RIP1K INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of the earlier filing date of U.S. Provisional Application No. 63/004,404, filed on April 2, 2020.

FIELD

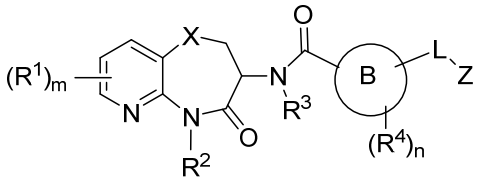
The present disclosure concerns compounds and methods of making and using the compounds, such as for inhibiting receptor-interacting protein-1 kinase ("RIP1"), and for treating diseases and/or conditions related to RIP1.

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 according to Formula I



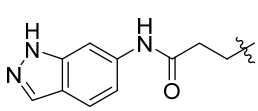
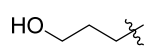
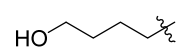
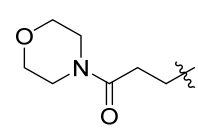
wherein ring B is 5-membered or 6-membered heteroaryl;

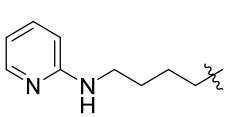
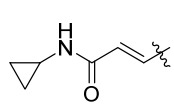
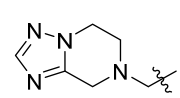
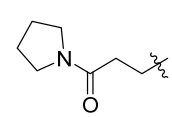
X is CH_2 or O;

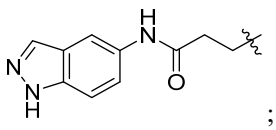
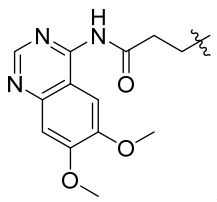
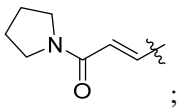
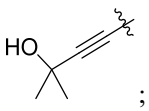
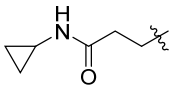
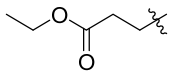
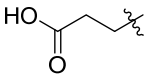
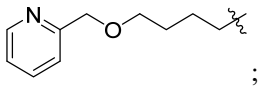
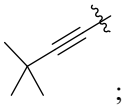
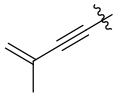
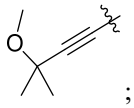
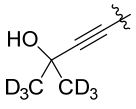
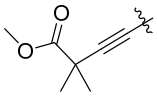
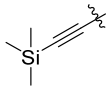
L is O, NH, S, or C_{1-10}alkyl;

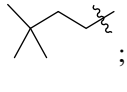
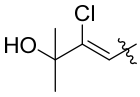
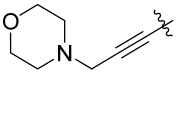
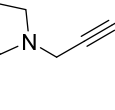
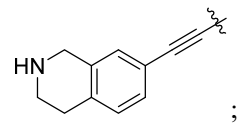
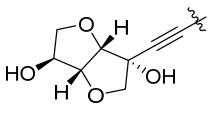
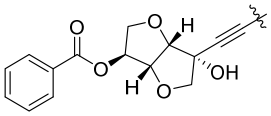
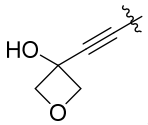
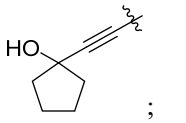
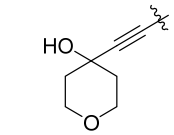
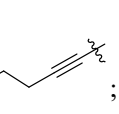
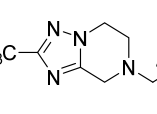
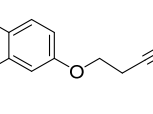
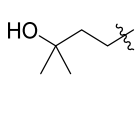
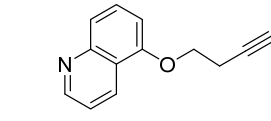
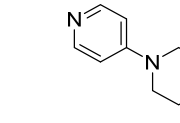
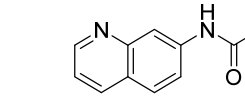
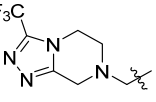
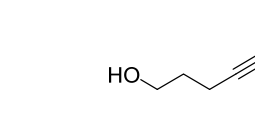
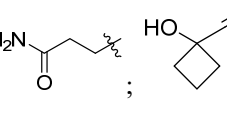
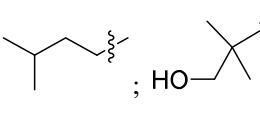
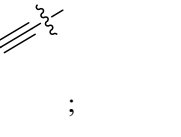
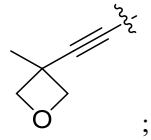
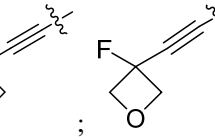
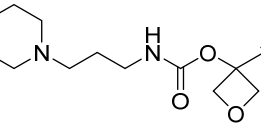
Z is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-6}cycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R^5 group;

R^1 is independently for each occurrence

 ;  ;  ;  ;

 ;  ;  ;  ;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

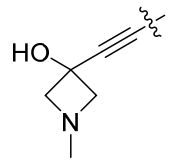
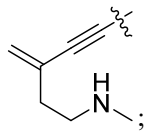
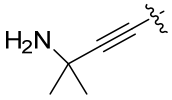
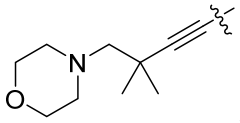
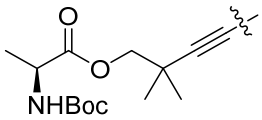
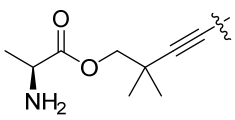
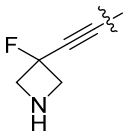
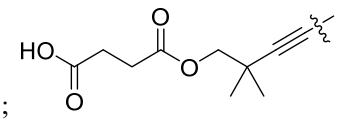
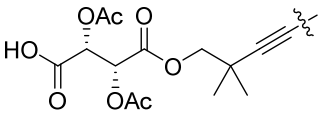
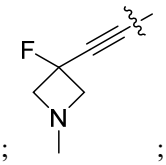
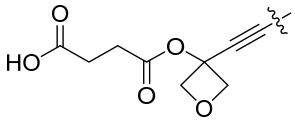
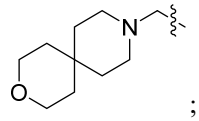
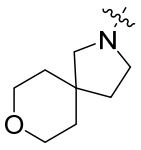
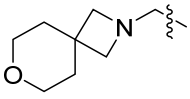
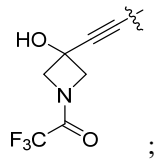
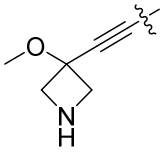
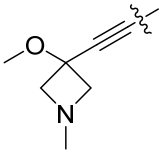
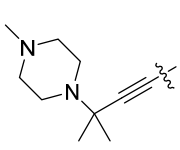
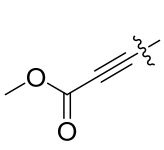
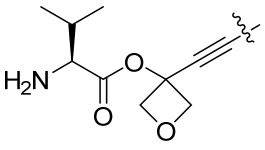
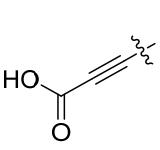
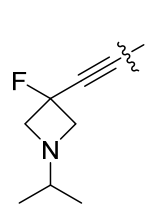
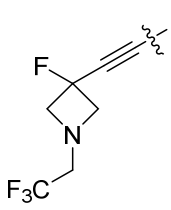
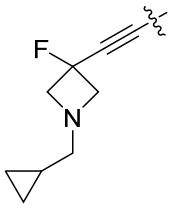
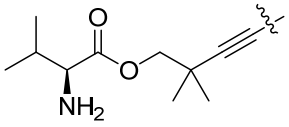
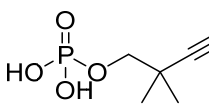
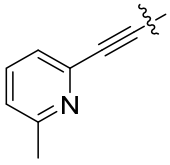
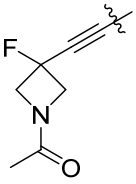
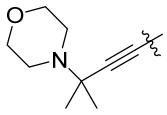
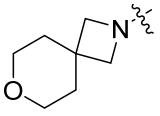
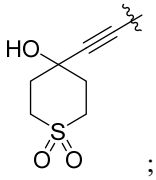
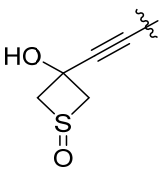
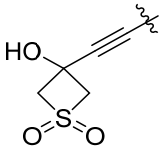
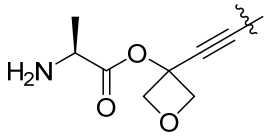
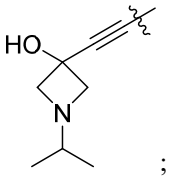
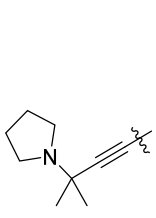
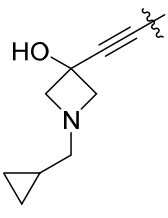
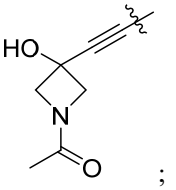
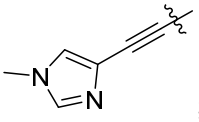
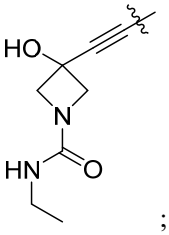
;

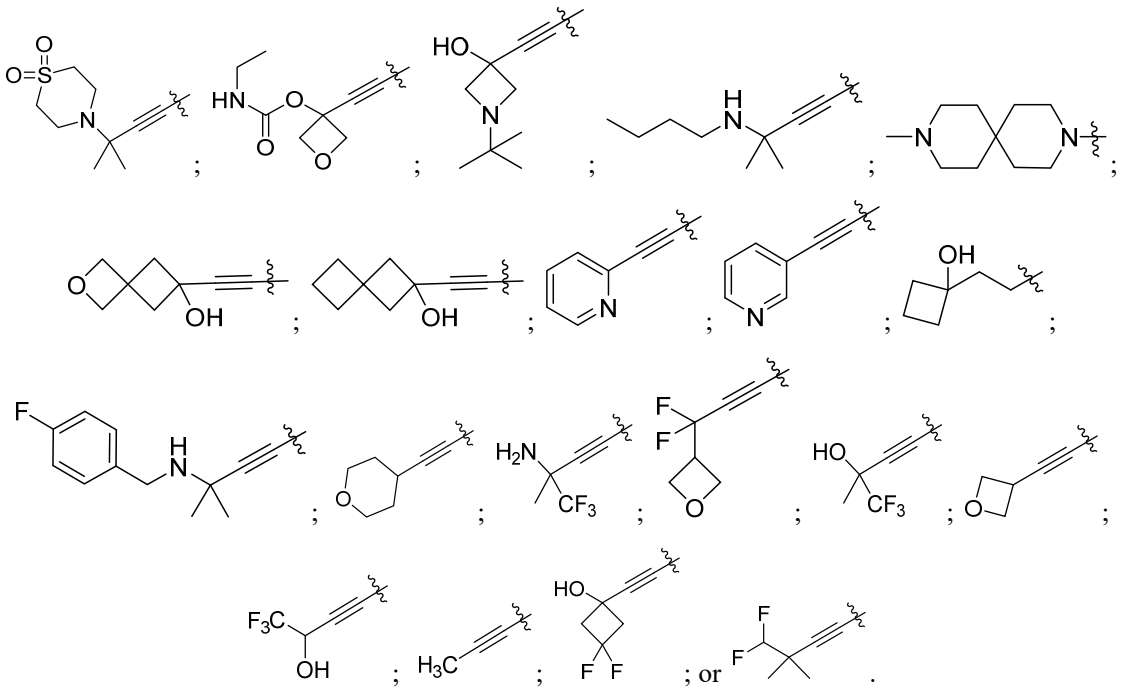
;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;



R^2 and R^3 independently are for each occurrence, H or $C_{1\text{-}3}$alkyl;

R^4 and R^5 independently are, for each occurrence, halo or $C_{1\text{-}10}$alkyl;

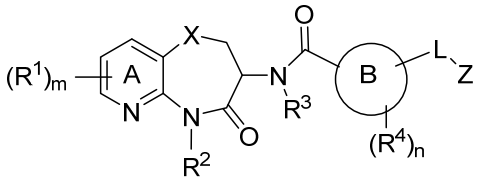
m is 1 to 4; and

n is 0, 1 or 2

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, in the manufacture of a medicament for the treatment of a disease, wherein the disease is amyotrophic lateral sclerosis (ALS), multiple sclerosis, Parkinson's disease, or Alzheimer's disease.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in the treatment of a disease, wherein the disease is amyotrophic lateral sclerosis (ALS), multiple sclerosis, Parkinson's disease, or Alzheimer's disease.

Disclosed herein are compounds according to Formula I



wherein ring B is 5-membered or 6-membered heteroaryl;

X is CH_2 or O;

L is a heteroatom or R^a, provided that R^a is not hydrogen;

Z is $C_{1\text{-}10}$aliphatic (such as $C_{1\text{-}10}$alkyl, $C_{2\text{-}10}$alkenyl, $C_{2\text{-}10}$alkynyl, $C_{3\text{-}6}$cycloalkyl); aryl or heteroaryl, each optionally substituted with one or more R^5 group;

R^1 is independently for each occurrence $-NR^dR^d$ wherein the two R^d groups together with the nitrogen bound thereto provide a C_{3-10}heterocyclic group; $-C{\equiv}CH$, or a -linker-R^6 group, wherein the linker is a divalent C_{1-10}aliphatic moiety (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl) or C_{1-10}cycloaliphatic moiety, and R^6 is R^b, $-C(R^f)_3$, or $-C(R^f){=}C(R^f)_2$; C_{5-10}aromatic, or C_{3-6}heterocyclic, each linker optionally substituted with one or more halo, R^a, or both;

R^2 and R^3 independently are R^a In some examples, R^2 is hydrogen or C_{1-10}aliphatic, such as H or C_{1-6}alkyl, and in certain examples, R^2 is C_{1-6}alkyl, such as CH_3 or CD_3;

R^4 and R^5 independently are, for each occurrence, R^e;

R^a is independently for each occurrence hydrogen, C_{1-10}aliphatic (such as C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, or C_{3-6}cycloalkyl), C_{1-10}haloaliphatic, C_{5-10}aromatic, or C_{3-6}heterocyclic;

R^b is independently for each occurrence -OH, -SH, $-OR^c$, $-SR^c$, $-NR^eR^e$, $-Si(R^a)_3$, -C(O)OH, $-C(O)OR^c$, or $-C(O)NR^eR^e$

R^c is independently for each occurrence C_{1-10}alkyl (optionally substituted with 1, 2 or 3 R^e), C_{2-10}alkenyl (optionally substituted with 1, 2 or 3 R^e), C_{2-10}alkynyl (optionally substituted with 1, 2 or 3 R^e), C_{3-6}cycloalkyl (optionally substituted with 1, 2 or 3 R^e), or C_{5-10}aromatic (optionally substituted with 1, 2 or 3 R^e);

R^d is C_{1-9}aliphatic optionally substituted with 1, 2, or 3 R^a, R^b and/or R^e groups;

R^e is independently for each occurrence oxo (=O), $-OR^a$, $N(R^a)_2$, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}heteroalkyl, C_{3-6}cycloalkyl, or two R^e groups join together to provide a C_{3-10}heterocyclic group with a nitrogen to which the two R^e groups are bound;

m is 1 to 4; and

n is 0, 1 or 2.

The foregoing and other objects, features, and advantages 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.

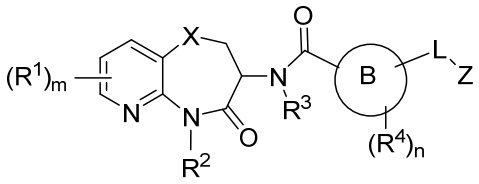
Unless otherwise indicated, all numbers expressing quantities of components, molecular weights, percentages, temperatures, times, and so forth, as used in the specification or claims are to be understood as

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 according to Formula I



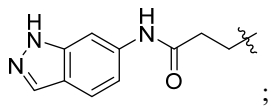
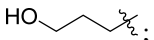
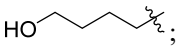
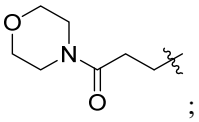
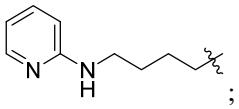
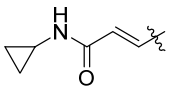
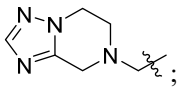
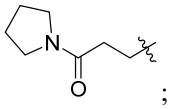
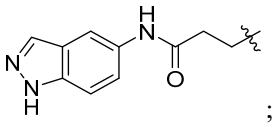
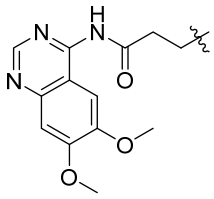
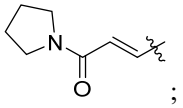
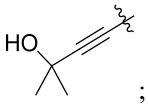
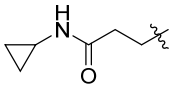
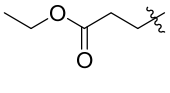
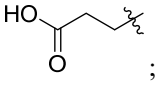
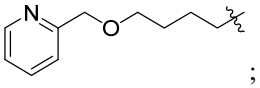
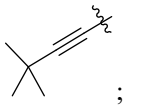
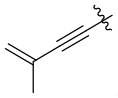
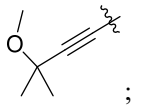
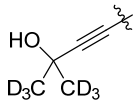
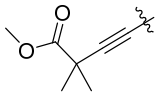
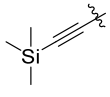
wherein ring B is 5-membered or 6-membered heteroaryl;

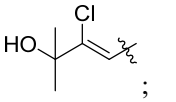
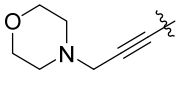
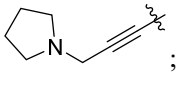
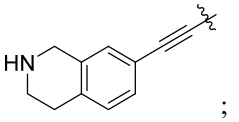
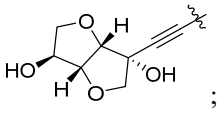
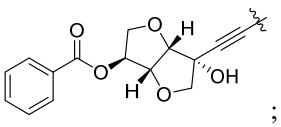
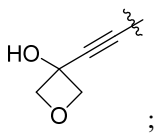
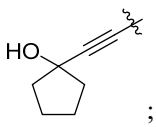
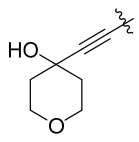
X is CH_2 or O;

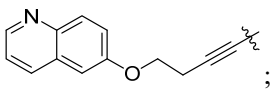
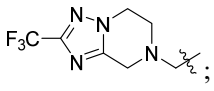
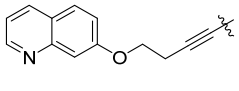
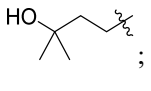
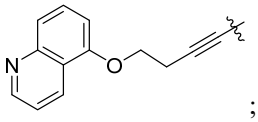
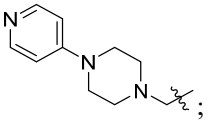
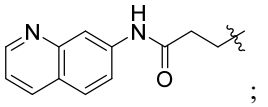
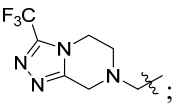
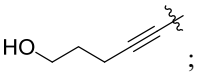
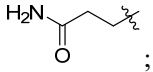
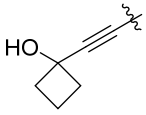
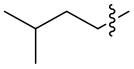
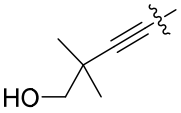
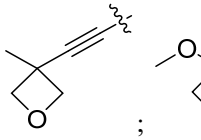
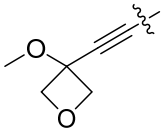
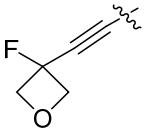
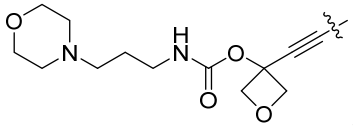
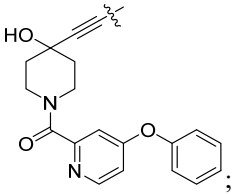
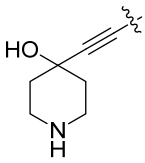
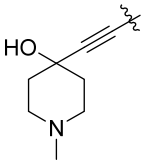
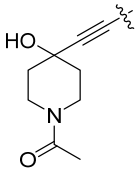
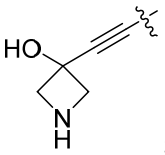
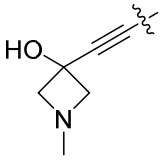
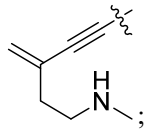
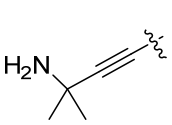
L is O, NH, S, or $C_{1\text{-}10}$alkyl;

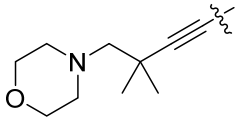
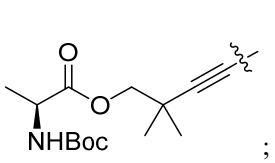
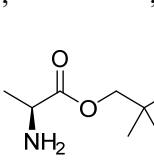
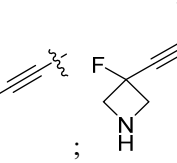
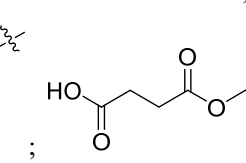
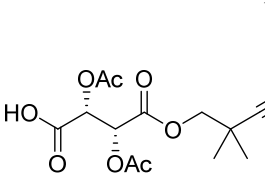
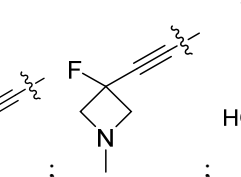
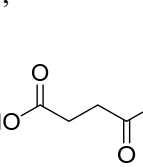
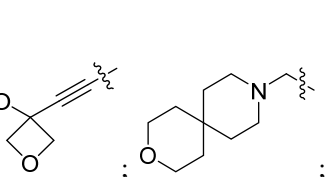
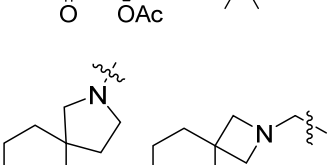
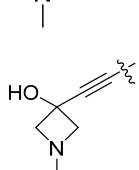
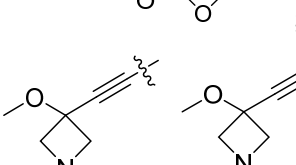
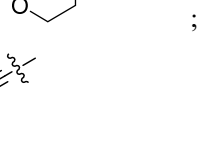
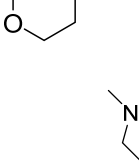
Z is $C_{1\text{-}10}$alkyl, $C_{2\text{-}10}$alkenyl, $C_{2\text{-}10}$alkynyl, $C_{3\text{-}6}$cycloalkyl, aryl, or heteroaryl, each optionally substituted with one or more R^5 group;

R^1 is independently for each occurrence


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

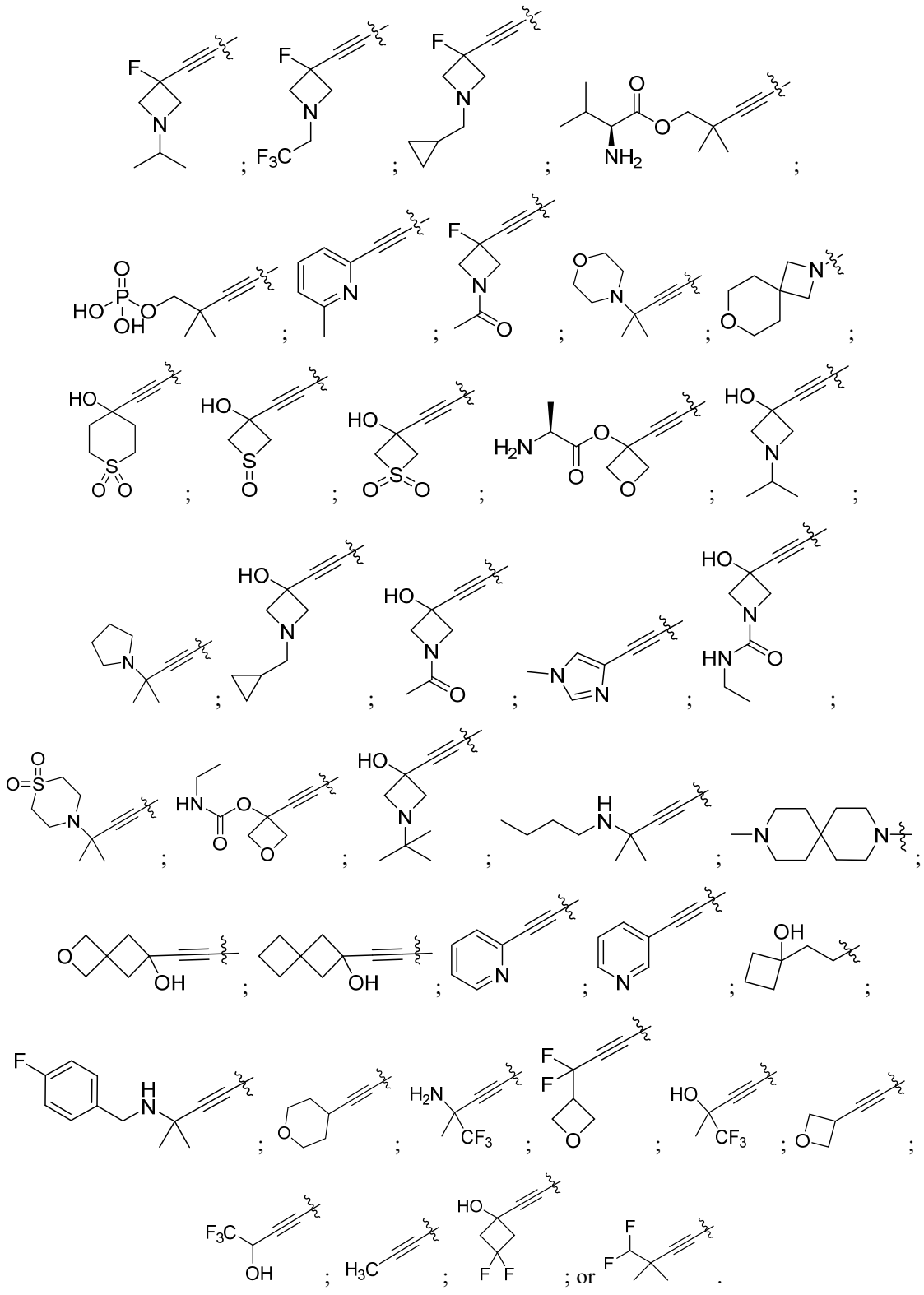
;

;

;

;

;



R^2 and R^3 independently are for each occurrence, H or $C_{1\text{-}3}$alkyl;

R^4 and R^5 independently are, for each occurrence, halo or $C_{1\text{-}10}$alkyl;

m is 1 to 4; and

n is 0, 1 or 2.

2. The compound of claim 1, wherein ring B is a 5-membered heteroaryl.

3. The compound of claim 2, wherein ring B is a triazole, a diazole, an oxazole or an oxadiazole.

4. The compound of claim 1, wherein ring B is pyrazolyl, and the -N(R^3)C(O)- moiety is attached to ring B at a ring nitrogen atom on ring B.

5. The compound of claim 1, wherein ring B is 6-membered heteroaryl.

6. The compound of claim 5, wherein ring B is pyridinyl.

7. The compound of claim 1, wherein R^2 is C_{1-3}alkyl.

8. The compound of claim 1, wherein R^2 is methyl.

9. The compound of claim 8, wherein R^2 is CD_3.

10. The compound of claim 1, wherein R^3 is H.

11. The compound of claim 1, wherein n is 0.

12. The compound of claim 1, wherein n is 1.

13. The compound of claim 1, wherein at least one R^4 is C_{1-6}alkyl.

14. The compound of claim 1, wherein at least one R^4 is fluoro.

15. The compound of claim 12, wherein R^4 is C_{1-6}alkyl or fluoro.

16. The compound of claim 1, wherein X is O.

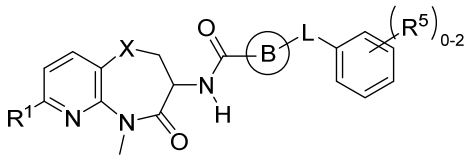
17. The compound of claim 1, wherein X is -CH_2-.

18. The compound of claim 1, wherein L is a O, NH, or S.

19. The compound of claim 11, wherein L is O.

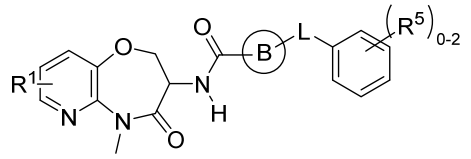
20. The compound of claim 1, wherein L is C_{1-6}alkyl.

21. The compound of claim 1, having Formula II



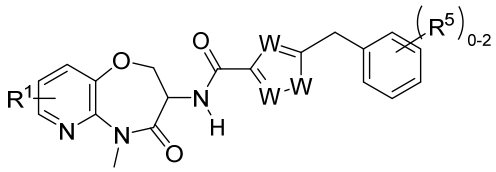
Formula II.

22. The compound of claim 1, having Formula IIA

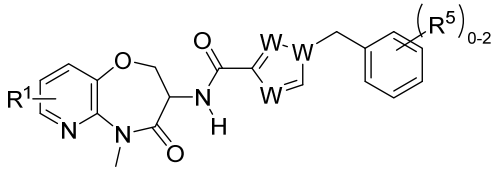


Formula IIA.

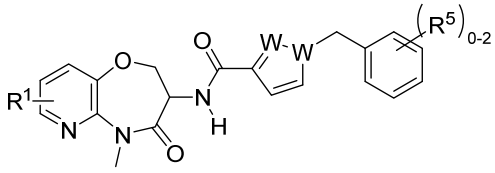
23. The compound of claim 1, having Formula IIB, IIC, IID or IIE



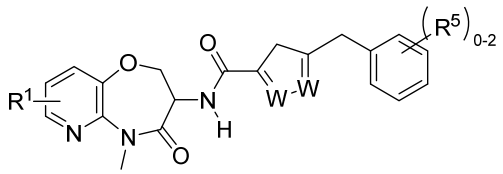
Formula IIB



Formula IIC



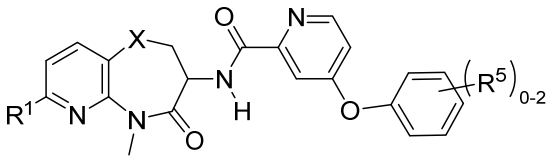
Formula IID



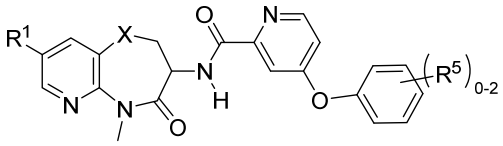
Formula IIE

wherein each W is independently N or O.

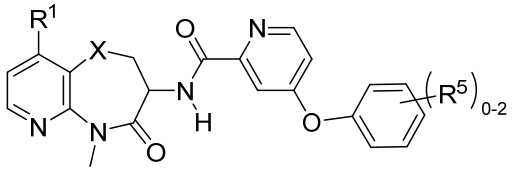
24. The compound of claim 1, having Formula IIF, IIG, IIH



Formula IIF

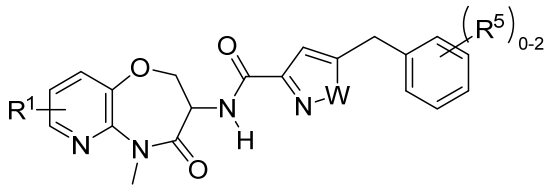


Formula IIG.



Formula IIH.

25. The compound of claim 1, having Formula IIK

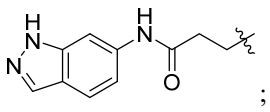
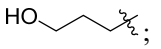
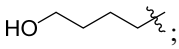
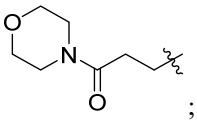
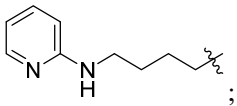
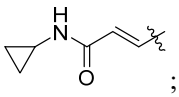
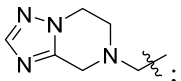
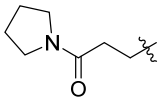
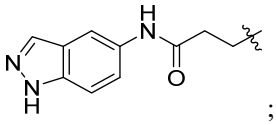
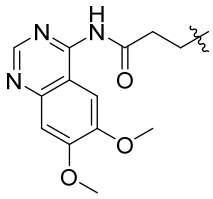
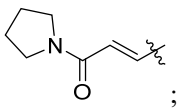
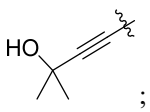
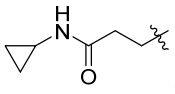
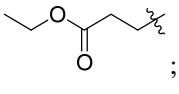
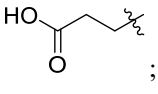
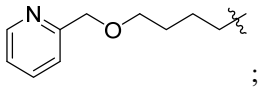
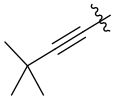
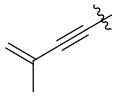
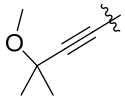
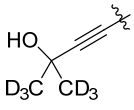
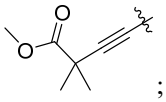
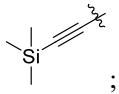


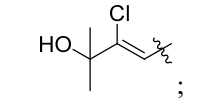
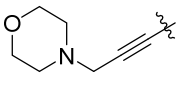
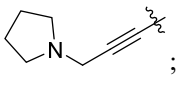
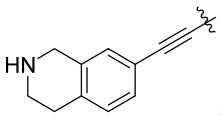
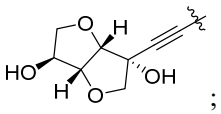
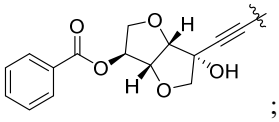
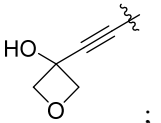
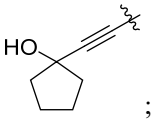
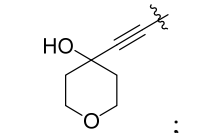
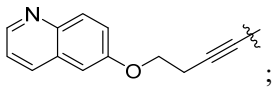
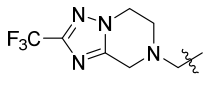
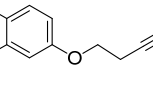
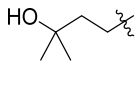
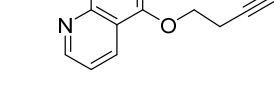
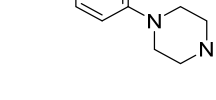
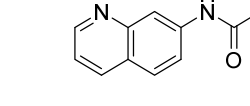
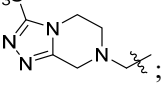
Formula IIK

wherein W is N or O.

26. The compound of claim 1, wherein m is 1.

27. The compound of claim 1, wherein at least one R^1 is selected from the following:


;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

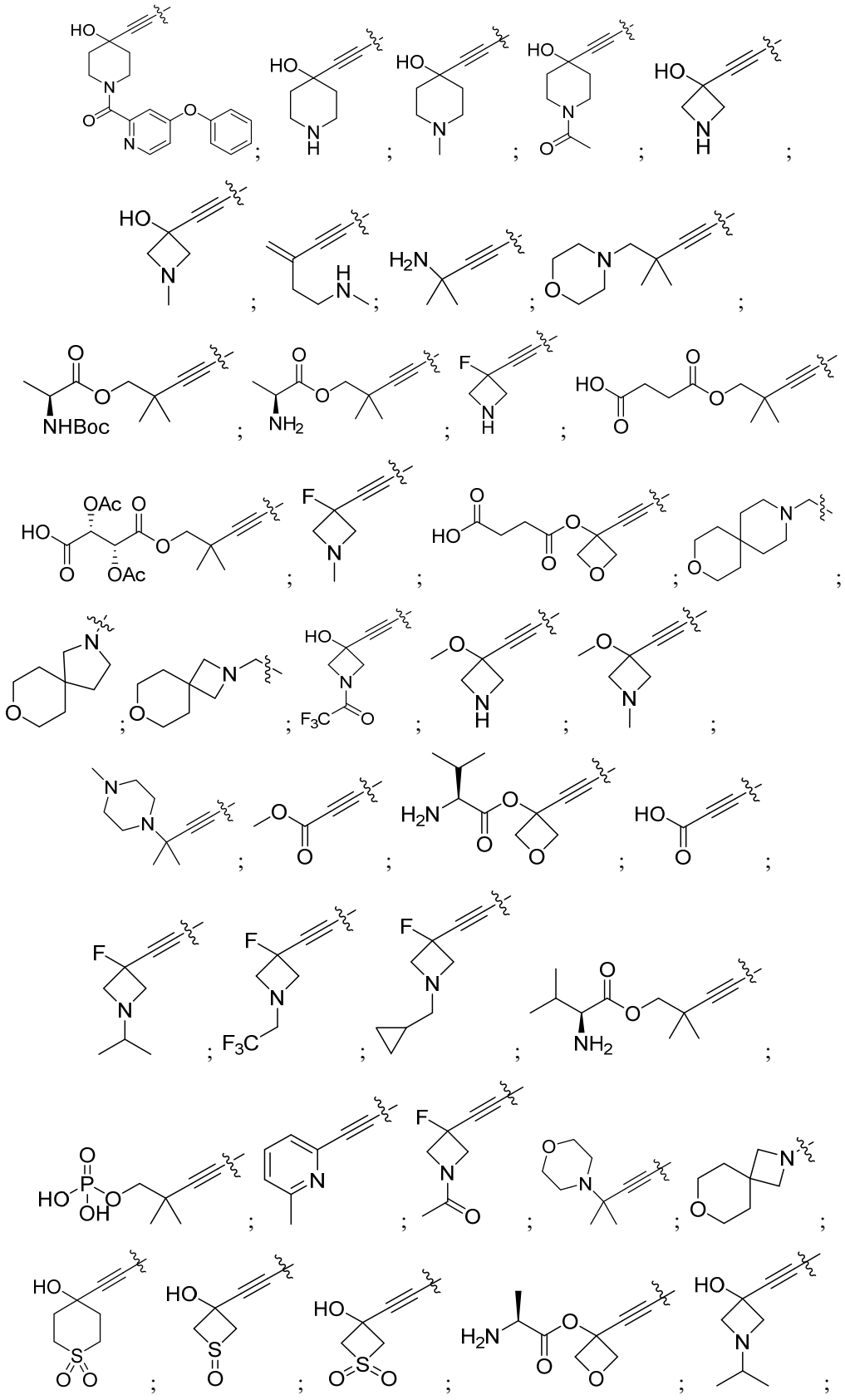
;

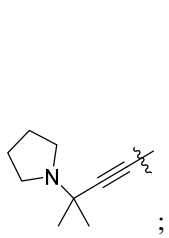
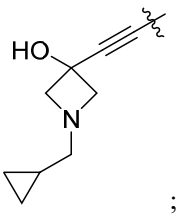
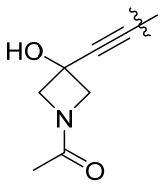
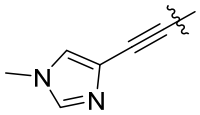
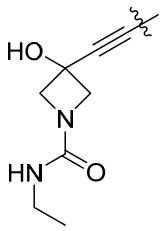
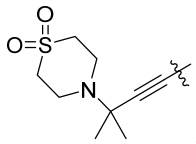
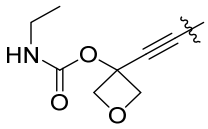
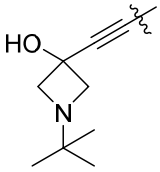
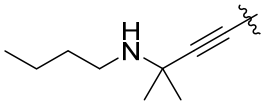
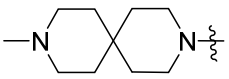
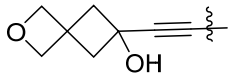
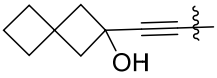
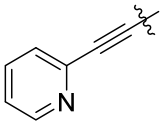
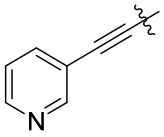
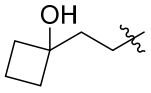
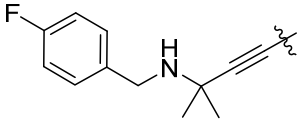
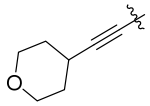
;

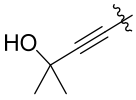
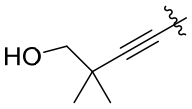
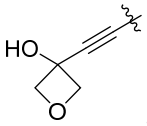
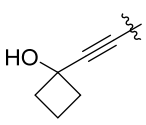
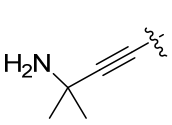
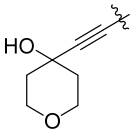
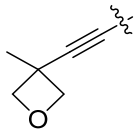
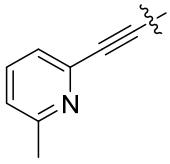
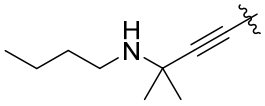
;

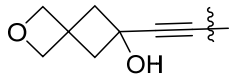
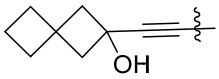
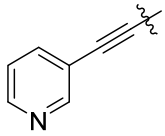
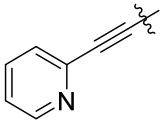
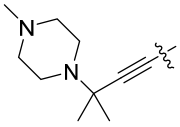
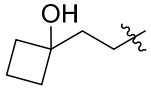
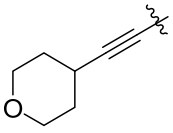
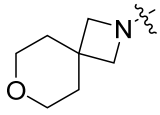
;

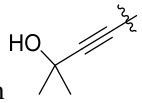
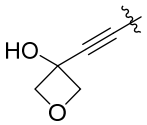
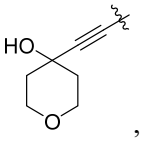
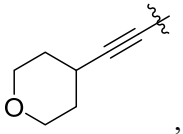
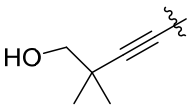
;




;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

; or

.

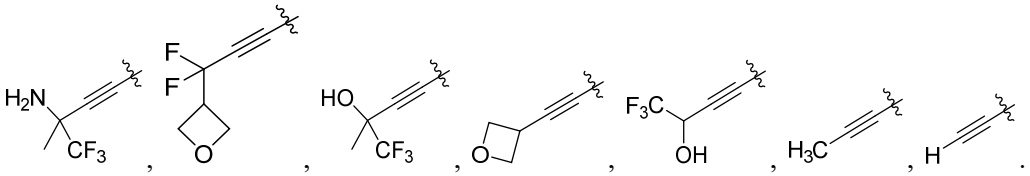
28. The compound of claim 1, wherein at least one R^1 is

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

, or

.

29. The compound of claim 1, wherein at least one R^1 is selected from

,

,

,

,

, or

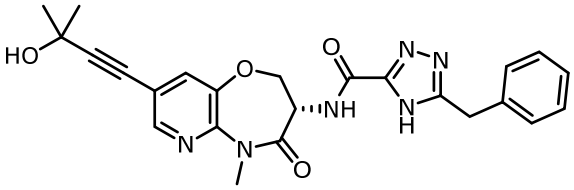
.

30. The compound of claim 1, wherein at least one R^1 is selected from

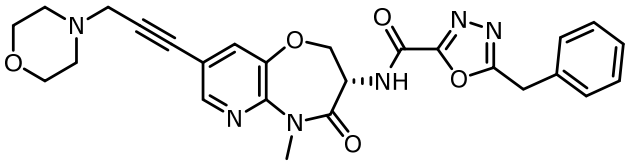


31. The compound of claim 1, having the formula

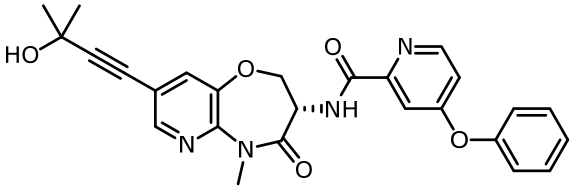
I-3



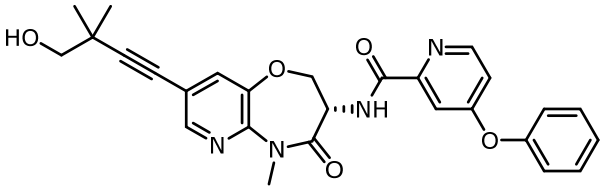
I-5



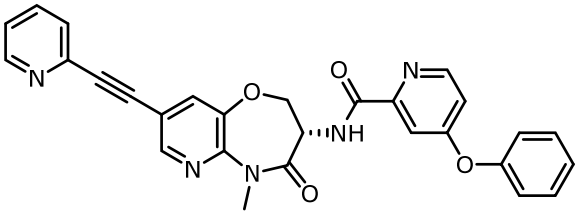
I-7

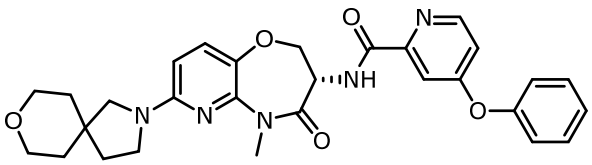


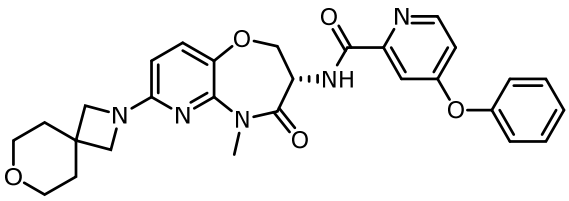
I-8

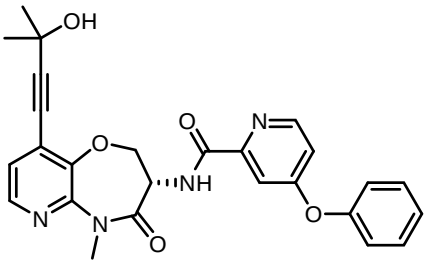


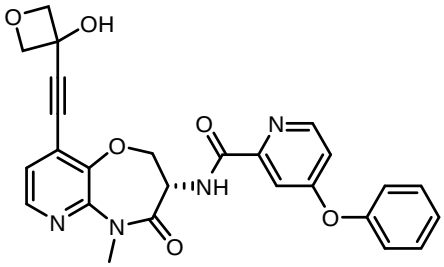
I-9

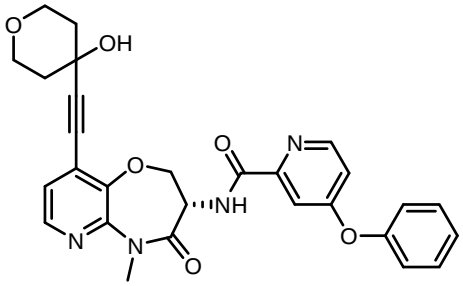


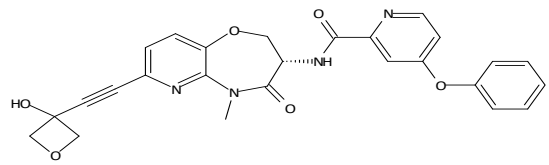
I-12 

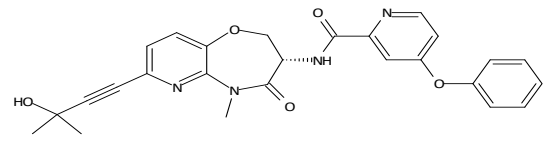
I-13 

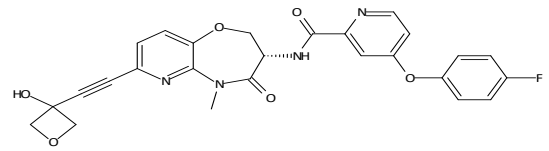
I-14 

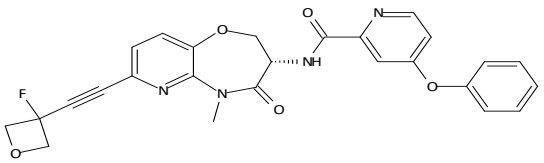
I-15 

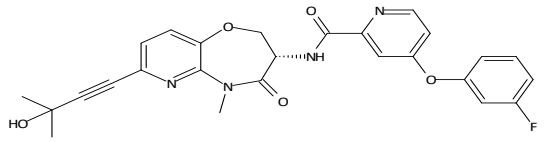
I-16 

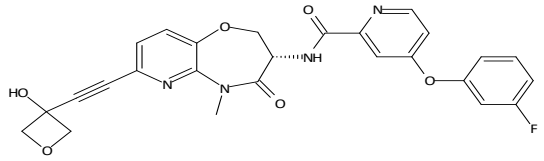
I-17 

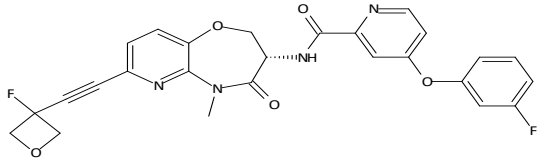
I-18 

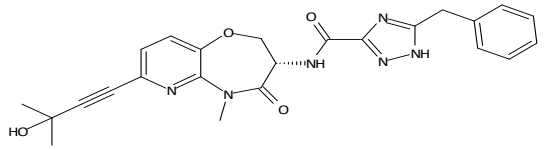
I-19 

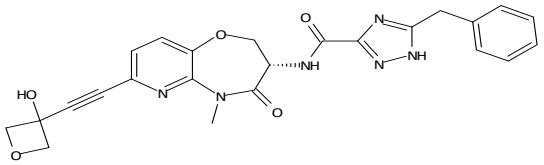
I-20 

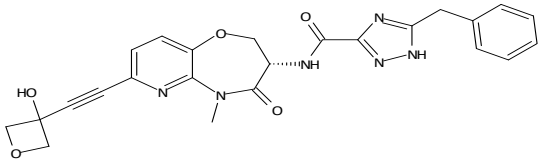
I-21 

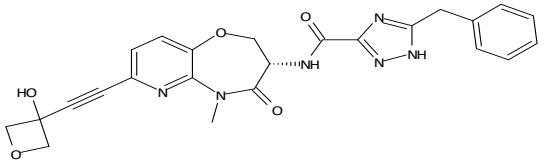
I-22 

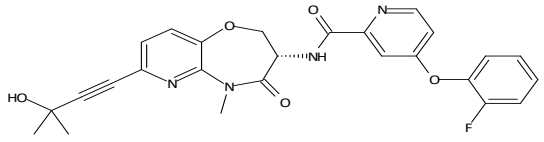
I-23 

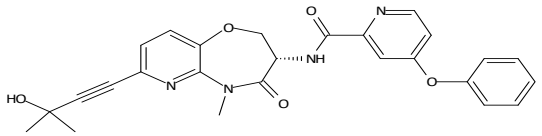
I-24 

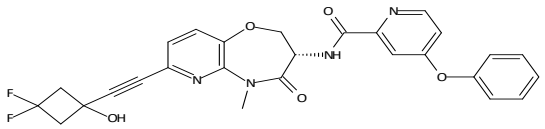
I-25 

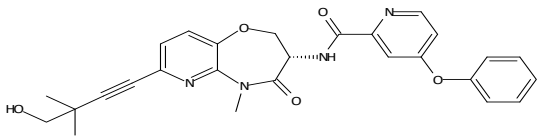
I-26 

I-27 

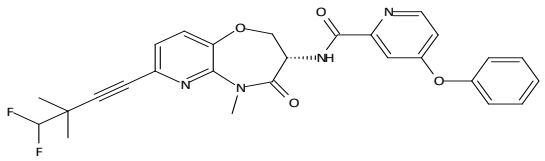
I-28 

I-29 

I-30 

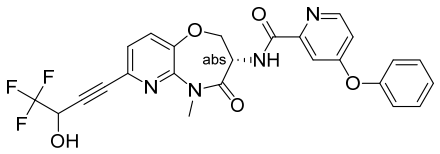
I-31 

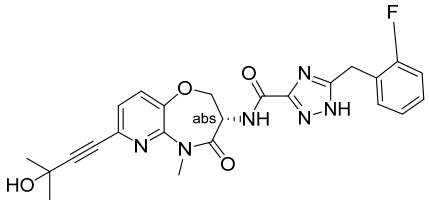
or

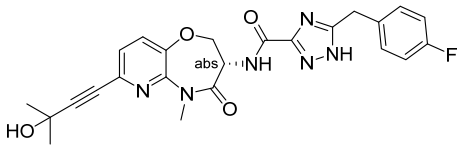
I-32 

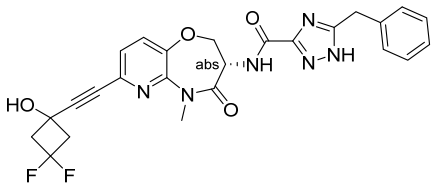
.

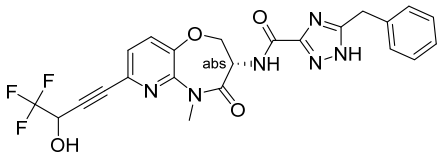
32. The compound of claim 1, having the formula

I-33 

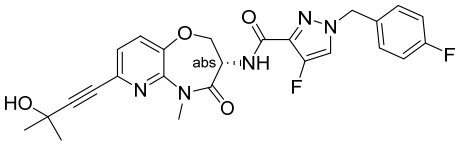
I-34 

I-35 

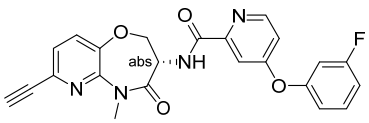
I-36 

I-37 

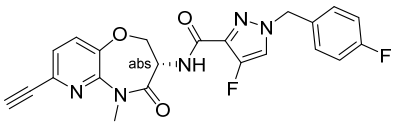
I-38



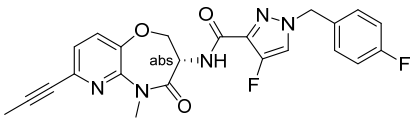
I-39



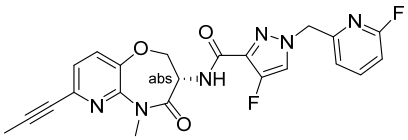
I-40



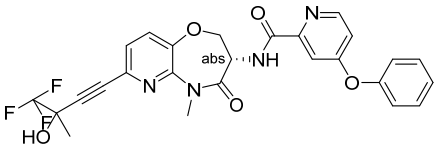
I-41



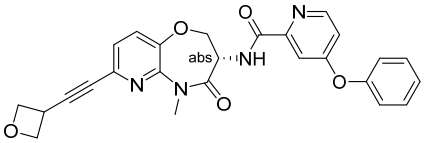
I-42



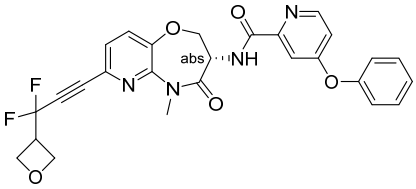
I-43



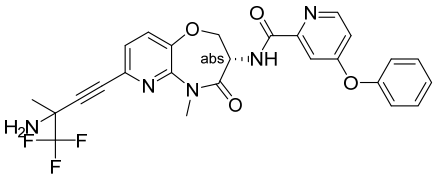
I-44



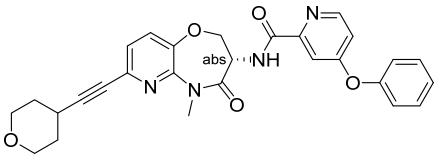
I-45

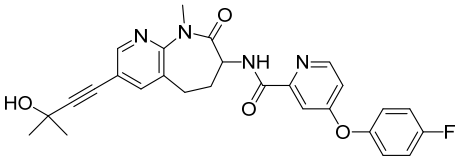


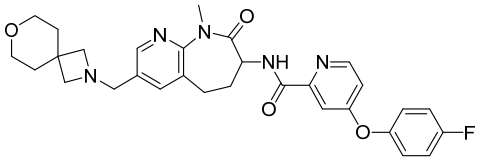
I-46

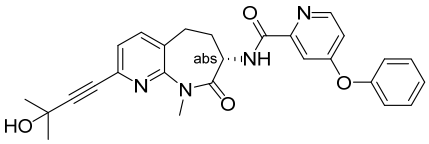


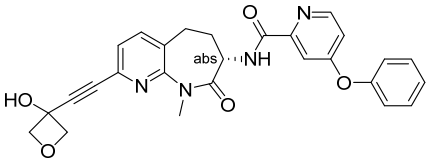
I-47

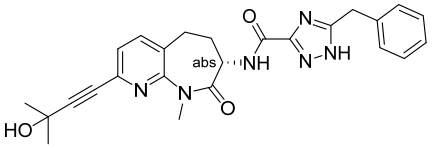


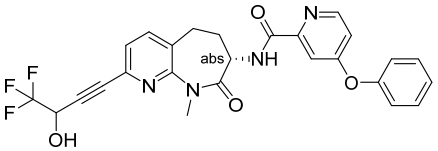
I-49 

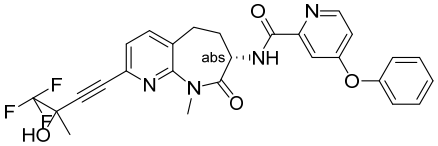
I-50 

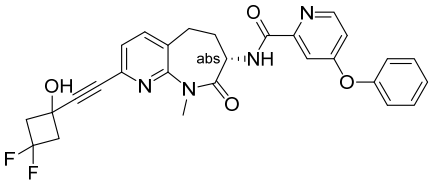
I-52 

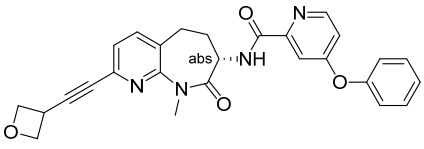
I-53 

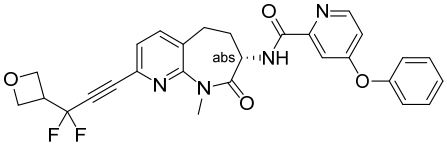
I-54 

I-55 

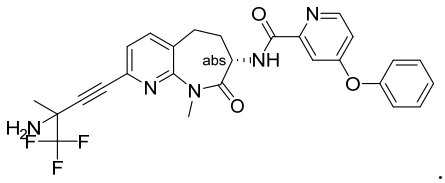
I-56 

I-57 

I-58 

I-59 

or

I-60 

.

33. Use of a compound according to any one of claims 1 – 32, in the manufacture of a medicament for the treatment of a disease, wherein the disease is amyotrophic lateral sclerosis (ALS), multiple sclerosis, Parkinson's disease, or Alzheimer's disease.

34. The compound of any one of claims 1-32 for use in the treatment of a disease, wherein the disease is amyotrophic lateral sclerosis (ALS), multiple sclerosis, Parkinson's disease, or Alzheimer's disease.