

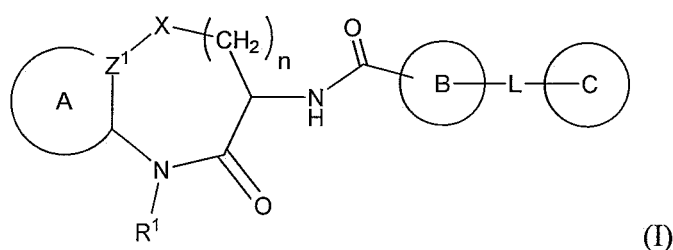
provided that if the A ring is 6 membered aryl or 6 membered heteroaryl, L is absent such that the B ring and the C ring are fused;

further provided that if the A ring is a 5 to 6 membered heteroaryl having 3 heteroatoms, two of said heteroatoms must be nitrogen;

- 5 further provided that if the A ring is unsubstituted 6 membered aryl and L is absent, the fused B and C rings are not unsubstituted indolyl or indolyl substituted by one or two halogen atoms; and

further provided that if the B ring is tetrazolyl, L is selected from the group consisting of CH₂, CH(CH₃), C(CH₃)₂, CF₂; and the C ring is phenyl.

- 10 In one aspect, the present disclosure relates to a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein

R¹ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl;

- the A ring is selected from the group consisting of cyclopropyl, 5 to 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:

- (a) 1 to 3 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;
- (b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or
- (c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

the B ring is tetrazolyl or a 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the B ring is optionally substituted with 1 to 2 substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and cyano; and wherein if a
5 nitrogen atom in the B ring is substituted, the substituent is not halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or cyano;

the C ring is selected from the group consisting of phenyl, 5 to 6 membered heteroaryl, 5 to 7 membered cycloalkyl, and 5 to 7 membered heterocyclyl; wherein the C ring is optionally substituted with:

10 (a) 1 to 4 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the C ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;

15 (b) 1 to 2 substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), and unsubstituted C₅-C₆ heteroaryl; or

(c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

20 L is selected from the group consisting of a bond, O, S, NH, NCH₃, (CH₂)_m, CH(CH₃), C(CH₃)₂, CF₂, CH₂O, CH₂S, CH(OH), CH₂NH, and CH₂N(CH₃), or L is absent such that the B ring and the C ring are fused;

X is selected from the group consisting of O, S, SO, SO₂, CH₂, C(CH₃)₂, CF₂ and CHCF₃;

Z¹ is selected from the group consisting of:

- 25 (i) C and N when the A ring is a 5 or 6 membered heteroaryl,
(ii) C when the A ring is a 5 or 6 membered aryl, and
(iii) CH when the A ring is cyclopropyl;

m is 1 or 4; and

n is 1 or 2;

30 provided that if the A ring is 6 membered aryl or 6 membered heteroaryl, L is absent such that the B ring and the C ring are fused;

further provided that if the A ring is a 5 to 6 membered heteroaryl having 3 heteroatoms, two of said heteroatoms must be nitrogen;

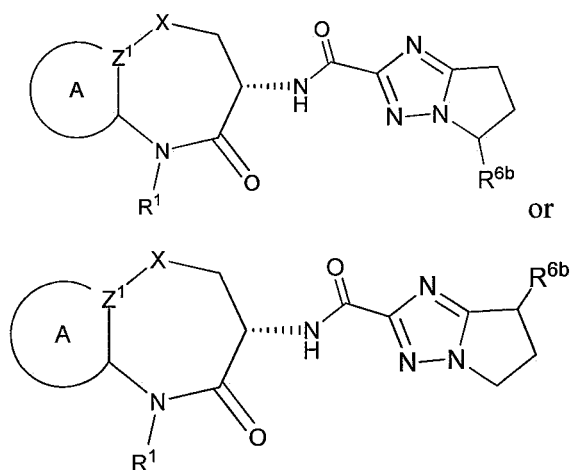
further provided that if the A ring is unsubstituted 6 membered aryl and L is absent, the fused B and C rings are not unsubstituted indolyl or indolyl substituted by one or two halogen atoms; and

further provided that if the B ring is tetrazolyl, L is selected from the group consisting of CH₂CH(CH₃), C(CH₃)₂, CF₂; and the C ring is phenyl.

In the following description, all references to formula I also include subembodiments of formula I (i.e., formulae 1a, 1b, etc.).

Also provided herein are pharmaceutical compositions comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients. Specific embodiments include pharmaceutical compositions suitable for intravenous or oral delivery.

In another aspect, the present disclosure relates to a compound according to the formula:



wherein

the A ring is selected from the group consisting of cyclopropyl, 5 to 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:

- (a) 1 to 3 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;

(b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or

(c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

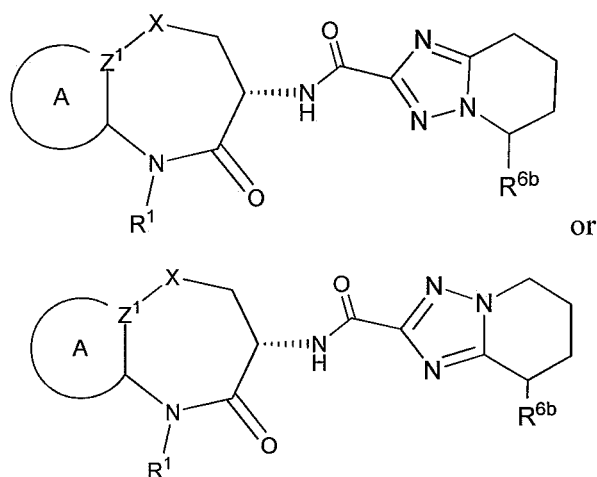
Z¹ is selected from the group consisting of:

- (i) C and N when the A ring is a 5 or 6 membered heteroaryl,
- (ii) C when the A ring is a 5 or 6 membered aryl, and
- (iii) CH when the A ring is cyclopropyl;

R¹ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl; and

R^{6b} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono- or di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl.

In another aspect, the present disclosure relates to a compound according to the formula:



wherein

the A ring is selected from the group consisting of cyclopropyl, 5 to 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:

(a) 1 to 3 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;

(b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or

(c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

Z¹ is selected from the group consisting of:

(i) C and N when the A ring is a 5 or 6 membered heteroaryl,

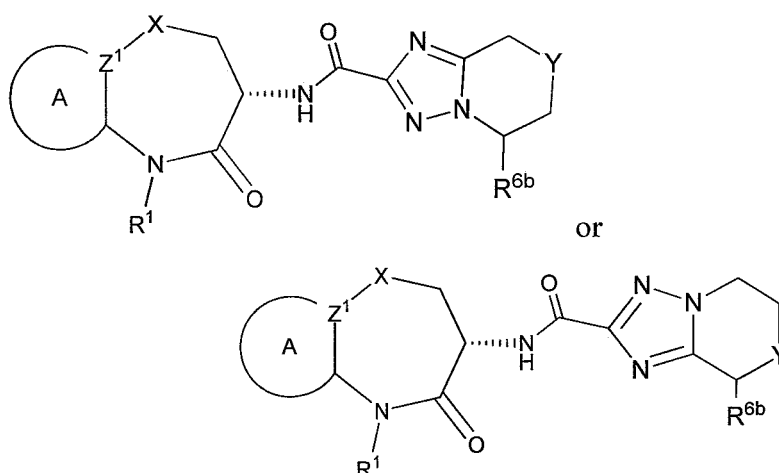
(ii) C when the A ring is a 5 or 6 membered aryl, and

(iii) CH when the A ring is cyclopropyl;

R¹ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl; and

R^{6b} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono- or di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl.

In another aspect, the present disclosure relates to a compound according to the formula:



wherein

the A ring is selected from the group consisting of cyclopropyl, 5 to 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:

(a) 1 to 3 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;

(b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or

(c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

Z¹ is selected from the group consisting of:

- (i) C and N when the A ring is a 5 or 6 membered heteroaryl,
- (ii) C when the A ring is a 5 or 6 membered aryl, and
- (iii) CH when the A ring is cyclopropyl;

R¹ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl;

Y is NH or O; and

R^{6b} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono- or di-fluorophenyl, benzyl, -CH₂-(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as defined herein or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

In another aspect, the present disclosure relates to the use of a compound as defined herein in the manufacture of a medicament for the treatment of a disease or disorder selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD).

In another aspect, the present disclosure relates to a compound as defined herein for the treatment of a disease or disorder selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD).

Also provided herein are oral formulations of a compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients suitable for oral delivery.

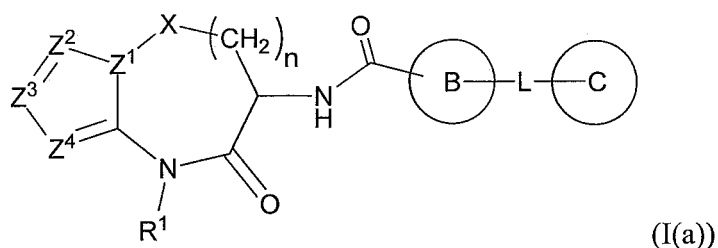
Also provided herein are parenteral formulations of a compound of formula I, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or excipients suitable for parenteral delivery.

In some embodiments, provided herein are uses of a compound of formula I, or a pharmaceutically acceptable salt thereof, for the treatment of diseases and disorders. In some embodiments, the diseases and disorders to be treated are selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia-reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD).

In some embodiments, the disease or disorder to be treated is selected from the group consisting of inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), psoriasis, retinal detachment, retinitis pigmentosa, macular degeneration, pancreatitis, atopic dermatitis, arthritis (including rheumatoid arthritis, osteoarthritis, spondylarthritis, gout, systemic onset juvenile idiopathic arthritis (SoJIA), psoriatic arthritis), systemic lupus

the B ring is tetrazolyl or a 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the B ring is optionally substituted with 1 to 2 substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₃-C₄ cycloalkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy and cyano; and wherein if a nitrogen atom in the B ring is substituted, the substituent is not halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, or cyano;

the C ring is selected from the group consisting of phenyl, 5 to 6 membered heteroaryl, 5 to 7 membered cycloalkyl, and 5 to 7 membered heterocyclyl; wherein the C ring is optionally substituted with:



or a pharmaceutically acceptable salt thereof, wherein

Z^2 , Z^3 , and Z^4 are each independently selected from the group consisting of CR^Z and NR^8 ;

each R^Z is independently selected from the group consisting of H, halogen, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, CH_2 (C_3 - C_6 cycloalkyl), C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 thioalkyl, CH_2 (C_4 - C_6 cycloalkoxy), CH_2 (C_4 - C_6 thiocycloalkyl), phenyl, benzyl, 4 to 6 memberd heterocyclyl; and 5 to 6 membered heteroaryl;

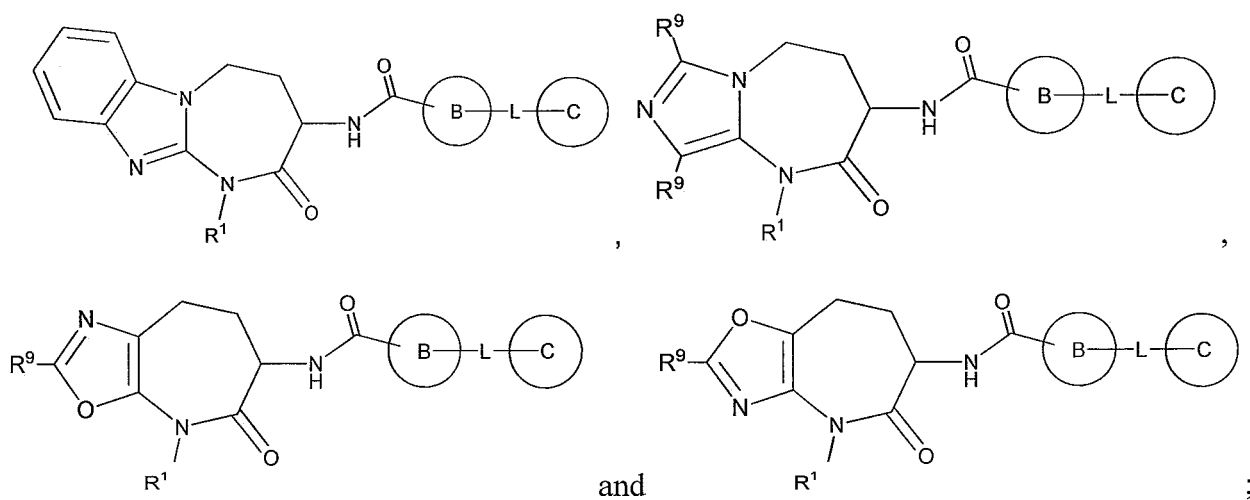
each R^8 is absent;

wherein Z^1 is N only if X is CH_2 , CF_2 , $CH(CH_3)$, $CH(CF_3)$, $C(CH_3)_2$, or $CH(OH)$;

wherein if Z^1 is N, at least one of Z^2 , Z^3 or Z^4 is CR^Z ;

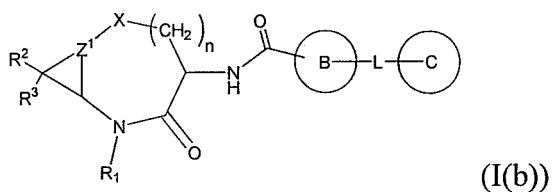
wherein, when Z^2 and Z^3 are each independently selected from CR^Z and NR^8 , Z^2 and Z^3 together with their respective R^Z and R^8 substituents may form a 6 membered aryl, 6 membered heteroaryl, 5 to 6 membered cycloalkyl or 5 to 6 membered heterocyclyl group;

wherein, when Z^3 and Z^4 are each independently selected from CR^Z and NR^8 , Z^3 and Z^4 together with their respective R^Z and R^8 substituents may form a 6 membered aryl, 6 membered heteroaryl, 5 to 6 membered cycloalkyl or 5 to 6 membered heterocyclyl group.



wherein each R⁹ is independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl substituted by 1 to 2 fluorine atoms, C₁-C₆ haloalkyl, (C₁-C₂ alkoxy)-C₁-C₂ alkyl, phenyl, benzyl, C₄-C₆ heterocyclyl, CH₂-(C₃-C₆ cycloalkyl), CH₂-(C₃-C₆ cycloalkyl substituted by 1 to 2 fluorine atoms), and CH₂-(C₄-C₆ heterocyclyl).

4. A compound according to claim 1 of formula I(b):

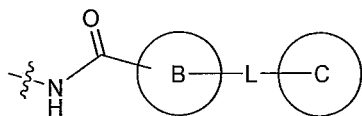


or a pharmaceutically acceptable salt thereof, wherein

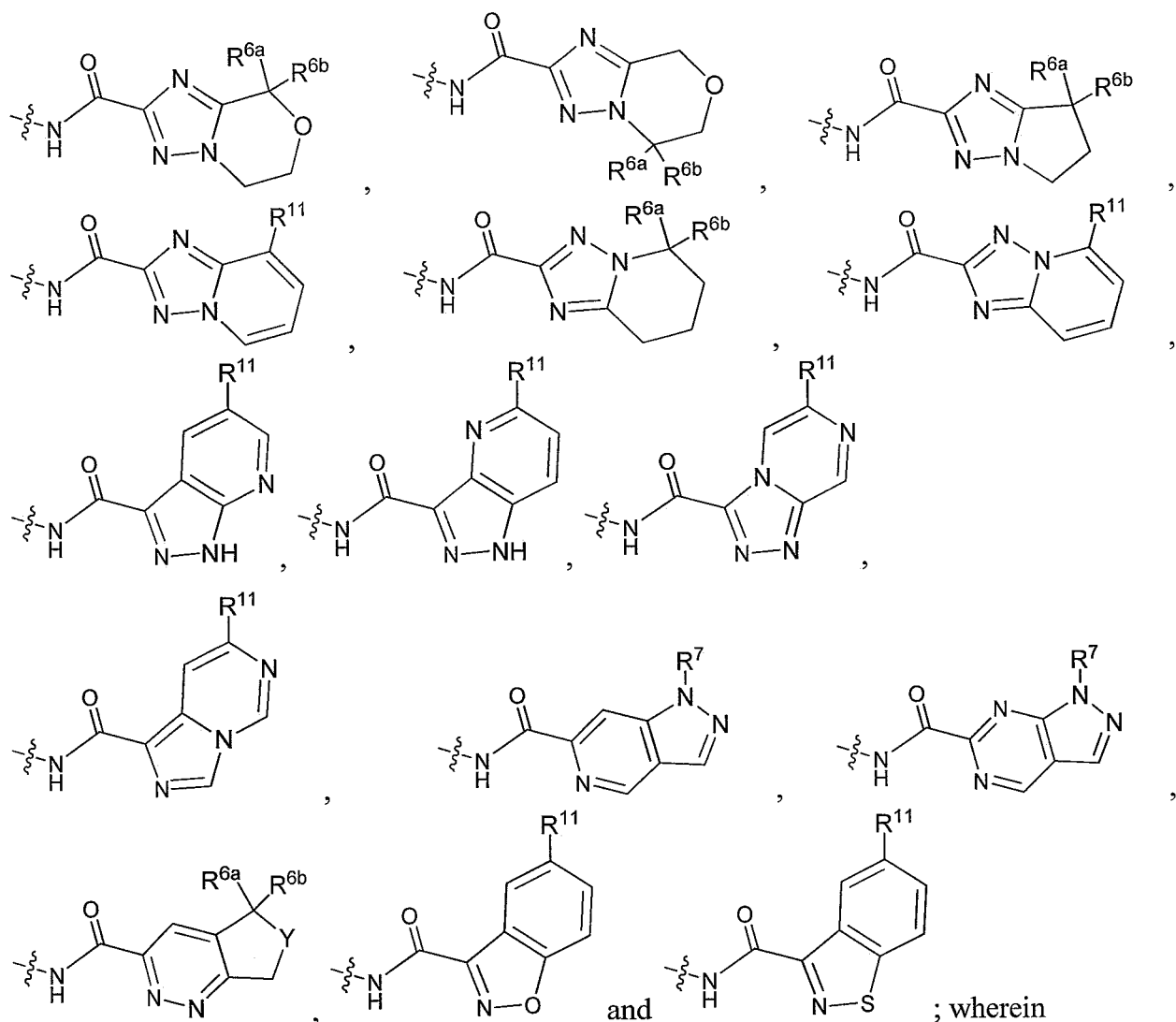
Z¹ is CH; and

R^2 and R^3 are each independently selected from the group consisting of H, halo, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, phenyl, benzyl, 5 to 6 membered heterocyclyl, 5 to 6 membered heteroaryl, $-CH_2(C_3$ - C_6 cycloalkyl), and $-CH_2(C_4$ - C_6 heterocyclyl); provided that when each of R^2 and R^3 are other than H, one must be C_1 - C_4 alkyl.

5. A compound according to any one of claims 1, wherein:



is selected from the group consisting of:



Y is selected from the group consisting of O, S, SO and SO₂;

X¹, X² and X³ are each independently N or CH, wherein 1 or 2 of X¹, X² and X³ is N;

X⁴ and X⁵ are each independently N or CH;

R^{5a} and R^{5b}, are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl); and 5 to 6 membered heteroaryl; wherein R^{5a} and R^{5b} together with the carbon to which they are attached may form a 4 membered cycloalkyl;

R^{6a} and R^{6b} are each independently selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl; wherein R^{6a} and R^{6b} together with the carbon to which they are attached may form a 4 membered cycloalkyl;

wherein when R^{5a} and R^{6a} are each H, R^{5b} and R^{6b} may together form a 4 membered cycloalkyl;

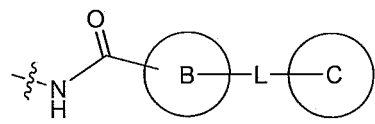
and wherein only two of R^{5a}, R^{5b}, R^{6a} and R^{6b} may be other than H in each instance;

R⁷ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl;

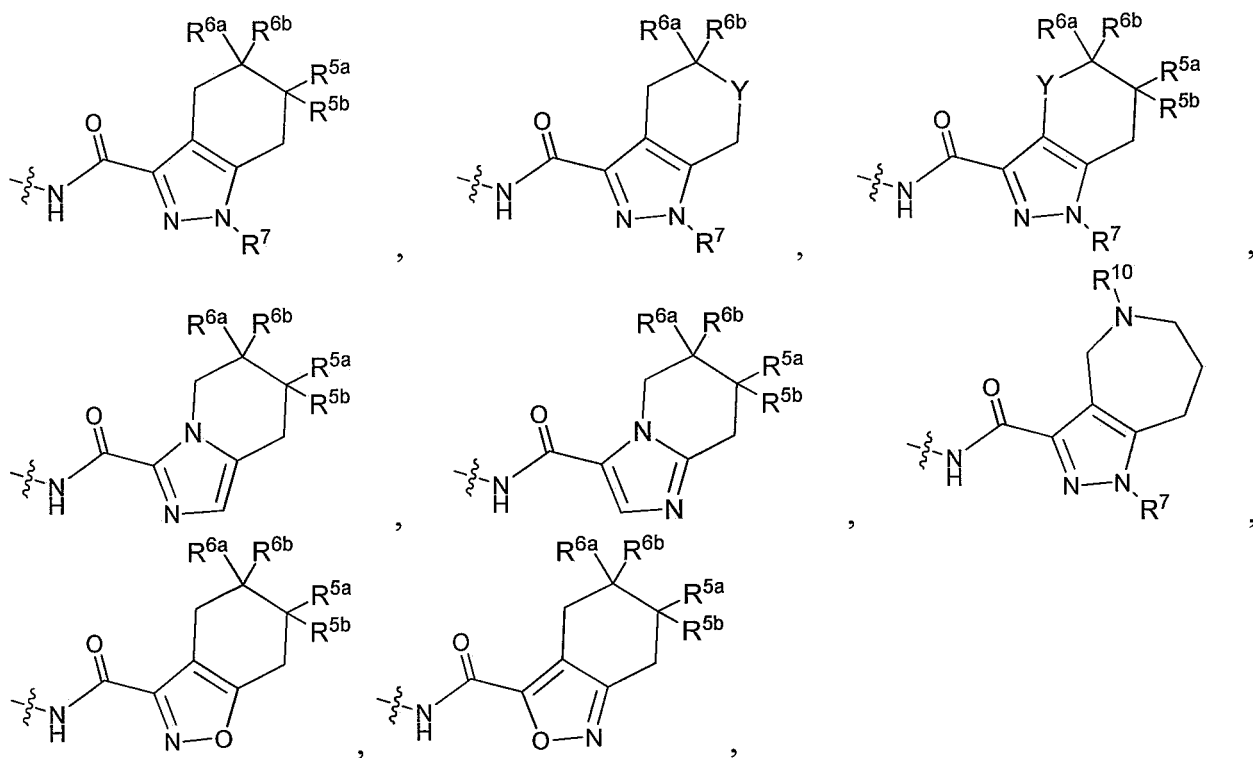
R¹⁰ is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, phenyl, and benzyl; and

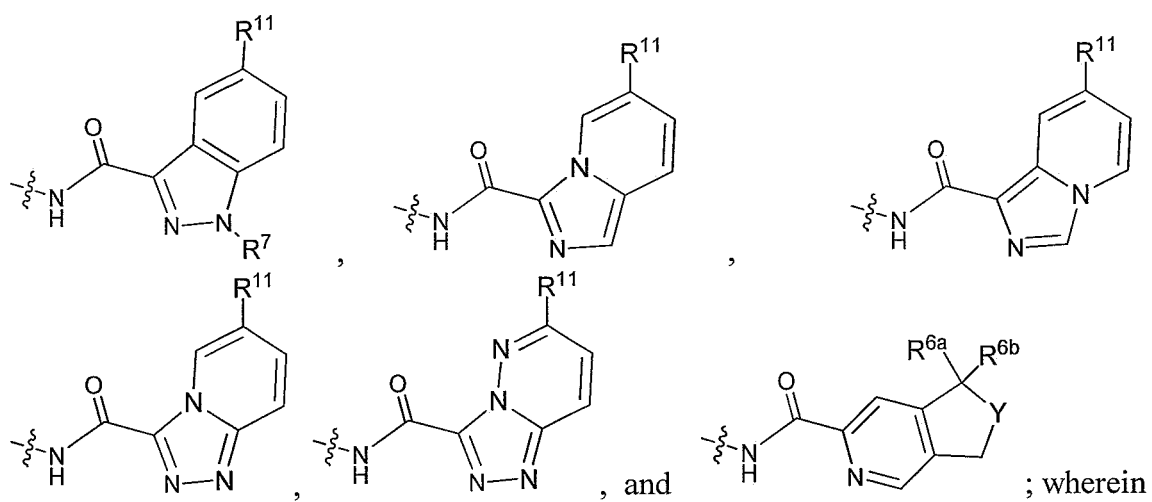
R¹¹ is selected from the group consisting of H, halogen, C₁-C₄ alkyl, and C₁-C₄ haloalkyl.

6. A compound according to claim 5, wherein:



is selected from the group consisting of:

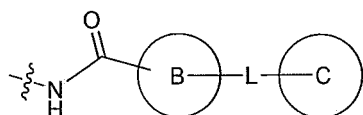




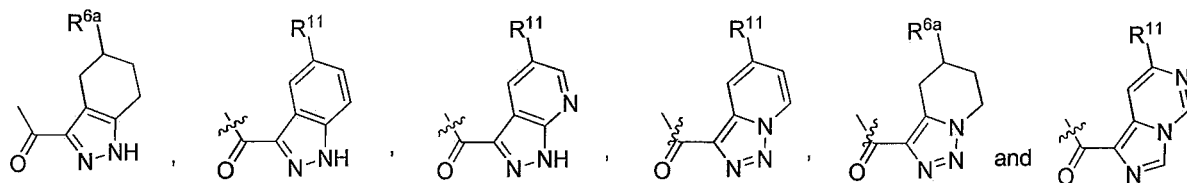
R^{5a} and R^{5b} are each H.

7. A compound according to claim 5, wherein Y is O.

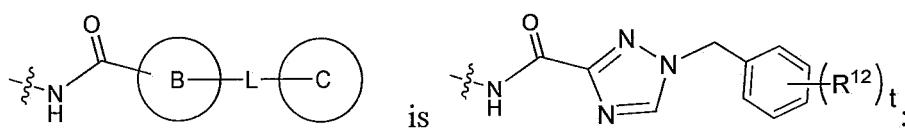
8. A compound according to claim 2, wherein



is selected from the group consisting of:



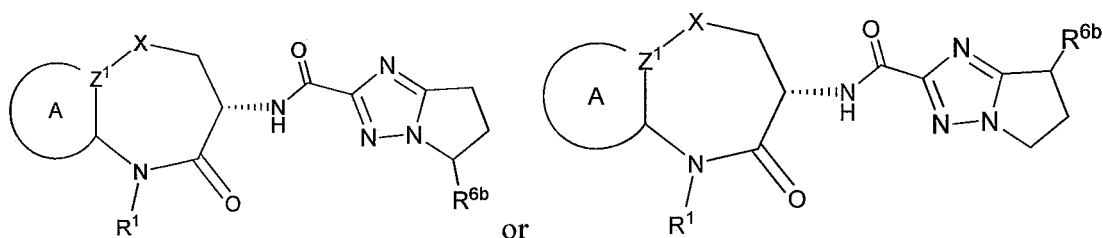
9. A compound according to claim 2, wherein



R^{12} is selected from the group consisting of halogen and methyl; and

t is 0, 1 or 2.

10. A compound according to the formula:



wherein

the A ring is selected from the group consisting of cyclopropyl, 5 to 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:

- (a) 1 to 3 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;
- (b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or
- (c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

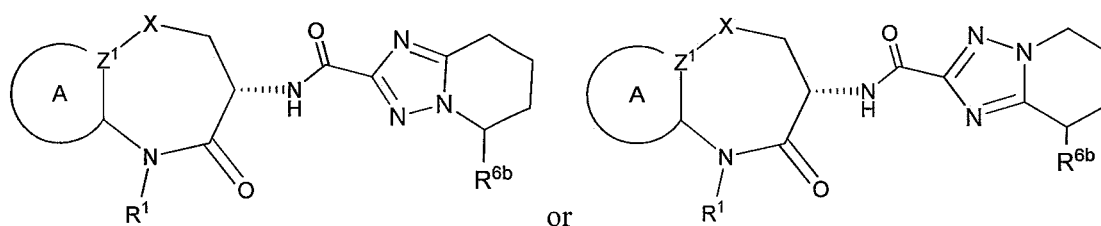
Z¹ is selected from the group consisting of:

- (i) C and N when the A ring is a 5 or 6 membered heteroaryl,
- (ii) C when the A ring is a 5 or 6 membered aryl, and
- (iii) CH when the A ring is cyclopropyl;

R¹ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl; and

R^{6b} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono- or di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl.

11. A compound according to the formula:



wherein

the A ring is selected from the group consisting of cyclopropyl, 5 to 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:

- (a) 1 to 3 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;
- (b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or
- (c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

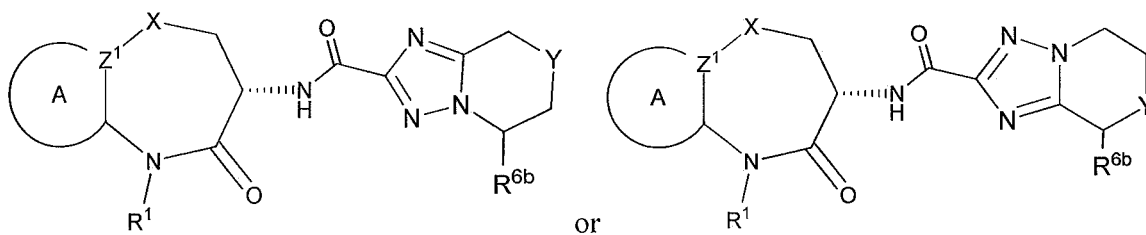
Z¹ is selected from the group consisting of:

- (i) C and N when the A ring is a 5 or 6 membered heteroaryl,
- (ii) C when the A ring is a 5 or 6 membered aryl, and
- (iii) CH when the A ring is cyclopropyl;

R¹ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl; and

R^{6b} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono- or di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl.

12. A compound according to the formula:



wherein

the A ring is selected from the group consisting of cyclopropyl, 5 to 6 membered aryl, and 5 to 6 membered heteroaryl having 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; wherein the A ring is optionally substituted with:

- (a) 1 to 3 substituents selected from the group consisting of halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, cyano, phenyl, benzyl, CH₂-(C₃-C₆ cycloalkyl), and CH₂CH₂-(C₃-C₆ cycloalkyl); wherein if a nitrogen atom in the A ring is substituted, the substituent is not halogen, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ thioalkyl, or cyano;
- (b) 1 substituent selected from the group consisting of C₄-C₆ heterocyclyl, C₅-C₆ heteroaryl, CH₂-(C₄-C₆ heterocyclyl), CH₂CH₂-(C₄-C₆ heterocyclyl), CH₂-(C₅-C₆ heteroaryl), CH₂CH₂-(C₅-C₆ heteroaryl); and optionally a second substituent selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy; or
- (c) two adjacent substituents which together form phenyl, C₅-C₆ heteroaryl, C₄-C₆ heterocyclyl or C₄-C₆ cycloalkyl;

Z¹ is selected from the group consisting of:

- (i) C and N when the A ring is a 5 or 6 membered heteroaryl,
- (ii) C when the A ring is a 5 or 6 membered aryl, and
- (iii) CH when the A ring is cyclopropyl;

R¹ is selected from the group consisting of H and unsubstituted C₁-C₄ alkyl;

Y is NH or O; and

R^{6b} is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, phenyl, mono- or di-fluorophenyl, benzyl, -CH₂(C₃-C₆ cycloalkyl), and 5 to 6 membered heteroaryl.

13. A compound according to claim 10, wherein R¹ is H or methyl; and the A ring is 6 membered aryl or 5 membered heteroaryl.

14. A compound according to claim 11, wherein R¹ is H or methyl; and the A ring is 6 membered aryl or 5 membered heteroaryl.

15. A compound according to claim 12, wherein R¹ is H or methyl; and the A ring is 6 membered aryl or 5 membered heteroaryl.

16. A compound according to claim 1, wherein the compound is selected from the group consisting of Table 1, Table 2, Table 3, Table 4 and Table 5.

17. A compound according to claim 16, wherein the compound selected from the group consisting of Table 1, Table 2, Table 3, Table 4 and Table 5 has a K_i in the RIP1 kinase inhibitory assay of less than or equal to 0.1 μM.

18. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier.

19. The use of a compound of claim 1 for the preparation of a medicament for the treatment of a disease or disorder selected from the group consisting of

irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia–reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD).

20. A compound of claim 1 for the treatment of a disease or disorder selected from the group consisting of irritable bowel disorders (IBD), irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, myocardial infarction, stroke, traumatic brain injury, atherosclerosis, ischemia–reperfusion injury of kidneys, liver and lungs, cisplatin-induced kidney injury, sepsis, systemic inflammatory response syndrome (SIRS), pancreatitis, psoriasis, retinitis pigmentosa, retinal degeneration, chronic kidney diseases, acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD).