

RIP1 INHIBITORY COMPOUNDS AND METHODS FOR MAKING AND USING THE SAME

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of the earlier filing date of U.S. Provisional Application No. 62/666,462, filed on May 3, 2018, the entirety of which is incorporated herein by reference.

FIELD

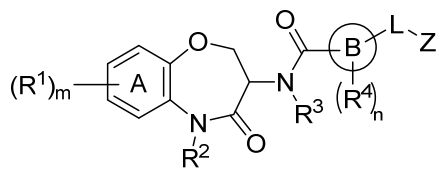
The present disclosure concerns compounds and methods of making and using the compounds, such as for inhibiting receptor-interacting protein-1 kinase ("RIP1"), and for treating diseases and/or conditions related to RIP1.

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

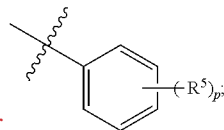


or a pharmaceutically acceptable salt thereof, wherein:

ring B is substituted or non-substituted 5-membered or 6-membered heteroaryl;

L is a heteroatom, CH₂, or R^a, provided that R^a is not H or D;

Z is substituted or non-substituted C₁₋₁₀aliphatic or



R¹ is -C≡CH, or a -linker-R⁶ group, wherein the linker is CH₂ or R^a, provided that R^a is not H or

D, and R⁶ is R^b, -C(R^f)₃, or -C(R^f)=C(R^f)₂;

R² and R³ independently are R^a;

R⁴ and R⁵ independently are R^c;

R^a is independently for each occurrence H, D, C₁alkyl, substituted or non-substituted C₂₋₁₀aliphatic, substituted or non-substituted C₁₋₁₀haloaliphatic, substituted or non-substituted C₅₋₁₀aromatic, or substituted or non-substituted C₃₋₆heterocyclic;

R^b is independently for each occurrence -OH, -SH, -OR^c, -SR^c, -NR^dR^d, -Si(R^a)₃, -C(O)OH, -C(O)OR^c, or -C(O)NR^dR^d;

R^c is independently for each occurrence substituted or non-substituted C₁₋₁₀alkyl, substituted or non-substituted C₂₋₁₀alkenyl, substituted or non-substituted C₂₋₁₀alkynyl, or substituted or non-substituted C₃₋₆cycloalkyl;

R^d is independently for each occurrence H; substituted or non-substituted C₁₋₆alkyl; substituted or non-substituted C₃₋₆cycloalkyl; substituted or non-substituted C₃₋₆heterocyclic; substituted or non-substituted C₅₋₁₀aryl; substituted or non-substituted C₅₋₁₀heteroaryl; or two R^d groups together with the nitrogen bound thereto provide a substituted or non-substituted C₃₋₉heterocyclic group, or a substituted or non-substituted C₅₋₁₀heteroaryl;

R^e is independently for each occurrence halogen, substituted or non-substituted C₁₋₆alkyl, substituted or non-substituted C₂₋₁₀alkenyl, substituted or non-substituted C₂₋₁₀alkynyl, substituted or non-substituted C₁₋₆haloalkyl, substituted or non-substituted C₃₋₆cycloalkyl, substituted or non-substituted C₅₋₁₀heteroaryl, or -OR^a;

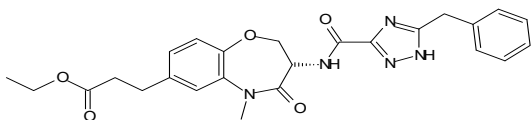
R^f is independently for each occurrence R^a, R^b, or R^c, or two R^f groups together with the carbon atom bound thereto provide a substituted or non-substituted C₃₋₆cycloalkyl group, or a substituted or non-substituted C₃₋₁₀heterocyclic group;

m is 1 to 4;

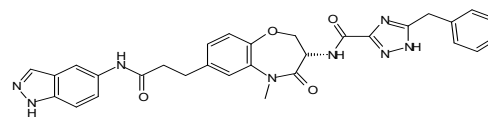
n is 0, 1 or 2; and

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

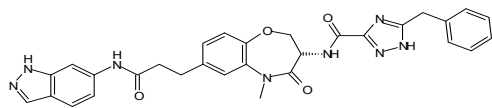
In another aspect of the present disclosure, there is provided a compound selected from:



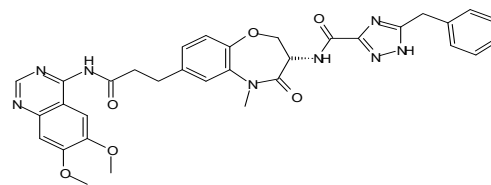
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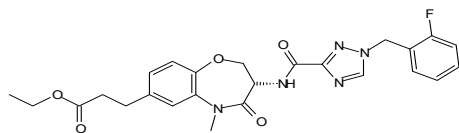
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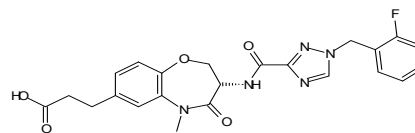
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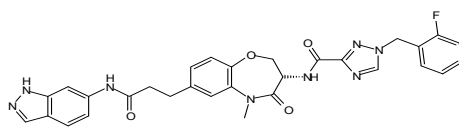
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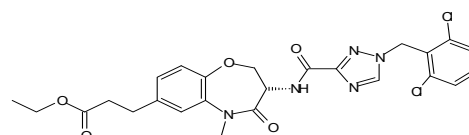
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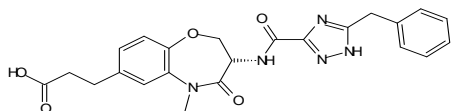
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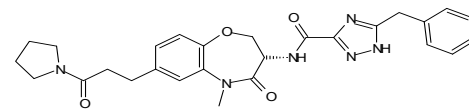
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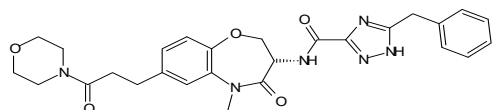
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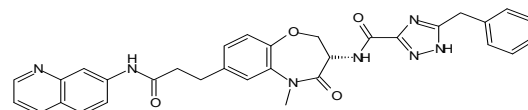
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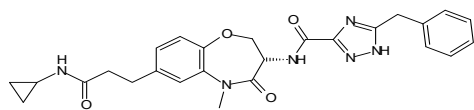
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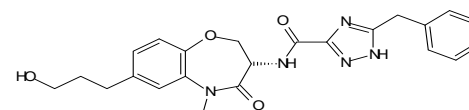
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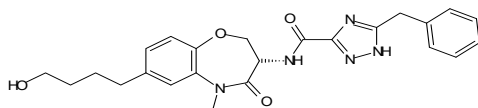
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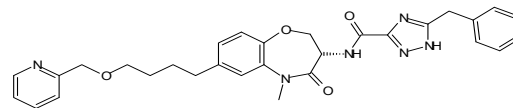
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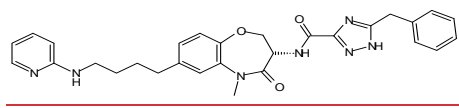
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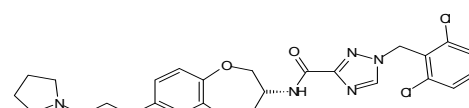
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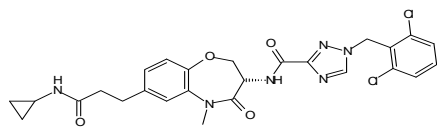
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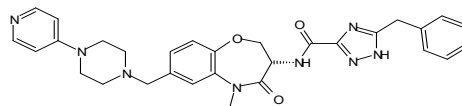
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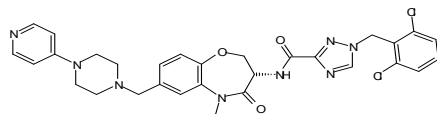
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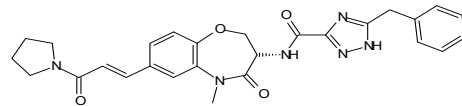
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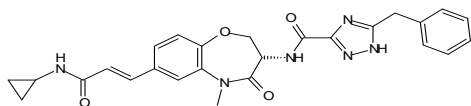
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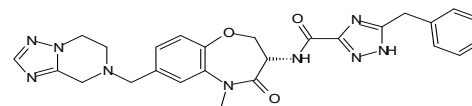
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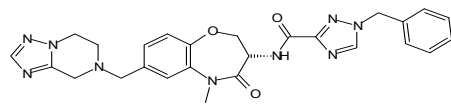
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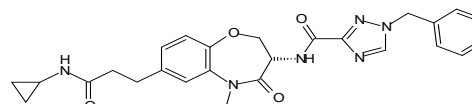
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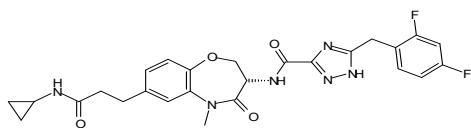
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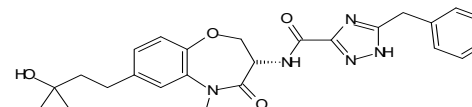
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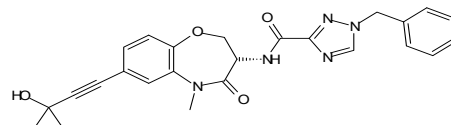
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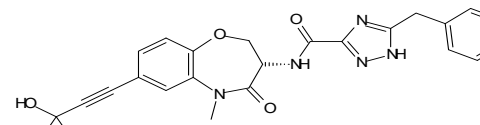
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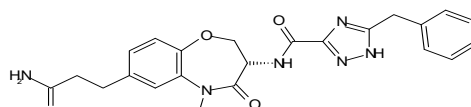
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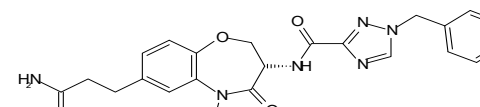
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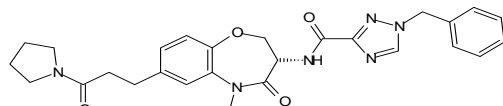
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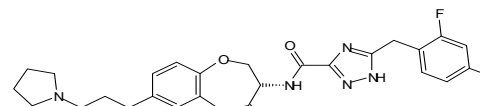
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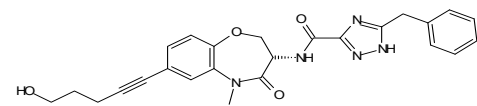
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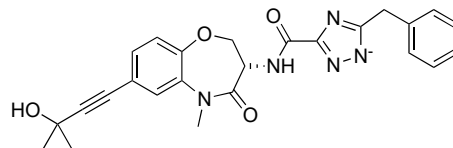
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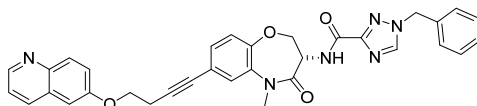
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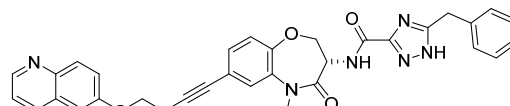
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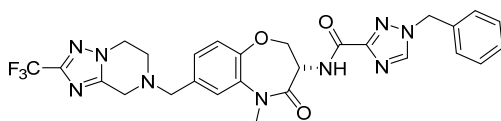
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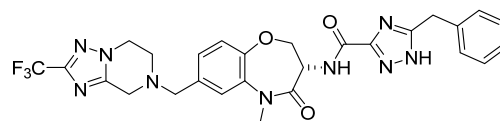
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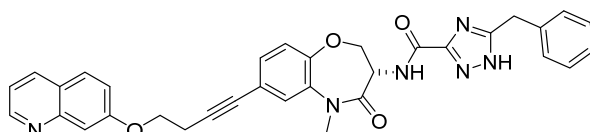
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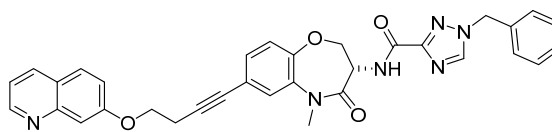
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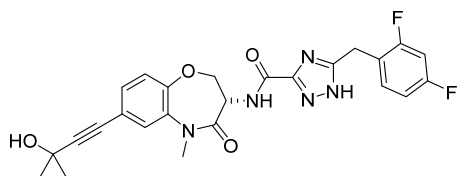
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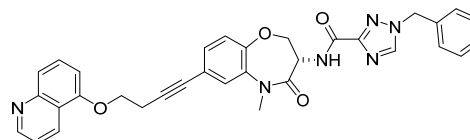
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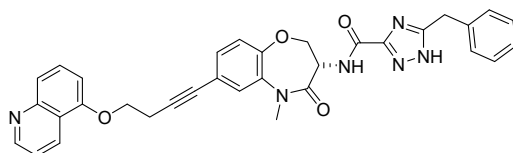
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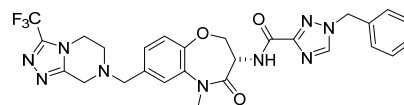
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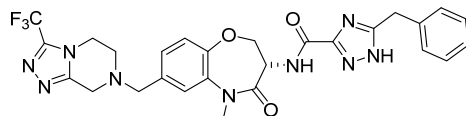
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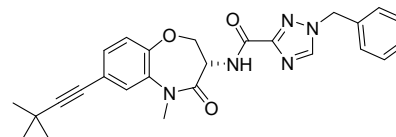
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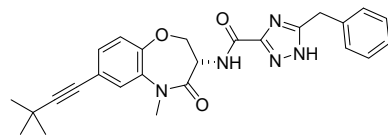
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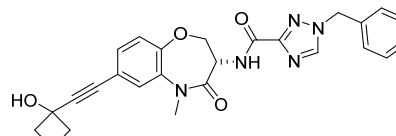
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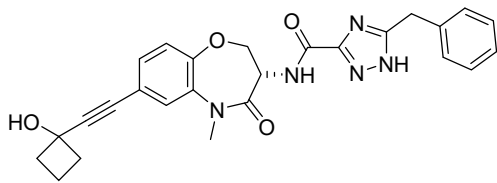
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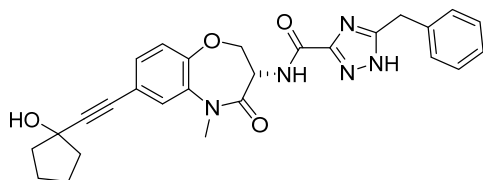
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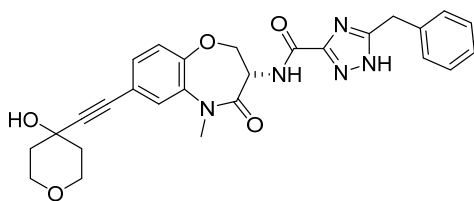
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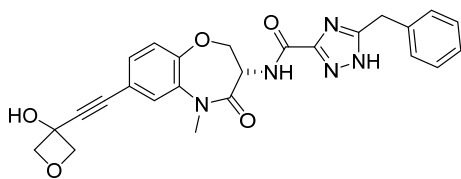
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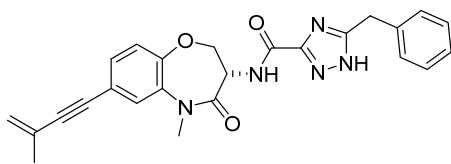
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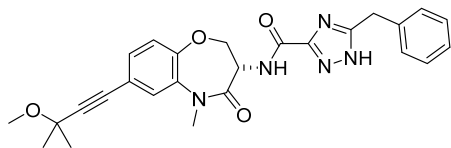
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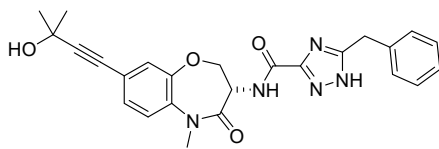
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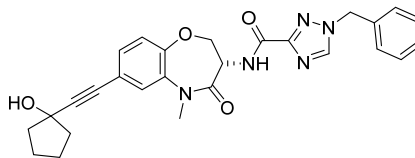
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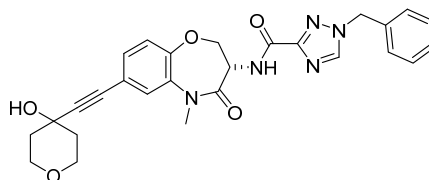
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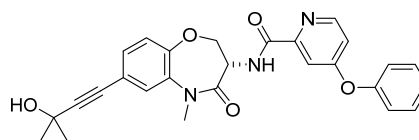
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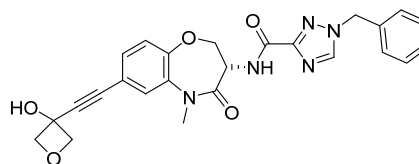
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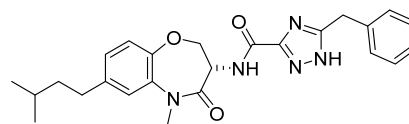
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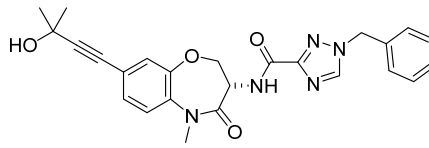
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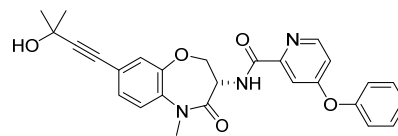
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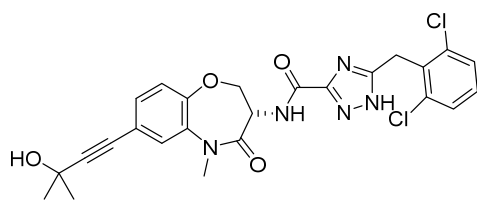
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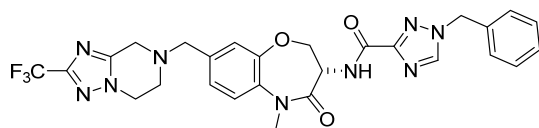
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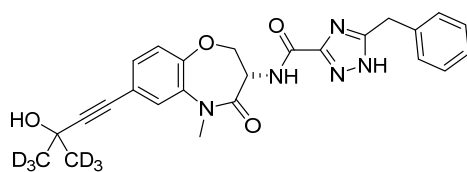
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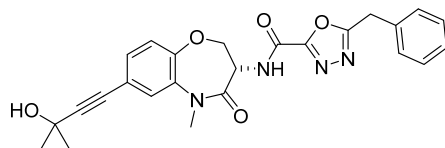
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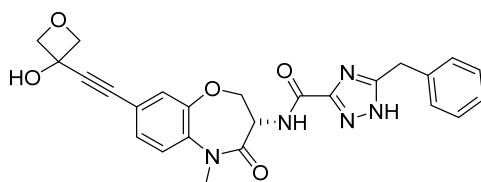
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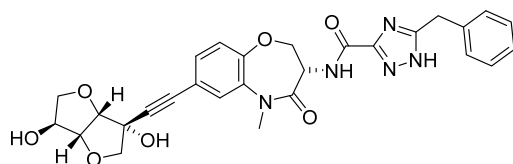
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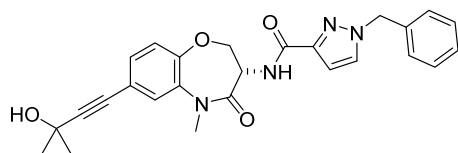
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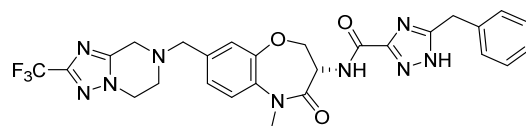
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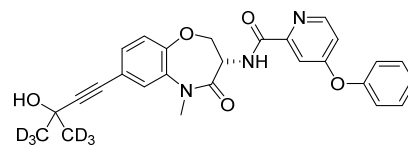
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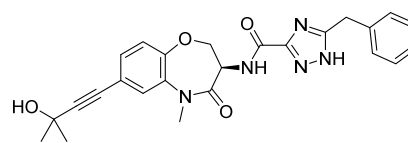
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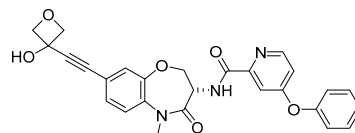
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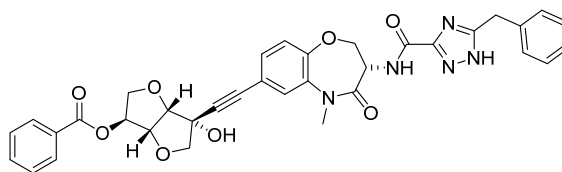
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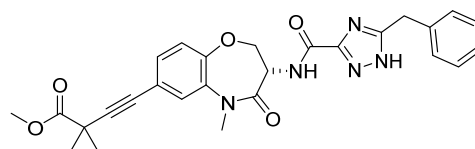
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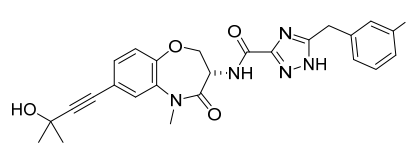
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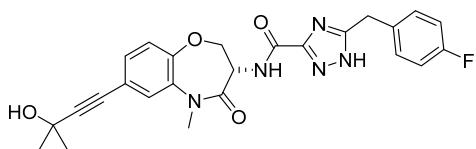
I-74;



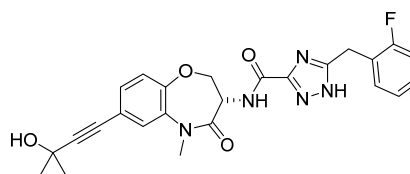
I-76;



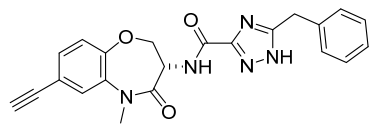
I-78;



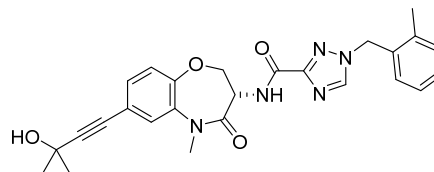
I-79;



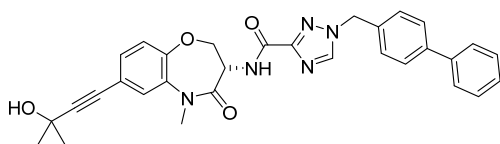
I-80;



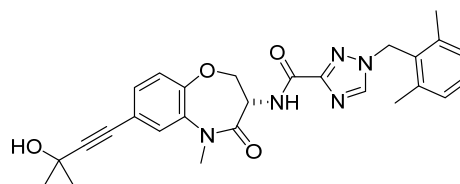
I-81;



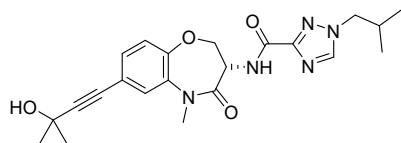
I-82;



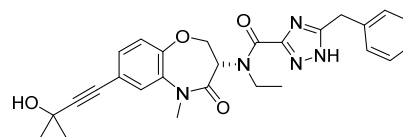
I-83;



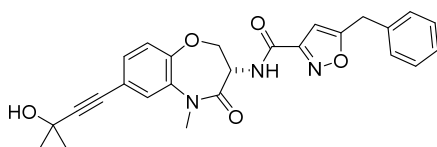
I-84;



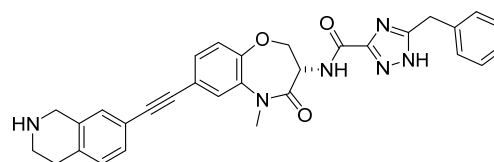
I-85;



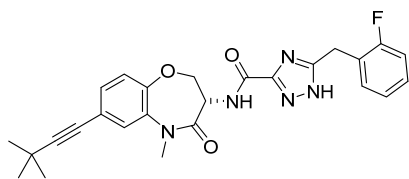
I-86;



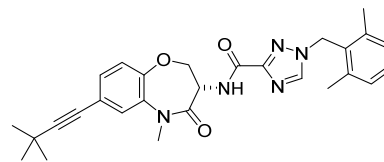
I-87;



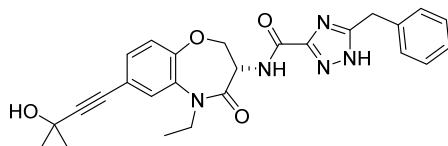
I-88;



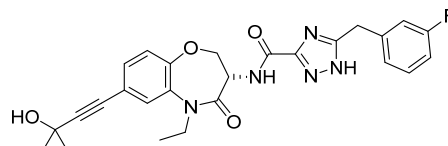
I-89;



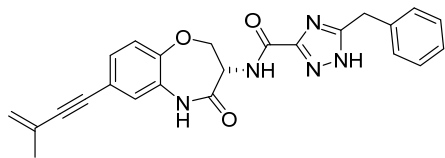
I-90;



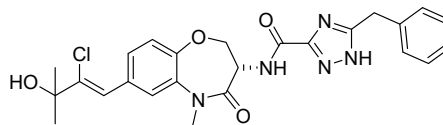
I-91;



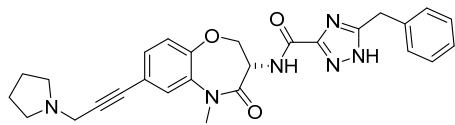
I-92;



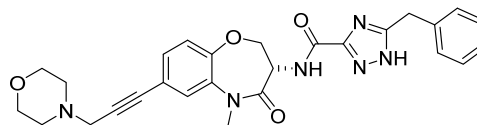
I-93:



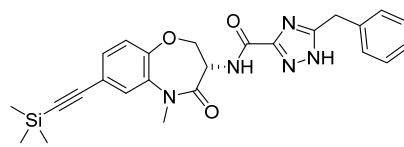
I-94:



I-95:

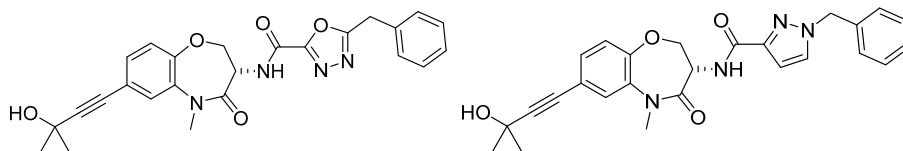
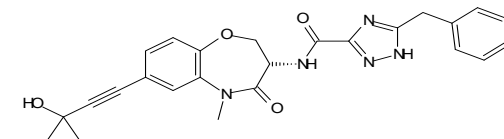


I-96; or

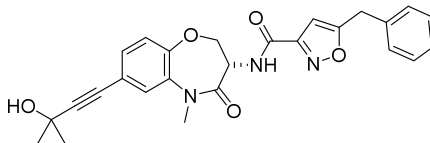


I-97.

In a further aspect of the present disclosure, there is provided a compound selected from:



, or



5

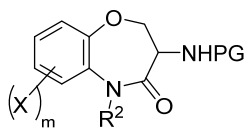
In another aspect of the present disclosure, there is provided a method for making a compound disclosed herein, comprising:

coupling a starting material having a Formula A with an R¹-containing reagent, by combining the starting material and the R¹-containing reagent, wherein R¹ comprises a linker-R⁶ group, with a transition metal catalyst, a base, and a solvent to form a functionalized product;

10

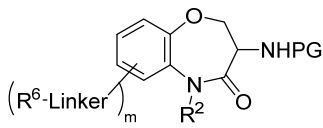
deprotecting an amine group of the functionalized product to provide an amine compound; and forming an amide bond between the amine compound and an acid-containing coupling partner to provide an amide-containing compound;

wherein Formula A is



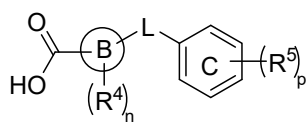
Formula A:

the 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 herein.

In a further aspect of the present disclosure, there is provided a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide or a pharmaceutically acceptable salt thereof.

In another aspect of the present disclosure, there is provided a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide.

In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease in a subject wherein the disease is a disease involving a receptor-interacting protein-1 (RIP 1) kinase, wherein the disease involving the RIP1 kinase is selected from ankylosing spondylitis, rheumatoid arthritis, atopic dermatitis, psoriasis, and any combination thereof.

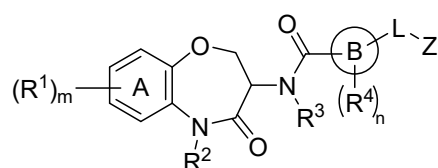
In a further aspect of the present disclosure, there is provided a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide for use in therapy.

In another aspect of the present disclosure, there is provided a use of a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide in the manufacture of a medicament for treating a disease in a subject wherein the disease is a disease involving a receptor-interacting protein-1 (RIP 1) kinase, wherein the disease involving the RIP1 kinase is psoriasis.

In a further aspect of the present disclosure, there is provided a use of a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide in the manufacture of a medicament for treating a disease in a subject wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase, wherein the disease involving the RIP1 kinase is rheumatoid arthritis.

In another aspect of the present disclosure, there is provided a use of a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide in the manufacture of a medicament for treating a disease in a subject wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase, wherein the disease involving the RIP1 kinase is atopic dermatitis.

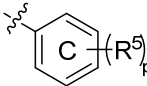
Disclosed herein are compound ~~embodiments~~ examples having a Formula I



Formula I,

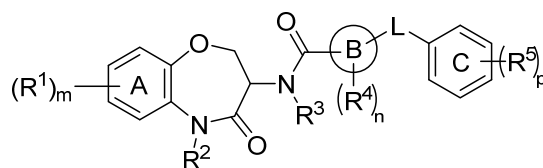
or a pharmaceutically acceptable salt thereof. A person of ordinary skill in the art will appreciate that compounds within the scope of Formula I also include stereoisomers, N-oxides, tautomers, hydrates, solvates, isotopes, and/or prodrugs thereof.

With reference to Formula I, ring B is 5-membered or 6-membered heteroaryl; L is a heteroatom or R^a, provided that R^a is not H or D; Z is C₁₋₁₀aliphatic (such as C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, or

C₃₋₆cycloalkyl); or ; R¹ is a halogen, -C≡CH, or a -linker-R⁶ group, wherein the linker is R^a, provided that R^a is not H or D, and R⁶ is R^b, -C(R^f)₃, or -C(R^f)=C(R^f)₂; R² and R³ independently are R^a; R⁴ and R⁵ independently are R^c; R^a is independently for each occurrence H, D, C₁₋₁₀aliphatic, C₁₋₁₀haloaliphatic, C₅₋₁₀aromatic, or C₃₋₆heterocyclic; R^b is independently for each occurrence -OH, -SH, -OR^c, -SR^c, -NR^dR^d, -Si(R^a)₃, -C(O)OH, -C(O)OR^c, or -C(O)NR^dR^d; R^c is independently for each occurrence C₁₋₁₀alkyl, C₂₋

₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₆cycloalkyl (which can be substituted with 1, 2 or 3 R^e), or C₅₋₁₀aromatic (which can be substituted with 1, 2 or 3 R^e); R^d is independently for each occurrence H; C₁₋₆alkyl (which can be substituted with 1, 2 or 3 R^e); C₃₋₆cycloalkyl (which can be substituted with 1, 2 or 3 R^e); C₃₋₆heterocyclic (which can be substituted with 1, 2 or 3 R^e); C₅₋₁₀aryl (which can be substituted with 1, 2 or 3 R^b); C₅₋₁₀heteroaryl (which can be substituted with 1, 2 or 3 R^b); or two R^d groups together with the nitrogen bound thereto provide a C₃₋₉heterocyclic (which can be substituted with one or more R^e), or a C₅₋₁₀heteroaryl (which can be substituted with one or more R^e); R^e is independently for each occurrence halogen, C₁₋₆alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₅₋₁₀heteroaryl, or -OR^a; R^f is independently for each occurrence R^a, R^b, or R^e, or two R^f groups together with the carbon atom bound thereto provide a C₃₋₆cycloalkyl group (which can be substituted with one or more R^e), or a C₃₋₁₀heterocyclic (which can be substituted with one or more R^e); m is 1 to 4; n is 0, 1 or 2; and p is 0, 1, 2, 3, 4, or 5.

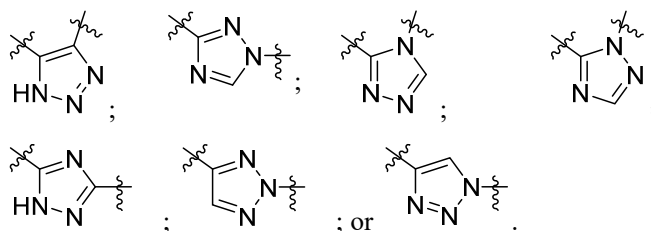
Disclosed compounds may have a structure satisfying the formula below



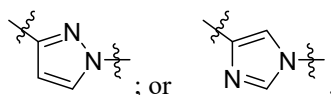
In any or all of the above embodimentsexamples, ring B can have a structure satisfying a formula



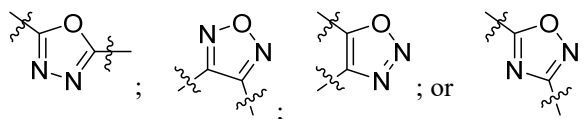
wherein at least one W is nitrogen, and each remaining W independently is selected from carbon, CH, oxygen, sulfur, nitrogen, or NH, with particular ring B examples embodiments being a diazole, a triazole, an oxadiazole, an oxazole, or a pyridinyl. Suitable exemplary triazoles include any of the following:



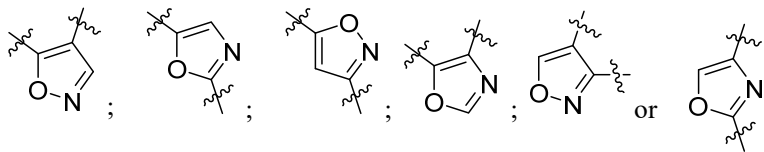
Suitable exemplary diazole include any of the following:



Suitable exemplary oxadiazoles include any of the following:



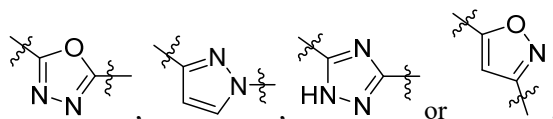
Suitable exemplary oxazoles include any of the following:



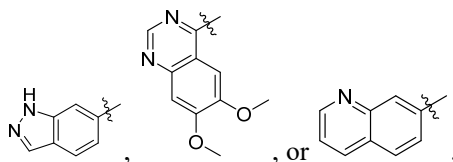
Certain disclosed compounds comprise an R^5 group that is an R^e group, wherein R^e is C_1 - C_4 aliphatic, or halogen, R^2 is R^a wherein R^a is C_1 - C_4 aliphatic, and R^3 is R^a , wherein R^a is hydrogen.

For certain disclosed embodimentexamples, R^1 is a linker- R^6 group wherein the linker is R^a and R^a is a C_1 , C_2 , C_3 , or C_4 aliphatic group. The C_2 aliphatic group may be an alkyl, alkenyl, or alkynyl group.

- 5 The R^6 group may be R^b wherein R^b is $-C(R^f)_3$, wherein one R^f is R^e , particularly $-OR^a$, wherein R^a is H; and each other R^f independently for each occurrence is R^a , wherein R^a is C_1 -alkyl, particularly methyl. In particular embodimentexamples, the C_2 group is an alkyne. In any or all of the above embodimentexamples, ring B can be selected from



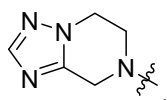
- 10 In some embodimentexamples, R^6 may be R^b wherein R^b is $-C(O)OEt$; or R^b may be $-C(O)NR^dR^d$, wherein each R^d is independently for each occurrence H, C_{5-10} heteroaryl (which can be substituted with 1, 2 or 3 R^e), C_{1-6} alkyl (which can be substituted with 1, 2 or 3 R^e), or two R^d groups together with the nitrogen bound thereto provide a C_{3-9} heterocyclic (which can be substituted with one or more R^e), or a C_{5-10} heteroaryl (which can be substituted with one or more R^e). More particularly, one R^d is H and the other R^d is aromatic,
- 15 such as



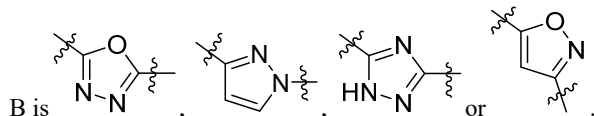
- Certain compounds can comprise an R^6 group that is R^b wherein R^b is $-OH$; OR^e , wherein R^e is C_1 - C_{10} alkyl (which can be substituted with 1, 2 or 3 R^e), C_{2-10} alkenyl (which can be substituted with 1, 2 or 3 R^e), C_{2-10} alkynyl (which can be substituted with 1, 2 or 3 R^e), or C_{5-10} aromatic (which can be substituted with 1, 2 or 3 R^e); or NR^dR^d , wherein one R^d is H and the other R^d is C_{5-10} aromatic (which can be substituted with 1, 2 or 3 R^e). In some embodimentexamples, R^b is OR^e , wherein R^e is C_2 alkyl substituted with pyridinyl. In some other embodimentexamples, R^b may be $-NR^dR^d$, wherein one R^d is H and the other R^d is pyridinyl.
- 20

- The linker group of the linker- R^6 group can be a C_1 group and the corresponding R^6 group is R^b wherein R^b is $-NR^dR^d$, wherein two R^d groups together with the nitrogen bound thereto provide a C_3 - C_9 heterocyclic (which can be substituted with one or more R^e), or a C_{5-10} heteroaryl (which can be substituted with one or more R^e), particularly wherein two R^d groups together with the nitrogen bound thereto provide a C_{3-9} heterocyclic substituted with one R^e . In such embodimentexamples, R^e may be C_{5-10} heteroaryl, such as pyridinyl. In other embodimentexamples, the two R^d groups together with the nitrogen to which they are bound may provide a
- 25

C₅₋₁₀heteroaryl optionally may be substituted with one or more R^e. The C₅₋₁₀heteroaryl without R^e substituents can be

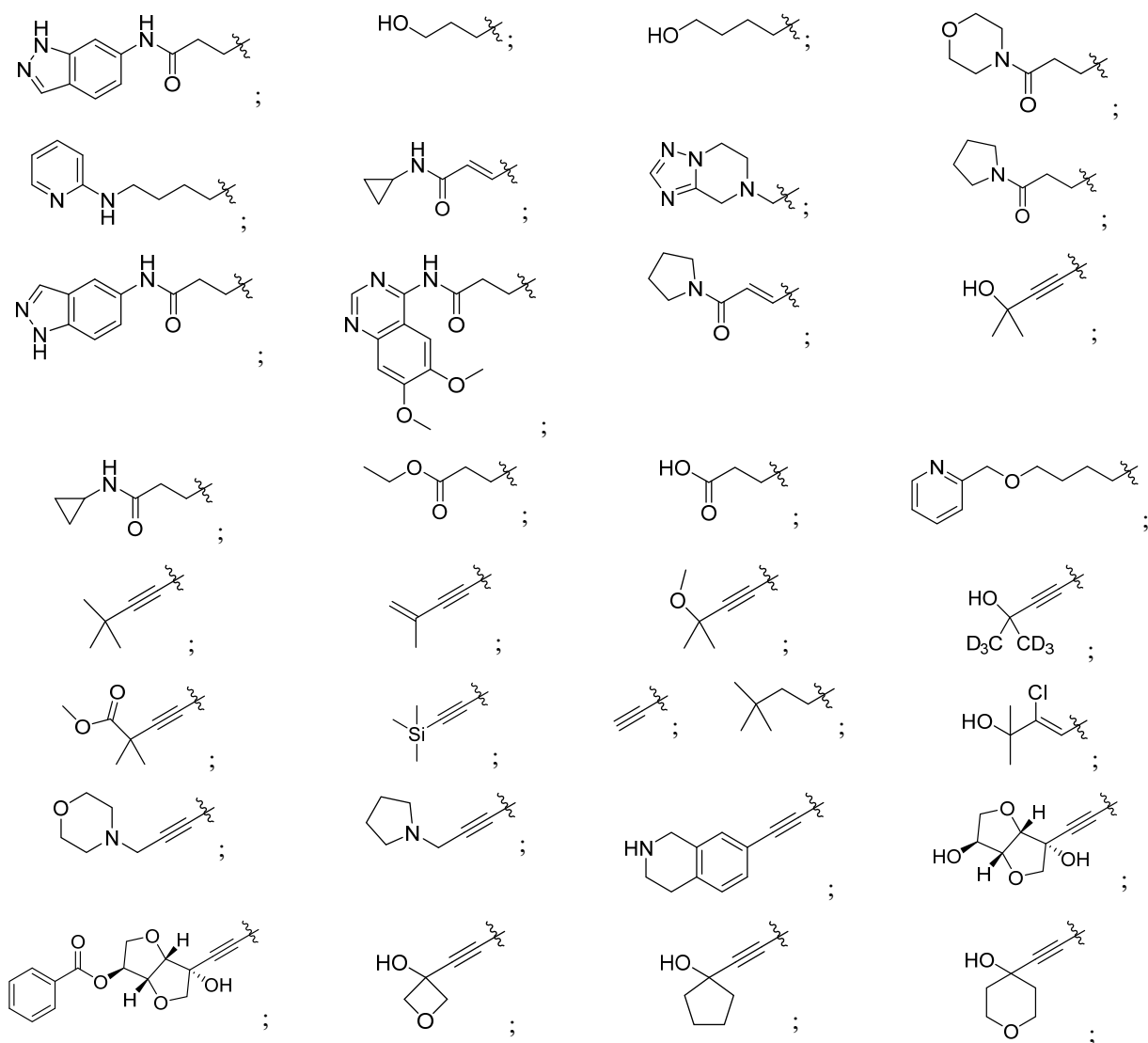


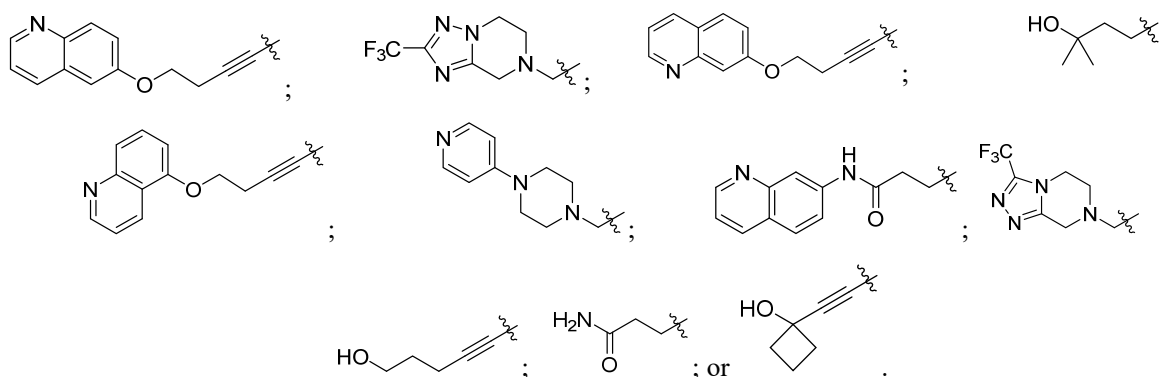
In some embodiment examples, R⁵ is R^e, wherein R^e is halogen or methyl. In some embodiment examples, the linker of the linker-R⁶ group is R^a wherein R^a is a C₁, C₂, C₃, or C₄ aliphatic group comprising an alkyl, alkenyl, or alkynyl group. In some such embodiment examples, the C₂ group comprises an alkyne and wherein R⁶ is R^b wherein R^b is -C(R^f)₃, wherein one R^f is R^e and each other R^f independently for each occurrence is R^a, wherein R^a is C₁₋₄alkyl. In particular embodiment examples, R^e is -OR^a, wherein R^a is H. R^a is methyl in some such embodiment examples and ring



R¹ can be positioned on any suitable carbon atom(s) of phenyl ring A, such as at the 1, 2, 3, or 4 position,

10 illustrated in Formula I. Exemplary R¹ groups are as follows:





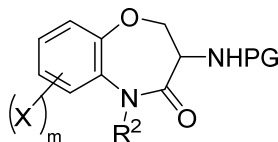
Exemplary compound species are provided herein.

Also disclosed herein are pharmaceutical composition **embodimentexamples** comprising a compound (or compounds) according to any of the formulas and/or species disclosed herein (or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof), and at least one additional active and/or non-active agent, such as an excipient, a therapeutic agent, an adjuvant, or combinations thereof.

Also disclosed herein are **embodimentexamples** of a method for using disclosed compounds. One such **embodimentexample** comprises contacting a receptor-interacting protein-1 (RIP1) kinase with a compound according to any of the formulas and/or species disclosed herein (or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof), or a pharmaceutical composition **embodimentexample** described herein. Contacting can occur *ex vivo* or *in vivo*.

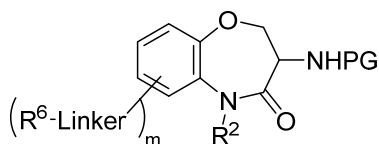
Also disclosed is a method for treating a disease in a subject, comprising administering to the subject (i) a therapeutically effective amount of the compound according to any of the formulas and/or species disclosed herein (or a pharmaceutically acceptable salt, a stereoisomer, an N-oxide, a tautomer, a hydrate, a solvate, an isotope, or a prodrug thereof); and/or (ii) a therapeutically effective amount of a pharmaceutical composition **embodimentexample** described herein; wherein the subject has, or is suspected of having or developing a disease involving a receptor-interacting protein-1 (RIP1) kinase.

Method **embodimentexamples** for making the compound **embodimentexamples** disclosed herein also are described. In some **embodimentexamples**, the method can comprise coupling a starting material having a Formula A with an R¹-containing reagent, by combining the starting material and the R¹-containing reagent, wherein R¹ comprises a linker-R⁶ group, with a transition metal catalyst, a base, and a solvent to form a functionalized product; deprotecting an amine group of the functionalized product to provide an amine compound; and forming an amide bond between the amine compound and an acid-containing coupling partner to provide an amide-containing compound; wherein Formula A is



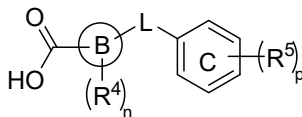
Formula A;

the 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 any one or more of the above compound embodiment examples.

The foregoing and other objects and features of the present disclosure will become more apparent from the following detailed description.

DETAILED DESCRIPTION

I. Overview of Terms

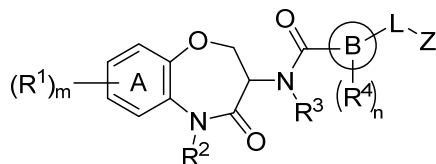
The following explanations of terms and methods are provided to better describe the present disclosure and to guide those of ordinary skill in the art in the practice of the present disclosure. The singular forms “a,” “an,” and “the” refer to one or more than one, unless the context clearly dictates otherwise. The term “or” refers to a single element of stated alternative elements or a combination of two or more elements, unless the context clearly indicates otherwise. As used herein, “comprises” means “includes.” Thus, “comprising A or B,” means “including A, B, or A and B,” without excluding additional elements. All references, including patents and patent applications cited herein, are incorporated by reference.

Unless otherwise indicated, all numbers expressing quantities of components, molecular weights, percentages, temperatures, times, and so forth, as used in the specification or claims are to be understood as being modified by the term “about.” Accordingly, unless otherwise indicated, implicitly or explicitly, the numerical parameters set forth are approximations that may depend on the desired properties sought and/or limits of detection under standard test conditions/methods. When directly and explicitly distinguishing embodiments from discussed prior art, the embodiment numbers are not approximates unless the word “about” is expressly recited.

Unless explained otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the

We claim:

1. A compound, having a formula

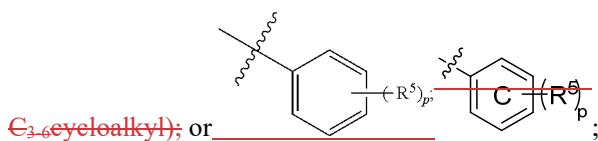


- 5 or a pharmaceutically acceptable salt thereof, wherein:

ring B is substituted or non-substituted 5-membered or 6-membered heteroaryl;

L is a heteroatom, CH₂, or R^a, provided that R^a is not H or D;

Z is substituted or non-substituted C₁₋₁₀aliphatic (~~such as C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, or~~



- 10 R¹ is ~~a halogen~~, -C≡CH, or a -linker-R⁶ group, wherein the linker is CH₂ or R^a, provided that R^a is not H or D, and R⁶ is R^b, -C(R^f)₃, or -C(R^f)=C(R^f)₂;

R² and R³ independently are R^a;

R⁴ and R⁵ independently are R^c;

- 15 R^a is independently for each occurrence H, D, C₁alkyl, substituted or non-substituted C₄₋₁₂-
aliphatic, substituted or non-substituted C₁₋₁₀haloaliphatic, substituted or non-substituted
C₅₋₁₀aromatic, or substituted or non-substituted C₃₋₆heterocyclic;

R^b is independently for each occurrence -OH, -SH, -OR^c, -SR^c, -NR^dR^d, -Si(R^a)₃, -C(O)OH, -
C(O)OR^c, or -C(O)NR^dR^d;

- 20 R^c is independently for each occurrence substituted or non-substituted C₁₋₁₀alkyl, substituted or
non-substituted C₂₋₁₀alkenyl, substituted or non-substituted C₂₋₁₀alkynyl, or substituted or non-
substituted C₃₋₆cycloalkyl, ~~or C₅₋₁₀aromatic~~;

- 25 R^d is independently for each occurrence H; substituted or non-substituted C₁₋₆alkyl; substituted
or non-substituted C₃₋₆cycloalkyl; substituted or non-substituted C₃₋₆heterocyclic; substituted or non-
substituted C₅₋₁₀aryl; substituted or non-substituted C₅₋₁₀heteroaryl; or two R^d groups together with
the nitrogen bound thereto provide a substituted or non-substituted C₃₋₉heterocyclic group, or a
substituted or non-substituted C₅₋₁₀heteroaryl;

- 30 R^e is independently for each occurrence halogen, substituted or non-substituted C₁₋₆alkyl,
substituted or non-substituted C₂₋₁₀alkenyl, substituted or non-substituted C₂₋₁₀alkynyl, substituted or
non-substituted C₁₋₆haloalkyl, substituted or non-substituted C₃₋₆cycloalkyl, substituted or non-
substituted C₅₋₁₀heteroaryl, or -OR^a;

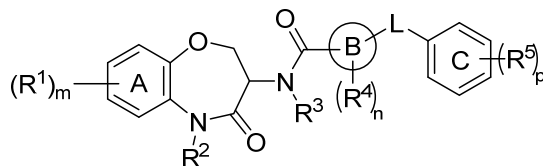
R^f is independently for each occurrence R^a , R^b , or R^e , or two R^f groups together with the carbon atom bound thereto provide a substituted or non-substituted C_{3-6} cycloalkyl group, or a substituted or non-substituted C_{3-10} heterocyclic group;

m is 1 to 4;

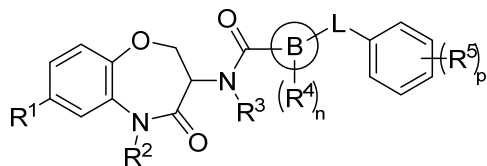
n is 0, 1 or 2; and

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

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



3. The compound ~~claim or claim 2~~claim 1, wherein the compound has a structure satisfying a formula



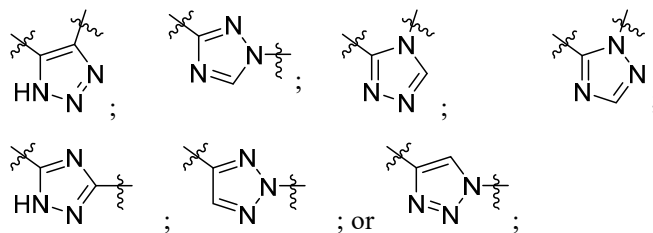
wherein L is oxygen or CH_2 .

4. The compound of claim 1~~any one of claims 1-3~~, wherein ring B has a structure satisfying a

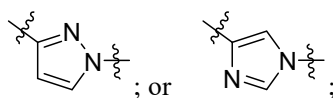
formula , wherein at least one W is nitrogen, and each remaining W independently is selected from carbon, CH, oxygen, sulfur, nitrogen, or NH.

5. The compound of claim 1~~any one of claims 1-4~~, wherein ring B is a diazole, a triazole, an oxadiazole, an oxazole, or a pyridinyl.

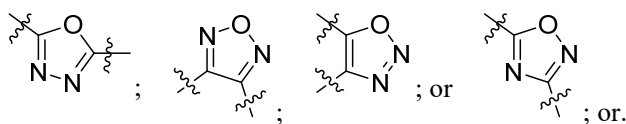
6. The compound of claim 5, wherein the triazole is



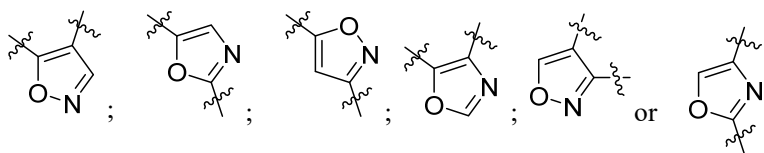
the diazole is



the oxadiazole is



the oxazole is



7. The compound of ~~claim 1~~ any one of claims 1-6, wherein R^5 is R^e , wherein R^e is halogen or methyl.

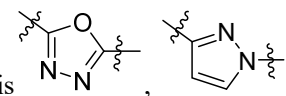
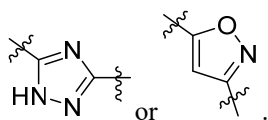
8. The compound of ~~claim 1~~ any one of claims 1-7, wherein the linker of the linker- R^6 group is CH_2 , or non-substituted R^a wherein R^a is a C_{1-4} , C_2 , C_3 , or C_4 aliphatic group comprising an alkyl, alkenyl, or alkynyl group.

9. The compound of claim 8, wherein the substituted or non-substituted C_2 aliphatic group comprises a substituted or non-substituted alkyne and wherein R^6 is ~~R^b wherein R^b is~~ $-C(R^f)_3$, wherein one R^f is R^e and each other R^f independently for each occurrence is substituted or non-substituted R^a wherein R^a is C_{1-4} alkyl.

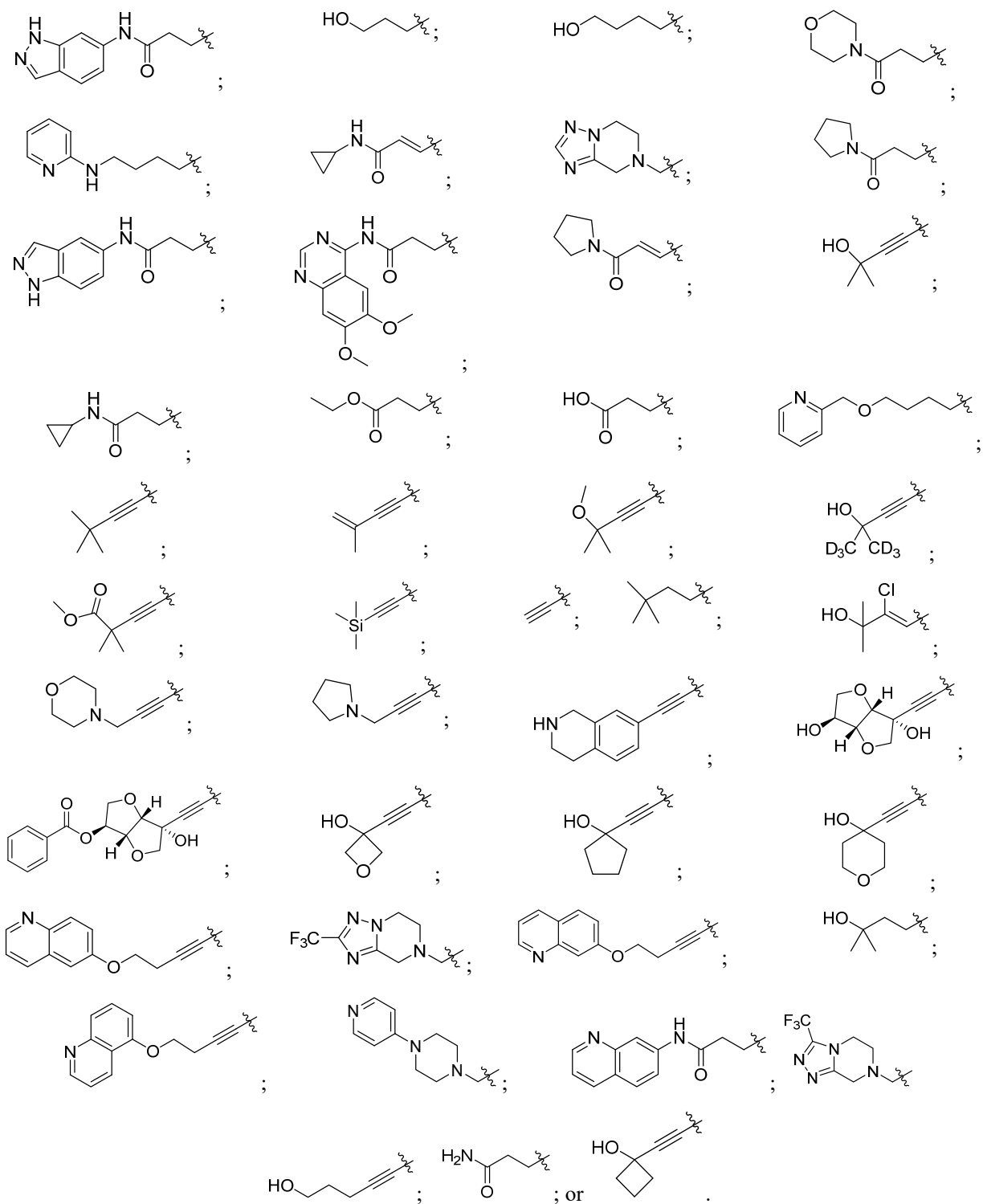
10. The compound of claim 9, wherein R^e is $-OR^a$, wherein R^a is H.

11. The compound of claim ~~9~~ or claim 10, wherein the substituted or non-substituted C_{1-4} alkyl R^a is methyl.

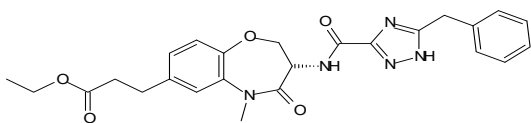
12. The compound of ~~any one of claims 9-11~~ claim 9, wherein ring B is



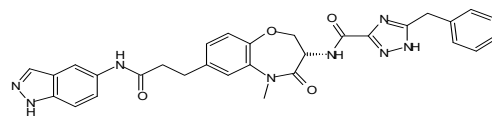
13. The compound of ~~any one of claims 1-12~~ claim 1, wherein R^1 is



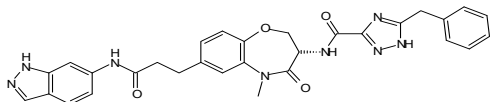
14. A compound selected from: ~~The compound of any one of claims 1-13, wherein the~~
~~compound is~~



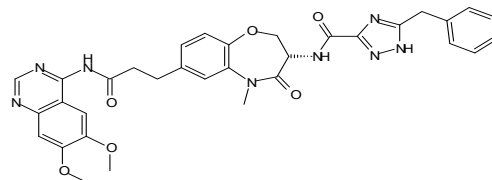
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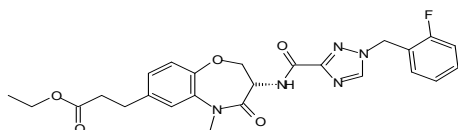
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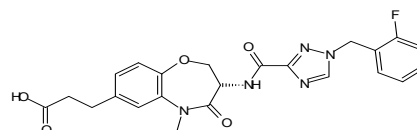
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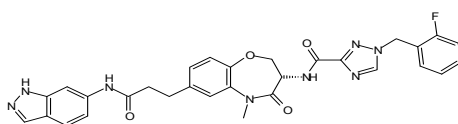
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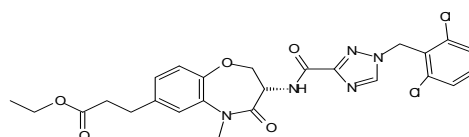
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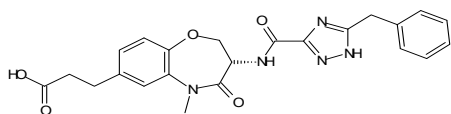
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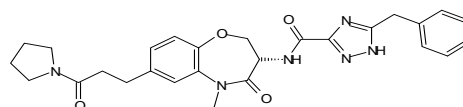
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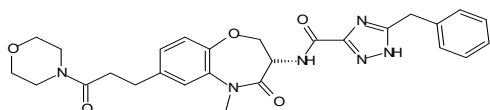
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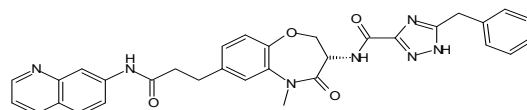
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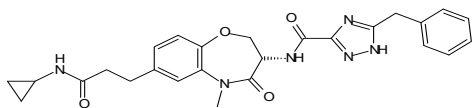
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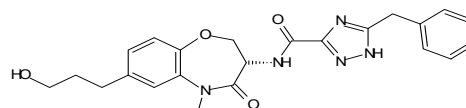
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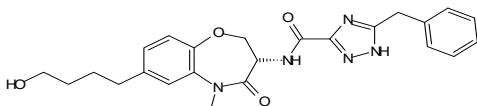
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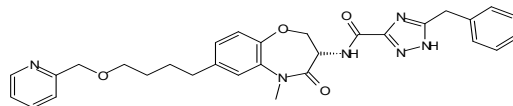
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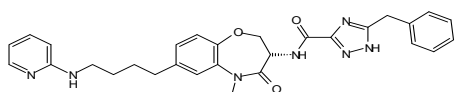
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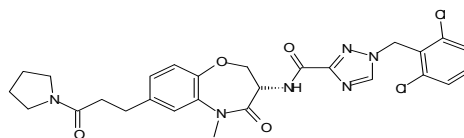
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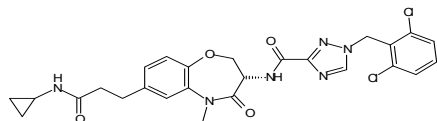
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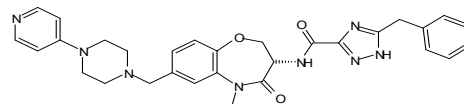
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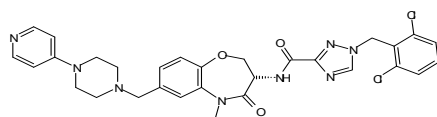
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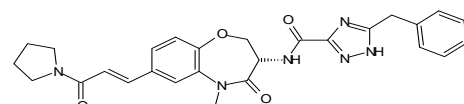
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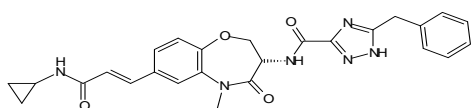
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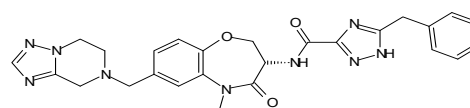
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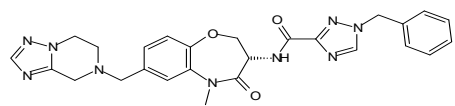
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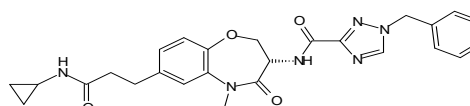
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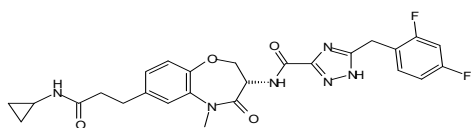
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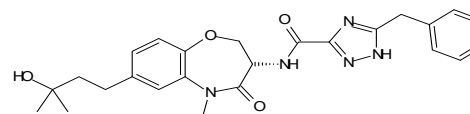
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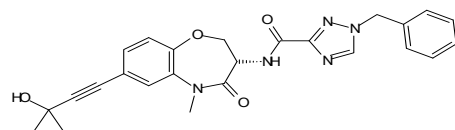
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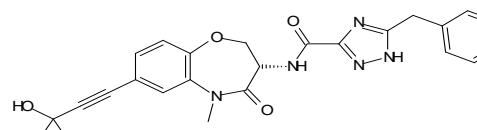
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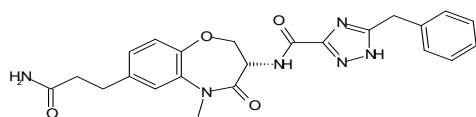
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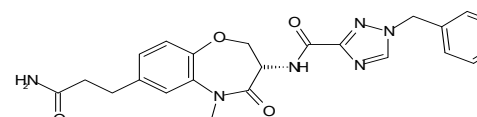
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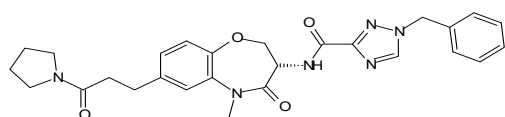
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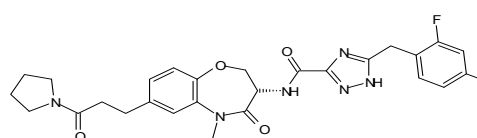
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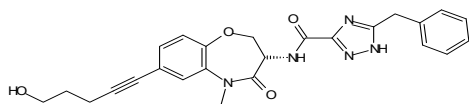
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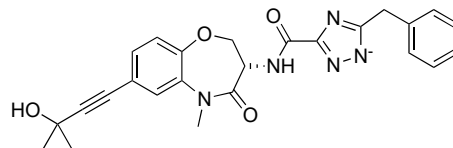
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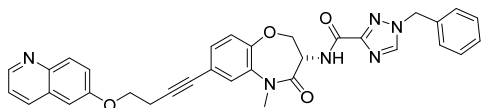
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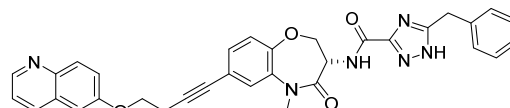
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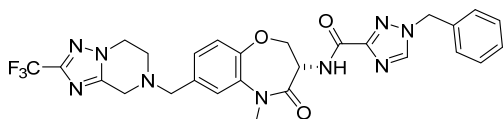
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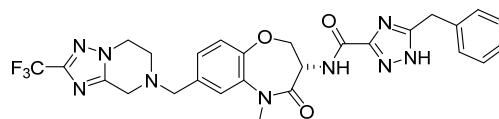
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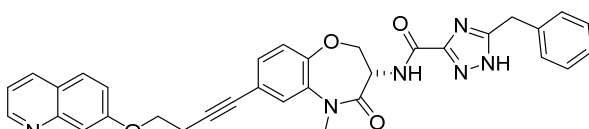
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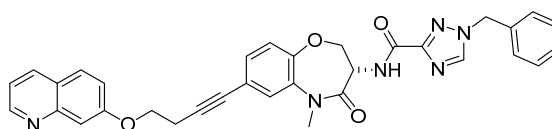
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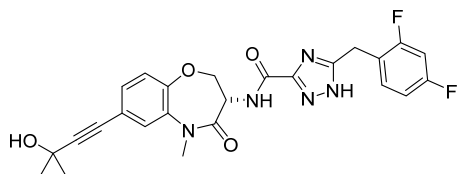
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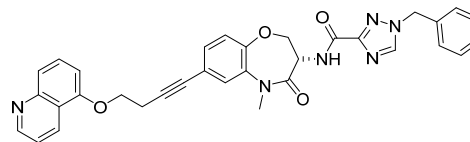
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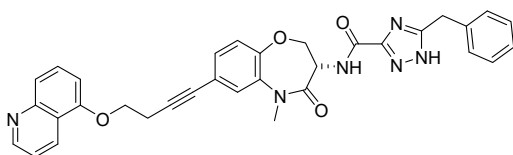
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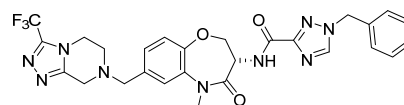
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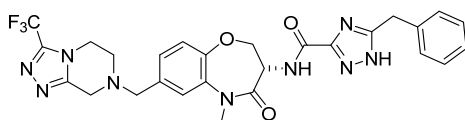
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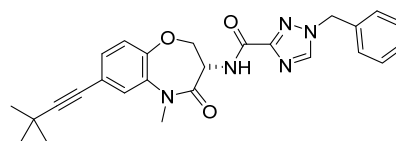
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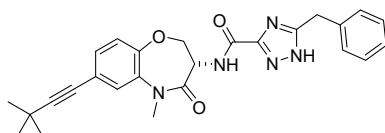
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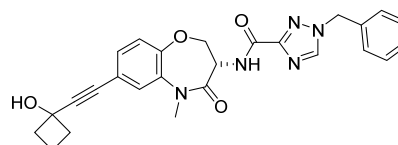
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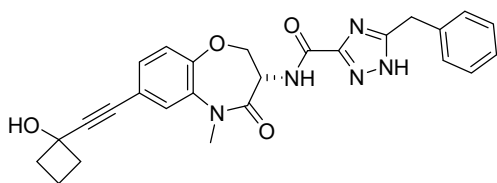
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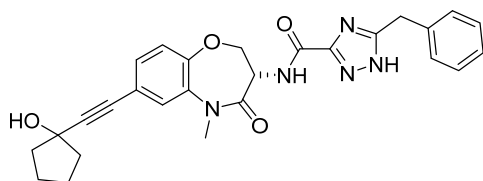
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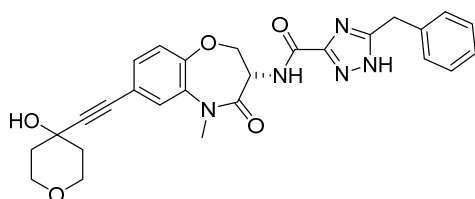
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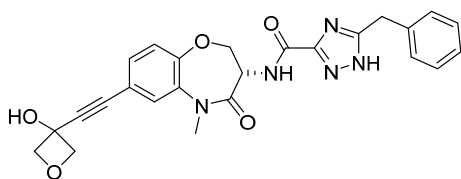
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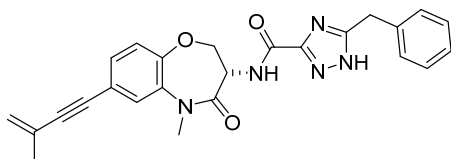
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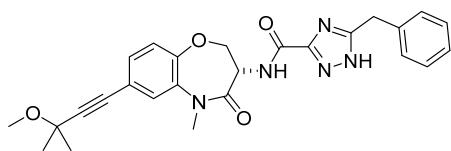
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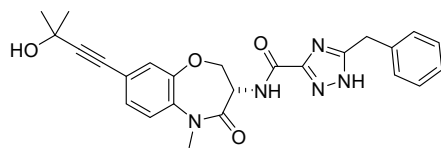
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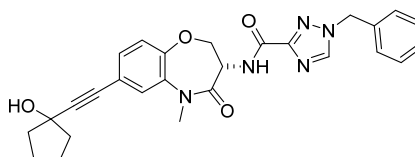
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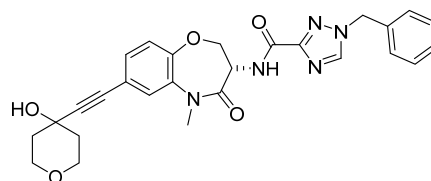
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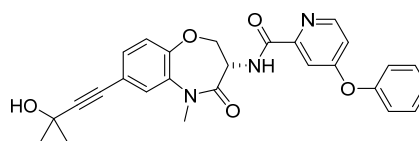
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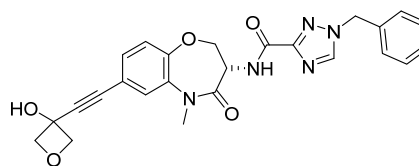
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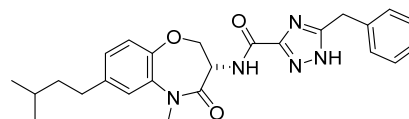
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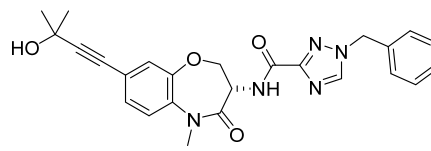
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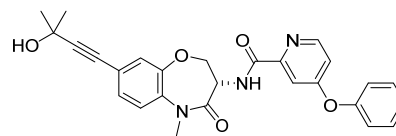
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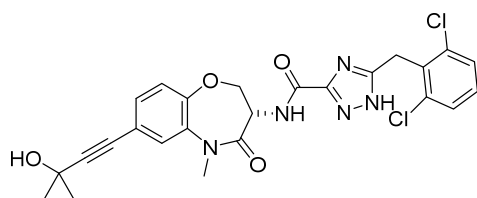
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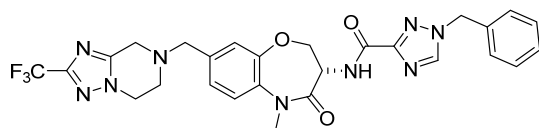
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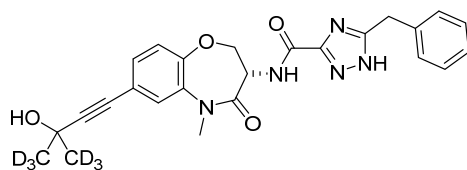
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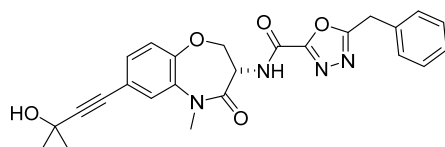
I-65;



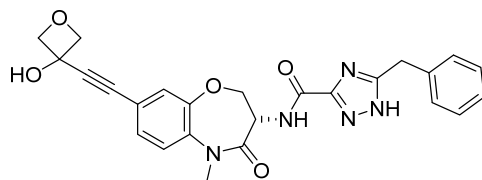
I-67;



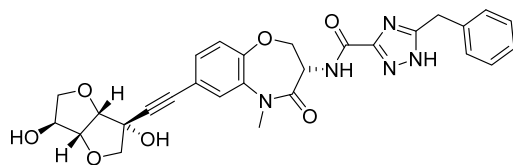
I-69;



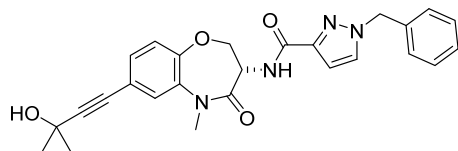
I-71;



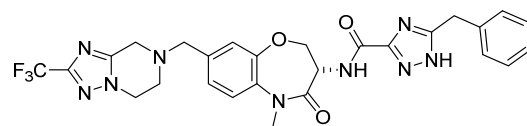
I-73;



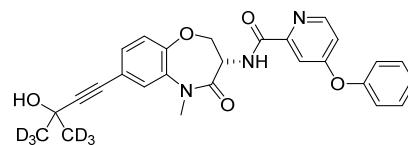
I-75;



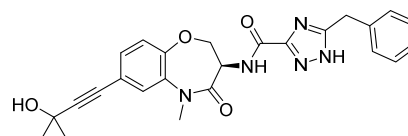
I-77;



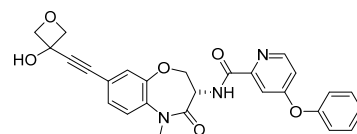
I-66;



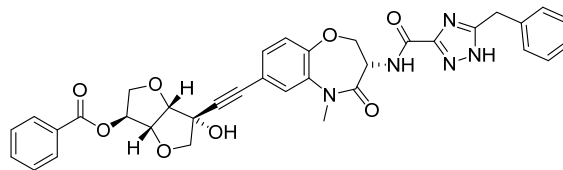
I-68;



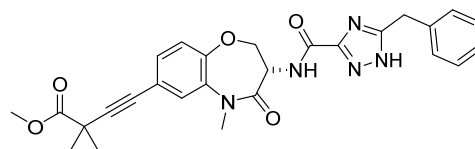
I-70;



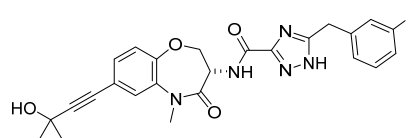
I-72;



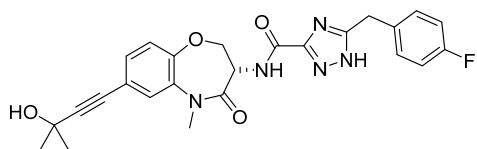
I-74;



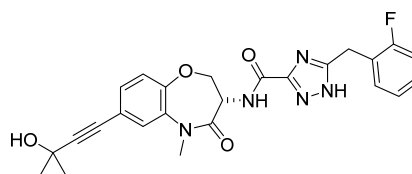
I-76;



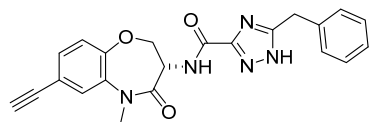
I-78;



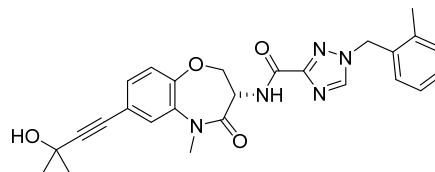
I-79;



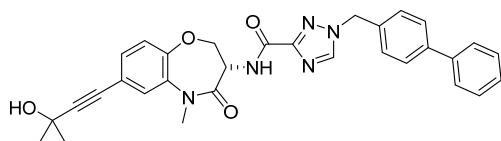
I-80;



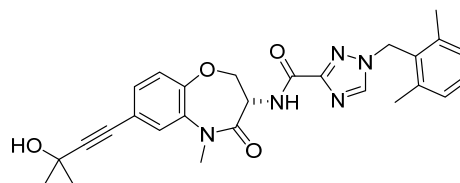
I-81;



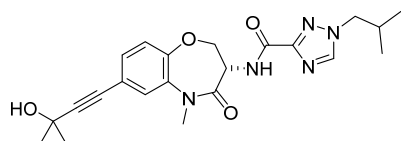
I-82;



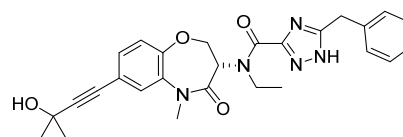
I-83;



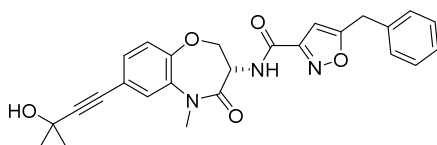
I-84;



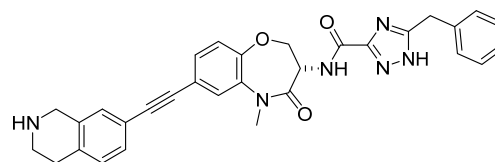
I-85;



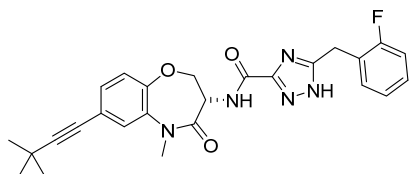
I-86;



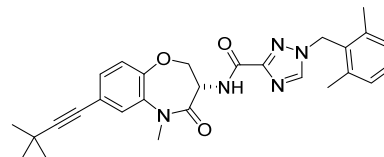
I-87;



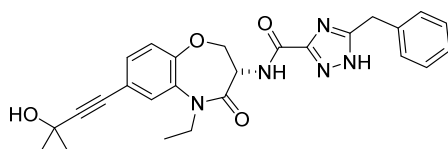
I-88;



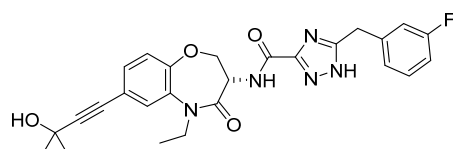
I-89;



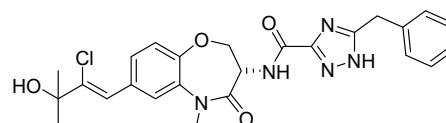
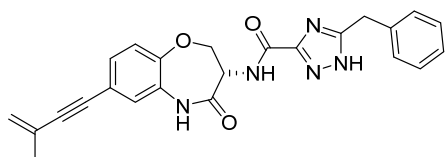
I-90;



I-91;

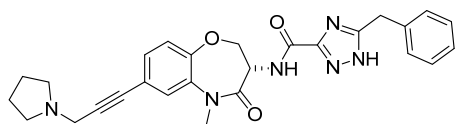


I-92;

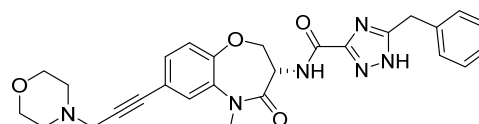


I-93;

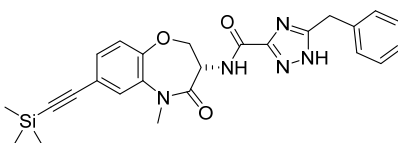
I-94;



I-95;

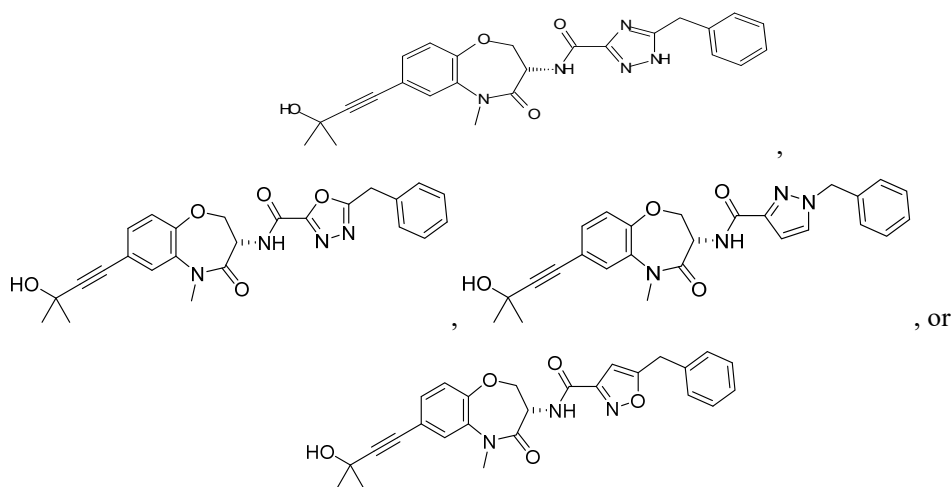


I-96; or



I-97.

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



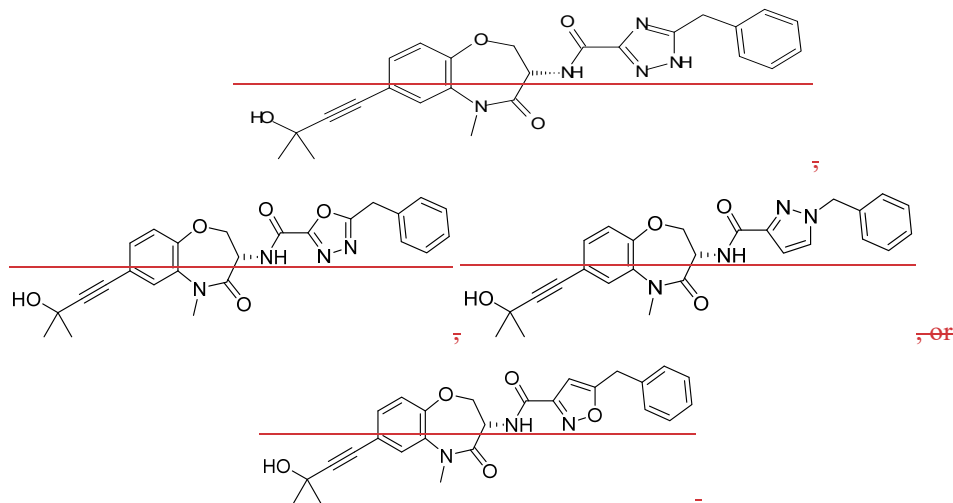
16. ~~—A pharmaceutical composition, comprising a compound according to any one of claims 1-15, an excipient, a therapeutic agent, or combinations thereof.~~

17. ~~—A method, comprising contacting a receptor-interacting protein-1 (RIP1) kinase with a compound according to any one of claims 1-15, or a pharmaceutical composition according to claim 16.~~

18. ~~—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.~~

~~19. The method of claim 17 or claim 18, wherein the compound is~~



2016. A method for making the compound of ~~claim 1~~~~any one of claims 1-15~~, comprising:

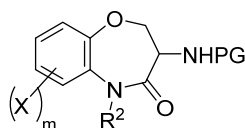
coupling a starting material having a Formula A with an R¹-containing reagent, by combining the starting material and the R¹-containing reagent, wherein R¹ comprises a linker-R⁶ group, with a transition metal catalyst, a base, and a solvent to form a functionalized product;

deprotecting an amine group of the functionalized product to provide an amine compound; and

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

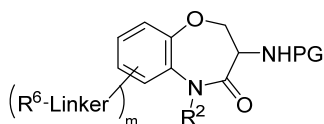
provide an amide-containing compound;

wherein Formula A is



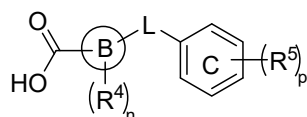
Formula A;

the 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 ~~any one of claims 1-15~~claim 1.

5

17. The compound of claim 1, wherein the linker of the linker-R⁶ group is R^a wherein R^a is a substituted or non-substituted C₂ alkyl, alkenyl, or alkynyl group; a substituted or non-substituted C₃ alkyl group; a substituted or non-substituted C₃ aliphatic group comprising a substituted or non-substituted alkenyl or alkynyl group; a substituted or non-substituted C₄ alkyl group; or a substituted or non-substituted C₄ aliphatic group comprising a substituted or non-substituted alkenyl or alkynyl group.

10

18. A compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide or a pharmaceutically acceptable salt thereof.

15

19. A compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide.

20 A compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, for use in therapy.

20

21. Use of a compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease in a subject wherein the disease is a disease involving a receptor-interacting protein-1 (RIP 1) kinase, wherein the disease involving the RIP1 kinase is selected from ankylosing spondylitis, rheumatoid arthritis, atopic dermatitis, psoriasis, and any combination thereof.

25

22. The use of claim 21, wherein the disease involving the RIP1 kinase is ankylosing spondylitis.

23. The use of claim 21, wherein the disease involving the RIP1 kinase is rheumatoid arthritis.

30

24. The use of claim 21, wherein the disease involving the RIP1 kinase is atopic dermatitis.

25. The use of claim 21, wherein the disease involving the RIP1 kinase is psoriasis.

26. A compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide for use in therapy.

35

27. Use of a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide in the manufacture of a medicament for treating a disease in a subject wherein the disease is a disease involving a receptor-interacting protein-1 (RIP 1) kinase, wherein the disease involving the RIP1 kinase is psoriasis.

5

28. Use of a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide in the manufacture of a medicament for treating a disease in a subject wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase, wherein the disease involving the RIP1 kinase is rheumatoid arthritis.

10

29. Use of a compound of (S)-5-benzyl-N-(7-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-1,2,4-triazole-3-carboxamide in the manufacture of a medicament for treating a disease in a subject wherein the disease is a disease involving a receptor-interacting protein-1 (RIP1) kinase, wherein the disease involving the RIP1 kinase is atopic dermatitis.

15