
19.	 and	20.	

or a pharmaceutically acceptable salt or a stereoisomer thereof.

11. A pharmaceutical composition comprising a compound of any one of claims 1-10 and a pharmaceutically acceptable carrier or excipient.

12. A use of a compound of any one of claims 1-10 in the manufacture of a medicament for the treatment of cancer.

13. The pharmaceutical composition or medicament of claims 11 or 12 for use in treating cancer, bacterial, viral or fungal infection or an immunological condition.

14. A method of treating cancer, comprising administering to a subject in need thereof a compound of any one of claims 1-10.

15. The method of claim 14, wherein the cancer is selected from lung cancer, breast cancer, colon cancer, renal cancer, bladder cancer, thyroid cancer, prostate cancer, osteosarcoma and Hodgkin's lymphoma.

16. The method of any one of the claims 14-15, comprising an additional step of administering to the subject in need thereof one or more additional chemotherapeutic agents independently selected from anti-proliferative agents, anti-cancer agents, immunosuppressant agents and pain-relieving agents.

17. A method of inhibiting the PD-1 pathway (e.g., PD-1, PD-L1 or PD-L2) in a subject, comprising administering to the subject a compound of any one of claims 1-10.

18. A method of treating disorders by inhibiting an immunosuppressive signal induced by PD-1, PD-L1 or PD-L2, comprising administering to a subject in need thereof a compound of any one of claims 1-10.

19. A method of treating a bacterial, viral or fungal infection or an immunological condition, comprising administering to a subject in need thereof a compound of any one of claims 1-10.

20. The method of any one of the claims 14-19, wherein the subject is a mammal e.g., a human.

21. A use of a compound of any one of claims 1-10 in inhibiting the PD-1 pathway (e.g., PD-1, PD-L1 or PD-L2).

22. A use of a compound of any one of claims 1-10 in the manufacture of a medicament for the treatment of bacterial, viral or fungal infection or an immunological condition in a subject.

23. The use of claim 12, wherein the cancer is selected from lung cancer, breast cancer, colon cancer, renal cancer, bladder cancer, thyroid cancer, prostate cancer, osteosarcoma and Hodgkin's lymphoma.

24. A compound of any one of the claims 1-10, for use as a medicament.

25. A compound of any one claims 1 to 10, for use in the treatment of cancer.

26. The compound according to claim 25, wherein the cancer is selected from lung cancer, breast cancer, colon cancer, renal cancer, bladder cancer, thyroid cancer, prostate cancer, osteosarcoma and Hodgkin's lymphoma.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/051268

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/395,A61K31/38 Version=2016.01

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)

A61K

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

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

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2015/033303 A1, (AURIGENE DISCOVERY TECHNOLOGIESLIMITED) 12 March 2015 page 2, line 5-20, page 9, table 1	1-13 and 21-26
A	WO 2013/170066 A1, (H. LEE MOFFITT CANCER CENTER & RESEARCH INSTITUTE, INC.) 14 November 2013 (14.11.2013) abstract, page 1, line 15-20, page 35, line 7-10	1-13 and 21-26
A	WO 2011/161699 A2, (AURIGENE DISCOVERY TECH LTD [IN];SASIKUMAR POTTAYIL GOVINDAN NAIR [IN) 29 December 2011 (29.12.2011) abstract, page 1, line 21-22, claims 1-25	1-13 and 21-26

☐ 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
27-06-2016	27-06-2016
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Md Atiqullah Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/051268

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.: 14-20
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 14-20 are directed to methods for the treatment of the human/animal body by therapy. Thus, the subject-matter of claims 14-20 is not required to be searched by this Authority accordance with PCT Article 17(2)(a)(i) and [Rule 39.1(iv)].

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

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2016/051268

Citation	Pub.Date	Family	Pub.Date
WO 2015/033303 A1	12-03-2015	CA 2922982 A1	12-03-2015
		US 20160113901 A1	28-04-2016
WO 2013/170066 A1	14-11-2013	US 20150071918 A1	12-03-2015
WO 2011/161699 A2	29-12-2011	EP 2585099 A2	01-05-2013
		US 8907053 B2	09-12-2014
		CN 103096915 A	08-05-2013