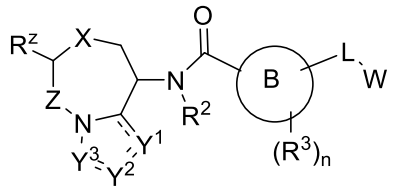
RIP1K INHIBITORS

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.

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 a first aspect of the present disclosure, there is provided a compound according to the formula



wherein

X is selected from CH_2, O, S, S(O), $S(O)_2$ and NR^a;

R^a is for each occurrence selected from hydrogen, C_{1-6}alkyl and C_{1-6}acyl;

Y^1, Y^2 and Y^3 are independently selected from the group consisting of N, $N(R^a)$, O, $C(R^b)_{1-2}$ and C=O;

R^b is selected from hydrogen, C_{1-6}alkyl and halo;

Z is $C(R^c)$ or NR^c;

R^c is a C_{1-4} unsaturated carbon chain optionally substituted with one or more R^1 groups, optionally interrupted by 1 or 2 heteroatoms selected from O, N and S;

R^z is N, CH or $C(R^1)$ and together with ZR^c and the carbon to which they are bound form a 5 or 6 membered heteroaryl or 6-membered aryl ring substituted with m R^1 groups;

R^1 is a linker-R^6 group, wherein the linker is a bond, (C1-C4) alkanyl, (C1-C4) alkenyl or (C1-C4) alkynyl, optionally substituted by one or more R^b and R^6 is R^e, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$;

R^2 is R^a;

ring B is 5 – 10-membered heteroaryl;

R^3 is, for each occurrence, independently selected from R^b and OR^a;

L is O, NR^a or alkylene;

W is 5 – 10 membered aryl or heteroaryl optionally substituted by p R^4;

R^4 is for each occurrence selected from R^b and OR^a;

R^d is for each occurrence independently selected from hydrogen, C_{1-6}alkyl, aralkyl, C_{5-10} aryl or heteroaryl, or two R^d together with a nitrogen to which they are both attached form a C_{3-10}heterocyclic group optionally substituted by one or more R^e;

R^e is independently for each occurrence halo, $-OR^d$, $-SR^d$, $-S(O)_2R^d$, $-NR^dR^d$, $-Si(R^a)_3$, -C(O)OH, $-C(O)OR^a$, or $-C(O)NR^dR^d$;

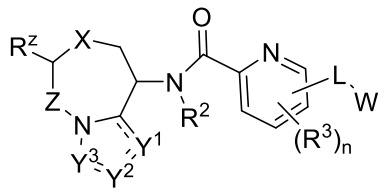
R^f is independently for each occurrence R^a, R^b, or R^e, or two R^f groups together with the carbon atom bound thereto provide a C_{3-6}cycloalkyl group or a C_{3-10}heterocyclic group each optionally substituted with one or more R^e;

m is 1, 2, 3, or 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 according to the formula



wherein

X is selected from CH_2, O, S, S(O), $S(O)_2$ and NR^a;

R^a is for each occurrence selected from hydrogen, C_{1-6}alkyl and C_{1-6}acyl;

Y^1, Y^2 and Y^3 are independently selected from the group consisting of N, $N(R^a)$, O, $C(R^b)_{1-2}$ and C=O;

R^b is selected from hydrogen, C_{1-6}alkyl and halo;

Z is $C(R^c)$ or NR^c;

R^c is a C_{1-4} unsaturated carbon chain optionally substituted with one or more R^1 groups, optionally interrupted by 1 or 2 heteroatoms selected from O, N and S;

R^z is N, CH or $C(R^1)$ and together with ZR^c and the carbon to which they are bound form a 5 or 6 membered heteroaryl or 6-membered aryl ring optionally substituted with m R^1 groups;

R^1 is halo or a linker-R^6 group, wherein the linker is a bond, (C1-C4) alkanyl, (C1-C4) alkenyl or (C1-C4) alkynyl, optionally substituted by one or more R^b and R^6 is R^e, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$;

R^2 is R^a;

ring B is 5 – 10-membered heteroaryl;

R^3 is, for each occurrence, independently selected from R^b and OR^a;

L is O, NR^a or alkylene;

W is 5 – 10 membered aryl or heteroaryl optionally substituted by p R^4;

R^4 is for each occurrence selected from R^b and OR^a;

R^d is for each occurrence independently selected from hydrogen, C_{1-6}alkyl, aralkyl, C_{5-10} aryl or heteroaryl, or two R^d together with a nitrogen to which they are both attached form a C_{3-10}heterocyclic group optionally substituted by one or more R^e;

R^e is independently for each occurrence halo, $-OR^d$, $-SR^d$, $-S(O)_2R^d$, $-NR^dR^d$, $-Si(R^a)_3$, -C(O)OH, $-C(O)OR^a$, or $-C(O)NR^dR^d$;

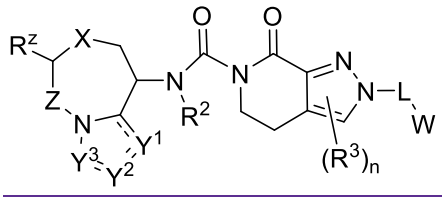
R^f is independently for each occurrence R^a, R^b, or R^e, or two R^f groups together with the carbon atom bound thereto provide a C_{3-6}cycloalkyl group or a C_{3-10}heterocyclic group each optionally substituted with one or more R^e;

m is 1, 2, 3, or 4;

n is 0, 1 or 2; and

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

In yet another aspect of the present disclosure, there is provided a compound according to the formula



wherein

X is selected from CH_2, O, S, S(O), $S(O)_2$ and NR^a;

R^a is for each occurrence selected from hydrogen, C_{1-6}alkyl and C_{1-6}acyl;

Y^1, Y^2 and Y^3 are independently selected from the group consisting of N, $N(R^a)$, O, $C(R^b)_{1-2}$ and C=O;

R^b is selected from hydrogen, C_{1-6}alkyl and halo;

Z is $C(R^c)$ or NR^c;

R^c is a C_{1-4} unsaturated carbon chain optionally substituted with one or more R^1 groups, optionally interrupted by 1 or 2 heteroatoms selected from O, N and S;

R^z is N, CH or $C(R^1)$ and together with ZR^c and the carbon to which they are bound form a 5 or 6 membered heteroaryl or 6-membered aryl ring optionally substituted with m R^1 groups;

R^1 is halo or a linker-R^6 group, wherein the linker is a bond, (C1-C4) alkanyl, (C1-C4) alkenyl or (C1-C4) alkynyl, optionally substituted by one or more R^b and R^6 is R^e, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$;

R^2 is R^a;

ring B is 5 – 10-membered heteroaryl;

R^3 is, for each occurrence, independently selected from R^b and OR^a;

L is O, NR^a or alkylene;

W is 5 – 10 membered aryl or heteroaryl optionally substituted by p R^4;

R^4 is for each occurrence selected from R^b and OR^a;

R^d is for each occurrence independently selected from hydrogen, C_{1-6}alkyl, aralkyl, C_{5-10} aryl or heteroaryl, or two R^d together with a nitrogen to which they are both attached form a C_{3-10}heterocyclic group optionally substituted by one or more R^e;

R^e is independently for each occurrence halo, $-OR^d$, $-SR^d$, $-S(O)_2R^d$, $-NR^dR^d$, $-Si(R^a)_3$, -C(O)OH, $-C(O)OR^a$, or $-C(O)NR^dR^d$;

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 C_{3-6}cycloalkyl group or a

C_{3-10}heterocyclic group each optionally substituted with one or more R^e;

m is 1, 2, 3, or 4;

n is 0, 1 or 2; and

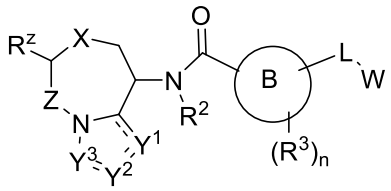
p is 0, 1, 2, 3, 4, or 5.

In a further aspect of the present disclosure, there is provided a use of the compound as disclosed herein in the manufacture of a medicament for the treatment of a condition, wherein the condition is associated with RIP1K.

In another aspect of the present disclosure, there is provided the compound as disclosed herein for use in the treatment of a condition associated with RIP1K.

DESCRIPTION

Disclosed herein are compounds according to the formula



wherein

X is selected from CH_2, O, S, S(O), $S(O)_2$ and NR^a;

R^a is for each occurrence selected from hydrogen, C_{1-6}alkyl and C_{1-6}acyl;

Y^1, Y^2 and Y^3 are independently selected from the group consisting of N, $N(R^a)$, O, $C(R^b)_{1-2}$ and C=O;

R^b is selected from hydrogen, C_{1-6}alkyl and halo;

Z is $C(R^c)$ or NR^c;

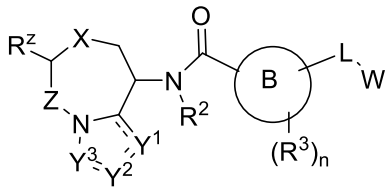
R^c is a C_{1-4} unsaturated carbon chain optionally substituted with one or more R^1 groups, optionally interrupted by 1 or 2 heteroatoms selected from O, N and S;

R^z is N, CH or $C(R^1)$ and together with ZR^c and the carbon to which they are bound form a 5 or 6 membered heteroaryl or 6-membered aryl ring optionally substituted with m R^1 groups;

R^1 is a halogen, a linker-R^6 group, wherein the linker is a bond, (C1-C4) alkanyl, (C1-C4) alkenyl or (C1-C4) alkynyl, optionally substituted by one or more R^b and R^6 is R^e, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$;

We claim:

1. A compound according to the formula



wherein

X is selected from CH_2, O, S, S(O), $S(O)_2$ and NR^a;

R^a is for each occurrence selected from hydrogen, C_{1-6}alkyl and C_{1-6}acyl;

Y^1, Y^2 and Y^3 are independently selected from the group consisting of N, $N(R^a)$, O, $C(R^b)_{1-2}$ and C=O;

R^b is selected from hydrogen, C_{1-6}alkyl and halo;

Z is $C(R^c)$ or NR^c;

R^c is a C_{1-4} unsaturated carbon chain optionally substituted with one or more R^1 groups, optionally interrupted by 1 or 2 heteroatoms selected from O, N and S;

R^z is N, CH or $C(R^1)$ and together with ZR^c and the carbon to which they are bound form a 5 or 6 membered heteroaryl or 6-membered aryl ring substituted with m R^1 groups;

R^1 is a linker-R^6 group, wherein the linker is a bond, (C1-C4) alkanyl, (C1-C4) alkenyl or (C1-C4) alkynyl, optionally substituted by one or more R^b and R^6 is R^e, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$;

R^2 is R^a;

ring B is 5 – 10-membered heteroaryl;

R^3 is, for each occurrence, independently selected from R^b and OR^a;

L is O, NR^a or alkylene;

W is 5 – 10 membered aryl or heteroaryl optionally substituted by p R^4;

R^4 is for each occurrence selected from R^b and OR^a;

R^d is for each occurrence independently selected from hydrogen, C_{1-6}alkyl, aralkyl, C_{5-10} aryl or heteroaryl, or two R^d together with a nitrogen to which they are both attached form a C_{3-10}heterocyclic group optionally substituted by one or more R^e;

R^e is independently for each occurrence halo, $-OR^d$, $-SR^d$, $-S(O)_2R^d$, $-NR^dR^d$, $-Si(R^a)_3$, -C(O)OH, $-C(O)OR^a$, or $-C(O)NR^dR^d$;

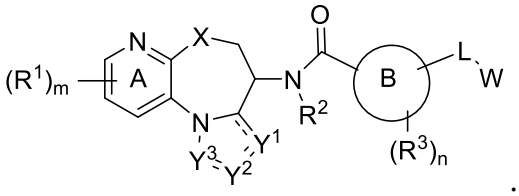
R^f is independently for each occurrence R^a, R^b, or R^e, or two R^f groups together with the carbon atom bound thereto provide a C_{3-6}cycloalkyl group or a C_{3-10}heterocyclic group each optionally substituted with one or more R^e;

m is 1, 2, 3, or 4;

n is 0, 1 or 2; and

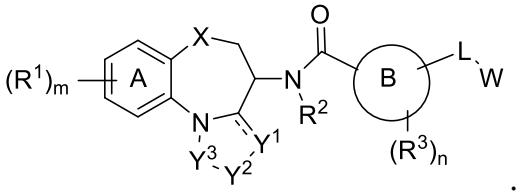
p is 0, 1, 2, 3, 4, or 5.

2. The compound of claim 1, having the formula



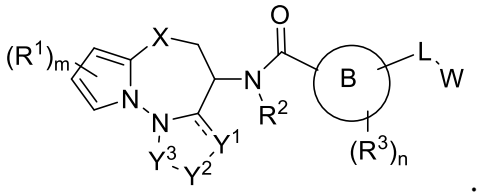
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3. The compound of claim 1, having the formula



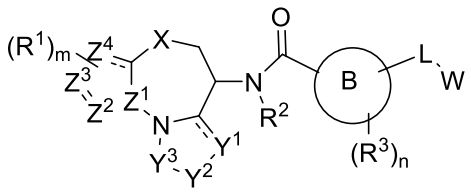
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4. The compound of claim 1, having the formula



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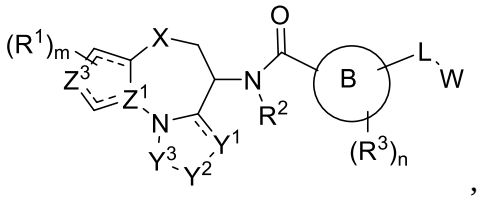
5. The compound of claim 1, having the formula



wherein Z^1 is selected from C and N; and

Z^2, Z^3 and Z^4 independently are selected from O, S, $S(O)_2$, CH, N, $N(R^a)$ and CR^1.

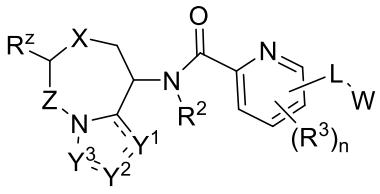
6. The compound of claim 1, having the formula



,

wherein Z^1 is C or N and Z^3 is O, S, N or $N(R^a)$.

7. A compound according to the formula



wherein

X is selected from CH_2, O, S, S(O), $S(O)_2$ and NR^a;

R^a is for each occurrence selected from hydrogen, $C_{1\text{-}6}$alkyl and $C_{1\text{-}6}$acyl;

Y^1, Y^2 and Y^3 are independently selected from the group consisting of N, $N(R^a)$, O, $C(R^b)_{1\text{-}2}$ and C=O;

R^b is selected from hydrogen, $C_{1\text{-}6}$alkyl and halo;

Z is $C(R^c)$ or NR^c;

R^c is a $C_{1\text{-}4}$ unsaturated carbon chain optionally substituted with one or more R^1 groups, optionally interrupted by 1 or 2 heteroatoms selected from O, N and S;

R^z is N, CH or C(R^1) and together with ZR^c and the carbon to which they are bound form a 5 or 6 membered heteroaryl or 6-membered aryl ring optionally substituted with m R^1 groups;

R^1 is halo or a linker-R^6 group, wherein the linker is a bond, (C1-C4) alkanyl, (C1-C4) alkenyl or (C1-C4) alkynyl, optionally substituted by one or more R^b and R^6 is R^e, -$C(R^f)_3$, or -$C(R^f)=C(R^f)_2$;

R^2 is R^a;

ring B is 5 – 10-membered heteroaryl;

R^3 is, for each occurrence, independently selected from R^b and OR^a;

L is O, NR^a or alkylene;

W is 5 – 10 membered aryl or heteroaryl optionally substituted by p R^4;

R^4 is for each occurrence selected from R^b and OR^a;

R^d is for each occurrence independently selected from hydrogen, C_{1-6}alkyl, aralkyl, C_{5-10} aryl or heteroaryl, or two R^d together with a nitrogen to which they are both attached form a C_{3-10}heterocyclic group optionally substituted by one or more R^e;

R^e is independently for each occurrence halo, -OR^d, -SR^d, -$S(O)_2R^d$, -NR^dR^d, -$Si(R^a)_3$, -C(O)OH, -$C(O)OR^a$, or -$C(O)NR^dR^d$;

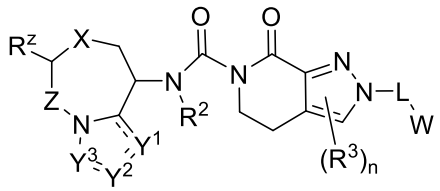
R^f is independently for each occurrence R^a, R^b, or R^e, or two R^f groups together with the carbon atom bound thereto provide a C_{3-6}cycloalkyl group or a C_{3-10}heterocyclic group each optionally substituted with one or more R^e;

m is 1, 2, 3, or 4;

n is 0, 1 or 2; and

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

8. A compound according to the formula



wherein

X is selected from CH_2, O, S, S(O), $S(O)_2$ and NR^a;

R^a is for each occurrence selected from hydrogen, C_{1-6}alkyl and C_{1-6}acyl;

Y^1, Y^2 and Y^3 are independently selected from the group consisting of N, $N(R^a)$, O, $C(R^b)_{1-2}$ and C=O;

R^b is selected from hydrogen, C_{1-6}alkyl and halo;

Z is $C(R^c)$ or NR^c;

R^c is a C_{1-4} unsaturated carbon chain optionally substituted with one or more R^1 groups, optionally interrupted by 1 or 2 heteroatoms selected from O, N and S;

R^z is N, CH or $C(R^1)$ and together with ZR^c and the carbon to which they are bound form a 5 or 6 membered heteroaryl or 6-membered aryl ring optionally substituted with m R^1 groups;

R^1 is halo or a linker-R^6 group, wherein the linker is a bond, (C1-C4) alkanyl, (C1-C4) alkenyl or (C1-C4) alkynyl, optionally substituted by one or more R^b and R^6 is R^e, $-C(R^f)_3$, or $-C(R^f)=C(R^f)_2$;

R^2 is R^a;

ring B is 5 – 10-membered heteroaryl;

R^3 is, for each occurrence, independently selected from R^b and OR^a;

L is O, NR^a or alkylene;

W is 5 – 10 membered aryl or heteroaryl optionally substituted by p R^4;

R^4 is for each occurrence selected from R^b and OR^a;

R^d is for each occurrence independently selected from hydrogen, C_{1-6}alkyl, aralkyl, C_{5-10} aryl or heteroaryl, or two R^d together with a nitrogen to which they are both attached form a C_{3-10}heterocyclic group optionally substituted by one or more R^e;

R^e is independently for each occurrence halo, $-OR^d$, $-SR^d$, $-S(O)_2R^d$, $-NR^dR^d$, $-Si(R^a)_3$, -C(O)OH, $-C(O)OR^a$, or $-C(O)NR^dR^d$;

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 C_{3-6}cycloalkyl group or a C_{3-10}heterocyclic group each optionally substituted with one or more R^e;

m is 1, 2, 3, or 4;

n is 0, 1 or 2; and

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

9. The compound according to any one of claims 1-8, wherein X is O.

10. The compound of any of claims 1-8, wherein Y^1 is N.

11. The compound of any of claims 1-8, wherein Y^1, Y^2 and Y^3 are each N.

12. The compound of any of claims 1-8, wherein Y^2 is O.

13. The compound of any of claims 1 – 8, wherein Y^3 is C=O.

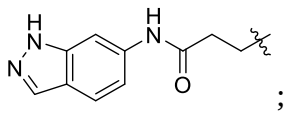
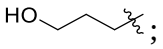
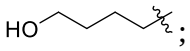
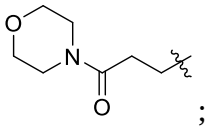
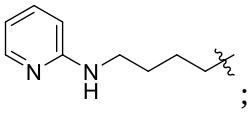
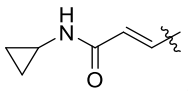
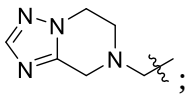
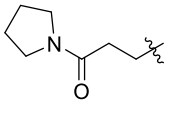
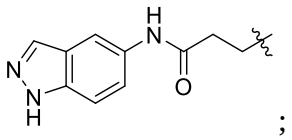
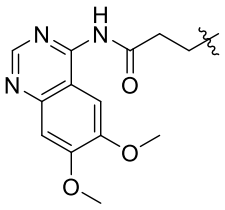
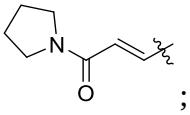
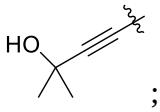
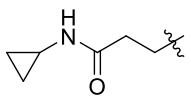
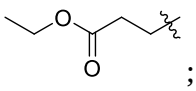
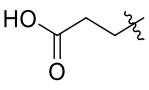
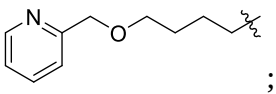
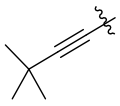
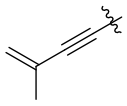
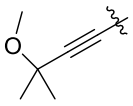
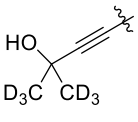
14. The compound of any of claims 1-8, wherein Y^1, Y^2 and Y^3 are each $C(R^b)_{1-2}$.

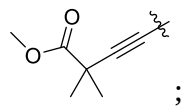
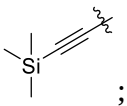
15. The compound of claim 14, wherein at least one R^b of Y^1, Y^2 and Y^3 is halo.

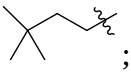
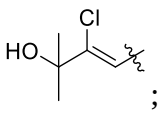
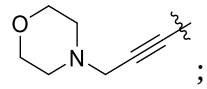
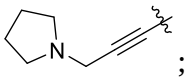
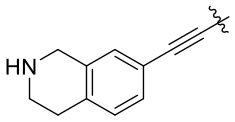
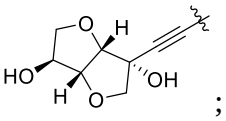
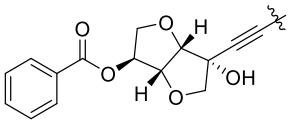
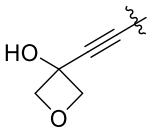
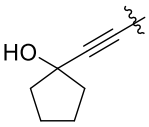
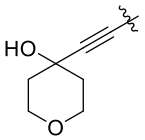
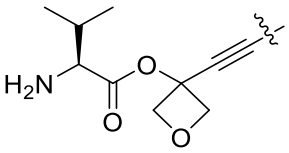
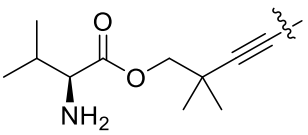
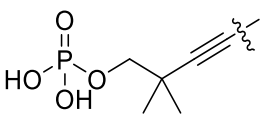
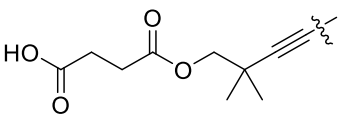
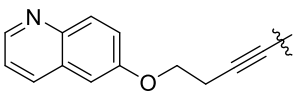
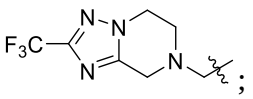
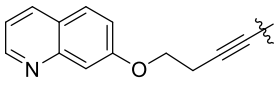
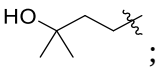
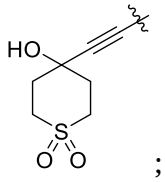
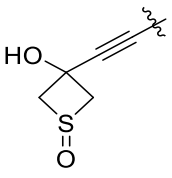
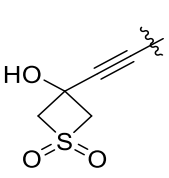
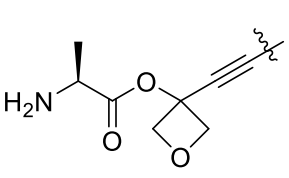
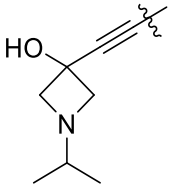
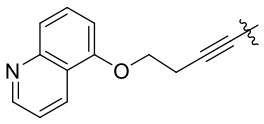
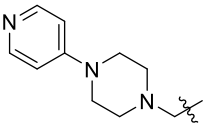
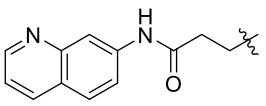
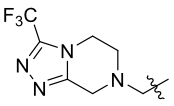
16. The compound of any of claims 1-8, wherein m is zero.

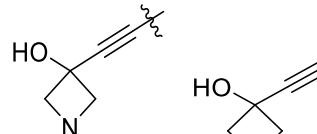
17. The compound of any of claims 1-8, wherein at least one R^1 is a linker-R^6 group and the R^6 group is selected from the group consisting of

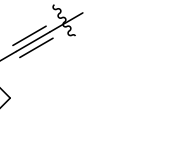
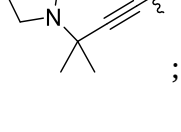
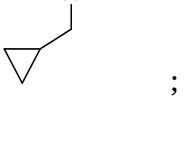
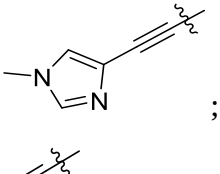
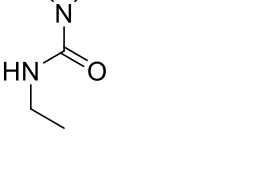
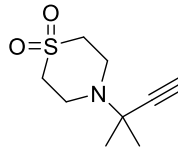
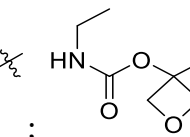
18. The compound of any one of claims 1-8, wherein at least one R^1 is


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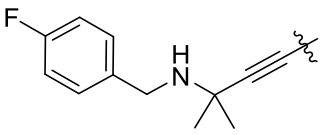
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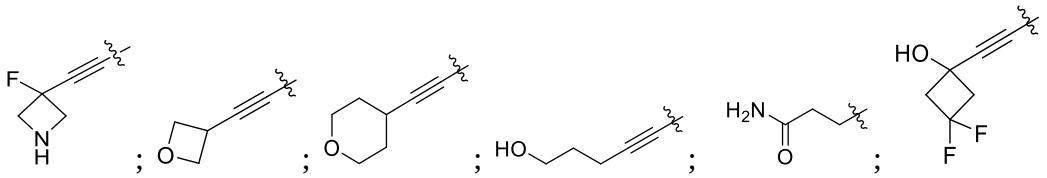
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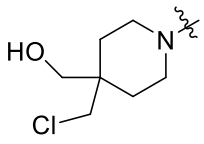
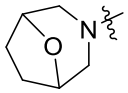
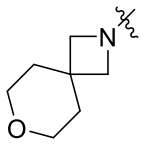
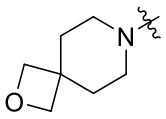
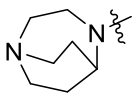
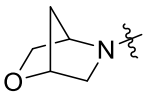
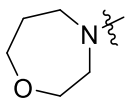
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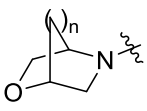
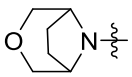
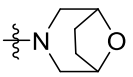


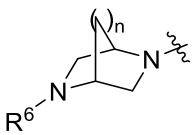
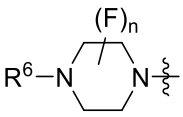
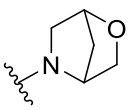
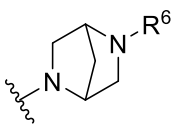
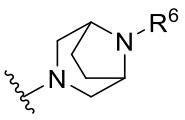
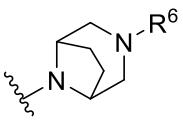
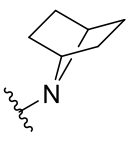
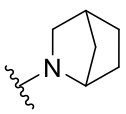
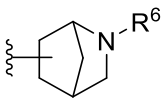
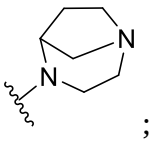
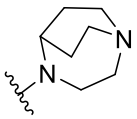
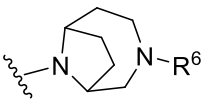


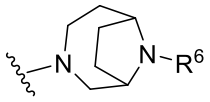
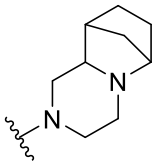
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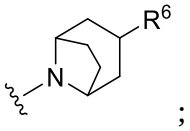
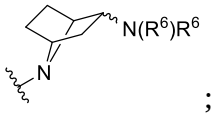
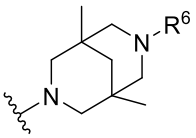
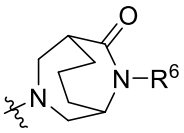
19. The compound of any one of claims 1-8, wherein at least one R^1 is

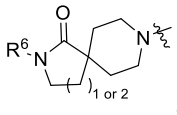
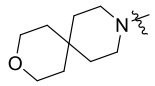
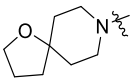
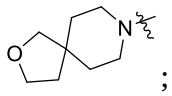
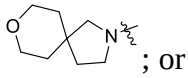
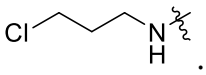

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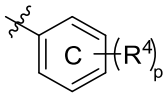
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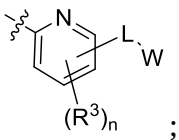
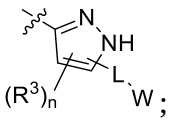
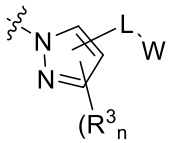
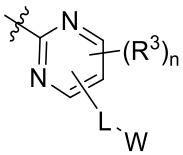
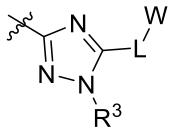
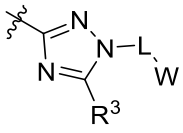

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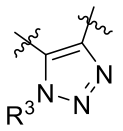
20. The compound according to any of claims 1-8, wherein W is

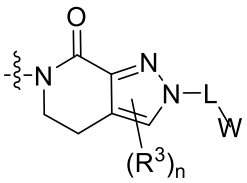

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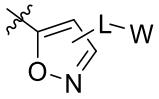
21. The compound according to any of claims 1-8, wherein W is pyridyl.

22. The compound according to any of claims 1-6, wherein the B ring has the formula

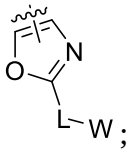

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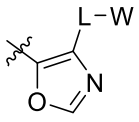




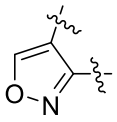
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or



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23. The compound according to any one of claims 1-8, wherein the compound is present in a salt form.

~~24. A method for treating a RIP1K associated condition in a subject, comprising administering to the subject a therapeutically effective amount of a compound according to any one of claims 1-6.~~

24. Use of the compound of any one of claims 1-23 in the manufacture of a medicament for the treatment of a condition, wherein the condition is associated with RIP1K.

25. The compound according to any one of claims 1-23 for use in the treatment of a condition associated with RIP1K.