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

(72) Inventors: SASIKUMAR, Pottayil Govindan Nair; # 5, Deccan Palms, Ananth Nagar Phase, II, Electronic city Post, Bangalore 560100 (IN). PRASAD, Ap-pukkuttan; S-2, Navnit Sphatika, Meenakshi Layout, Kalena Agrahara, Bannerghatta Road, Bangalore 560076 (IN). NAREMADDEPALLI, Seetharamaiah Setty Sudarshan; 33/A, Shenimahathama temple compound, R., K. Layout, K. G. Nagar, Bangalore 560019 (IN). RA-MACHANDRA, Muralidhara; V173, Adarsh Palm Retreat, Outer Ring, Road, Bellandur Post, Bangalore 560103 (IN).

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(54) Title: CYCLIC SUBSTITUTED-1,3,4-OXADIAZOLE AND THIADIAZOLE COMPOUNDS AS IMMUNOMODULATORS

(57) Abstract: The present invention relates to cyclic substituted 1,3,4-oxadiazole and thiadiazole compounds of formula (I) and their use to inhibit the programmed cell death 1 (PD1) signaling pathway and/or for treatment of disorders by inhibiting an immunosuppressive signal induced by PD-1, PD-L1 or PD-L2.



WO 2018/051255 A1

CYCLIC SUBSTITUTED-1,3,4-OXADIAZOLE AND THIADIAZOLE COMPOUNDS AS IMMUNOMODULATORS

RELATED APPLICATIONS

This application claims the benefit of priority to Indian provisional application
5 number 201641031319, filed September 14, 2016, the contents of which are hereby
incorporated by reference.

TECHNICAL FIELD

The present invention relates to cyclic substituted 1,3,4-oxadiazole and
thiadiazole compounds and their derivatives therapeutically useful as immune
10 modulators. The invention also relates to pharmaceutical compositions comprising cyclic
substituted 1,3,4-oxadiazole and thiadiazole compounds and their derivatives as
therapeutic agents.

BACKGROUND OF THE INVENTION

Immune system in mammals sustains the ability to control the homeostasis
15 between the activation and inactivation of lymphocytes through various regulatory
mechanisms during and after an immune response. Among these mechanisms, there are
mechanisms that specifically modulate the immune response as and when required.
Mechanism via PD-1 pathway relates to almost every aspect of immune responses
including autoimmunity, tumour immunity, infectious immunity, transplantation
20 immunity, allergy and immunological privilege. PD-1 (or Programmed Cell Death 1 or
PDCD1) is a ~55kD type I membrane glycoprotein and is a receptor of the CD28
superfamily that negatively regulates T cell antigen receptor signalling by interacting
with the specific ligands and is suggested to play significant role in the maintenance of
self-tolerance.

25 The PD-1 protein's structure comprises of an extracellular IgV domain followed
by a trans-membrane region and an intracellular tail. The intracellular tail contains
two phosphorylation sites located in an immunoreceptor tyrosine-based inhibitory motif
and an immunoreceptor tyrosine-based switch motif, which suggests that PD-1
negatively regulates TCR signals. Also, PD-1 is expressed on the surface of activated T
30 cells, B cells, and macrophages, (Y. Agata et al., Int Immunol, May 1996, 8, 765)
suggesting that compared to CTLA-4 [(Cytotoxic T-Lymphocyte Antigen 4), also known
as CD152 (Cluster of differentiation 152), a protein that also plays an important

regulatory role in the immune system], PD-1 more broadly negatively regulates immune responses.

Indeed, functional “exhaustion” (immune dysfunction) among T and B cell subsets is a well-described feature of chronic viral infections, such as hepatitis B and C and HIV viruses. T cell exhaustion was initially described for CD8 T cells in mice chronically infected with lymphocytic choriomeningitis virus clone 13. In the lymphocytic choriomeningitis virus mouse model, repeated antigen stimulation through the T cell antigen receptor drives the sustained expression of T cell inhibitory receptors, including programmed cell death-1 (PD-1) and lymphocyte activation gene-3 (LAG-3), on virus-specific CD8 T cells (Joseph Illingworth et al., *Journal of Immunology* (2013), 190(3), 1038-1047).

Blockade of PD-1, an inhibitory receptor expressed by T cells, can overcome immune resistance. PD-1 is a key immune check point receptor expressed by activated T cells, and it mediates immune suppression. PD-1 functions primarily in peripheral tissues, where T cells may encounter the immune suppressive PD-1 ligands; PD-L1 (B7-H1) and PD-L2 (B7-DC), which are expressed by tumor cells, stromal cells, or both. Inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity (Suzanne L. Topalian et al., *N Engl J Med*. 2012, 366(26): 2443-2454).

PD-1 plays critical roles in the regulation of the immune response to cancer, allergy, and chronic viral infection (Julie R. Brahmer et al., *N Engl J Med*. 2012, 366(26): 2455-2465).

Tumour cells and virus (including HCV and HIV) infected cells are known to exploit the PD-1 signalling pathway (to create Immunosuppression) in order to escape immune surveillance by host T cells. It has been reported that the PD-1 gene is one of genes responsible for autoimmune diseases like systemic lupus erythematosus (Prokunina et al., *Nature Genetics*, 2002, Vol. 32, No. 4, 666-669).

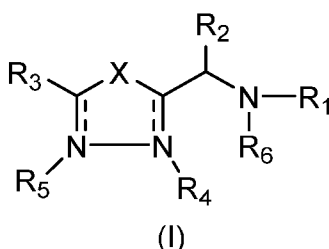
International applications WO2011161699 and WO2012168944 report peptides and their derivatives derived from PD1 ectodomain capable of inhibiting the programmed cell death 1 (PD1) signalling pathway. Further, WO2013144704 and WO2013132317 report cyclic peptides and peptidomimetic compounds as therapeutic agents capable of inhibiting the programmed cell death 1 (PD1) respectively.

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

SUMMARY OF INVENTION

The present invention relates to cyclic substituted 1,3,4-oxadiazole and
5 thiadiazole compounds or a stereoisomer thereof or a pharmaceutically acceptable salt thereof. The compounds of present invention are capable of suppressing and/or inhibiting the programmed cell death 1 (PD1) signalling pathway.

In one aspect, the present invention provides compound of formula (I):



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

X is O or S;

each dotted line ---- represents an optional bond;

R₁ is -CO-Aaa, -C(=W)R_a, -SO₂R_a, -SO₂-Aaa, heterocycloalkyl, heteroaryl,
(heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or
15 arylalkyl-; wherein the heterocycloalkyl-, heteroaryl, (heterocycloalkyl)alkyl-,
(heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl and arylalkyl- are each optionally
substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy,
amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, -SH, -S(alkyl),
aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl;

20 W is O or S;

R₂ is a side chain of an amino acid or is alkyl, alkenyl, alkynyl, cycloalkyl,
(cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or
(heterocycloalkyl)alkyl-; wherein the alkyl, alkenyl, alkynyl, cycloalkyl,
(cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl and
25 (heterocycloalkyl)alkyl- are each optionally substituted with 1 to 4 substituents selected
from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl,
cycloalkyl, aryl, -CONR₇R₈, -aryl-COOH, heterocycloalkyl, heteroaryl, guanidino,

amidino, -SH and -S(alkyl); optionally wherein two or three carbon atoms of the alkyl, alkenyl, or alkynyl form part of a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with 1 to 4 substituents, each independently selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl;

5 R₃ represents aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl-, (heteroaryl)alkyl-, -alkyl-COOH, -(CH₂)₂-NH₂ or a group represented by the formula -CH(OR_b)(CH₂OR_b), -C(R₇R₈)(NR₉R₁₀) or -N(R₁₁)₂; wherein the aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl- and (heteroaryl)alkyl- is optionally substituted with 1 to 4 occurrences of R_e;

10 R₄ and R₅ independently are hydrogen or absent;

R₆ is hydrogen or alkyl; or R₆ and R_c taken together with the atoms to which they are attached form a 5- to 7-membered ring optionally substituted with one or more groups independently selected from hydroxyl, halo, amino, cyano and alkyl;

15 R₇, R₈ and R₁₁ each independently represent hydrogen, alkyl, heteroalkyl, alkoxy, aryl, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-, each optionally substituted with -alkyl-COOH, -aryl-alkoxy, hydroxy, halo, amino, cyano or alkyl; or

R₇ and R₈ taken together with the atoms to which they are attached form a 5- to 7-membered cycloalkyl ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

20 R₉ and R₁₀ independently is hydrogen, alkyl or acyl; or R₉ and R₁₀ taken together with the atoms to which they are attached form a 5- to 7-membered carbocyclic ring or heterocyclic ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

Aaa represents an amino acid residue;

25 R_a is -NR_cR_d, aminoalkyl-, aminoaryl-, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl are each optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, -CONR₇R₈, carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy;

30 R_b and R_c each independently represent hydrogen, alkyl or alkoxyalkyl;

R_d represents hydrogen, alkyl, acyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the said aryl, heterocycloalkyl and heteroaryl are optionally substituted with one or more hydroxyl, cyano, alkyl or alkoxy;

5 R_e, at each occurrence, is alkyl, alkoxy, halo, hydroxyl, -C(O)OH, arylalkyl-, aryl, heteroarylalkyl-, heteroaryl, cycloalkyl, (cycloalkyl)alkyl-, hydroxyalkyl, alkoxyalkyl or acyl; wherein the alkyl, alkoxy, arylalkyl, aryl, heteroarylalkyl, heteroaryl, cycloalkyl, (cycloalkyl)alkyl- and hydroxyalkyl are optionally substituted with halo, hydroxyl, amido, cyano or alkoxy; or

10 two R_e groups attached to same carbon atom together represent an oxo (=O) or thioxo (=S);

wherein either:

A) R₁ represents -C(=W)R_a, -SO₂R_a, -SO₂-Aaa, heterocycloalkyl, (heterocycloalkyl)alkyl-, heteroaryl, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-, wherein R_a is -NR_cR_d or is alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl substituted with carboxylate, thioacid, thiocarboxylate, oxo, halo, cyano or haloalkyl;

or

B) R₃ represents optionally substituted arylalkyl-, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted (heteroaryl)alkyl-, -alkyl-(COOH), -CH₂)₂-NH₂, or a group represented by the general formula -CH(OR_b)(CH₂OR_b) or -N(R₁₁)₂.

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

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

30 In yet another aspect of the present invention, it provides use of cyclic substituted 1,3,4-oxadiazole and thiadiazole compounds and derivatives of formula (I), salts and stereoisomers thereof, which are capable of suppressing and/or inhibiting the

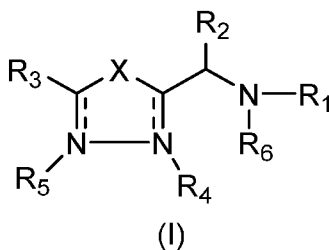
programmed cell death 1 (PD1) signaling pathway. For example, these compounds can be used to treat one or more diseases characterized by aberrant or undesired activity of the PD1 signaling pathway.

DETAILED DESCRIPTION OF THE INVENTION

5 The present invention provides cyclic substituted 1,3,4-oxadiazole and thiadiazole compounds and their derivatives as therapeutic agents useful for treatment of disorders via immunopotentialization 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
10 way of limitation of the invention. In fact, it will be apparent to those skilled in the art that various modification and variations can be made in the present invention without departing from the scope or spirit of the invention. For instance, features illustrated or described as part of one embodiment can be used on another embodiment to yield a still further embodiment. Thus it is intended that the present invention cover such
15 modifications and variations as come within the scope of the appended claims and their equivalents. Other objects, features and aspects of the present invention are disclosed in, or are obvious from, the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only, and is not to be construed as limiting the broader aspects of the
20 present invention.

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



or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein

25 X is O or S;

each dotted line ---- represents an optional bond;

R₁ is -CO-Aaa, -C(=W)R_a, -SO₂R_a, -SO₂-Aaa, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-; wherein the heterocycloalkyl-, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl and arylalkyl- are each optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, -SH, -S(alkyl), aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl;

W is O or S;

R₂ is a side chain of an amino acid or is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl-; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl and (heterocycloalkyl)alkyl- are each optionally substituted with 1 to 4 substituents selected from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl, cycloalkyl, aryl, -CONR₇R₈, -aryl-COOH, heterocycloalkyl, heteroaryl, guanidino, amidino, -SH and -S(alkyl); optionally wherein two or three carbon atoms of the alkyl, alkenyl, or alkynyl form part of a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with 1 to 4 substituents, each independently selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl;

R₃ represents aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl-, (heteroaryl)alkyl-, -alkyl-COOH, -(CH₂)₂-NH₂, or a group represented by the formula -CH(OR_b)(CH₂OR_b), -C(R₇R₈)(NR₉R₁₀) or -N(R₁₁)₂; wherein the aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl and (heteroaryl)alkyl- is optionally substituted with 1 to 4 occurrences of R_e;

R₄ and R₅ independently are hydrogen or absent;

R₆ is hydrogen or alkyl; or R₆ and R_c taken together with the atoms to which they are attached form a 5- to 7-membered ring optionally substituted with one or more groups independently selected from hydroxyl, halo, amino, cyano and alkyl;

R₇, R₈ and R₁₁ each independently represent hydrogen, alkyl, heteroalkyl, alkoxy, aryl, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-, each optionally substituted with -alkyl-COOH, -aryl-alkoxy, hydroxy, halo, amino, cyano or alkyl; or

R₇ and R₈ taken together with the atoms to which they are attached form a 5- to 7-membered cycloalkyl ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

R₉ and R₁₀ independently is hydrogen, alkyl or acyl; or R₉ and R₁₀ taken together with the atoms to which they are attached form a 5- to 7-membered carbocyclic ring or heterocyclic ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

Aaa represents an amino acid residue;

R_a is -NR_cR_d, aminoalkyl-, aminoaryl-, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl are each optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, -CONR₇R₈, carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy;

R_b and R_c each independently represent hydrogen, alkyl or alkoxyalkyl;

R_d represents hydrogen, alkyl, acyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the said aryl, heterocycloalkyl, and heteroaryl are optionally substituted with one or more hydroxyl, cyano, alkyl or alkoxy;

R_e, at each occurrence, is alkyl, alkoxy, halo, hydroxyl, -C(O)OH, arylalkyl-, aryl, heteroarylalkyl-, heteroaryl, cycloalkyl, (cycloalkyl)alkyl-, hydroxyalkyl, alkoxyalkyl or acyl; wherein the alkyl, alkoxy, arylalkyl, aryl, heteroarylalkyl, heteroaryl, cycloalkyl, (cycloalkyl)alkyl- and hydroxyalkyl are optionally substituted with halo, hydroxyl, amido, cyano or alkoxy; or

two R_e groups attached to same carbon atom together represent an oxo (=O) or thioxo (=S);

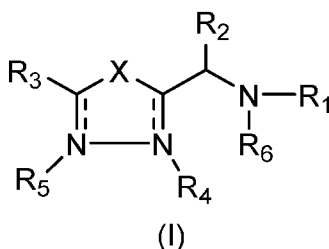
wherein either:

A) R₁ represents -C(=W)R_a, -SO₂R_a, -SO₂-Aaa, heterocycloalkyl, (heterocycloalkyl)alkyl-, heteroaryl, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-, wherein R_a is -NR_cR_d or is alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl substituted with carboxylate, thioacid, thiocarboxylate, oxo, halo, cyano or haloalkyl;

or

- B) R_3 represents optionally substituted arylalkyl-, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted (heteroaryl)alkyl-, -alkyl- (COOH), $-(CH_2)_2-NH_2$, or a group represented by the general formula -
 5 $CH(OR_b)(CH_2OR_b)$, or $-N(R_{11})_2$.

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



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

- 10 X is O or S;

each dotted line ---- represents an optional bond;

- R_1 is $-C(=W)R_a$, $-SO_2R_a$, $-SO_2-Aaa$, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-; wherein the heterocycloalkyl-, heteroaryl, (heterocycloalkyl)alkyl-,
 15 (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl and arylalkyl- are each optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, $-SH$, $-S(alkyl)$, aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl;

W is O or S;

- 20 R_2 is a side chain of an amino acid or is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl-; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl and (heterocycloalkyl)alkyl- are each optionally substituted with 1 to 4 substituents selected
 25 from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl, cycloalkyl, aryl, $-CONR_7R_8$, $-aryl-COOH$, heterocycloalkyl, heteroaryl, guanidino, amidino, $-SH$ and $-S(alkyl)$; optionally wherein two or three carbon atoms of the alkyl,

alkenyl, or alkynyl form part of a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with 1 to 4 substituents, each independently selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl;

5 R_3 represents aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl-, (heteroaryl)alkyl-, -alkyl-COOH, $-(CH_2)_2-NH_2$, or a group represented by the formula $-CH(OR_b)(CH_2OR_b)$, $-C(R_7R_8)(NR_9R_{10})$ or $-N(R_{11})_2$; wherein the aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl and (heteroaryl)alkyl- is optionally substituted with 1 to 4 occurrences of R_e ;

R_4 and R_5 independently are hydrogen or absent;

10 R_6 is hydrogen or alkyl; or R_6 and R_c taken together with the atoms to which they are attached form a 5- to 7-membered ring optionally substituted with one or more groups independently selected from hydroxyl, halo, amino, cyano and alkyl;

R_7 , R_8 and R_{11} each independently represent hydrogen, alkyl, heteroalkyl, alkoxy, aryl, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-, each optionally substituted with -
15 alkyl-COOH, -aryl-alkoxy, hydroxy, halo, amino, cyano or alkyl; or

R_7 and R_8 taken together with the atoms to which they are attached form a 5- to 7-membered cycloalkyl ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

20 R_9 and R_{10} independently is hydrogen, alkyl or acyl; or R_9 and R_{10} taken together with the atoms to which they are attached form a 5- to 7-membered carbocyclic ring or heterocyclic ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

Aaa represents an amino acid residue;

25 R_a is $-NR_cR_d$, aminoalkyl-, aminoaryl-, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl are each optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, $-CONR_7R_8$, carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy;

R_b and R_c each independently represent hydrogen, alkyl or alkoxyalkyl;

30 R_d represents hydrogen, alkyl, acyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the

said aryl, heterocycloalkyl, and heteroaryl are optionally substituted with one or more hydroxyl, cyano, alkyl or alkoxy;

R_e , at each occurrence, is alkyl, alkoxy, halo, hydroxyl, $-C(O)OH$, arylalkyl-, aryl, heteroarylalkyl-, heteroaryl, cycloalkyl, (cycloalkyl)alkyl-, hydroxyalkyl, alkoxyalkyl or acyl; wherein the alkyl, alkoxy, arylalkyl, aryl, heteroarylalkyl, heteroaryl, cycloalkyl, (cycloalkyl)alkyl- and hydroxyalkyl are optionally substituted with halo, hydroxyl, amido, cyano or alkoxy; or

two R_e groups attached to same carbon atom together represent an oxo ($=O$) or thioxo ($=S$).

In certain preferred embodiments of formula (I), X is O. In certain such embodiments, the ring containing X is 1,3,4-oxadiazole ring.

In certain embodiments, R_1 is $-C(=W)R_a$, $-SO_2R_a$, $-SO_2-Aaa$, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-; wherein the heterocycloalkyl-, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl and arylalkyl- are each optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, $-SH$, $-S(alkyl)$, aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl.

In certain embodiments, R_1 is (heteroaryl)alkyl-, optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, $-SH$, $-S(alkyl)$, aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl.

In certain embodiments, R_1 is $-C(=X)R_a$, $-SO_2R_a$, $-SO_2-Aaa$, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or arylalkyl; wherein the said heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or arylalkyl is substituted with 0-4 same or different groups selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl.

In certain such embodiments, Aaa represents an amino acid residue wherein the amino acid residue comprises a side chain that includes a $-OH$, $-O$ -acyl, $-SH$, $-NH_2$ or $-NH(alkyl)$ moiety.

In certain embodiments, R_1 is $-C(=X)R_a$, wherein X and R_a are same as defined in formula (I).

In certain embodiments, R_1 is $-C(=O)R_a$, wherein R_a is $-NR_cR_d$, aminoalkyl-, aminoaryl-, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the alkyl, aryl, cycloalkyl, heterocycloalkyl, and heteroaryl are each optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, $-CONR_7R_8$,
5 carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy.

In certain embodiments, R_1 is $-C(=O)R_a$, wherein R_a is $-NR_cR_d$, aminoaryl-, aryl, heterocycloalkyl or heteroaryl; wherein the said aryl, heterocycloalkyl, and heteroaryl are optionally substituted with 1 to 4 substituents, each independently selected from
10 alkyl, amido, amino, carboxylic acid, carboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy.

In certain embodiments, R_1 is $-C(=O)R_a$, wherein R_a is aryl, heterocycloalkyl or heteroaryl; each optionally substituted with carboxylic acid, carboxylate, hydroxyl, alkyl, or oxo.

15 In certain embodiments, R_1 is $-C(=S)R_a$ wherein R_a is same as defined in formula (I).

In certain embodiments, R_1 is $-C(=S)R_a$, wherein R_a is $-NR_cR_d$; and R_c and R_d are defined in compound of formula (I).

20 In certain embodiments, R_1 is $-SO_2R_a$ or $-SO_2Aaa$, wherein R_a and Aaa are same as defined in formula (I).

In certain embodiments, R_1 is $-SO_2R_a$; wherein R_a is aryl, cycloalkyl, heterocycloalkyl or heteroaryl; each optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, $-CONR_7R_8$, carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and
25 alkoxy.

In certain embodiments, R_1 is $-SO_2Aaa$ wherein Aaa is as defined in compound of formula (I).

In certain embodiments, Aaa is an amino acid residue selected from Ala, Phe, Thr, Ser, and Val.

30 In certain embodiments, R_1 is heterocycloalkyl, (heterocycloalkyl)alkyl-, heteroaryl, (heteroaryl)alkyl-, aryl or arylalkyl-; wherein each optional substituent

independently represents 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate thiocarboxylate, thioacid, -SH and -S(alkyl), aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl.

In certain embodiments, R_1 is heterocycloalkyl, (heterocycloalkyl)alkyl-,
 5 heteroaryl or (heteroaryl)alkyl-; wherein the heterocycloalkyl, (heterocycloalkyl)alkyl-, heteroaryl or (heteroaryl)alkyl- are optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate thiocarboxylate, thioacid, -SH and -S(alkyl), aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl.

10 In certain preferred embodiments, when R_1 represents $-C(=W)R_a$, $-SO_2R_a$, $-SO_2$ -Aaa, heterocycloalkyl, (heterocycloalkyl)alkyl-, heteroaryl, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-; wherein heterocycloalkyl-, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl- aryl and arylalkyl- are optionally substituted with 1 to 4 substituents each independently selected
 15 from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate thiocarboxylate, thioacid, -SH and -S(alkyl), aryl, heteroaryl, heterocycloalkyl, cycloalkyl or hydroxyl; and R_3 represents aryl, heterocycloalkyl, heteroaryl or cycloalkyl; wherein the aryl, heterocycloalkyl, heteroaryl and cycloalkyl are optionally substituted with 1 to 4 occurrences of R_e ; and W, R_e , R_a , Aaa and R_e are same as defined in formula (I).

20 In certain preferred embodiments, when R_1 represents $-C(=W)R_a$, R_3 represents aryl, heterocycloalkyl, heteroaryl or cycloalkyl; wherein the aryl, heterocycloalkyl, heteroaryl and cycloalkyl are optionally substituted with 1 to 4 occurrences of R_e ; and W, R_e , R_a and R_e are same as defined in formula (I).

In further embodiments, when R_1 represents $-CO$ -Aaa, R_3 represents
 25 (heterocycloalkyl)alkyl-, arylalkyl-, (heteroaryl)alkyl-, -alkyl-COOH, $-(CH_2)_2-NH_2$, or a group represented by the formula, $-CH(OR_b)(CH_2OR_b)$, or $-N(R_{11})_2$; wherein each optional substituent independently represents 1 to 4 occurrences of R_e ; and Aaa, R_b , R_7 , R_8 , R_9 , R_{10} and R_{11} are same as defined in formula (I).

In further embodiments, when R_1 represents $-CO$ -Aaa, and R_3 represents -alkyl-
 30 COOH, $-(CH_2)_2-NH_2$, or a group represented by the formula, $-CH(OR_b)(CH_2OR_b)$, $-C(R_7R_8)(NR_9R_{10})$ or $-N(R_{11})_2$; and Aaa, R_b , R_7 , R_8 , R_9 , R_{10} and R_{11} are same as defined in formula (I).

In certain embodiments, R_1 is $-\text{CO}-\text{Aaa}$, wherein Aaa is same as defined in formula (I).

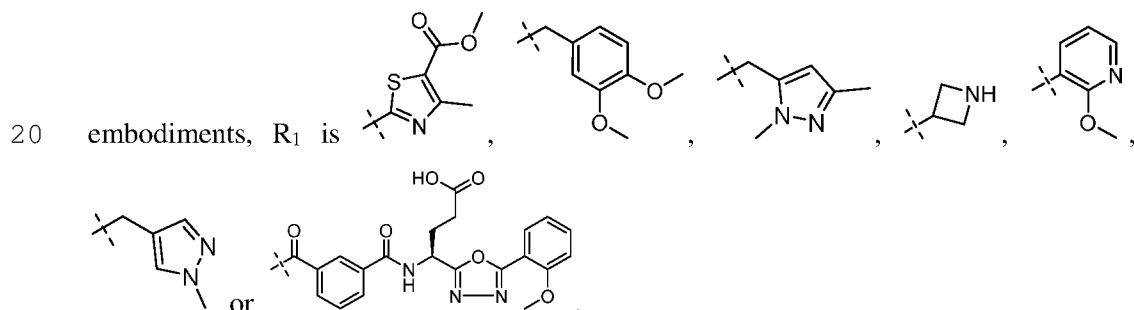
In certain embodiments, R_1 is $-\text{CO}-\text{Aaa}$ and Aaa is a natural amino acid residue.

In alternative embodiments, R_1 is $-\text{CO}-\text{Aaa}$ and Aaa represents an amino acid residue, wherein the amino acid residue comprises a side chain that does not include a -OH, -O-acyl, -SH, $-\text{NH}_2$ or $-\text{NH}(\text{alkyl})$ moiety.

In certain embodiments, Aaa is an amino acid residue wherein a C-terminal carboxyl group of the amino acid residue may be a free C-terminal carboxyl group ($-\text{COOH}$) or a modified C-terminal carboxyl group. For example, the modified C-terminal carboxyl group may be esterified or amidated. Similarly, if connectivity allows, an N-terminal amino group of the amino acid residue may be a free N-terminus ($-\text{NH}_2$) or a modified N-terminal amino group (e.g., an alkylated amino group).

In certain embodiments, R_1 is $-\text{SO}_2\text{R}_a$, wherein R_a is optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl or optionally substituted heteroaryl; wherein each optional substituent represents 1 to 4 substituents, each independently selected from halo, oxo, cyano and acyl.

In certain embodiments, R_1 is $-\text{C}(=\text{O})\text{NR}_c\text{R}_d$, wherein R_c is hydrogen or alkyl and R_d is aryl, arylalkyl or alkoxyalkyl; wherein the said aryl or arylalkyl is optionally substituted with one or more hydroxyl, cyano, alkyl or alkoxy. In certain



In certain embodiments, R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl-; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl and (heterocycloalkyl)alkyl- are each optionally substituted with 1 to 4 substituents selected from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl,

cycloalkyl, aryl, -CONR₇R₈, -aryl-COOH, heterocycloalkyl, heteroaryl, guanidino, amidino, -SH and -S(alkyl); optionally wherein two or three carbon atoms of the alkyl, alkenyl, or alkynyl form part of a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with 1 to 4 substituents, each independently selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl.

In certain embodiments, R₂ is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl-; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl- are each optionally substituted with 1 to 4 substituents selected from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl, cycloalkyl, aryl, -CONR₇R₈, -aryl-COOH, heterocycloalkyl, heteroaryl, guanidino, amidino, -SH or -S(alkyl);

In certain embodiments, R₂ is alkyl, alkenyl or alkynyl; wherein two or three carbon atoms of the alkyl, alkenyl, or alkynyl form part of a 3- to 7-membered carbocyclic ring or heterocyclic ring, optional substituted with 1 to 4 substituents, each independently selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl.

In certain embodiments, R₂ is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl-; wherein each optional substituent independently represents 1 to 4 substituents selected from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl, cycloalkyl, aryl, -CONR₇R₈, -aryl-COOH, heterocycloalkyl, heteroaryl, guanidino, amidino, -SH or -S(alkyl).

In certain embodiments, R₂ is a side chain of an amino acid.

In certain embodiments, R₂ represents side chain of Asn, Ser, Asp, Glu, Gln, Lys, or Ala.

In certain embodiments, R₃ represents (heterocycloalkyl)alkyl-, arylalkyl, (heteroaryl)alkyl, -alkyl-COOH, -(CH₂)₂-NH₂, or a group represented by the formula, -CH(OR_b)(CH₂OR_b), -C(R₇R₈)(NR₉R₁₀) or -N(R₁₁)₂; wherein (heterocycloalkyl)alkyl-, arylalkyl and (heteroaryl)alkyl- are optionally substituted with 1 to 4 occurrences of R_c; and R_b, R₇, R₈, R₉, R₁₀ and R₁₁ are same as defined in formula (I).

In certain embodiments, R_3 represents aryl, heterocycloalkyl, heteroaryl or cycloalkyl; wherein the said aryl, heterocycloalkyl, heteroaryl or cycloalkyl are optionally substituted with 1 to 4 occurrences of R_e ; and R_e is same as defined in formula (I).

5 In certain embodiments, R_3 represents aryl, heterocycloalkyl, or heteroaryl; wherein the said aryl, heterocycloalkyl, and heteroaryl are optionally substituted with 1 to 4 occurrences of R_e ; and R_e is same as defined in formula (I).

10 In certain embodiments, R_3 represents aryl, heterocycloalkyl, or heteroaryl; wherein the said aryl, heterocycloalkyl, and heteroaryl are optionally substituted with 1 to 4 occurrences of R_e ; wherein R_e , at each occurrence, is alkyl, alkoxy, halo, hydroxyl, -C(O)OH, hydroxyalkyl, alkoxyalkyl or acyl.

In certain embodiments, R_3 represents aryl, or heteroaryl; each optionally substituted with R_e ; wherein R_e is alkyl, alkoxy, halo, hydroxyl, or -C(O)OH.

In certain embodiments, both R_4 and R_5 are absent.

15 In certain embodiments, R_6 is hydrogen. In further embodiments, R_6 and R_e taken together with the atoms to which they are attached form a 5- to 7-membered ring optionally substituted with one or more groups independently selected from hydroxyl, halo, amino, cyano and alkyl.

20 In certain embodiments, R_7 , R_8 and R_{11} independently represents alkyl, alkoxy, aryl, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-; each optionally substituted with -alkyl-COOH, -aryl-alkoxy, hydroxy, halo, amino, cyano and alkyl.

25 In another embodiments, R_7 and R_8 taken together with the atoms to which they are attached form a 5- to 7-membered cycloalkyl ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino and alkyl;

30 In certain embodiments, R_a is aminoalkyl, aminoaryl, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl or optionally substituted heteroaryl; wherein each optional substituent represents 1 to 4 substituents, each independently selected from alkyl, amino, -CONR₇R₈, carboxylic acid, carboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy.

In certain embodiments, R_a is $-NR_cR_d$, wherein R_c represents hydrogen or alkyl; and R_d represents hydrogen, alkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the said aryl, heterocycloalkyl, and heteroaryl, are optionally substituted with one or more hydroxyl, alkyl or alkoxy.

In certain embodiments, R_e represents alkyl, alkoxy, halo, hydroxyl, $-C(O)OH$, arylalkyl-, aryl, heteroarylalkyl, heteroaryl, cycloalkyl, (cycloalkyl)alkyl-, hydroxyalkyl, alkoxyalkyl or acyl; wherein each optional substituent independently represents halo, hydroxyl or amido.

In certain embodiments, two R_e groups attached to same carbon atom together represent an oxo ($=O$) or thioxo ($=S$).

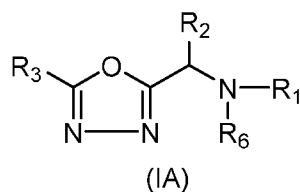
In certain embodiments, in compound of formula (I), either:

A) R_1 represents $-C(=W)R_a$, $-SO_2R_a$, $-SO_2-Aaa$, heterocycloalkyl, (heterocycloalkyl)alkyl-, heteroaryl, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or optionally substituted arylalkyl-; wherein R_a is $-NR_cR_d$ or is alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl substituted with carboxylate, thioacid, thiocarboxylate, oxo, halo, cyano or haloalkyl;

or

B) R_3 represents arylalkyl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, -alkyl- $(COOH)$, $-(CH_2)_2-NH_2$, or a group represented by the general formula, $-CH(OR_b)(CH_2OR_b)$ or $-N(R_{11})_2$.

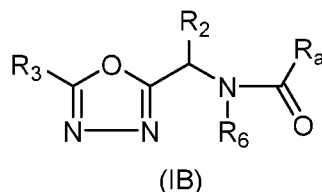
In certain embodiments, the present invention provides compounds of formula (IA):



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

R_1 , R_2 , R_3 and R_6 are same as defined in formula (I).

In certain embodiments, compound of formula (I) having compounds of formula (IB):



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

- 5 R_3 represents aryl, heterocycloalkyl, heteroaryl or cycloalkyl; each optionally substituted with 1 to 4 occurrences of R_e ; and R_2 , R_e , R_6 and R_a are same as defined as formula (I).

- In certain embodiments of the compounds of formula (IB), R_a is $-NR_cR_d$, aminoaryl-, aryl, heterocycloalkyl or heteroaryl; wherein the said aryl, heterocycloalkyl,
 10 and heteroaryl are optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, carboxylic acid, carboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy.

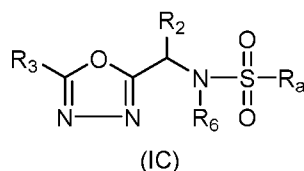
In further such embodiments, R_a is $-NR_cR_d$;

R_c represents hydrogen; and

- 15 R_d represents alkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the said aryl, heterocycloalkyl and heteroaryl are optionally substituted with one or more hydroxyl, cyano, alkyl or alkoxy.

- In certain embodiments of the compounds of formula (IB), R_3 represents aryl,
 20 heterocycloalkyl, heteroaryl or cycloalkyl; wherein the said aryl, heterocycloalkyl, heteroaryl or cycloalkyl are optionally substituted with 1 to 4 occurrences of R_e . In certain such embodiments, R_e is alkyl, alkoxy, halo, hydroxyl, $-C(O)OH$, hydroxyalkyl, alkoxyalkyl or acyl.

- In certain embodiments, compound of formula (I) having compounds of formula
 25 (IC):

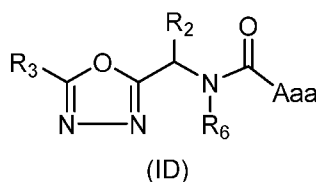


or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

R_3 represents aryl, heterocycloalkyl, heteroaryl or cycloalkyl, each optionally substituted with 1 to 4 occurrences of R_e ; and R_2 , R_e , R_6 and R_a are same as defined in formula (I).

In certain embodiments of the compounds of Formula (IC), R_a is aryl, cycloalkyl, heterocycloalkyl or heteroaryl; each optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, $-\text{CONR}_7\text{R}_8$, carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy.

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

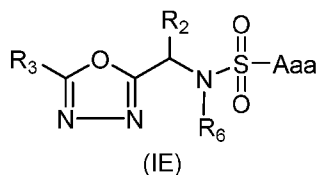


or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

R_3 represents arylalkyl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, -alkyl-(COOH), $-(\text{CH}_2)_2\text{-NH}_2$, or a group represented by the general formula, $-\text{CH}(\text{OR}_b)(\text{CH}_2\text{OR}_b)$, or $-\text{N}(\text{R}_{11})_2$; and Aaa, R_2 , R_6 , R_b and R_{11} are same as defined in formula (I).

In certain such embodiments, R_3 represents -alkyl(COOH), $-(\text{CH}_2)_2\text{-NH}_2$, (heterocycloalkyl)alkyl-, $-\text{N}(\text{R}_{11})_2$; and R_{11} represents heteroalkyl.

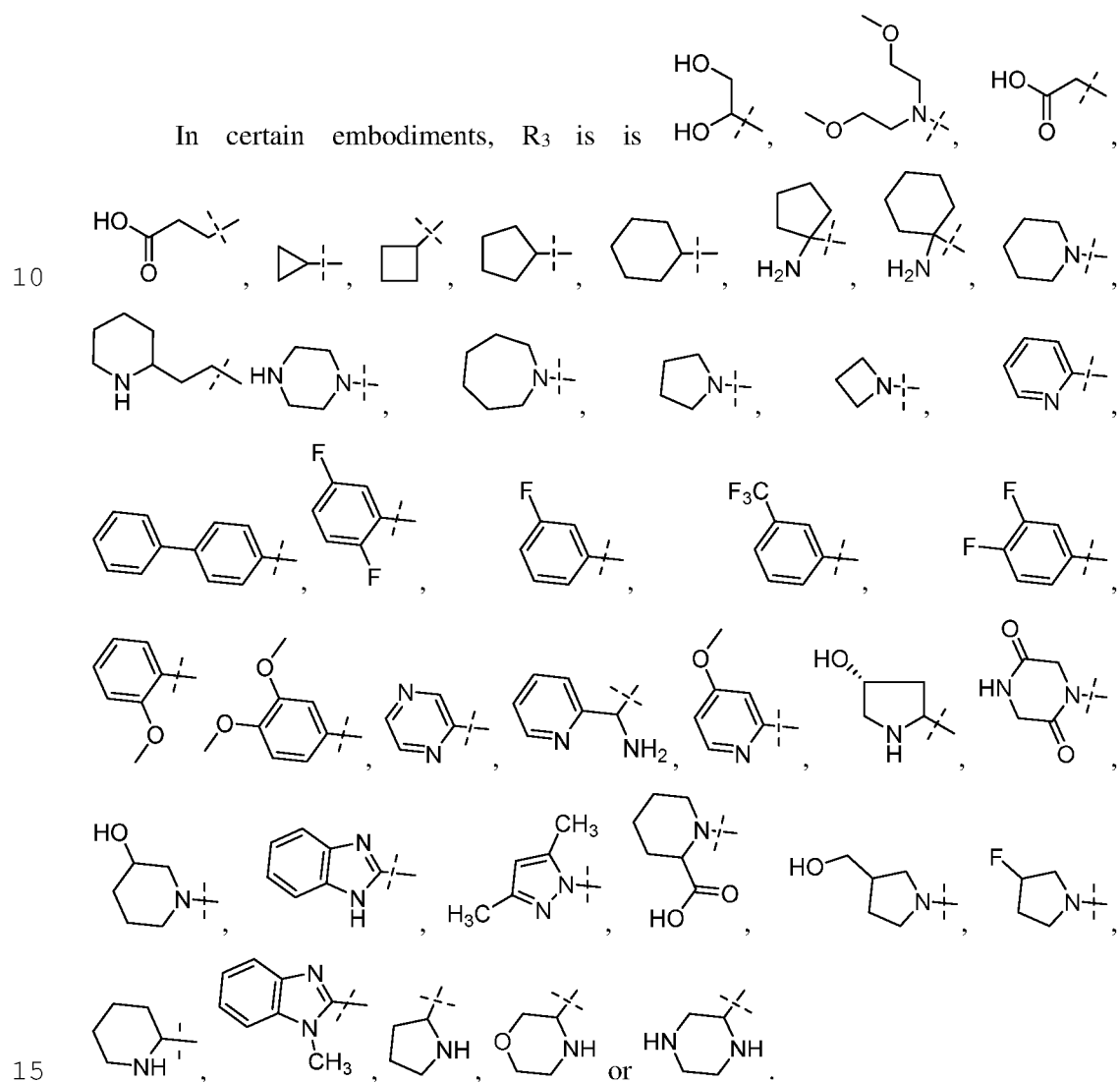
In certain embodiments, the present invention provides compounds of formula (IE):



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

R₃ represents arylalkyl-, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, -alkyl-, (COOH), -(CH₂)₂-NH₂, or a group represented by the general formula, -CH(OR_b)(CH₂OR_b) or -N(R₁₁)₂; and Aaa, R₂, R₆, R_b and R₁₁ are same as defined in formula (I).

In certain such embodiments, R₃ represents arylalkyl-, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, -alkyl-(COOH), -(CH₂)₂-NH₂, or a group represented by the general formula, -CH(OR_b)(CH₂OR_b) or -N(R₁₁)₂.



In certain embodiments, R₃ is a group of the formula, -CH(R₈)(N(R₉)R₁₀) in which R₈, R₉ and R₁₀ are same as defined in formula (I).

In certain embodiments, R_2 is optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl wherein each optional substituent represents one or more substituents selected from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino and amidino.

- 5 In certain embodiments, R_2 is (C₁-C₆)alkyl substituted by carboxylic acid or amido.

An amino acid residue is understood in the art to mean a carboxylic acid, substituted at the alpha, beta, or gamma carbon by an amino (-NH₂) group. In the group -CO-Aaa, the amino acid residue Aaa is connected to the carbonyl group CO via a covalent bond between the carbonyl carbon and the amino group of the amino acid residue. In preferred embodiments, the amino acid is an alpha-amino acid, and the amino acid residue Aaa is connected to the carbonyl group CO via a covalent bond between the carbonyl carbon and the alpha-amino group of the amino acid residue.

15 In certain embodiments, one, more or all amino acid residues are D amino acid residues.

In certain embodiments, one, more than one, or all amino acid residues are L amino acid residues.

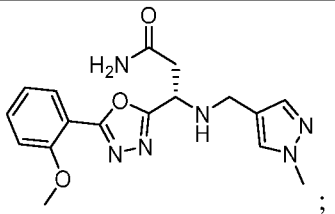
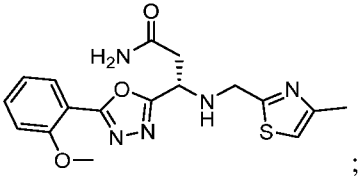
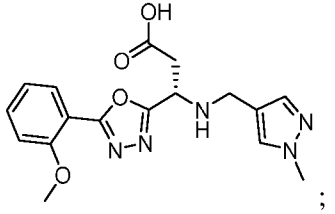
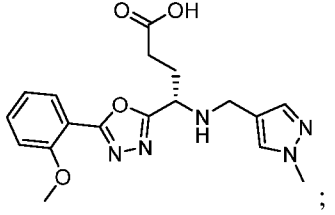
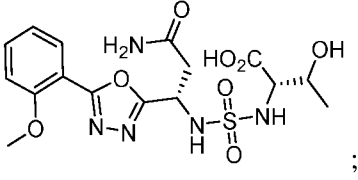
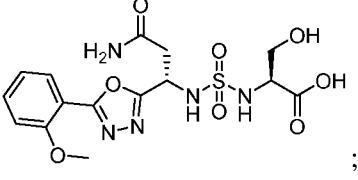
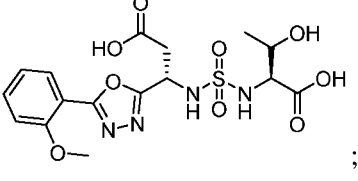
In certain embodiments, the present invention provides a compound, or a pharmaceutically acceptable salt or a stereoisomer thereof, selected from:

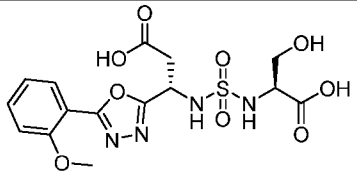
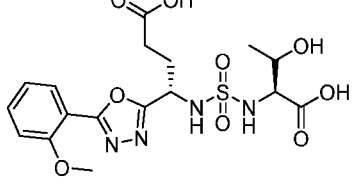
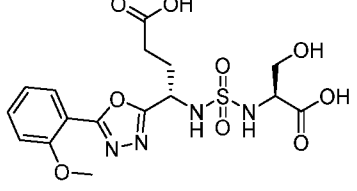
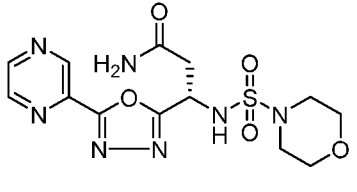
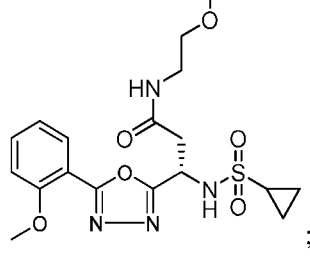
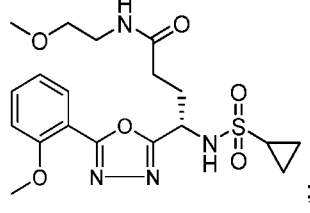
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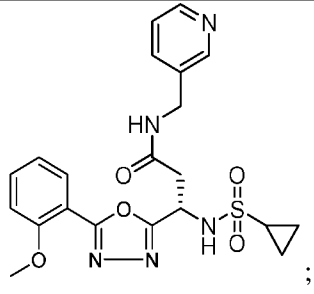
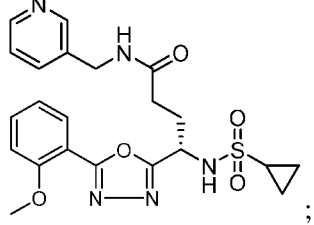
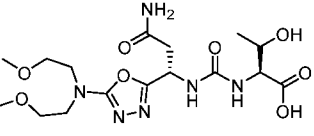
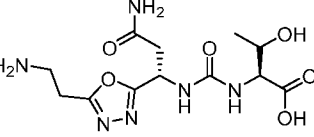
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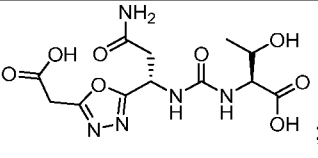
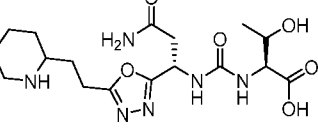
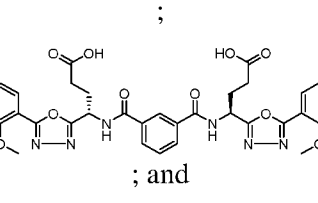
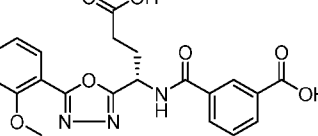
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Comp	Structure
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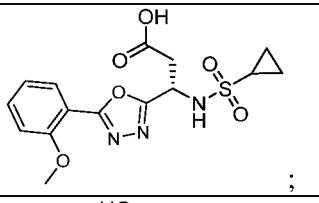
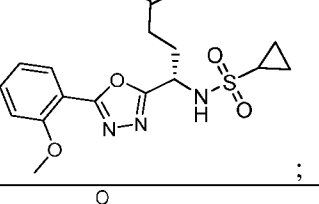
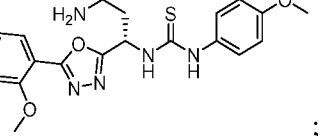
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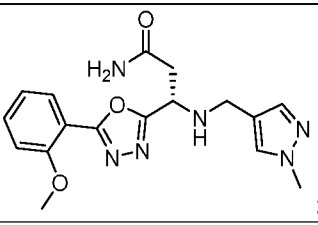
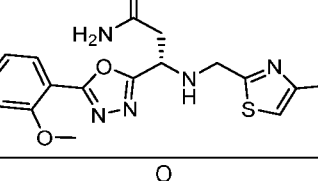
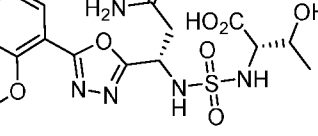
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In certain embodiments, the preferred compound, or a pharmaceutically acceptable salt or a stereoisomer thereof is selected from:

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Comp	Structure	Comp	Structure
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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 in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated in order to facilitate the understanding of the present invention.

The singular forms “a”, “an” and “the” encompass plural references unless the context clearly indicates otherwise.

As used herein, the term “or” refers to “and/or”, unless stated otherwise.

As used herein, the terms “optional” or “optionally” mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, “optionally substituted alkyl” refers to when the alkyl may be substituted as well as the event or circumstance where the alkyl is not substituted.

The term “substituted” refers to moieties having substituents replacing hydrogen on one or more carbons of the backbone. Thus, a moiety that is optionally substituted may have one or more hydrogens of the indicated moiety be replaced by a substituent, each of which may be the same or different. 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, 5 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 10 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 alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, 15 an imine, a cyano, a nitro, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, and 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, 20 reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

As used herein, the term “optionally substituted” refers to the replacement of one to six hydrogen radicals on the same carbon or on different carbons in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, 25 hydroxyalkyl, alkoxy, alkoxyalkyl, halogen, alkyl, aryl, aryloxy, aralkyl, heteroaryl, heteroaryloxy, heteroaralkyl, cycloalkyl, cycloalkoxy, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, amino, aminoalkyl, alkylamino, dialkylamino, acyl, -C(O)₂H, -O(acyl), -NH(acyl), -N(alkyl)(acyl), cyano, phosphinate, phosphate, phosphonate, sulfonate, sulfonamido, sulfate, haloalkyl or haloalkoxy. Preferably, 30 “optionally substituted” refers to the replacement of one to four hydrogen radicals in a given structure with the substituents mentioned above. More preferably, one to three hydrogen radicals are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

As used herein, the term “alkyl” refers to saturated aliphatic groups, including, but not limited to, C₁-C₁₀ straight-chain alkyl groups or C₃-C₁₀ branched-chain alkyl groups. Preferably, the “alkyl” group refers to C₁-C₆ straight-chain alkyl groups or C₃-C₆ branched-chain alkyl groups. Most preferably, the “alkyl” group refers to C₁-C₄ straight-chain alkyl groups or C₃-C₄ branched-chain alkyl groups. Examples of “alkyl” include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. The “alkyl” group may be optionally substituted.

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

As used herein, the term “heteroalkyl” refers to a straight- or branched-chain alkyl group in which one or more of carbon atoms have been replaced by a heteroatom or a heterogroup selected from S, O, P, N and -(CO)-; wherein the ‘alkyl’ group is as defined above. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary alkyl amines, amides, alkyl sulfides, alkyl disulfides, and the like. The group, may be a terminal group or a bridging group.

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 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 “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 “acyl” refers to a group R-CO- wherein R is an optionally substituted alkyl group defined above. Examples of ‘acyl’ groups are, but not limited to, CH₃CO-,
5 CH₃CH₂CO-, CH₃CH₂CH₂CO- or (CH₃)₂CHCO-.

The term “acylamino” refers to an amino group substituted with acyl. Acylamino groups include -N(H)C(O)CH₃, -N(H)C(O)CH₂CH₃ and the like.

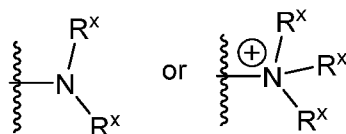
As used herein, the term “alkoxy” refers to alkyl groups (as defined above) bonded to an oxygen atom that is attached to a core structure. Preferably, alkoxy groups
10 have one to six carbon atoms. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, 3-methyl butoxy and the like.

As used herein, the term “haloalkyl” refers to alkyl group (as defined above) is substituted with one or more halogens. A monohaloalkyl radical, for example, may have
15 a chlorine, bromine, iodine or fluorine atom. Dihalo and polyhaloalkyl radicals may have two and more of the same or different halogen atoms respectively. Examples of haloalkyl include, but are not limited to, chloromethyl, dichloromethyl, trichloromethyl, dichloroethyl, dichloropropyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl,
20 difluoroethyl, difluoropropyl and the like.

As used herein, the term “haloalkoxy” refers to radicals wherein one or more of the hydrogen atoms of the alkoxy group are substituted with one or more halogens. Representative examples of “haloalkoxy” groups include, but are not limited to, difluoromethoxy (-OCHF₂), trifluoromethoxy (-OCF₃) or trifluoroethoxy (-OCH₂CF₃).

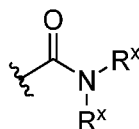
25 As used herein, the term “aryl” alone or in combination with other term(s) means a 6- to 10-membered carbocyclic aromatic system containing one or two rings wherein such rings may be fused. The term “fused” means that the second ring is attached or formed by having two adjacent atoms in common with the first ring. The term “fused” is equivalent to the term “condensed”. Examples of aryl groups include but are not limited
30 to phenyl, naphthyl or indanyl. Unless otherwise specified, all aryl groups described herein may be optionally substituted.

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



- 5 wherein each R^x independently represents hydrogen or a hydrocarbyl group, or two R^x are taken together with the N atom to which they are attached to form a heterocycle having from 4 to 8 atoms in the ring structure.

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



- 10 wherein each R^x independently represent a hydrogen or hydrocarbyl group, or two R^x 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.

- As used herein, “aminoalkyl” refers to an amino group, as defined above, in which one or two hydrogen atoms are substituted with alkyl group. A carbon atom of the alkyl group is attached to the parent molecular group. Aminoalkyl groups include -
 15 CH_2NH_2 , $-(\text{CH}_2)_2\text{NH}_2$, $-(\text{CH}_2)_3\text{NH}_2$, $-(\text{CH}_2)_4\text{NH}_2$ and the like.

As used herein, “aminoaryl” refers to an amino group, as defined above, in which one or two hydrogen atoms are substituted with aryl group.

As used herein, “nitro” refers to an $-\text{NO}_2$ group.

- 20 As used herein, the term “guanidino” refers to $-\text{NH}-\text{C}(=\text{NH})-\text{NH}_2$ group.

- As used herein, “alkylamino” and “cycloalkylamino”, refer to an $-\text{N}$ -group, wherein nitrogen atom of said group being attached to alkyl or cycloalkyl respectively. Representative examples of an “alkylamino” and “cycloalkylamino” groups include, but are not limited to, $-\text{NHCH}_3$ and $-\text{NH}$ -cyclopropyl. An amino group can be optionally
 25 substituted with one or more of the suitable groups.

As used herein the term “cycloalkyl” alone or in combination with other term(s) means $\text{C}_3\text{-C}_{10}$ saturated cyclic hydrocarbon ring. A cycloalkyl may be a single ring,

which typically contains from 3 to 7 carbon ring atoms. Examples of single-ring cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. A cycloalkyl may alternatively be polycyclic or contain more than one ring. Examples of polycyclic cycloalkyls include bridged, fused, and spirocyclic carbocyclyls.

5 As used herein, “cycloalkyloxy” refers to an -O-cycloalkyl group wherein the cycloalkyl group is as defined above.

As used herein, the term “cyano” refers to a -CN group.

As used herein, the term “hydroxy” or “hydroxyl” refers to -OH group.

As used herein, the term “oxo” refers to a =O group.

10 The term “glycinate”, as used herein, refers to a group -C(O)ONH₂(CH₂).

As used herein, the term “thiol” or “sulfhydryl” refers to a -SH group.

As used herein, the term “hydroxyalkyl” or “hydroxylalkyl” means alkyl substituted with one or more hydroxyl groups, wherein the alkyl groups are as defined above. Examples of “hydroxyalkyl” include, but are not limited to, hydroxymethyl, hydroxyethyl, hydroxypropyl, propan-2-ol and the like.

As used herein, the term “halo” or “halogen” alone or in combination with other term(s) means fluorine, chlorine, bromine or iodine.

The term “carboxy” or “carboxylic acid”, as used herein, refers to a group represented by the formula —CO₂H.

20 The term “thioacid”, “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)⁻.

The term “carboxylate” refers to a group represented by the formula -(CO₂)⁻.

The term “amidino”, as used herein, refers to -C(=NH)NH₂ group.

25 The term “ester”, as used herein, refers to a group -C(O)OR^y wherein R^y represents a hydrocarbyl group.

The term “thioester”, as used herein, refers to a group —C(O)SR^z or —SC(O)R^z wherein R^z represents a hydrocarbyl.

30 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.

The terms “aralkyl” and “arylalkyl”, as used herein, refers to an alkyl group substituted with an aryl group. Arylalkyl groups include benzyl and the like.

As used herein, the term “heterocycloalkyl” refers to a non-aromatic, saturated or partially saturated, monocyclic or polycyclic ring system of 3 to 15 members having at least one heteroatom or heterogroup selected from O, N, S, S(O), S(O)₂, NH and C(O) with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. The term “heterocycloalkyl” also refers to a bridged bicyclic ring system having at least one heteroatom or heterogroup selected from O, N, S, S(O), S(O)₂, NH or C(O). The “monocyclic heterocycloalkyl” refers to non-aromatic, saturated or partially saturated, monocyclic heterocycloalkyl rings having 4 to 7 member atoms. Examples of “monocyclic heterocycloalkyl” include, but are not limited to, azetidiny, oxetanyl, imidazolidiny, pyrrolidiny, oxazolidiny, thiazolidiny, pyrazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl, morpholiny, thiomorpholiny, 1,4-dioxanyl, dioxidothiomorpholiny, oxapiperaziny, oxapiperidiny, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiophenyl, dihydropyranyl and N-oxides thereof. The “bicyclic heterocycloalkyl” refers to non-aromatic, saturated or partially saturated, monocyclic heterocycloalkyl rings having 7 to 11 member atoms. Examples of “bicyclic heterocycloalkyl” include, but are not limited to, benzo[d][1,3]dioxole, indoliny, indolinylmethyl, indolin-2-one, aza-bicyclooctanyl, azociny, chromanyl, xanthenyl and N-oxides thereof. Attachment of a heterocycloalkyl substituent can occur via either a carbon atom or a heteroatom. A heterocycloalkyl group can be optionally substituted by one or more aforesaid groups.

Preferably, “heterocycloalkyl” refers to a 5- to 6-membered ring selected from azetidiny, oxetanyl, imidazolidiny, pyrrolidiny, oxazolidiny, thiazolidiny, pyrazolidiny, tetrahydrofuranyl, piperidiny, piperaziny, tetrahydropyranyl, morpholiny, thiomorpholiny, 1,4-dioxanyl and N-oxides thereof. More preferably,

“heterocycloalkyl” includes azetidiny, pyrrolidinyl, morpholinyl and piperidinyl. All heterocycloalkyl groups are optionally substituted by one or more aforesaid groups.

As used herein, the term “heteroaryl” refers to an aromatic heterocyclic ring system containing 5 to 20 ring atoms, preferably 5 to 10 ring atoms, which can be a monocyclic heteroaryl or bicyclic heteroaryl or polycyclic heteroaryl fused together or linked covalently. The rings may contain from 1 to 4 heteroatoms selected from N, O and S, wherein the N or S atom is optionally oxidized or the N atom is optionally quarternized. Any suitable ring position of the heteroaryl moiety may be covalently linked to the parent molecular structure.

The “monocyclic heteroaryl” refers to a 5- or 6- membered heteroaryl ring. The 5 membered ring consists of two double bonds and one, two, three or four heteroatoms selected from N, O and S, wherein the N or S atom is optionally oxidized or the N atom is optionally quarternized. The 6 membered ring consists of three double bonds and one, two, three or four N atoms wherein the N atom is optionally oxidized or quarternized. The 5 or 6 membered heteroaryl is connected to the parent molecular moiety through any carbon atom or any nitrogen atom contained within the heteroaryl. Representative examples of monocyclic heteroaryl include, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, and triazinyl. All monocyclic heteroaryls are optionally substituted by one or more aforesaid groups.

As used herein, the term “bicyclic heteroaryl” refers to a monocyclic heteroaryl fused to a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocycloalkyl, or a monocyclic heteroaryl. The fused cycloalkyl or heterocycloalkyl portion of the bicyclic heteroaryl group is optionally substituted. When the bicyclic heteroaryl is a monocyclic heteroaryl fused to a phenyl ring, then the bicyclic heteroaryl group is attached to the parent molecular moiety through any carbon atom or nitrogen atom within the bicyclic ring system. When the bicyclic heteroaryl contains a fused cycloalkyl, cycloalkenyl, heteroaryl or heterocycloalkyl, then the bicyclic heteroaryl group is attached to the parent molecular moiety through any carbon or nitrogen atom contained within the monocyclic heteroaryl portion of the bicyclic ring system.

As used herein, the term “heterocyclyl” includes definitions of “heterocycloalkyl” and “heteroaryl”.

As used herein, the term ‘(cycloalkyl)alkyl’, ‘arylalkyl’, ‘(heterocycloalkyl)alkyl’ or ‘heteroaralkyl’ refers to an alkyl group which is further substituted by cycloalkyl, aryl, heterocycloalkyl or heteroaryl respectively, wherein cycloalkyl, aryl, heterocycloalkyl and heteroaryl are as above defined.

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

The term “haloalkyl”, as used herein, refers to an alkyl group substituted with a halogen group.

As used herein, the term “nitro” refers to -NO₂ 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).

In certain embodiments, 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 in to compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine and iodine, such as ^2H ("D"), ^3H , ^{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.

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 diluent.

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
5 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
10 (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;
15 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.
20 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
25 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,
30 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.

5 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
10 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
15 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,
20 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)
25 absorbents, such as kaolin and bentonite clay; (9) lubricants, such as 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
30 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.

5 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.

10 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.

15 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.

20 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.

25 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.

30 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 compatible 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
5 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
10 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
15 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
20 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.
25 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.

30 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
5 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
10 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,
15 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.

20 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
25 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
30 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).

5 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.

10 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.

15 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.

20 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.

25 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

30 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-L1 or PD-L2, leads to anti-tumor activity in various cancers, including lung, breast, colon, renal, bladder, thyroid, prostate, osteosarcoma, and Hodgkin's lymphoma.

5 Furthermore, PD-1 activity has also been associated with autoimmune conditions, such as lupus erythematosus, 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.

10 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.

15 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
20 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
25 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.
30

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
5 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
10 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 present invention provides methods for treating infectious disease in a subject comprising administering a therapeutically effective
15 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
20 virus), adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, coronavirus, 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,
25 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,
30 Coccidioides immitis and Histoplasma capsulatum, and pathogenic infection by the parasites Entamoeba histolytica, Balantidium coli, Naegleria fowleri, Acanthamoeba sp.,

Giardia lamblia, *Cryptosporidium* sp., *Pneumocystis carinii*, *Plasmodium vivax*, *Babesia microti*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Leishmania donovani*, *Toxoplasma gondi*, *Nippostrongylus brasiliensis*.

5 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.

10 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, 15 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 20 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 25 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 30 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, 5 concomitantly or in a mixture form. Chemotherapeutic agents that may be conjointly administered with compounds of the invention include: aminoglutethimide, amsacrine, anastrozole, asparaginase, bcr, bicalutamide, bleomycin, bortezomib, buserelin, busulfan, campothecin, capecitabine, carboplatin, carfilzomib, carmustine, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, 10 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, 15 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, perfosine, plicamycin, pomalidomide, porfimer, procarbazine, raltitrexed, rituximab, 20 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 25 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 30 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-TGF β 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.

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.

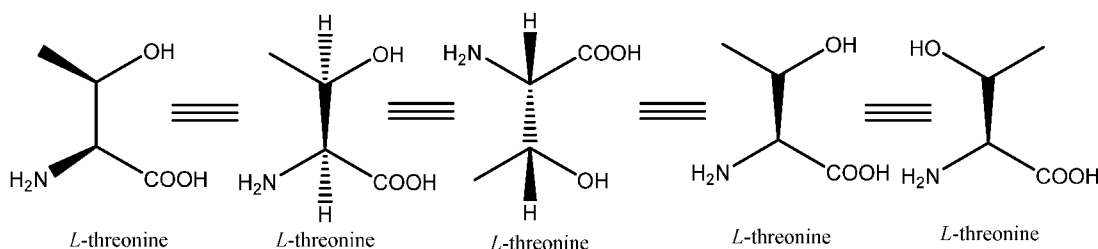
As used herein, the term “amino acid” means a molecule containing both an amino group and a carboxyl group, and includes its salts, esters, combinations of its various salts, as well as tautomeric forms. In solution, at neutral pH, amino and acid groups of an amino acid can exchange a proton to form 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 $\text{CH}(\text{COOH})(\text{NH}_2)$ -(side chain), having the L-configuration. The term “D-amino acid” similarly denotes a carboxylic acid of general formula $-\text{CH}(\text{COOH})(\text{NH}_2)$ -(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 $-\text{NH}_2$ or $-\text{OH}$ is replaced by a bond to another chemical moiety).

Amino acids include the twenty standard amino acids used by most biological organisms in protein synthesis. Unnatural amino acid residues 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, (heteroaryl)alkyl 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 NH₂ 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 capreomycin. 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' mentioned in compound of formula (I) or compounds of the present invention and/or preparation thereof can be represented by any one of the following formulae.



20

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.

25

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.

5 Further exemplary amino acids include penicillamine and betamethoxyvaline.

Further examples of unnatural amino acids include the amino acids wherein the side chain comprises amino, alkylamino, acylamino, -COO-alkyl, cycloalkyl, heterocyclyl, heteroaryl, guanidino, (cycloalkyl)alkyl, (heterocyclyl)alkyl and (heteroaryl)alkyl.

10 “Modified N-terminal amino group” and “modified C-terminal carboxyl group” mean that the amino group or carboxyl group is altered.

Modification of the N-terminal amino group is preferably with the general formula -NR_xR_y; wherein R_x is hydrogen or alkyl and R_y is alkyl, alkenyl, -C(=NH)NH₂, alkynyl or acyl.

15 Examples of N-terminal modifications include, but are not limited to, are acetylated, formylated or guanylated N-termini.

Modification of the C-terminal carboxyl group is preferably with the general formula -COR' (R' replaces the hydroxyl group of the last amino acid); wherein R' is alkoxy, amino or an imide. For example, the C-terminus may be esterified or amidated.

20 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,
25 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
30 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
5 adventitious to such solvent.

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
10 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
15 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
20 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
25 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%
30 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 I: Amino acid codes

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

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

°C (degree Celsius); % (percentage); brine (NaCl solution); CH₂Cl₂/DCM (Dichloromethane); Boc (Tert-butyloxycarbonyl); Cs₂CO₃ (Caesium carbonate); HATU (N-[(Dimethylamino)-1H-1,2,3-triazolo-[4,5-b]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide); DIC (N,N'-
10 Diisopropylcarbodiimide); DIPEA (N,N-Diisopropylethylamine); DMF (Dimethyl formamide); EtOH (Ethanol); Et₂NH (Diethylamine); Fmoc (9-Fluorenylmethyloxycarbonyl); g or gr (gram); HOBT (1-Hydroxy benzotriazole); h or hr (Hours); HPLC (High-performance liquid chromatography); K₂CO₃ (Potassium carbonate); LCMS (Liquid chromatography mass spectroscopy); Liq.NH₃ (Liquid
15 ammonia); mmol (Millimoles); M (Molar); µl (Microlitre); mL (Millilitre); mg (Milligram); MS (ES) (Mass spectroscopy-electro spray); min (Minutes); Na (Sodium); NaHCO₃ (Sodium bicarbonate); NH₂NH₂.H₂O (Hydrazine hydrate); Na₂SO₄ (Sodium sulphate); NH₂OH.HCl (Hydroxylamine hydrochloride); PD1/PD-1 (Programmed cell death 1); PD-L1 (Programmed death-ligand 1); PD-L2 (Programmed cell death 1 ligand
20 2); prep-HPLC/preparative HPLC (Preparative High-performance liquid chromatography); TEA/Et₃N (Triethylamine); (Tifluoroacetic anhydride); TLC (Thin Layer Chromatography); THF (Tetrahydrofuran); TIPS (Triisopropylsilane); TFA (Trifluoroacetic acid); t_R (Retention time); Trt (Trityl or Triphenylmethyl), MeI (Methyl Iodide), etc.

EXPERIMENTAL

General Information on Analytical Methods

LCMS Conditions:

Method A:

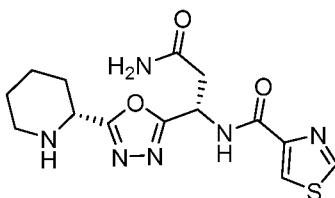
- 5 LC-MSD (Agilent 1100 series with Single Quad, Dual Mode mass spectrometer/ API 2000, Triple Quad, ESI/ APCI SHIMADZU LCMS-2020 WITH SINGLE QUAD)
Column: Mercury MS Synergi 2 μ , 20X4.0mm; Gradient: A- 0.1% formic acid in water/B-MeCN; 0-0.5min 70A-30B; 1.5-2.4min 5A-95B; 2.5-3.0min 70A-30B; Flow 2.0mL/min; Column temperature 30°C.

10 **Method B:**

- LC-MSD (Agilent 1100 series with Single Quad, Dual Mode mass spectrometer/API 2000, Triple Quad, ESI/APCI SHIMADZU LCMS-2020 WITH SINGLE QUAD)
Column: Mercury MS Synergi 2 μ , 20X4.0mm; Gradient: A-0.1% formic acid in water/B-MeCN; 0-0.5min 30A-70B; 1.5-2.4min 100B-0A; 2.5-3.0min 30A-70B; Flow
15 2.0mL/min; Column temperature 30°C.

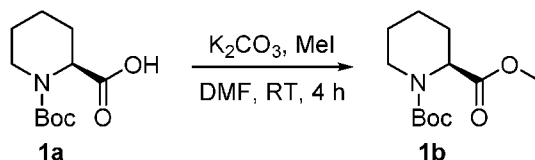
¹H-NMR Instrument: Varian Mercury 300 MHz and Varian 400 MHz (MR-400)

Example 1: N-((S)-3-amino-3-oxo-1-(5-((R)-piperidin-2-yl)-1,3,4-oxadiazol-2-yl)propyl)thiazole-4-carboxamide (Compound 1)



20

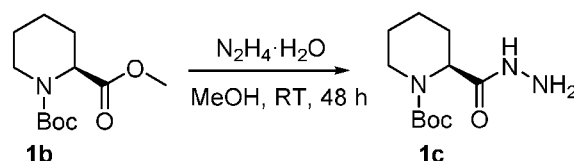
Step 1: Preparation of compound 1b



- To a stirred solution of N-Boc-L-Homoproline (compound **1a**) (10.0 g, 43.6 mmol) in dry DMF (100.0 mL) was added K₂CO₃ (6.80 g, 49.2 mmol) followed by methyl iodide (18.0 g, 126.7 mmol) and the resultant mixture was stirred at ambient
25 temperature for 4 h. When TLC-analysis has indicated the completion of the reaction, the reaction mixture was then partitioned between water and EtOAc (ca. 200 mL each), the

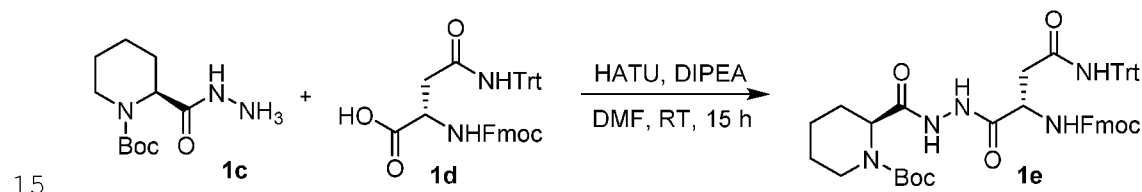
organic layer was separated and washed with water and brine, dried over Na₂SO₄ and the solvents were removed under reduced pressure to furnish the ester **1b** (9.80 g). **LCMS:** 244.1 (M+H)⁺.

Step 2: Preparation of compound 1c



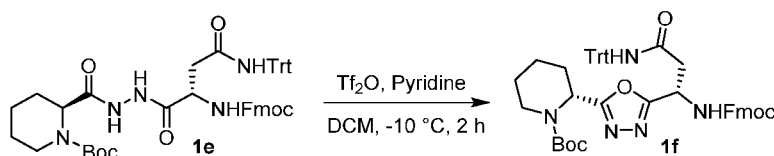
To a stirred solution of compound **1b** (9.8 g, 40.3 mmol) in methanol (50.0 mL) was added hydrazine hydrate (20.1 g, 403.2 mmol) the resultant mixture was stirred at ambient temperature for 48 h, when TLC-analysis has indicated the completion of the reaction. The reaction mixture was concentrated under reduced pressure and the crude residue was partitioned between water and EtOAc (ca. 200 mL each). The organic layer was separated and washed with water and brine; dried over Na₂SO₄ and the solvents were removed under reduced pressure to furnish the compound **1c** (10.1 g). LCMS: 244.1 (M+H)⁺.

Step 3: Preparation of compound 1e



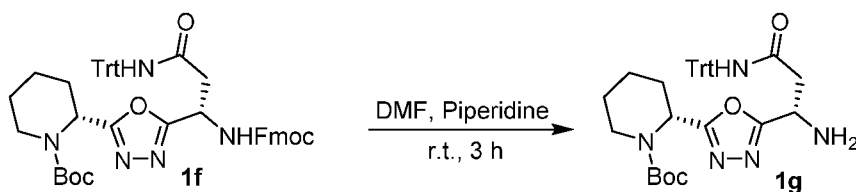
To a stirred solution of compound **1c** (1.00 g, 4.12 mmol) in DMF (25.0 mL) under inert atmosphere was added HATU (2.30 g, 6.17 mmol) and DIPEA (1.30 g, 10.05 mmol), followed by amino acid (compound **1d**) (2.45 g, 4.12 mmol), and the reaction mixture was stirred at ambient temperature for 15 h, then the reaction mixture was poured into ice-cold water. The precipitate thus generated was collected by filtration, washed with water, and the traces of solvents were removed under reduced pressure to furnish the compound **1e** (2.90 g). **LCMS**: 722.6 (M+H-Boc)⁺.

Step 4: Preparation of compound 1f



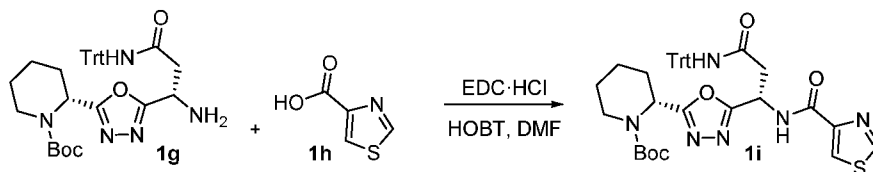
To a stirred solution of compound **1e** (1.90 g, 2.31 mmol) in dry DCM (20.0 mL) and pyridine (10.0 mL) at -10°C was added trifluoromethanesulfonic anhydride (0.98 g, 3.47 mmol) in a drop-wise manner and the resultant mixture was stirred at -10 °C for a further 2 h, until completion of the reaction. To the reaction was added ice-cold water and after stirring for ca. 5 min, the mixture was extracted with DCM (ca. 100 mL). The organic phase was washed with brine; dried over Na₂SO₄ and the solvent was removed under reduced pressure to furnish the crude product, which was further purified by MPLC (CombiFlash®, Gradient: 2:3 to 3:2 EtOAc-Hexane) to furnish compound **1f** (0.55 g). LCMS: 804.0 (M+H)⁺.

Step 5: Preparation of compound **1g**



To a stirred solution of compound **1f** (0.55 g) in dry DMF (2.0 mL) under inert atmosphere was added piperidine (0.55 mL) and the resultant mixture was stirred at room temperature for 3 h. When TLC-analysis has indicated the completion of the reaction, the reaction mixture was diluted with ice-cold water and was extracted with EtOAc, washed with water and brine and was dried over Na₂SO₄. After removing the solvents under reduced pressure, the solid material was stirred for 10-15 min with diethyl ether and pentane, decanted and the traces of solvents remained was removed *in vacuo* to furnish compound **1g** (0.41 g). LCMS: 582.1 (M+H)⁺.

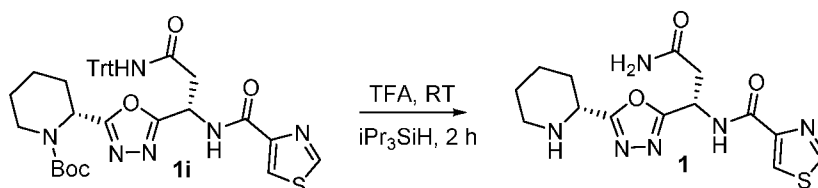
Step 6: Preparation of compound **1i**



To a stirred solution of compound **1h** (18.0 mg), EDC·HCl (40.0 mg) and HOBT (28.0 mg) in dry DMF (1.5 mL) under inert atmosphere was added compound **1g** (80.0 mg) and the resultant mixture was stirred at ambient temperature for 24 h, when TLC-

analysis has indicated the completion of the reaction. The reaction mixture was diluted with water and the solids generated were collected by vacuum filtration, washed with water and brine and dried under reduced pressure to furnish the desired amide **1i** (83.0 mg). **LCMS**: 693.0 (M+H)⁺.

5 **Step 7: Preparation of compound 1**



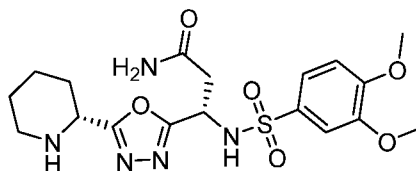
TFA (1.0 mL) was added to the compound **1i** (50.0 mg) dissolved in DCM (10.0 mL), followed by triisopropylsilane (0.05 mL) and the resultant mixture was stirred at ambient temperature for 2 h. The solvents were removed under reduced pressure, and the crude product thus obtained was agitated with diethyl ether (20.0 mL), before collecting the solid product by vacuum filtration. The solid was repeatedly washed with diethyl ether (2 x 10 mL) to furnish compound **1** (20 mg). **¹HNMR (DMSO, 300 MHz):** δ = 1.54-1.70 (m, 2H), 1.71-1.85 (m, 3H), 2.08-2.18 (m, 1H), 2.85-3.10 (m, 3H), 4.78-4.88 (m, 1H), 5.68-5.71 (m, 1H), 6.52-6.60 (bs, 1H), 7.06 (s, 1H), 7.59 (s, 1H), 8.42 (d, 1H), 9.22-9.26 (m, 2H), 9.34-9.60 (bs, 2H); **LCMS**: 351.4 (M+H)⁺.

The below compounds were prepared by procedure similar to the one described in Example-1 (Compound **1**) with appropriate variations in solvents, reactants or amino acids, quantities of reagents and reaction conditions. The analytical data of the compounds are summarized herein below table.

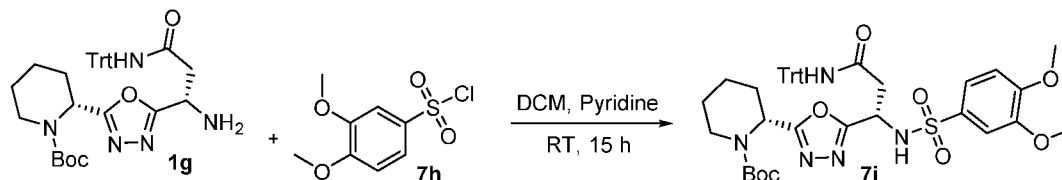
Comp	Structure	Analytical Data
2		¹HNMR (DMSO-D₆, 300 MHz): δ = 2.75-2.93 (m, 1H), 3.00-3.13 (m, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 5.70-5.75 (m, 1H), 7.08-7.16 (m, 2H), 7.25 (d, 1H), 7.58-7.63 (m, 2H), 7.77-7.80 (dd, 1H), 8.00 (d, 2H), 8.08 (d, 2H), 9.39-9.42 (d, 1H). LCMS : 425.2 (M+H) ⁺ .
3		¹H-NMR (DMSO-D₆, 300 MHz): δ = 2.81-2.87 (m, 1H), 3.01-3.09 (m, 1H), 3.79 (s, 3H), 5.70 (m, 1H), 7.04-7.12 (m, 2H), 7.22 (m, 1H), 7.55-7.61 (m, 2H), 7.74-7.77 (dd, 1H), 7.95 (d,

Comp	Structure	Analytical Data
		2H), 8.22 (d, 2H), 9.35 (d, 1H), 13.28 (bs, 1H); LCMS: 410.9 (M+H) ⁺
4		¹H-NMR (DMSO-D₆, 300 MHz): δ = 3.0-3.05 (t, 2H), 3.75 (s, 3H), 5.7-5.8 (m, 1H), 7.04-7.12 (m, 3H), 7.20-7.22 (d, 1H), 7.54-7.6 (m, 2H), 7.74-7.79 (m, 2H), 8.88 (s, 1H), 9.75-9.78 (d, 1H); LCMS: 408.0 (M+H) ⁺ ;
5		¹H-NMR (DMSO-D₆, 300 MHz): δ = 1.03-1.05 (d, 3H), 2.76-3.00 (m, 4H), 3.79-3.84 (m, 2H), 5.49-5.53 (t, 1H), 7.03 (s, 1H), 7.56 (s, 1H), 7.6-7.66 (m, 1H), 8.02-8.08 (m, 1H), 8.13-8.16 (d, 1H), 8.76-8.77 (d, 1H). LCMS: 334.9 (M+H) ⁺ ;
6		¹H-NMR (DMSO-D₆, 300 MHz): δ = 1.82-1.95 (m, 1H), 2.08-2.16 (m, 2H), 2.20-2.35 (m, 1H), 2.70-2.90 (m, 1H), 2.91-3.02 (m, 1H), 4.03-4.10 (m, 1H), 5.51 (q, 1H), 7.06 (s, 1H), 7.57 (s, 1H), 7.86 (s, 1H), 8.85-8.90 (m, 3H), 9.36 (d, 1H). LCMS: 346.0 (M+H) ⁺ ;

Example-2: (S)-3-((3,4-dimethoxyphenyl)sulfonamido)-3-(5-((R)-piperidin-2-yl)-1,3,4-oxdiazol-2-yl)propanamide (Compound 7)



5 Step 1: Preparation of Compound 7i



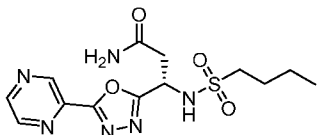
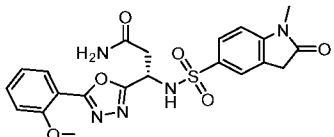
To a stirred solution of compound **1g** (80.0 mg) in DCM (2.0 mL) under inert atmosphere was added pyridine (27.0 mg) followed by 3,4-dimethoxybenzenesulfonyl chloride (compound **7h**) (39.0 mg) and the resultant mixture was stirred at ambient conditions for 15 h, when TLC-analysis has indicated the completion of the reaction. The reaction mixture was partitioned between water and EtOAc; the organic phase was washed with water and brine; dried under Na₂SO₄ and was concentrated under reduced pressure to furnish the compound **7i** (110.0 mg). **LCMS**: 804.0 (M+Na)⁺.

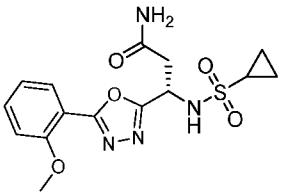
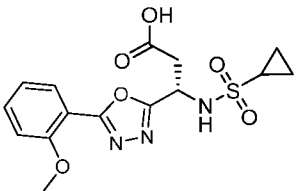
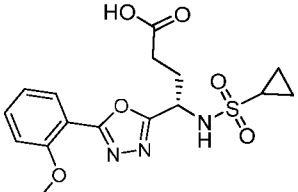
Step 2: Preparation of compound **7**

The compound **7** was prepared from compound **7i** according to the procedure described in step **7** of example - 1 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions.

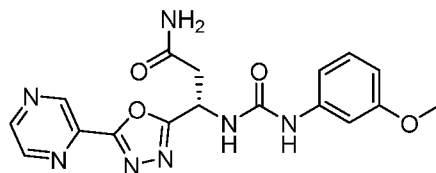
¹H-NMR (DMSO-D₆, 300 MHz): δ = 1.54-1.83 (m, 5H), 1.93-2.02 (m, 1H), 2.80-2.91 (m, 1H), 2.98-3.11 (m, 1H), 3.27-3.40 (m, 1H), 3.80 (s, 3H), 3.84 (s, 3H), 4.66-4.78 (m, 1H), 4.83-4.93 (m, 1H), 6.98 (s, 1H), 7.12 (d, 1H), 7.26 (d, 1H), 7.32-7.40 (dd, 1H), 7.52 (s, 1H), 8.59 (d, 1H), 9.40-9.60 (bs, 2H); **LCMS**: 440.2 (M+H)⁺;

The below compounds were prepared by procedure similar to the one described in Example-2 (Compound **7**) with appropriate variations in solvents, reactants or amino acids, quantities of reagents and reaction conditions. The analytical data of the compounds are summarized herein below table.

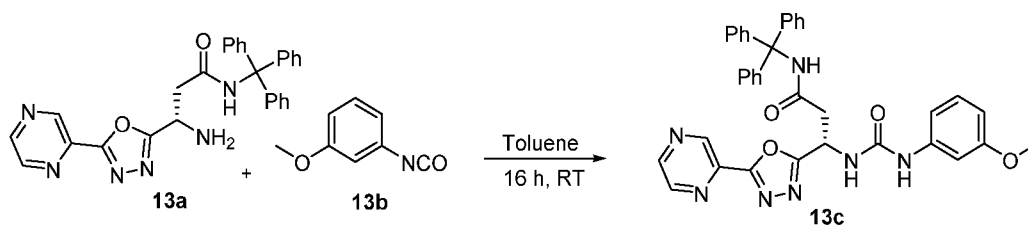
Comp	Structure	Analytical Data
8		¹H-NMR (DMSO-D₆, 300 MHz) : δ = 0.83 (t, 3H), 1.29-1.37 (m, 2H), 1.50-1.70 (m, 2H), 2.70-2.90 (m, 1H), 2.91-3.11 (m, 3H), 5.15-5.18 (t, 1H), 7.12 (s, 1H), 7.61 (s, 1H), 8.224 (d, 1H), 8.88-8.92 (m, 2H), 9.38 (d, 1H). LCMS : 355.2 (M+H) ⁺ ;
9		¹H-NMR (DMSO-D₆, 300 MHz) : δ = 2.71-2.73 (m, 2H), 2.85 (s, 3H), 3.25-3.3 (m, 2H), 3.84 (s, 3H), 4.953 (m, 1H), 6.84-6.87 (d, 1H), 6.99-7.04 (m, 2H), 7.17-7.20 (d, 1H), 7.36-7.42 (m, 2H), 7.52-7.57 (m, 3H), 8.64-8.67 (d, 1H). LCMS : 471.8 (M+H) ⁺ ;

Comp	Structure	Analytical Data
10		¹ H-NMR (CD ₃ OD, 300 MHz): δ = 0.92-0.95 (m, 2H), 1.05-1.08 (m, 2H), 2.56-2.62 (m, 1H), 2.93-2.95 (m, 1H), 2.99-3.10 (m, 1H), 3.97 (s, 3H), 5.27-5.3, (t, 1H), 7.09-7.12 (m, 1H), 7.21-7.23 (m, 1H) 7.56-7.60 (m, 1H), 7.87-7.89 (m, 1H). LCMS: 367.0 (M+H) ⁺ ;
11		¹ H-NMR (CD ₃ OD, 300 MHz): δ = 0.91-1.08 (m, 4H), 2.56-2.65 (m, 1H), 2.93-2.95 (m, 1H), 3.00-3.20 (m, 2H), 3.94 (s, 3H), 5.23-5.28, (t, 1H), 7.09-7.13 (m, 1H), 7.20-7.23 (m, 1H) 7.56-7.61 (m, 1H), 7.86-7.90 (m, 1H). LCMS: 367.9 (M+H) ⁺ ;
12		¹ H-NMR (CD ₃ OD, 400 MHz): δ = 0.88-0.92 (m, 2H), 1.01-1.04 (m, 2H), 2.18-2.25 (m, 1H), 2.25-2.34 (m, 1H), 2.36-2.58 (m, 3H), 3.94 (s, 3H), 4.93-4.96 (m, 1H), 7.09-7.13 (m, 1H), 7.21-7.23 (m, 1H) 7.56-7.61 (m, 1H), 7.87-7.890 (m, 1H). LCMS: 381.9 (M+H) ⁺ ;

Example-3: (S)-3-(3-(3-methoxyphenyl)ureido)-3-(5-(pyrazin-2-yl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 13)



5 Step 1: Preparation of Compound 13c

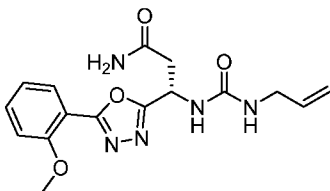
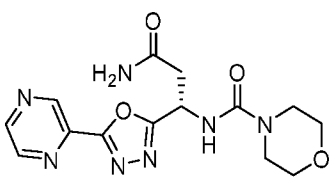


To a stirred solution of Compound **13a** (100.0 mg; prepared as per the procedure described in steps 1 to 5 of Example 1) in toluene (2.0 mL) under inert atmosphere was added 1-isocyanato-3-methoxybenzene (compound **13b**) (47.0 mg) and the resultant mixture was stirred at ambient temperature for 16 h. When TLC-analysis has indicated the completion of the reaction, the solvent was removed under reduced pressure; and the crude product was agitated with pentane for 10 min. The solid material was collected by vacuum filtration; repeatedly washed with pentane (3 x 10 mL) and was dried under reduced pressure to obtain the compound **13c** (77.0 mg). LCMS: 626.5 (M+H)⁺.

Step 2: Preparation of Compound 13

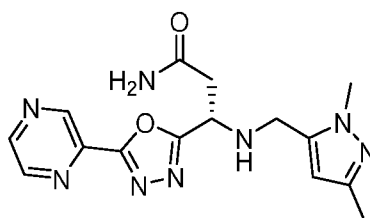
The Compound **13** was prepared from compound **13c** according to the procedure described in step 7 of example - 1 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. ¹H-NMR (DMSO-D₆, 300 MHz): δ = 2.88-2.94 (m, 2H), 3.69 (s, 3H), 4.95-5.05 (m, 1H), 6.48-6.53 (m, 1H), 6.84-6.91 (m, 1H), 7.05-7.18 (m, 4H), 7.62 (bs, 1H), 8.84-8.90 (m, 2H), 8.96 (s, 1H), 9.36 (s, 1H); LCMS: 384.2 (M+H)⁺

The below compounds were prepared by procedure similar to the one described in Example-3 (Compound **13**) with appropriate variations in solvents, reactants or amino acids, quantities of reagents and reaction conditions. The analytical data of the compounds are summarized herein below table.

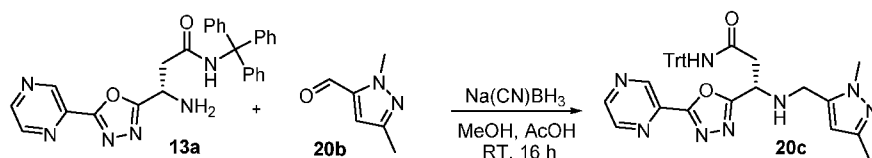
Comp	Structure	Analytical Data
14		¹ H-NMR (DMSO, 400 MHz): δ = 2.74-2.77 (t, 2H), 3.62-3.64 (t, 2H), 3.86 (s, 3H), 4.99-5.01 (m, 1H), 5.08—5.02 (m, 1H), 5.30-5.33 (m, 1H), 5.72-5.82 (m, 1H), 6.37-6.4 (t, 1H), 6.69-6.71 (d, 1H), 6.98 (s, 1H), 7.07-7.1 (m, 1H), 7.23-7.25 (d, 1H), 7.5 (s, 1H), 7.56-7.61 (m, 1H), 7.73-7.75 (m, 1H); LCMS: 346.2 (M+H) ⁺ ;
15		¹ H-NMR (DMSO, 400 MHz): δ = 2.73-2.80 (m, 1H), 2.91-3.00 (m, 1H), 3.28 (m, 4H), 3.54 (m, 4H), 5.41 (m, 1H), 7.02 (s, 1H), 7.35 (d, 1H), 7.51 (s, 1H), 8.88 (dt, 2H), 9.36 (d, 1H); LCMS: 370.2 (M+H+Na) ⁺ ;

Comp	Structure	Analytical Data
16		LCMS: 364.0 (M+H) ⁺ ;
17		¹ H-NMR (DMSO, 400 MHz): δ = 2.40 (m, 1H), 2.72-2.73 (m, 1H), 3.7 (s, 3H), 3.98 (s, 3H), 5.3 (m, 2H), 6.85-6.87 (d, 2H), 6.90 (s, 1H), 7.08-7.12 (t, 1H), 7.20-7.22 (d, 1H), 7.39 (s, 1H), 7.52-7.56 (m, 3H), 7.82-7.83 (d, 1H), 10.34 (s, 1H); LCMS: 427.9 (M+H) ⁺
18		LCMS: 426.9 (M+H) ⁺ ;
19		¹ H-NMR (DMSO-D ₆ , 300 MHz): δ = 0.87-0.93 (m, 5H), 1.61-1.82 (m, 6H), 2.15-2.48 (m, 2H), 3.03-3.07 (m, 4H), 3.30-3.52 (m, 3H), 4.82 (m, 1H), 5.40-5.43 (d, 1H), 6.53 (s, 1H), 9.34-9.49 (m, 2H); LCMS: 307.9 (M+H) ⁺

Example 4: (S)-3-(((1,3-dimethyl-1H-pyrazol-5-yl)methyl)amino)-3-(5-(pyrazin-2-yl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 20)



5 Step 1: Preparation of compound 20c



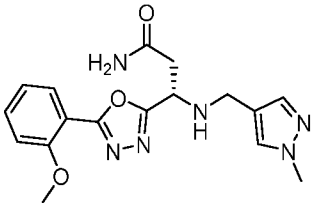
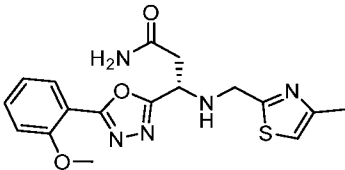
To a stirred solution of compound **13a** (100.0 mg) and compound **20b** (26.0 mg) in dry DCM (1.0 mL) under inert atmosphere at 0 °C was added sodium cyanoborohydride (133.0 mg) and the resultant mixture was warmed to ambient temperature and was stirred for 16 h, when TLC-analysis has indicated the completion of the reaction. The reaction mixture was diluted with DCM and was washed with water (3 x 25 mL), brine and was dried over Na₂SO₄. The solvent was removed under reduced pressure to furnish the crude product, which was triturated with diethyl ether and pentane to obtain compound **20c** (110.0 mg). LCMS: 585.3 (M+H)⁺.

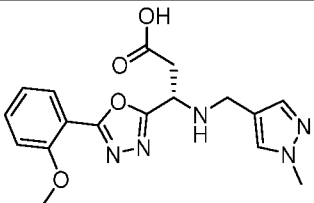
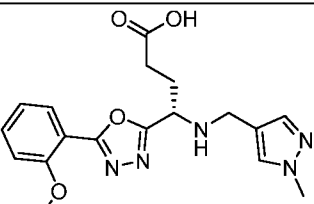
Step 2: Preparation of compound 20

The compound **20** was prepared from compound **20c** according to the procedure described in step 7 of Example - 1 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions.

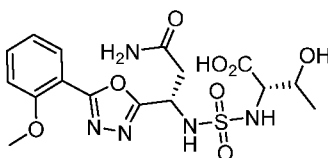
¹H-NMR (DMSO-D₆, 300 MHz): δ = 2.08 (s, 3H), 3.02 (m, 3H), 3.75 (m, 3H), 4.18 (m, 2H), 4.88-5.05 (m, 1H), 6.09 (s, 1H), 7.20 (s, 1H), 7.70 (s, 1H), 8.91 (d, 2H), 9.30 (s, 1H); LCMS: 343.2 (M+H)⁺

The below compounds were prepared by procedure similar to the one described in Example-4 (Compound **20**) with appropriate variations in solvents, reactants or amino acids, quantities of reagents and reaction conditions. The analytical data of the compounds are summarized herein below table.

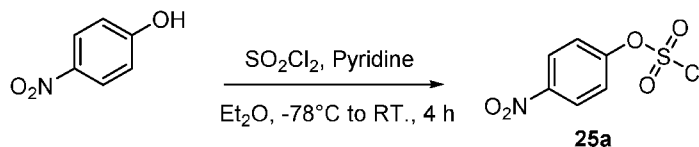
Comp	Structure	Analytical Data
21		¹ H-NMR (CD ₃ OD, 300 MHz): δ = 2.82-2.92 (m, 2H), 3.66-3.76 (m, 2H), 3.69 (s, 3H), 3.95 (s, 3H), 4.50 (m, 1H), 7.11 (t, 1H), 7.22 (d, 1H), 7.41 (s, 1H), 7.50 (s, 1H), 7.56-7.60 (dt, 1H), 7.86 (dd, 1H); LCMS: 357.1 (M+H) ⁺
22		¹ H-NMR (DMSO-D ₆ , 300 MHz): δ = 2.32 (s, 3H), 2.89-2.95 (m, 2H), 3.89 (m, 4H), 4.32 (s, 2H), 4.65-4.78 (m, 1H), 7.12-7.17 (m, 2H), 7.24-7.29 (m, 2H), 7.59-7.64 (m, 2H), 7.81-7.84 (dd, 1H); LCMS: 374.0 (M+H) ⁺

Comp	Structure	Analytical Data
23		LCMS: 357.9 (M+H) ⁺
24		LCMS: 372.0 (M+H) ⁺

Example-5: (N-((S)-3-amino-1-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-3-oxopropyl)sulfamoyl)-L-allothreonine (Compound 25)



Step 1: Preparation of Compound 25a



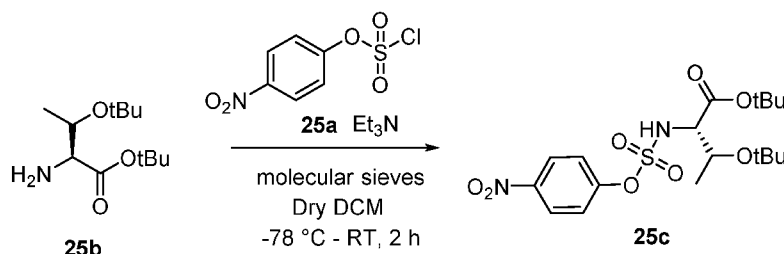
5

A solution of 4-nitrophenol (1.3 g, 9.35 mmol) and pyridine (0.8 mL, 9.99 mmol) in Et₂O (20 mL) was added dropwise to a solution of SO₂Cl₂ (0.8 mL, 9.99 mmol) in Et₂O (20 mL) at -78°C under argon. The reaction mixture allowed to warm to room temperature and stirred for 4 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel column chromatography (Eluent: 0-3% ethyl acetate in hexane) to afford 1.2 g of compound **25a**.

10

¹HNMR (400 MHz: CDCl₃): 8.39-8.36 (m 2H), 7.61- 7.57 (m 2H).

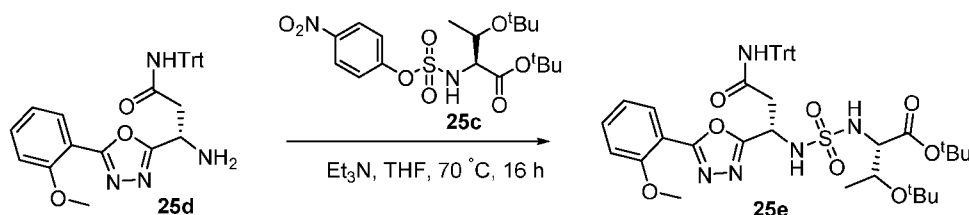
Step 2: Preparation of compound 25c



A solution of compound **5b** (0.6 g, 2.59 mmol), molecular sieves (1.0 g) and Et₃N (1.1 mL, 7.77 mmol) in dry CH₂Cl₂ (25.0 mL), was added dropwise to a solution of compound **5a** (1.2 g, 5.18 mmol) in dry CH₂Cl₂ (5.0 mL) at -78°C under argon. After being stirred for 30 minutes, the reaction mixture was allowed to warm to room temperature for 2 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was evaporated under reduced pressure to get crude compound. The crude compound was purified by silica gel column chromatography (Eluent: 0-7% ethyl acetate in hexane) to afford 0.7 g of compound **5c**.

¹HNMR (300 MHz; CDCl₃): 8.30-8.27 (m 2H), 7.52- 7.49(m 2H), 5.70-5.67 (1H d, J 9.6), 4.17-3.90 (1H, m), 1.49 (9H, s), 1.28-1.23 (3H, m), 1.15 (9H, s).

Step 3: Preparation of compound **5e**



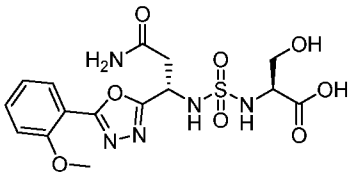
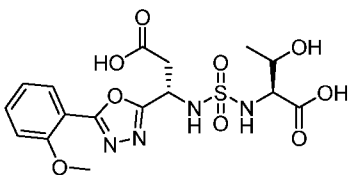
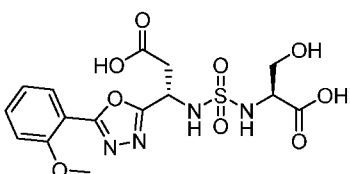
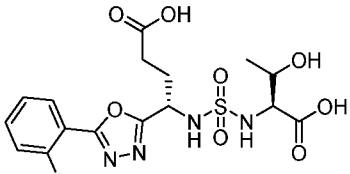
To a stirred solution of compound **25d** (0.3 g, 1.0 mmol) and Et₃N (0.4 mL, 2.95 mmol) in dry THF (3.0 mL) and was added a solution of compound **25c** (0.64 g, 1.47 mmol) in THF (3.0 mL), then the reaction mixture stirred at 70 °C for 16 h. The completeness of the reaction was confirmed by TLC analysis. The reaction mixture was evaporated under reduced pressure, diluted with ethyl acetate (25 mL) and was washed with water (20 mL) followed by sat. K₂CO₃ solution (20 mL) and brine (20 mL). After drying the organics over Na₂SO₄, solvents were removed under reduced pressure to obtain 0.35 g of compound **25e**, which was taken for further steps without purification. LCMS: 543.1 (M+H-(Trt, ^tBu)⁺.

Step 17: Preparation of compound **25**

The compound **25** was prepared from compound **25e** according to the procedure described in step 7 of example – 1 with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. **LCMS**: 444.7 (M+H)⁺;

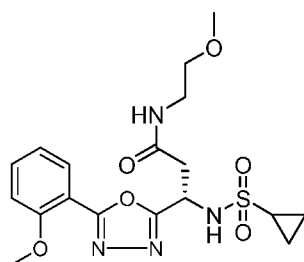
¹H-NMR (CD₃OD, 300 MHz): δ = 1.20-1.23 (d, 3H), 3.06-3.1 (m, 2H), 3.75-3.76 (d, 1H), 3.94 (s, 3H), 4.09-4.12 (m, 1H), 5.22-5.25 (t, 2H), 7.07-7.21 (m, 2H), 7.53-7.59 (m, 1H), 7.93-7.96 (dd, 1H); **LCMS**: 443.9 (M+H)⁺

The compounds mentioned in the below table were prepared by procedure similar to the one described in Example-5 (Compound **25**) with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. The characterization data of the compounds are summarized herein below table.

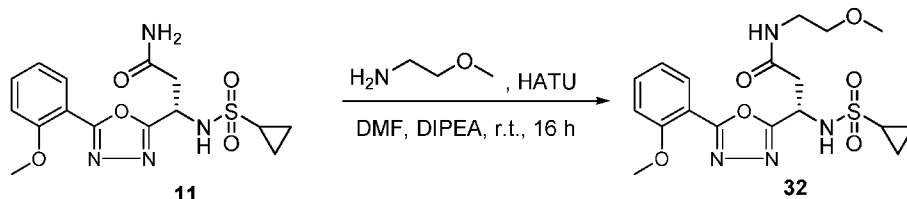
Comp	Structure	Analytical Data
26		¹H-NMR (CD ₃ OD, 300 MHz): δ = 3.06-3.08 (m, 2H), 3.82-3.85 (m, 3H), 3.94 (s, 3H), 5.21-5.23 (m, 2H), 7.11 (t, 1H), 7.18-7.20 (d, 1H), 7.50-7.62 (m, 1H), 7.92-7.95 (dd, 1H); LCMS : 429.9 (M+H) ⁺
27		¹H-NMR (CD ₃ OD, 300 MHz): δ = 1.27 (d, 3H), 3.17 (d, 2H), 3.89 (d, 1H), 3.95 (s, 3H), 4.18-4.22 (m, 1H), 5.22-5.26 (m, 1H), 7.10 (t, 1H), 7.21 (d, 1H), 7.54-7.60 (dt, 1H), 7.91-7.94 (dd, 1H); LCMS : 444.9 (M+H) ⁺
28		¹H-NMR (CD ₃ OD, 300 MHz): δ = 3.13-3.16 (d, 2H), 3.86-3.87 (d, 2H), 3.95 (s, 3H), 4.04-4.05 (m, 1H), 5.18-5.22 (t, 1H), 7.08-7.13 (m, 1H), 7.20-7.23 (d, 1H), 7.55-7.60 (m, 1H), 7.89-7.92 (dd, 1H); LCMS : 431.2 (M+H) ⁺
29		¹H-NMR (CD ₃ OD, 300 MHz): δ = 1.25 (d, 3H), 2.26-2.28 (m, 2H), 2.51-2.54 (m, 2H), 3.87 (d, 1H), 3.95 (s, 3H), 4.10-4.21 (m, 1H), 4.97 (m, 1H), 7.10 (m, 1H), 7.19-7.22 (d, 1H), 7.57 (m, 1H), 7.90-7.93 (dd, 1H); LCMS : 459.0 (M+H) ⁺

Comp	Structure	Analytical Data
30		¹ H-NMR (CD ₃ OD, 300 MHz): δ = 2.24-2.27 (m, 2H), 2.54 (t, 2H), 3.85 (d, 2H), 3.95 (s, 3H), 4.04 (d, 1H), 4.89 (m, 1H), 7.10 (m, 1H), 7.19-7.22 (d, 1H), 7.57 (m, 1H), 7.89-7.92 (dd, 1H); LCMS: 444.9 (M+H) ⁺
31		¹ H-NMR (DMSO-D ₆ , 300 MHz): δ = 2.8-3.00 (m, 6H), 3.53 (m, 4H), 5.04-5.06 (m, 1H), 7.09(s, 1H), 7.59 (s, 1H), 8.51-5.54 (d, 1H), 8.88-8.92 (m, 2H), 9.38-9.93 (s, 1H); LCMS: 384.1 (M+H) ⁺

Example-6: (S)-3-(cyclopropanesulfonamido)-N-(2-methoxyethyl)-3-(5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)propanamide (Compound 32)



Step 1: Preparation of Compound 32



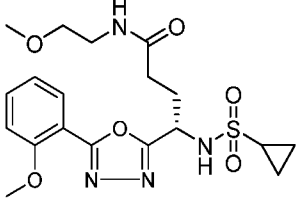
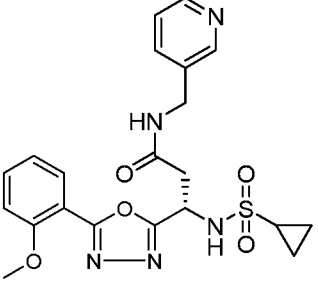
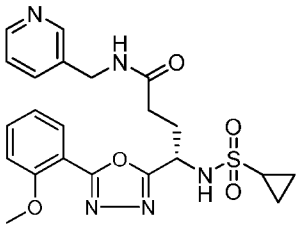
5

To a stirred solution of Compound **11** (0.15 g, 0.4 mmol) in DMF (5 mL.0) at RT was added 2-methoxyethan-1-amine (0.2 mL, 2.29 mmol), HATU (0.23 g, 0.6 mmol) and DIPEA (0.2 mL, 1.16 mmol). The reaction mixture was stirred at r.t. for 16 h, when TLC-analysis has indicated the completion of the reaction. The reaction mixture was diluted with EtOAc (25 mL) and was washed thoroughly with water (25 mL), followed by brine (25 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to furnish crude product, which was then purified by reverse-phase preparative HPLC (Column: Waters X-Bridge C-18 (250mmx21.20mm), 5.0μ; Phase A: MeCN; Phase B: Water; Flow Rate: 15 mL/min) to obtain the compound **32** as a brown viscous material (0.13 g).

15

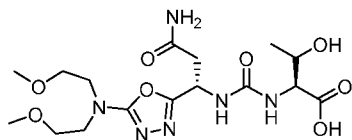
¹H-NMR (400 MHz, CD₃OD): δ = 0.91-0.96 (m, 2H), 1.03-1.07 (m, 2H), 2.55-2.59 (m, 1H), 2.91-3.08 (m, 2H), 3.22-3.41 (m, 4H), 3.30 (s, 3H), 3.94 (s, 3H), 5.30 (t, 1H), 7.12 (t, 1H), 7.22 (d, 1H), 7.56-7.61 (m, 1H), 7.87-7.90 (dd, 1H); **LCMS**: 425.1 (M+H)⁺.

- 5 The compounds mentioned in the below table were prepared by procedure similar to the one described in Example-6 (Compound **32**) with appropriate variations in reactants, quantities of reagents, solvents and reaction conditions. The characterization data of the compounds are summarized herein below table.

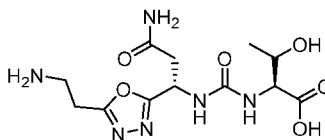
Comp	Structure	Analytical Data
33		¹H-NMR (CD ₃ OD, 400 MHz): δ = 0.86-0.892 (m, 2H), 1.01-1.04 (m, 2H), 2.18-2.53 (m, 5H), 2.54-3.34 (m, 4H), 3.41-3.44 (m, 2H), 3.94 (s, 3H), 4.93-4.96 (m, 1H), 7.090-7.095 (m, 1H), 7.21-7.24 (m, 1H), 7.56-7.62 (m, 1H), 7.87-7.91 (m, 1H); LCMS : 439.1 (M+H) ⁺ ;
34		¹H-NMR (CD ₃ OD, 400 MHz): δ = 0.91-1.11 (m, 4H), 2.58-2.64 (m, 1H), 3.01-3.18 (m, 2H), 3.95 (s, 3H), 4.60 (s, 2H), 5.29-5.34 (m, 1H), 7.1-7.15 (m, 1H), 7.23-7.25 (m, 1H), 7.57-7.63 (m, 1H), 7.86-7.891 (dd, 1H), 7.98-8.03 (dd, 1H), 8.54-8.57 (d, 1H), 8.72-8.74 (d, 1H), 8.85 (s, 1H); LCMS : 458.1 (M+H) ⁺
35		¹H-NMR (CD ₃ OD, 400 MHz): δ = 0.84-1.01 (m, 4H), 2.21-2.26 (m, 1H), 2.41-2.64 (m, 4H), 3.29-3.31 (m, 2H), 3.94 (s, 3H), 4.48-4.66 (dd, 2H), 4.84-4.89 (m, 2H), 7.09-7.15 (m, 1H), 7.21-7.24 (m, 1H), 7.56-7.62 (m, 1H), 7.86-7.89 (dd, 1H), 8.01-8.06 (m, 1H), 8.56-8.59 (d, 1H), 8.74-8.82 (m, 2H); LCMS : 472.2 (M+H) ⁺

- 10 Although the present application has been illustrated by certain of the 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

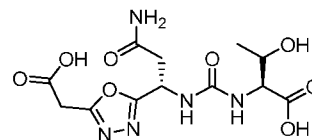
similar procedure as described above with suitable modification known to the one ordinary skilled in the art are also included in the scope of the present application:



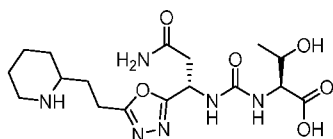
Compound 36



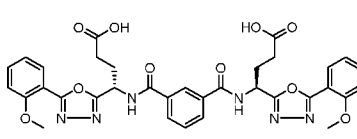
Compound 37



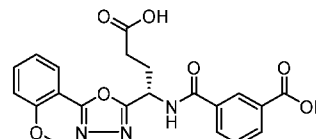
Compound 38



Compound 39



Compound 40



Compound 41

Example 7: Rescue of mouse splenocyte proliferation in the presence of recombinant PD-L1/PD-L2

- 5 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
- 10 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
- 15 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)
- 20 (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 C₂H₆SO, SIGMA-D-5879) and aliquoted in to tubes for

further use. Working concentrations were titrated from 10 μ M to 1 μ M. (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).

5 Protocol

Splenocyte preparation and culturing:

Splenocytes harvested in a 50 mL falcon tube by mashing mouse spleen in a 40 μ m 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-
10 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
15 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 10,000 μ g/mL streptomycin) and maintained in a CO₂ incubator with 5% CO₂ at 37 °C.

CFSE Proliferation assay:

20 CFSE is a dye that passively diffuses into cells and binds to intracellular proteins. 1x10⁶ cells/mL of harvested splenocytes were treated with 5 μ M 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
25 media. CFSE labelled 1x10⁵ splenocytes added to wells containing either MDA-MB231 cells (1x10⁵ cells cultured in high glucose DMEM medium) or recombinant human PDL-1 (100 ng/mL) and test compounds. Splenocytes were stimulated with anti-mouse CD3 and anti- mouse CD28 antibody (1 μ g/mL each), and the culture was further incubated for 72 h at 37 °C with 5% CO₂. Cells were harvested and washed thrice with ice cold FACS
30 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%.

- 5 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).

- 10 **Table II: Percent rescue of splenocyte proliferation at 100 nM of compounds of present invention)**

Compound	Percent rescue of splenocyte proliferation	Compound	Percent rescue of splenocyte proliferation
1	10.1	22	74.7
5	1.9	25	39.1
11	79.5	26	81.8
12	61.0	29	68.9
16	6.1	32	77.9
17	87.1	33	96.8
19	3.2	34	17.0
21	89.2	35	94.8

Incorporation by Reference

- 15 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.

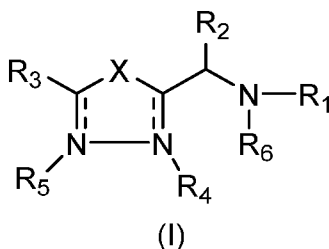
Equivalents

- 20 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):



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

X is O or S;

each dotted line ---- represents an optional bond;

R₁ is -CO-Aaa, -C(=W)R_a, -SO₂R_a, -SO₂-Aaa, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-; wherein the heterocycloalkyl-, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl and arylalkyl- are each optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, -SH, -S(alkyl), aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl;

W is O or S;

R₂ is a side chain of an amino acid or is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl-; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl and (heterocycloalkyl)alkyl- are each optionally substituted with 1 to 4 substituents selected from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl, cycloalkyl, aryl, -CONR₇R₈, -aryl-COOH, heterocycloalkyl, heteroaryl, guanidino, amidino, -SH and -S(alkyl); optionally wherein two or three carbon atoms of the alkyl, alkenyl, or alkynyl form part of a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with 1 to 4 substituents, each independently selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl;

R₃ represents aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl-, (heteroaryl)alkyl-, -alkyl-COOH, -(CH₂)₂-NH₂, or a

group represented by the formula $-\text{CH}(\text{OR}_b)(\text{CH}_2\text{OR}_b)$, $-\text{C}(\text{R}_7\text{R}_8)(\text{NR}_9\text{R}_{10})$ or $-\text{N}(\text{R}_{11})_2$; wherein the aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl- and (heteroaryl)alkyl- are optionally substituted with 1 to 4 occurrences of R_e ;

R_4 and R_5 independently are hydrogen or absent;

R_6 is hydrogen or alkyl; or R_6 and R_c taken together with the atoms to which they are attached form a 5- to 7-membered ring optionally substituted with one or more groups independently selected from hydroxyl, halo, amino, cyano and alkyl;

R_7 , R_8 and R_{11} each independently represent hydrogen, alkyl, heteroalkyl, alkoxy, aryl, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-, each optionally substituted with -alkyl-COOH, -aryl-alkoxy, hydroxy, halo, amino, cyano or alkyl; or

R_7 and R_8 taken together with the atoms to which they are attached form a 5- to 7-membered cycloalkyl ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

R_9 and R_{10} independently is hydrogen, alkyl or acyl; or R_9 and R_{10} taken together with the atoms to which they are attached form a 5- to 7-membered carbocyclic ring or heterocyclic ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

Aaa represents an amino acid residue;

R_a is $-\text{NR}_c\text{R}_d$, aminoalkyl-, aminoaryl-, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl are each optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, $-\text{CONR}_7\text{R}_8$, carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy;

R_b and R_c each independently represent hydrogen, alkyl or alkoxyalkyl;

R_d represents hydrogen, alkyl, acyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the said aryl, heterocycloalkyl and heteroaryl are optionally substituted with one or more hydroxyl, cyano, alkyl or alkoxy;

R_e , at each occurrence, is alkyl, alkoxy, halo, hydroxyl, $-\text{C}(\text{O})\text{OH}$, arylalkyl-, aryl, heteroarylalkyl-, heteroaryl, cycloalkyl, (cycloalkyl)alkyl-, hydroxyalkyl, alkoxyalkyl or acyl; wherein the alkyl, alkoxy, arylalkyl, aryl, heteroarylalkyl,

heteroaryl, cycloalkyl, (cycloalkyl)alkyl- and hydroxyalkyl are optionally substituted with halo, hydroxyl, amido, cyano or alkoxy; or

two R_e groups attached to same carbon atom together represent an oxo (=O) or thioxo (=S);

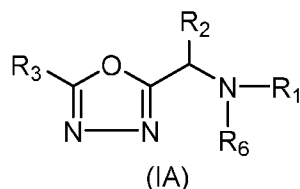
wherein either:

A) R₁ represents -C(=W)R_a, -SO₂R_a, -SO₂-Aaa, heterocycloalkyl, (heterocycloalkyl)alkyl-, heteroaryl, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-, wherein R_a is -NR_cR_d or is alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl substituted with carboxylate, thioacid, thiocarboxylate, oxo, halo, cyano or haloalkyl;

or

B) R₃ represents optionally substituted arylalkyl-, optionally substituted (heterocycloalkyl)alkyl-, optionally substituted (heteroaryl)alkyl-, -alkyl-(COOH), -(CH₂)₂-NH₂, or a group represented by the general formula -CH(OR_b)(CH₂OR_b) or -N(R₁₁)₂.

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



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

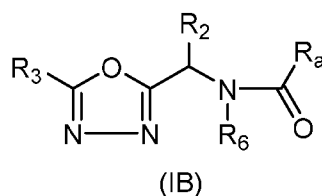
R₁, R₂, R₃ and R₆ are same as defined in claim 1.

3. The compound of claim 1 or 2, wherein R₁ is -C(=W)R_a, -SO₂R_a, -SO₂-Aaa, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-; wherein the heterocycloalkyl-, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl and arylalkyl- are each optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, -SH, -S(alkyl), aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl; and

R₂, R₃, R₆, R_a, Aaa are same as defined in claim 1.

4. The compound of claim 1 or 2, wherein R₁ is (heteroaryl)alkyl-, optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, -SH, -S(alkyl), aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl.

5. The compound of claim 1, wherein the compound is of formula (IB):



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

R₃ represents aryl, heterocycloalkyl, heteroaryl or cycloalkyl, each optionally substituted with 1 to 4 occurrences of R_e; and

R₂, R_e, R₆ and R_a are same as defined in claim 1.

6. The compound of claim 5, wherein R_a is -NR_cR_d, aminoaryl-, aryl, heterocycloalkyl or heteroaryl; wherein the said aryl, heterocycloalkyl, and heteroaryl are optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, carboxylic acid, carboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy.

7. The compound of claim 5, wherein R_a is -NR_cR_d;

R_c represents hydrogen; and

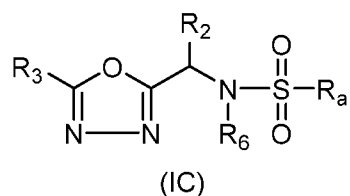
R_d represents alkyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the said aryl, heterocycloalkyl and heteroaryl are optionally substituted with one or more hydroxyl, cyano, alkyl or alkoxy.

8. The compound any one of claims 5-7, wherein, R₃ represents aryl, heterocycloalkyl, heteroaryl or cycloalkyl; wherein the said aryl, heterocycloalkyl,

heteroaryl or cycloalkyl are optionally substituted with 1 to 4 occurrences of R_e ; and R_e is same as defined in claim 5.

9. The compound of claim 8, wherein R_e is alkyl, alkoxy, halo, hydroxyl, $-C(O)OH$, hydroxyalkyl, alkoxyalkyl or acyl.

10. The compound of any one of claims 1-3, wherein the compound is of formula (IC):



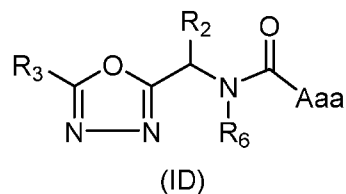
or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

R_3 represents aryl, heterocycloalkyl, heteroaryl or cycloalkyl, each optionally substituted with 1 to 4 occurrences of R_e ; and

R_2 , R_e , R_6 and R_a are same as defined in claim 1.

11. The compound of claim 10, wherein R_a is aryl, cycloalkyl, heterocycloalkyl or heteroaryl; each optionally substituted with with 1 to 4 substituents, each independently selected from alkyl, amido, amino, $-CONR_7R_8$, carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy.

12. The compound of any one of claims 1-3, wherein the compound is of formula (ID):



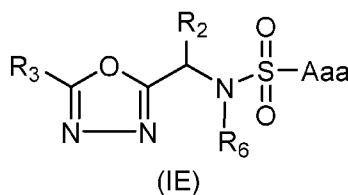
or a pharmaceutically acceptable salt or a stereoisomer thereof; wherein,

R_3 represents arylalkyl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl, -alkyl(COOH), $-(CH_2)_2-NH_2$, or a group represented by the general formula, $-CH(OR_b)(CH_2OR_b)$ or $-N(R_{11})_2$; and

Aaa, R_2 , R_6 , R_b and R_{11} are same as defined in claim 1.

13. The compound of claim 12, wherein R_3 represents -alkyl(COOH), $-(CH_2)_2-NH_2$, (heterocycloalkyl)alkyl-, $-N(R_{11})_2$; and R_{11} represents heteroalkyl.

14. The compound of any one of claims 1-3, wherein the compound is of formula (IE):



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

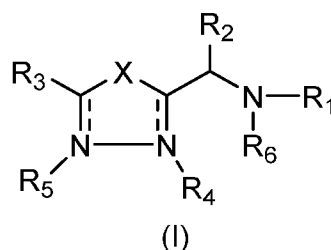
R_3 , Aaa, R_2 , and R_6 , are same as defined in claim 1.

15. The compound of claim 14, wherein R_3 represents arylalkyl-, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, -alkyl-(COOH), $-(CH_2)_2-NH_2$, or a group represented by the general formula, $-CH(OR_b)(CH_2OR_b)$ or $-N(R_{11})_2$; and R_b and R_{11} are same as defined in claim 1.

16. The compound of any one of claims 1 – 15, wherein R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl-; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl and (heterocycloalkyl)alkyl- are each optionally substituted with 1 to 4 substituents selected from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl, cycloalkyl, aryl, $-CONR_7R_8$, -aryl-COOH, heterocycloalkyl, heteroaryl, guanidino, amidino, -SH and -S(alkyl); optionally wherein two or three carbon atoms of the alkyl, alkenyl, or alkynyl form part of a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with 1 to 4 substituents, each independently selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl.

17. The compound of any one of claims 1 – 15, wherein R_2 is a side chain of an amino acid.

18. A compound of formula (I):



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

X is O or S;

each dotted line ---- represents an optional bond;

R₁ is -C(=W)R_a, -SO₂R_a, -SO₂-Aaa, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl or arylalkyl-; wherein the heterocycloalkyl-, heteroaryl, (heterocycloalkyl)alkyl-, (heteroaryl)alkyl-, cycloalkyl, (cycloalkyl)alkyl-, aryl and arylalkyl- are each optionally substituted with 1 to 4 substituents each independently selected from alkyl, alkoxy, amino, amido, carboxylic acid, carboxylate, thiocarboxylate, thioacid, -SH, -S(alkyl), aryl, heteroaryl, heterocycloalkyl, cycloalkyl and hydroxyl;

W is O or S;

R₂ is a side chain of an amino acid or is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl or (heterocycloalkyl)alkyl-; wherein the alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl-, (heteroaryl)alkyl-, heteroaryl, arylalkyl-, aryl, heterocycloalkyl and (heterocycloalkyl)alkyl- are each optionally substituted with 1 to 4 substituents selected from carboxylic acid, carboxylate, thiocarboxylate, thioacid, amido, amino, hydroxyl, cycloalkyl, aryl, -CONR₇R₈, -aryl-COOH, heterocycloalkyl, heteroaryl, guanidino, amidino, -SH and -S(alkyl); optionally wherein two or three carbon atoms of the alkyl, alkenyl, or alkynyl form part of a 3- to 7-membered carbocyclic or heterocyclic ring, optionally substituted with 1 to 4 substituents, each independently selected from alkyl, alkoxy, carboxylic acid, carboxylate and hydroxyl;

R₃ represents aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl-, (heteroaryl)alkyl-, -alkyl-COOH, -(CH₂)₂-NH₂, or a group represented by the formula -CH(OR_b)(CH₂OR_b), -C(R₇R₈)(NR₉R₁₀) or -N(R₁₁)₂;

wherein the aryl, heterocycloalkyl, heteroaryl, cycloalkyl, (heterocycloalkyl)alkyl-, arylalkyl and (heteroaryl)alkyl- is optionally substituted with 1 to 4 occurrences of R_e;

R₄ and R₅ independently are hydrogen or absent;

R₆ is hydrogen or alkyl; or R₆ and R_c taken together with the atoms to which they are attached form a 5- to 7-membered ring optionally substituted with one or more groups independently selected from hydroxyl, halo, amino, cyano and alkyl;

R₇, R₈ and R₁₁ each independently represent hydrogen, alkyl, heteroalkyl, alkoxy, aryl, heterocycloalkyl, heteroaryl or (heteroaryl)alkyl-, each optionally substituted with -alkyl-COOH, -aryl-alkoxy, hydroxy, halo, amino, cyano or alkyl; or

R₇ and R₈ taken together with the atoms to which they are attached form a 5- to 7-membered cycloalkyl ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

R₉ and R₁₀ independently is hydrogen, alkyl or acyl; or R₉ and R₁₀ taken together with the atoms to which they are attached form a 5- to 7-membered carbocyclic ring or heterocyclic ring which is optionally substituted with one or more substituents each independently selected from hydroxy, halo, amino, cyano and alkyl;

Aaa represents an amino acid residue;

R_a is -NR_cR_d, aminoalkyl-, aminoaryl-, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl; wherein the alkyl, aryl, cycloalkyl, heterocycloalkyl and heteroaryl are each optionally substituted with 1 to 4 substituents, each independently selected from alkyl, amido, amino, -CONR₇R₈, carboxylic acid, carboxylate, thioacid, thiocarboxylate, oxo, hydroxyl, halo, cyano, acyl, haloalkyl and alkoxy;

R_b and R_c each independently represent hydrogen, alkyl or alkoxyalkyl;

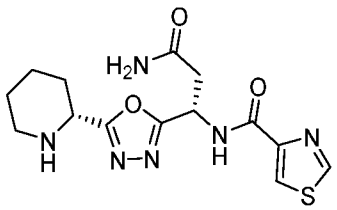
R_d represents hydrogen, alkyl, acyl, alkenyl, alkoxyalkyl, aryl, arylalkyl, heterocycloalkyl, heteroaryl, (heterocycloalkyl)alkyl- or (heteroaryl)alkyl-; wherein the said aryl, heterocycloalkyl, and heteroaryl are optionally substituted with one or more hydroxyl, cyano, alkyl or alkoxy;

R_e, at each occurrence, is alkyl, alkoxy, halo, hydroxyl, -C(O)OH, arylalkyl-, aryl, heteroarylalkyl-, heteroaryl, cycloalkyl, (cycloalkyl)alkyl-, hydroxyalkyl, alkoxyalkyl or acyl; wherein the alkyl, alkoxy, arylalkyl, aryl, heteroarylalkyl,

heteroaryl, cycloalkyl, (cycloalkyl)alkyl- and hydroxyalkyl are optionally substituted with halo, hydroxyl, amido, cyano or alkoxy; or

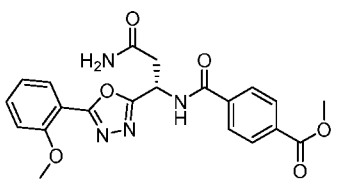
two R_e groups attached to same carbon atom together represent an oxo (=O) or thioxo (=S).

19. A compound having the structure:



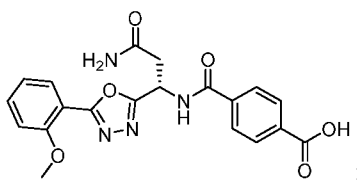
or a pharmaceutically acceptable salt or stereoisomer thereof.

20. A compound having the structure:



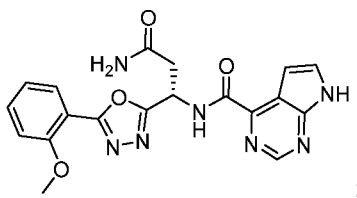
or a pharmaceutically acceptable salt or stereoisomer thereof.

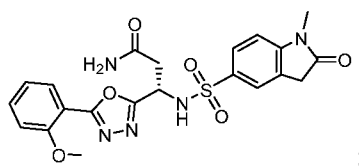
21. A compound having the structure:



or a pharmaceutically acceptable salt or stereoisomer thereof.

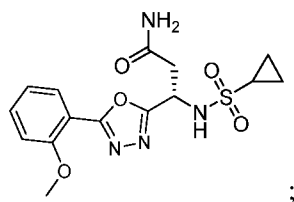
22. A compound having the structure:





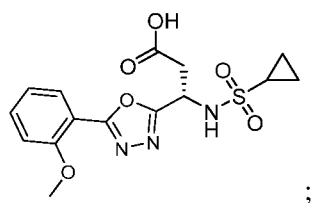
or a pharmaceutically acceptable salt or stereoisomer thereof.

28. A compound having the structure:



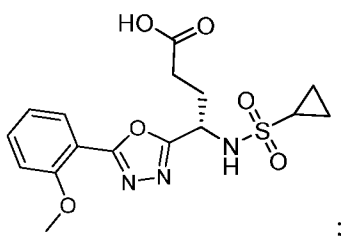
or a pharmaceutically acceptable salt or stereoisomer thereof.

29. A compound having the structure:



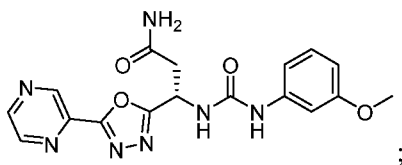
or a pharmaceutically acceptable salt or stereoisomer thereof.

30. A compound having the structure:



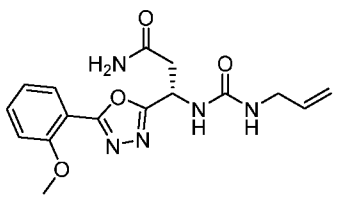
or a pharmaceutically acceptable salt or stereoisomer thereof.

31. A compound having the structure:



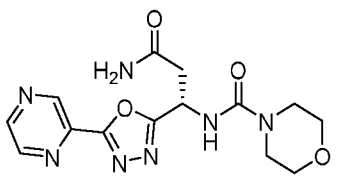
or a pharmaceutically acceptable salt or stereoisomer thereof.

32. A compound having the structure:



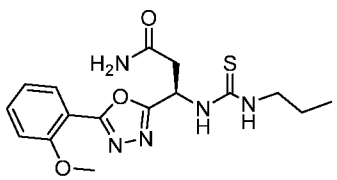
or a pharmaceutically acceptable salt or stereoisomer thereof.

33. A compound having the structure:



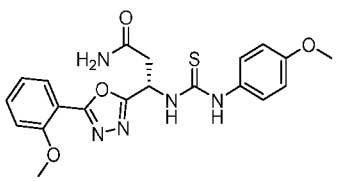
or a pharmaceutically acceptable salt or stereoisomer thereof.

34. A compound having the structure:



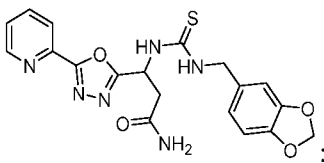
or a pharmaceutically acceptable salt or stereoisomer thereof.

35. A compound having the structure:



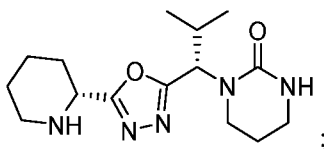
or a pharmaceutically acceptable salt or stereoisomer thereof.

36. A compound having the structure:



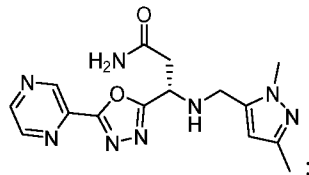
or a pharmaceutically acceptable salt or stereoisomer thereof.

37. A compound having the structure:



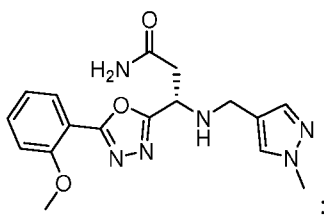
or a pharmaceutically acceptable salt or stereoisomer thereof.

38. A compound having the structure:



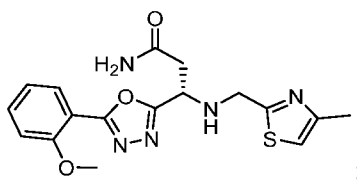
or a pharmaceutically acceptable salt or stereoisomer thereof.

39. A compound having the structure:



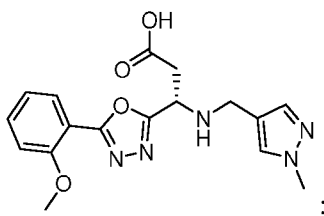
or a pharmaceutically acceptable salt or stereoisomer thereof.

40. A compound having the structure:



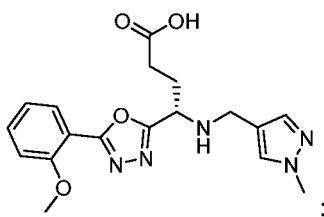
or a pharmaceutically acceptable salt or stereoisomer thereof.

41. A compound having the structure:



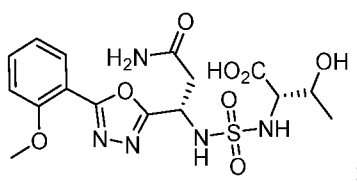
or a pharmaceutically acceptable salt or stereoisomer thereof.

42. A compound having the structure:



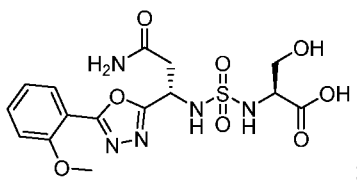
or a pharmaceutically acceptable salt or stereoisomer thereof.

43. A compound having the structure:



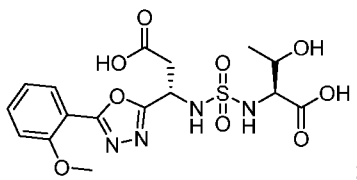
or a pharmaceutically acceptable salt or stereoisomer thereof.

44. A compound having the structure:



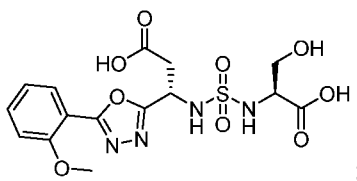
or a pharmaceutically acceptable salt or stereoisomer thereof.

45. A compound having the structure:



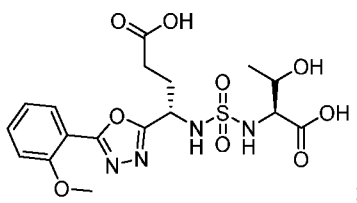
or a pharmaceutically acceptable salt or stereoisomer thereof.

46. A compound having the structure:



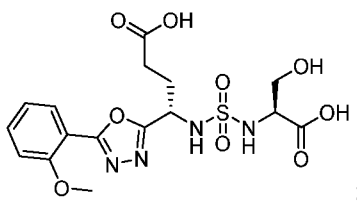
or a pharmaceutically acceptable salt or stereoisomer thereof.

47. A compound having the structure:



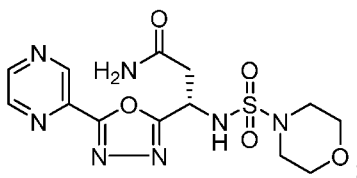
or a pharmaceutically acceptable salt or stereoisomer thereof.

48. A compound having the structure:



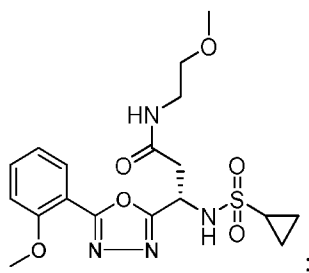
or a pharmaceutically acceptable salt or stereoisomer thereof.

49. A compound having the structure:



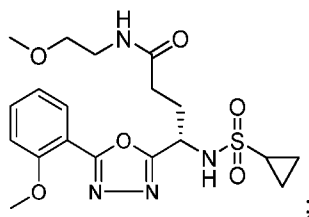
or a pharmaceutically acceptable salt or stereoisomer thereof.

50. A compound having the structure:



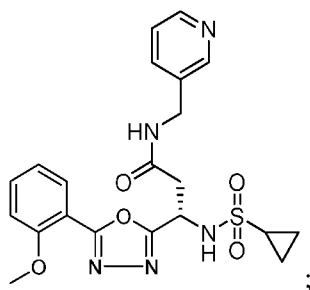
or a pharmaceutically acceptable salt or stereoisomer thereof.

51. A compound having the structure:



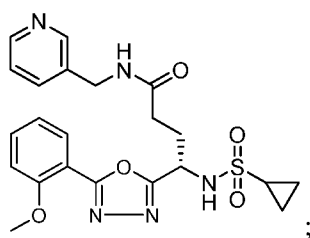
or a pharmaceutically acceptable salt or stereoisomer thereof.

52. A compound having the structure:



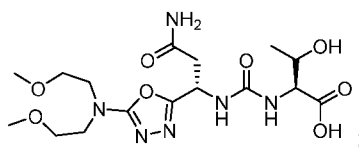
or a pharmaceutically acceptable salt or stereoisomer thereof.

53. A compound having the structure:



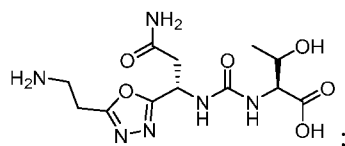
or a pharmaceutically acceptable salt or stereoisomer thereof.

54. A compound having the structure:



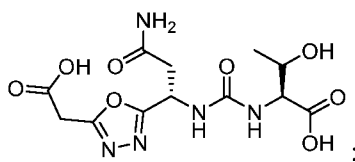
or a pharmaceutically acceptable salt or stereoisomer thereof.

55. A compound having the structure:



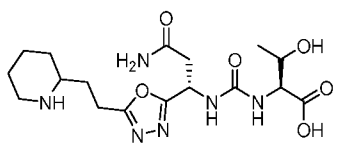
or a pharmaceutically acceptable salt or stereoisomer thereof.

56. A compound having the structure:



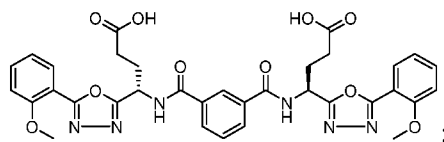
or a pharmaceutically acceptable salt or stereoisomer thereof.

57. A compound having the structure:



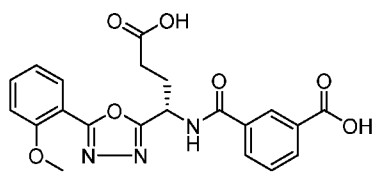
or a pharmaceutically acceptable salt or stereoisomer thereof.

58. A compound having the structure:



or a pharmaceutically acceptable salt or stereoisomer thereof.

59. A compound having the structure:



or a pharmaceutically acceptable salt or stereoisomer thereof.

60. A pharmaceutical composition comprising a compound of any one of claims 1-59, and a pharmaceutically acceptable carrier.

61. The pharmaceutical composition according to claim 60, further comprising at least one agent selected from an anticancer agent, a chemotherapy agent, and an antiproliferative compound.

62. A compound of any one of claims 1 to 59, for use as a medicament.
63. A method of treating cancer comprising administering to a subject in need thereof, the compound of formula (I) or a pharmaceutically acceptable salt or a stereoisomer thereof according to claim 1 to 59.
64. The method of claim 63, wherein the cancer is selected from 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.
65. The method of claim 63, wherein the cancer is selected from breast cancer, colon cancer, lung cancer, melanoma, prostate cancer, and renal cancer.
66. The method of any one of claims 63-65, wherein the subject is a mammal, e.g., a human.
67. The method of any one of claims 63-65, further comprising conjointly administering to the subject a second chemotherapeutic agent.

68. The method of any one of claims 63-65, further comprising conjointly administering to the subject one or more non-chemical cancer treatments, e.g., radiation therapy, surgery, thermoablation, focused ultrasound therapy or cryotherapy.

69. A method for 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 to 59.

70. A method for 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 to 59.

71. Use of a compound of any one of claims 1 - 59 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer.

72. The use of claim 71, wherein the cancer is selected from breast cancer, colon cancer, lung cancer, melanoma, prostate cancer, and renal cancer.

73. The use of claim 71, wherein the cancer is selected from bone cancer, cancer of the head or neck, pancreatic cancer, skin cancer, cutaneous or intraocular malignant melanoma, 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 tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, 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.

74. Use of a compound of any one of claims 1 - 59 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating an infectious disease.

75. The use of claim 74, wherein the infectious disease is a bacterial infectious disease, a viral infectious disease or a fungal infectious disease.

76. The use of claim 74, wherein the infectious disease is selected from 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*, *Naegleria fowleri*, *Acanthamoeba* sp., *Giardia lamblia*, *Cryptosporidium* sp., *Pneumocystis carinii*, *Plasmodium vivax*, *Babesia microti*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Leishmania donovani*, *Toxoplasma gondi*, or *Nippostrongylus brasiliensis*.

77. Use of a compound of any one of claims 1 - 59 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for modulating an immune response mediated by the PD-1 signaling pathway.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/055547

A. CLASSIFICATION OF SUBJECT MATTER
C07D291/00, C07D285/08, A61K31/4245, A61K31/433, A61P31/00, A61P35/00
Version=2017.01
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)

C07D, A61K, A61P

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, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/033301 A1, 12 March 2015 (12.03.2015), AURIGENE DISCOVERY TECHNOLOGIES LIMITED abstract, examples, and claims, pages 2-6	1-18 (in part), 60-62, 71-77
Y	examples, and claims, pages 2-6	19-59
X	SUSSAN K. ARDESTANI, FATEMAH POORRAJAB, SEPIDEH RAZMI, ALIREZA FOROUMADI, SOHEILA AJDARY, BEHNAZ GHAREGOZLOU ET AL.: "Cell death features induced in Leishmania major by 1, 3, 4-thiadiazole derivatives", EXPERIMENTAL PARASITOLOGY, vol.132, 14 August 2012 (14.08.2012), pages 116-122 Whole document	1 (in part), 18 (in part)
Y	Whole document	19-59



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

14-12-2017

Date of mailing of the international search report

14-12-2017

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/IB2017/055547

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.: 63-70
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 63-70 relates to a method for treatment of the human or animal body which does not require an international search by the International Searching Authority in accordance with PCT Article 17(2) (a) (i) and [Rule 39.1(iv)].
2. ☒ Claims Nos.: 1-18 (in part)
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:
The present claims 1-18 relates to an extremely large number of possible compounds. However, support and disclosure in the sense of Article 6 and 5 of PCT are found for only a very small proportion of the compounds. This covers few embodiments, examples 1-6.
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

International application No.

PCT/IB2017/055547

Continuation of Claims found unsearchable (Box II)

extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the claims (PCT Guidelines 9.19 and 9.23). The search of claims 1-18 was restricted to those claimed compounds which appear to be supported and a generalization of their structural formulae.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2017/055547

Citation	Pub.Date	Family	Pub.Date
WO 2015/033301 A1	12-03-2015	CA 2922655 A1	12-03-2015
		EP 3041828 A1	13-07-2016
		US 20160194295 A1	07-07-2016