

RIP1 INHIBITORY COMPOUNDS AND METHODS FOR MAKING AND USING THE SAME

This application claims the benefit of the earlier filing date of U.S. Provisional Application No. 62/666,452, filed on May 3, 2018, the entirety of which is incorporated herein by reference.

FIELD

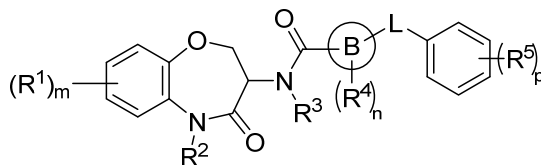
The present disclosure concerns compounds and methods of making and using the compounds, such as for inhibiting receptor-interacting protein-1 kinase (“RIP1”), and for treating diseases and/or conditions related to RIP1.

BACKGROUND

Receptor-interacting protein-1 kinase (referred to herein as“RIP1”) belongs to the tyrosine kinase-like family and is a serine/threonine protein kinase involved in innate immune signaling. RIP1 plays a central role in regulating cell signaling and its role in programmed cell death has been linked to various inflammatory diseases, such as inflammatory bowel disease, psoriasis, and other diseases and/or conditions associated with inflammation and/or necroptotic cell death.

SUMMARY

In one aspect of the present disclosure, there is provided a compound, having a formula



or a pharmaceutically acceptable salt thereof, wherein:

ring B is substituted or non-substituted 5-membered heteroaryl;

L is a substituted or non-substituted C₁₋₁₀aliphatic linker;

R^1 is R^a or R^b wherein at least one R^1 is R^b :

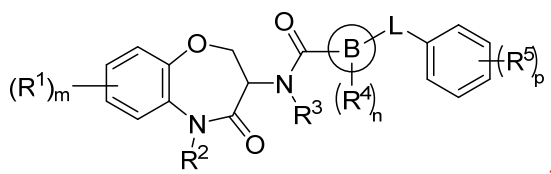
each of $\mathbb{R}^2$ and $\mathbb{R}^3$ independently are $\mathbb{R}^a$:

each R⁴ and each R⁵ independently are halogen, R^a or R^b:

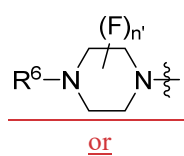
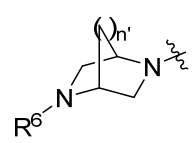
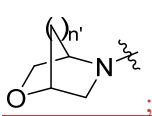
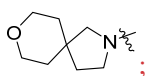
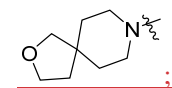
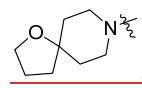
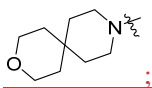
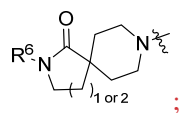
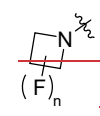
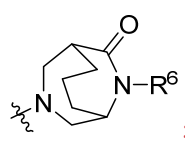
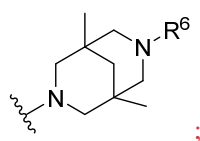
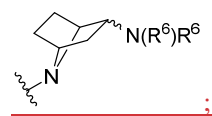
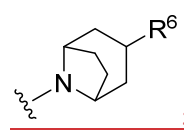
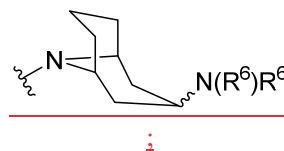
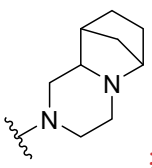
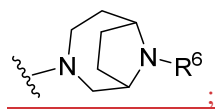
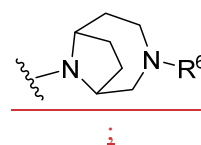
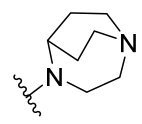
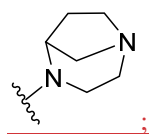
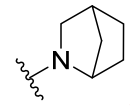
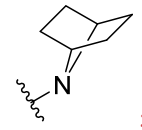
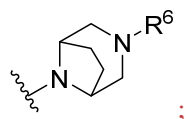
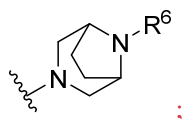
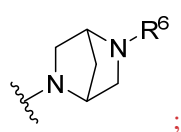
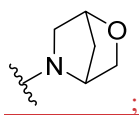
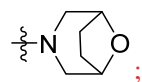
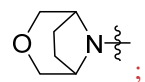
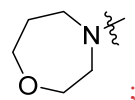
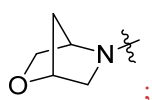
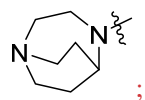
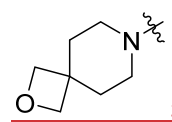
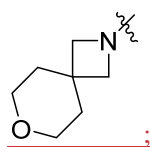
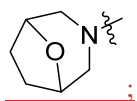
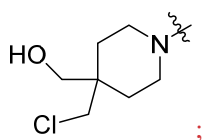
R^a is independently for each occurrence H, D, substituted or non-substituted C₁₋₁₀aliphatic, or substituted or non-substituted C₁₋₁₀cycloaliphatic;

R^b is independently for each occurrence -NR^dR^d wherein two R^d groups together with the nitrogen bound thereto provide a non-aromatic C₃₋₁₀heterocyclic group that is non-substituted or substituted with one or more R^c groups and/or one or more R^g groups, wherein R^c is independently for each occurrence -OR^a, N(R^a)₂, substituted or non-substituted C₁₋₆alkyl, substituted or non-substituted C₁₋₆haloalkyl, substituted or non-substituted C₁₋₆heteroalkyl, substituted or non-substituted C₃₋₆cycloalkyl, or two R^c groups join together to provide a substituted or non-substituted C₃₋₁₀heterocyclic group with the

p is 0, 1, 2, 3, 4, or 5.



each R^1 independently for each occurrence is



or



wherein each n' independently is an integer ranging from 0 to 4; and each R^6 independently is selected from hydrogen, substituted or non-substituted aliphatic, substituted or non-substituted aromatic, or substituted or non-substituted heteroaliphatic.

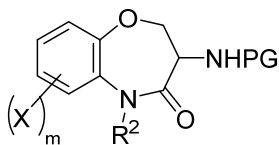
In a further aspect of the present disclosure, there is provided a method for making a compound disclosed herein, comprising:

coupling a starting material having a Formula A with an R^1 -containing reagent having a formula R^1 -H, by combining the starting material and the R^1 -containing reagent with a transition metal catalyst, a ligand component, and a solvent to form an R^1 -functionalized product;

deprotecting an amine group of the R^1 -functionalized product to provide an amine compound;
and

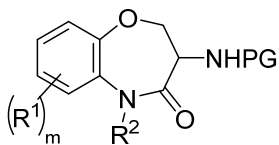
forming an amide bond between the amine compound and an acid-containing coupling partner;

wherein Formula A is



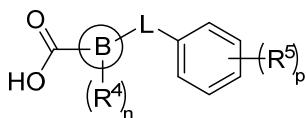
Formula A:

the R^1 -functionalized product has a structure satisfying Formula B



Formula B:

and the acid-containing coupling partner has a structure satisfying Formula C



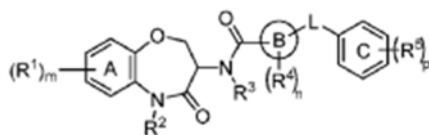
Formula C; and wherein

X is a halogen or a triflate;

PG is an amine protecting group;

and each of ring B, L, R^1 , R^2 , R^4 , R^5 , m, n, and p are as recited for claim 1.

Also disclosed herein are compound ~~embodiments~~ examples having a Formula I



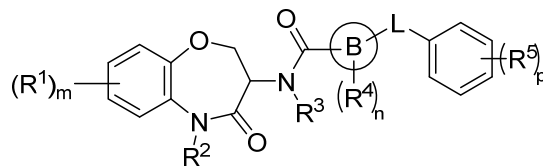
Formula I,

or a pharmaceutically acceptable salt thereof. A person of ordinary skill in the art will appreciate that compounds within the scope of Formula I also include stereoisomers, N-oxides, tautomers, hydrates, solvates, isotopes, and/or prodrugs thereof.

With reference to Formula I, ring B is 5-membered heteroaryl; L is a C₁₋₁₀aliphatic linker; R¹ is R^a or R^b wherein at least one R¹ is R^b; each of R² and R³ independently are R^a; each R⁴ and each R⁵ independently are R^a or R^b; R^a is independently for each occurrence H, D, C1-10aliphatic, or C1-10cycloaliphatic; R^b is independently for each occurrence halogen or -NR^dR^d wherein (i) each R^d independently is R^a or R^c; or (ii) two R^d groups together with the nitrogen bound thereto provide a C3-10heterocyclic group; R^c is independently for each occurrence -OR^a, -NR^a, C1-6alkyl, C1-6haloalkyl, C1-6heteroalkyl, C3-6cycloalkyl, or two R^c groups join together to provide a C₃₋₁₀heterocyclic group with the R^b group to which the two R^c

We claim:

1. A compound, having a formula



or a pharmaceutically acceptable salt thereof, wherein:

ring B is substituted or non-substituted 5-membered heteroaryl;

L is a substituted or non-substituted C₁₋₁₀ aliphatic linker;

R¹ is R^a or R^b wherein at least one R¹ is R^b;

each of R² and R³ independently are R^a;

each R⁴ and each R⁵ independently are halogen, R^a or R^b;

R^a is independently for each occurrence H, D, substituted or non-substituted C₁₋₁₀ aliphatic, or substituted or non-substituted C₁₋₁₀ cycloaliphatic;

R^b is independently for each occurrence ~~halogen or~~ -NR^dR^d wherein ~~(i) each R^d independently is R^a or R^b; or (ii)~~ two R^d groups together with the nitrogen bound thereto provide a non-aromatic C₃₋₁₀ heterocyclic group;

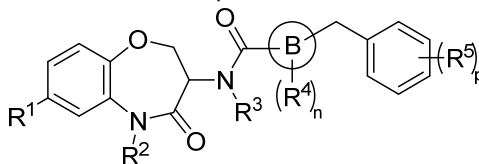
that is non-substituted or substituted with one or more R^e groups and/or one or more R^g groups, wherein R^e is independently for each occurrence -OR^a, -N(R^a)₂, substituted or non-substituted C₁₋₆ alkyl, substituted or non-substituted C₁₋₆ haloalkyl, substituted or non-substituted C₁₋₆ heteroalkyl, substituted or non-substituted C₃₋₆ cycloalkyl, or two R^e groups join together to provide a substituted or non-substituted C₃₋₁₀ heterocyclic group with the R^b group to which the two R^e groups are bound; and R^g is halogen, substituted or non-substituted C₁₋₁₀ aliphatic-C₅₋₁₀ aromatic, or =O;

m is 1 to 4;

n is 0, 1 or 2; and

p is 0, 1, 2, 3, 4, or 5.

2. The compound of claim 1, wherein the compound has a structure satisfying a formula

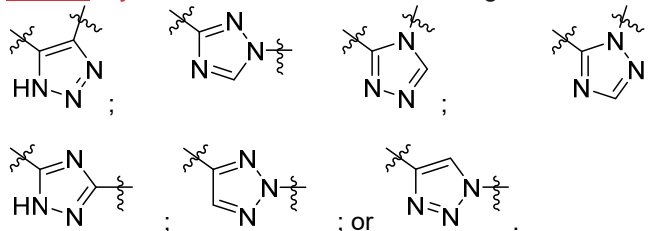


3. The compound of claim 1 ~~or claim 2~~, wherein ring B has a structure satisfying a

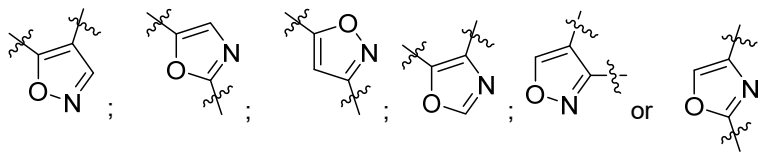


formula W_3 , wherein at least one W is nitrogen, and each remaining W independently is selected from carbon, CH, oxygen, sulfur, nitrogen, or NH.

4. The compound of claim 1 ~~any one of claims 1-3~~, wherein ring B is a triazole selected from



or an oxazole selected from



5. The compound of claim 1 ~~any one of claims 1-4~~, wherein R^5 is R^a , wherein R^a is substituted or non-substituted C_{1-4} aliphatic, or R^5 is ~~R^b , wherein R^b is~~ halogen; and/or wherein R^2 is R^a wherein R^a is substituted or non-substituted C_{1-4} aliphatic and R^3 is R^a , wherein R^a is hydrogen.

6. The compound of claim 1 ~~any one of claims 1-5~~, wherein R^1 is R^b wherein R^b is $-NR^dR^d$ wherein two R^d groups together with the nitrogen bound thereto provide a substituted or non-substituted non-aromatic C_{3-10} heterocyclic group comprising two R^e groups that join together to provide a second substituted or non-substituted C_{3-10} heterocyclic group.

7. The compound of claim 6, wherein the second substituted or non-substituted C_{3-10} heterocyclic group formed by the two R^e groups and the substituted or non-substituted non-aromatic C_{3-10} heterocyclic formed by the two R^d groups of R^b provide a substituted or non-substituted spirocyclic group or a substituted or non-substituted bicyclic group.

8. The compound of ~~claim 6 or~~ claim 7, wherein the substituted or non-substituted spirocyclic group comprises at least two rings, wherein a first ring and a second ring of the spirocyclic group have a different number of carbon atoms, a different number of heteroatoms, or both and wherein each ring of the spirocyclic group comprises a heteroatom in the ring.

9. The compound of claim 8 ~~any one of claims 6-8~~, wherein the substituted or non-substituted spirocyclic group comprises at least one oxygen atom and at least one nitrogen atom.

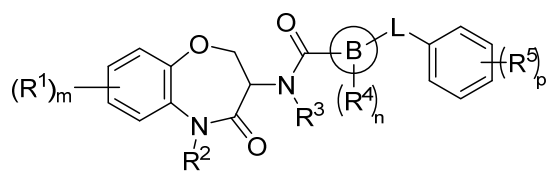
10. The compound of claim 7 ~~any one of claims 6-9~~, wherein the substituted or non-substituted spirocyclic group comprises a first ring and a second ring, wherein the first ring is coupled to a carbon atom of the compound and has, the first ring having from 3 to 7 atoms, and wherein the a second ring ~~having from~~ has 3 to 7 atoms.

11. The compound of claim 7 ~~any one of claims 6-10~~, wherein the substituted or non-substituted spirocyclic group comprises greater than 7 total atoms in the substituted or non-substituted spirocyclic ~~system~~ group.

12. The compound of ~~claim 7~~any one of claims 6-11, wherein the substituted or non-substituted C₃₋₁₀ heterocyclic formed by the two R^e groups and the substituted or non-substituted non-aromatic C₃₋₁₀ heterocyclic formed by the two R^d groups of R^b provide a substituted or non-substituted bicyclic group and the bicyclic group comprising ~~ing~~es two or more heteroatoms in the substituted or non-substituted bicyclic group.

13. The compound of claim 12, wherein the substituted or non-substituted bicyclic group is a fused substituted or non-substituted bicyclic group or a bridged substituted or non-substituted bicyclic group and wherein the substituted or non-substituted bicyclic group is attached to the compound ring A ~~phenyl group of Formula I~~ through a nitrogen atom of the substituted or non-substituted bicyclic group.

14. A compound, having a formula



or a pharmaceutically acceptable salt thereof, wherein:

ring B is substituted or non-substituted 5-membered heteroaryl;

L is a substituted or non-substituted C₁₋₁₀aliphatic linker;

each of R² and R³ independently are R^a;

each R⁴ and each R⁵ independently are halogen, R^a, or R^b;

R^a is independently for each occurrence H, D, substituted or non-substituted C₁₋₁₀aliphatic, or substituted or non-substituted C₁₋₁₀cycloaliphatic;

R^b is independently for each occurrence -NR^dR^d wherein (i) each R^d independently is R^a or R^e; or (ii) two R^d groups together with the nitrogen bound thereto provide a substituted or non-substituted C₃₋₁₀heterocyclic group;

R^e is independently for each occurrence -OR^a, -N(R^a)₂, substituted or non-substituted C₁₋₆alkyl, substituted or non-substituted C₁₋₆haloalkyl, substituted or non-substituted C₁₋₆heteroalkyl, substituted or non-substituted C₃₋₆cycloalkyl, or two R^e groups join together to provide a substituted or non-substituted C₃₋₁₀heterocyclic group with the R^b group to which the two R^e groups are bound;

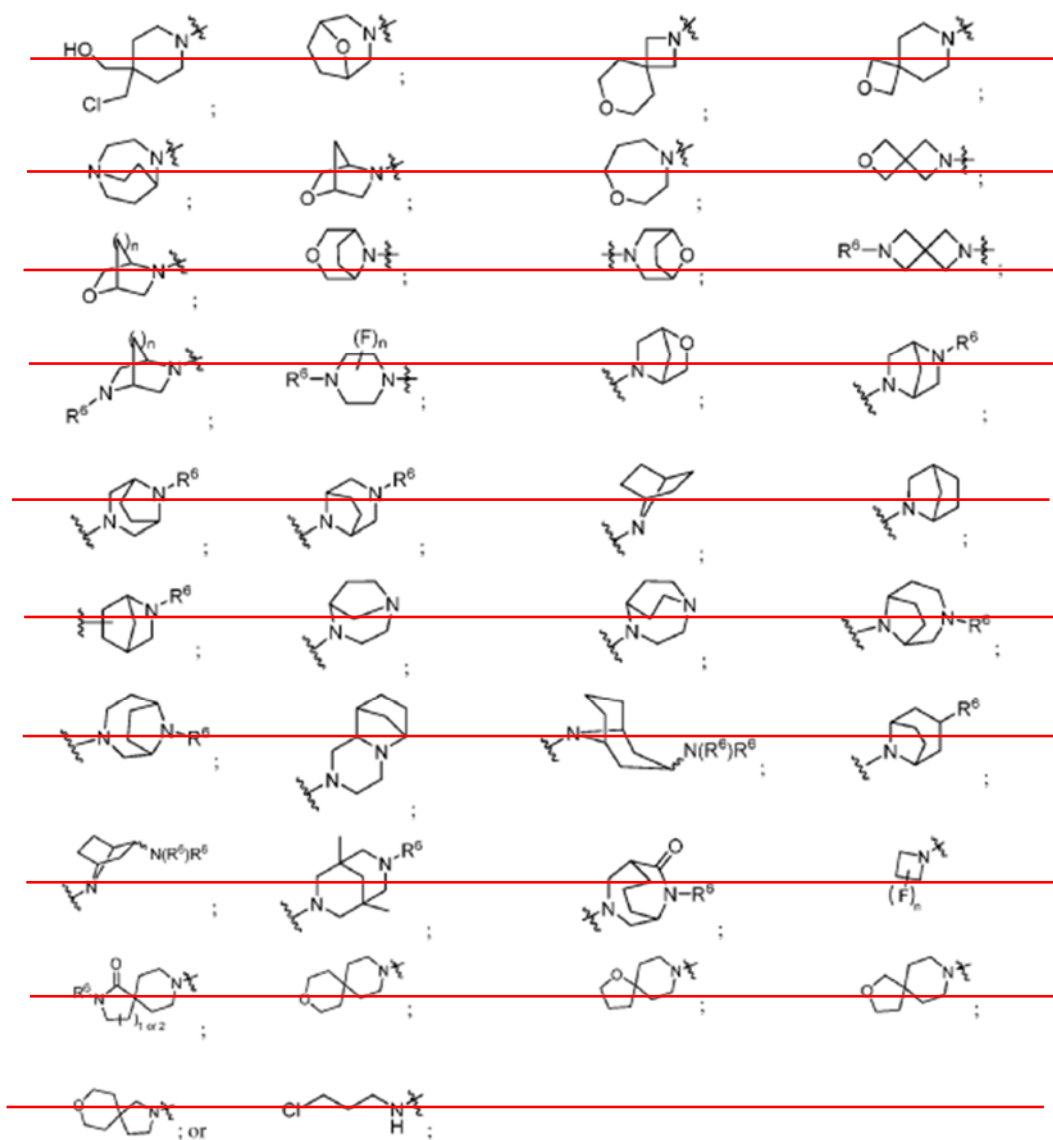
m is 1 to 4;

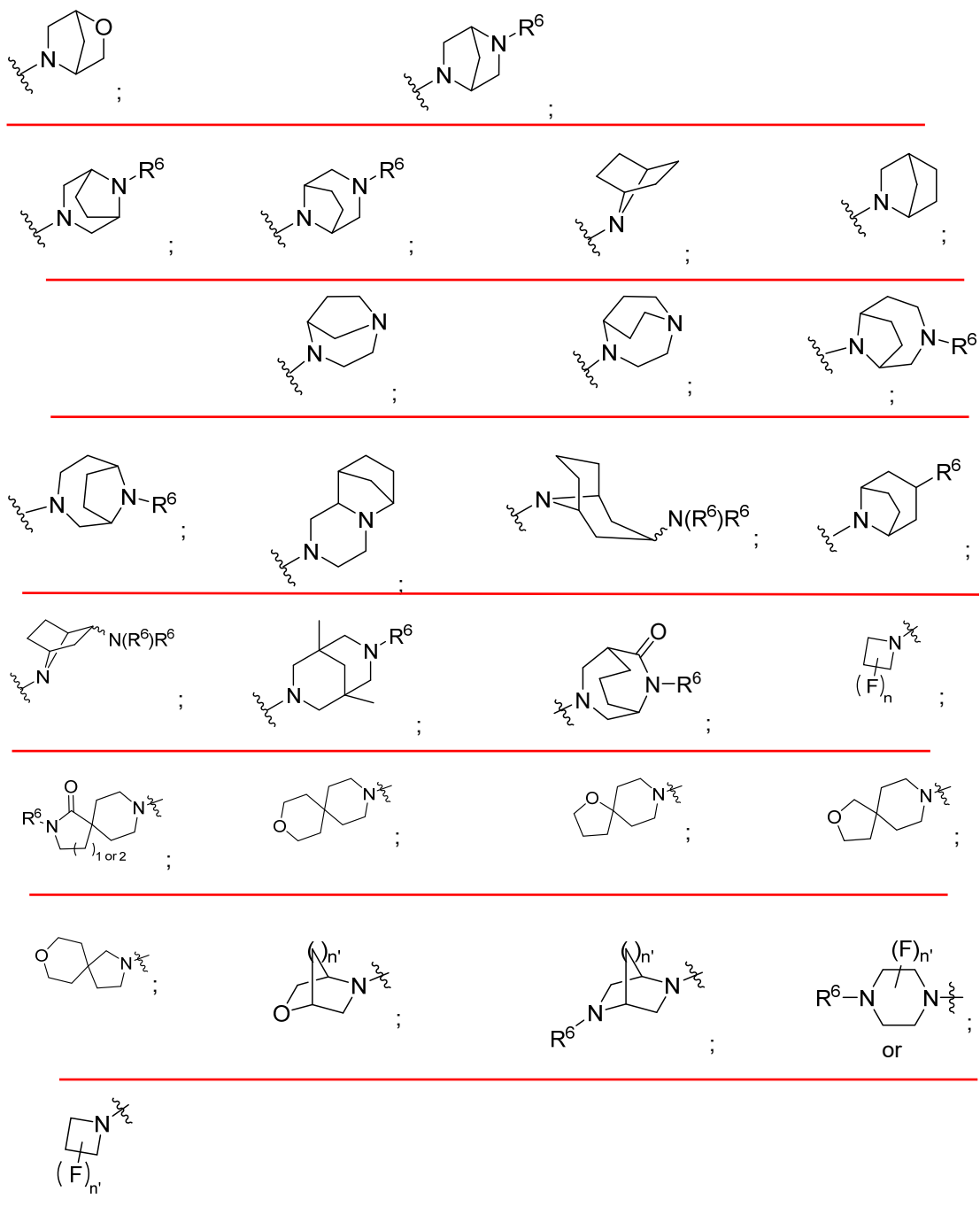
n is 0, 1 or 2;

p is 0, 1, 2, 3, 4, or 5; and

each R¹ independently for each occurrence is

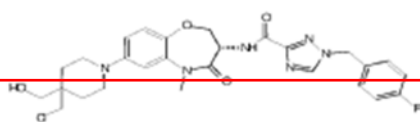
~~The compound of any one of claims 1-13, wherein R¹ is~~



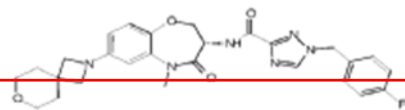


wherein each n' independently is an integer ranging from 0 to 4; and each R^6 independently is selected from hydrogen, substituted or non-substituted aliphatic, substituted or non-substituted aromatic, or substituted or non-substituted heteroaliphatic.

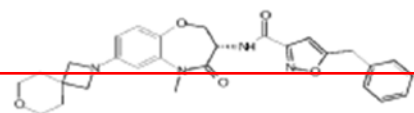
15. The compound of claim 14~~any one of claims 1-14~~, wherein the compound is selected from



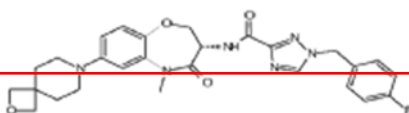
I-1;



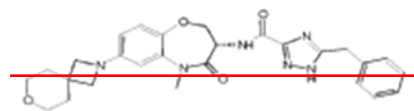
I-2;



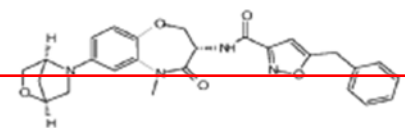
I-3;



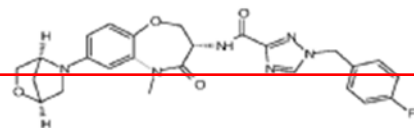
I-4;



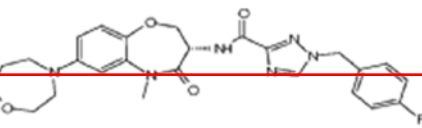
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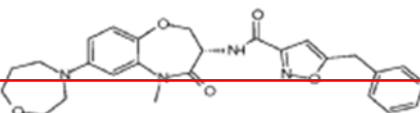
I-6;



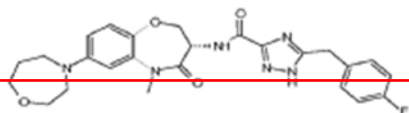
I-7;



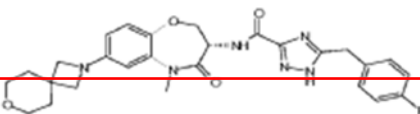
I-8;



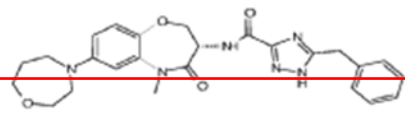
I-9;



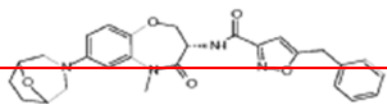
I-10;



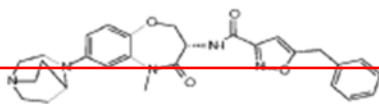
I-11;



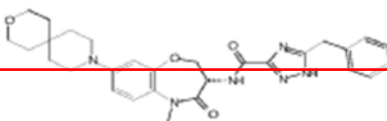
I-12;



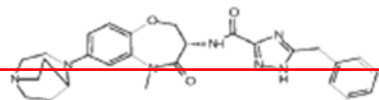
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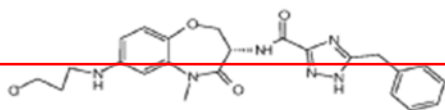
I-14;



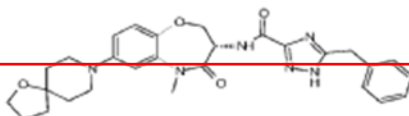
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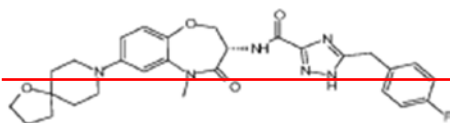
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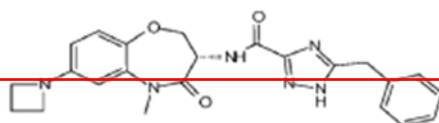
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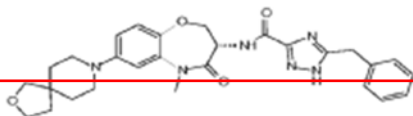
I-18;



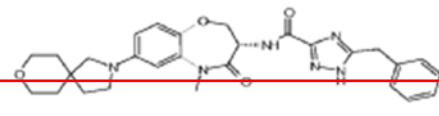
I-19;



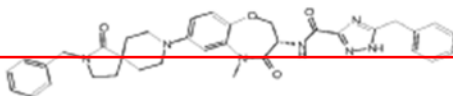
I-20;



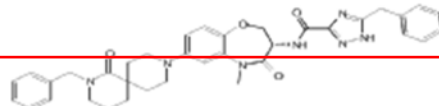
I-21;



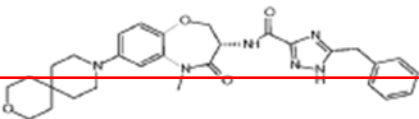
I-22;



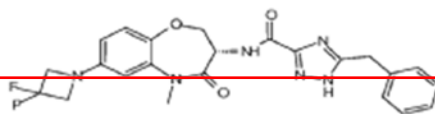
I-23;



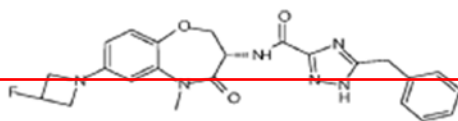
I-24;



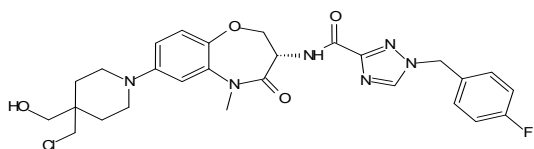
I-25;



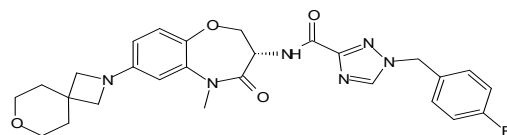
I-26; or



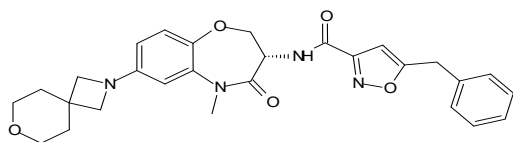
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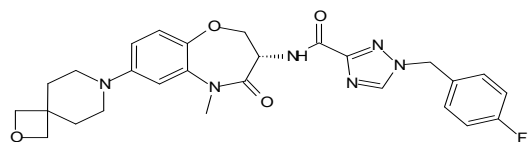
I-1;



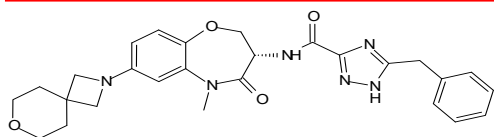
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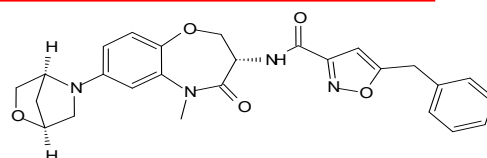
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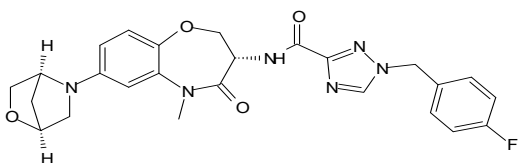
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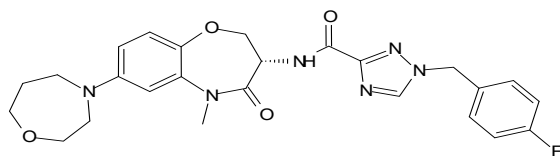
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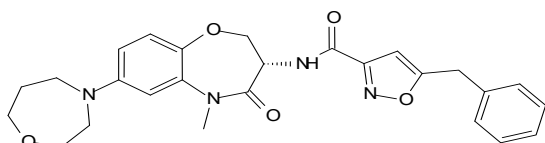
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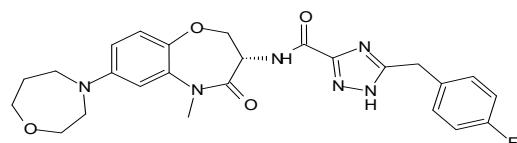
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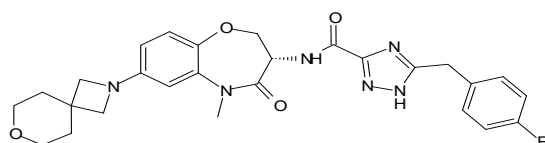
I-8;



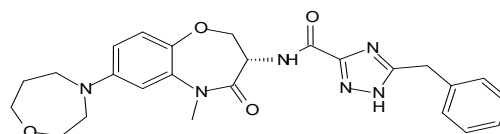
I-9;



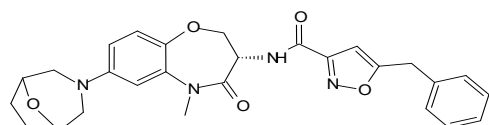
I-10;



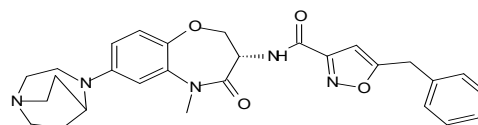
I-11;



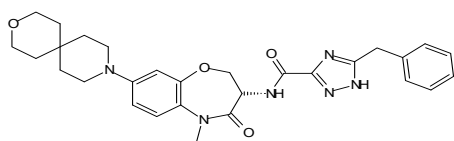
I-12;



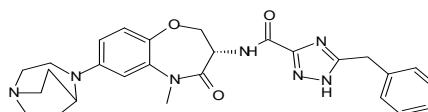
I-13;



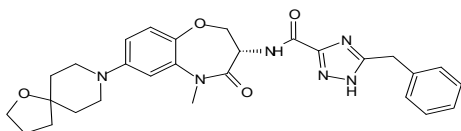
I-14;



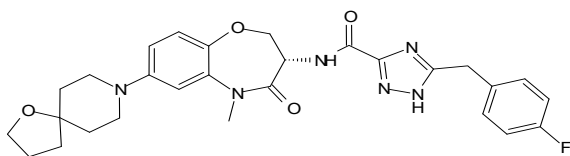
I-15;



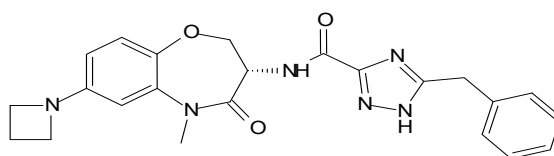
I-16;



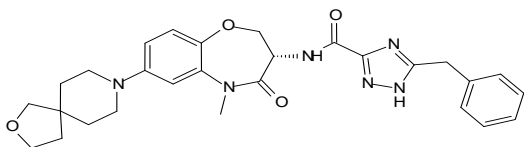
I-18;



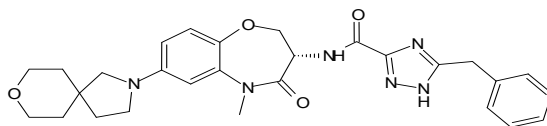
I-19;



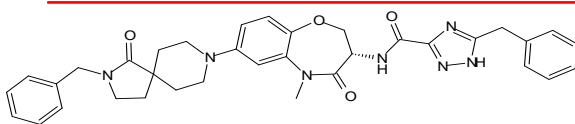
I-20;



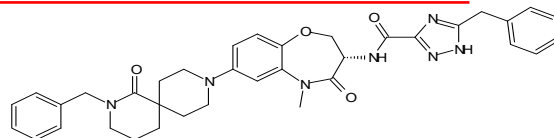
I-21;



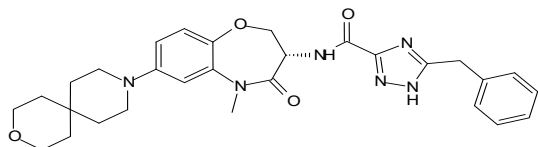
I-22;



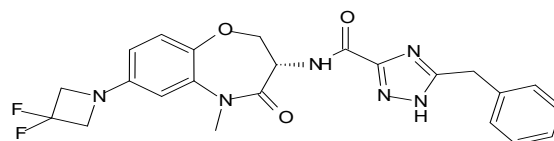
I-23;



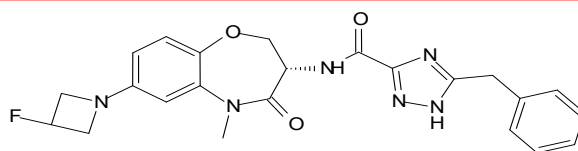
I-24;



I-25;

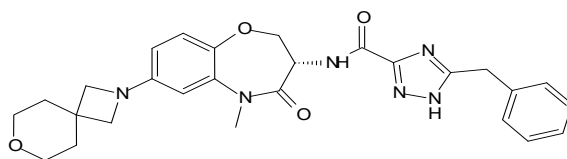


I-26; or



I-27.

16. The compound of claim 1 ~~any one of claims 1-15~~, wherein the compound is



~~17. A pharmaceutical composition, comprising a compound according to any one of claims 1-15, an excipient, a therapeutic agent, an adjuvant, or combinations thereof.~~

~~18. A method, comprising contacting a receptor-interacting protein-1 (RIP1) kinase with a compound according to any one of claims 1-15, or the pharmaceutical composition of claim 17.~~

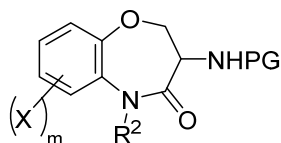
~~19. A method for treating a disease in a subject, comprising administering to the subject (i) a therapeutically effective amount of the compound of any one of claims 1-15, or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof; or (ii) a therapeutically effective amount of a pharmaceutical composition of claim 16; wherein the subject has, or is suspected of having or developing, the disease, wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase.~~

~~2017.~~ A method for making the compound of claim 1~~any one of claims 1-15~~, comprising:

coupling a starting material having a Formula A with an R¹-containing reagent having a formula R¹-H, by combining the starting material and the R¹-containing reagent with a transition metal catalyst, a ligand component, and a solvent to form an R¹-functionalized product;

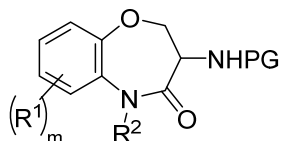
deprotecting an amine group of the R¹-functionalized product to provide an amine compound; and forming an amide bond between the amine compound and an acid-containing coupling partner;

wherein Formula A is



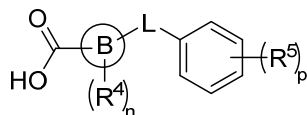
Formula A;

the R¹-functionalized product has a structure satisfying Formula B



Formula B;

and the acid-containing coupling partner has a structure satisfying Formula C



Formula C; and wherein

X is a halogen or a triflate;

PG is an amine protecting group;

and each of ring B, L, R¹, R², R⁴, R⁵, m, n, and p are as recited for claim 1.

~~2418~~. The method of claim ~~2017~~, wherein the amide bond is formed by coupling the amine compound and the acid-containing coupling partner in the presence of propylphosphonic anhydride and diisopropylethylamine.