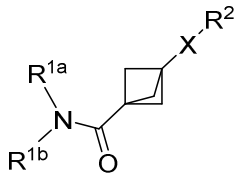
CLAIMS

What is claimed is:

1. A compound of structural Formula I:



(I)

or a salt thereof, wherein:

X is alkylene and is optionally substituted with one or more R^7,

or X is chosen from carbamoyl, carbonyl, and a bond;

R^{1a} and R^{1b}, together with the intervening nitrogen, combine to form a pyrazoline, which is optionally substituted with one R^3, and which is optionally substituted with one or more R^4;

R^2 is chosen from hydrogen, hydroxy, cyano, and halo,

or R^2 is chosen from alkyl, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, (cycloalkyl)oxy, (heterocycloalkyl)oxy, (aryl)oxy, (heteroaryl)oxy, (alkyl)carbonyl, (cycloalkyl)carbonyl, (heterocycloalkyl)carbonyl, (aryl)carbonyl, (alkyl)amino, (cycloalkyl)amino, (heterocycloalkyl)amino, (aryl)amino, and (heteroaryl)amino, any of which is optionally substituted with one or more R^5;

R^3 is chosen from aryl, (aryl)oxy, heteroaryl, (heteroaryl)oxy, cycloalkyl, and heterocycloalkyl, any of which is optionally substituted with one or more R^6;

each R^4 is independently chosen from alkyl, halo, cyano, and hydroxy;

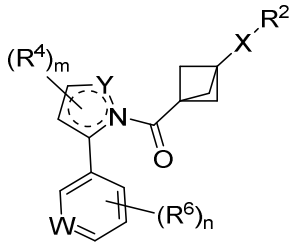
each R^5 is independently chosen from halo, cyano, amido, alkyl, alkoxy, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, $P(O)(CH_3)_2$, SO_2CH_3, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with one or more alkyl;

two R^5, together with the intervening atoms, optionally combine to form a cycloalkyl or heterocycloalkyl;

each R^6 is independently chosen from halo, alkyl, cycloalkyl, cyano, alkoxy, hydroxy, haloalkyl, hydroxyalkyl, and haloalkoxy; and

each R^7 is independently chosen from alkyl, cyano, halo, and hydroxy.

2. The compound as recited in claim 1, wherein R^3 is aryl optionally substituted with one or more R^6.
3. The compound as recited in claim 1, wherein R^3 is any one of phenyl, phenoxy, and pyridinyl, any of which is optionally substituted with 1 or 2 R^6.
4. The compound as recited in claim 2, wherein R^6 is halo.
5. The compound as recited in claim 2, wherein R^6 is fluoro.
6. The compound as recited in any one of claims 1 – 5, wherein X is alkylene and is optionally substituted with one or more R^7.
7. The compound as recited in claim 6, wherein X is $-CH_2-$.
8. The compound as recited in claim 7, wherein R^2 is chosen from aryl and heteroaryl.
9. The compound as recited in claim 8, wherein R^2 is 5-10 membered heteroaryl.
10. The compound as recited in claim 9, wherein R^2 is chosen from pyrazol-1-yl, 1*H*-indazol-1-yl, 2*H*-indazol-2-yl, 1*H*-pyrazolo[3,4-*c*]pyridin-1-yl, imidazol-1-yl, benzo[*d*]imidazol-1-yl, 1*H*-1,2,3-triazol-1-yl, 2*H*-1,2,3-triazol-2-yl, 1*H*-benzo[*d*][1,2,3]triazol-1-yl, and 2*H*- benzo[*d*][1,2,3]triazol-2-yl.
11. The compound as recited in any one of claims 1 – 10, wherein R^2 is optionally substituted with 1 or 2 R^5.
12. The compound as recited in claim 11, wherein each R^5 is independently chosen from fluoro, cyano, methyl, methoxy, hydroxymethyl, methoxymethyl, cyclopropyl, and trifluoromethyl.
13. The compound as recited in claim 1, having structural Formula II:



(II)

or a salt thereof, wherein:

m is chosen from 0, 1, and 2;

n is chosen from 0, 1, 2, and 3;

W is chosen from C(R^{6a}) and N;

X is alkylene and is optionally substituted with one or more R^7,

or X is chosen from carbamoyl, carbonyl, and a bond;

Y is NH and N;

Y and the intervening carbons and nitrogen combine to form a pyrazoline;

R^2 is chosen from hydrogen, hydroxy, cyano, and halo,

or R^2 is chosen from alkyl, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, (cycloalkyl)oxy, (heterocycloalkyl)oxy, (aryl)oxy, (heteroaryl)oxy, (alkyl)carbonyl, (cycloalkyl)carbonyl, (heterocycloalkyl)carbonyl, (aryl)carbonyl, (alkyl)amino, (cycloalkyl)amino, (heterocycloalkyl)amino, (aryl)amino, and (heteroaryl)amino, any of which is optionally substituted with one or more R^5;

each R^4 is independently chosen from halo, cyano, and hydroxy;

each R^5 is independently chosen from halo, cyano, amido, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, $P(O)(CH_3)_2$, SO_2CH_3, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with one or more alkyl;

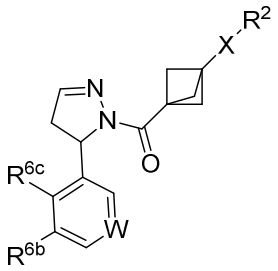
two R^5, together with the intervening atoms, optionally combine to form a cycloalkyl or heterocycloalkyl;

each R^6 is independently chosen from halo, alkyl, cycloalkyl, cyano, alkoxy, hydroxy, haloalkyl, hydroxyalkyl, and haloalkoxy;

R^{6a} is chosen from H, halo, alkyl, cyano, alkoxy, hydroxy, haloalkyl, and haloalkoxy; and

each R^7 is independently chosen from alkyl, cyano, halo, and hydroxy.

14. The compound as recited in claim 13, wherein m is chosen from 0 and 1.
15. The compound as recited in claim 14, wherein n is chosen from 0, 1, and 2.
16. The compound as recited in claim 14, wherein W is $C(R^{6a})$.
17. The compound as recited in claim 16, wherein R^{6a} is chosen from H, fluoro, methyl, cyano, and methoxy.
18. The compound as recited in any one of claims 14–17, wherein each R^6 is is independently chosen from fluoro, methyl, cyano, and methoxy.
19. The compound as recited in claim 18, wherein n is chosen from 1 and 2.
20. The compound as recited in claim 13, having structural Formula III:



(III)

or a salt thereof, wherein:

W is chosen from C(R^{6a}) and N;

X is alkylene and is optionally substituted with one or more R^7,

or X is chosen from carbamoyl, carbonyl, and a bond;

R^2 is chosen from hydrogen, hydroxy, cyano, and halo,

or R^2 is chosen from alkyl, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, (cycloalkyl)oxy, (heterocycloalkyl)oxy, (aryl)oxy, (heteroaryl)oxy, (alkyl)carbonyl, (cycloalkyl)carbonyl, (heterocycloalkyl)carbonyl, (aryl)carbonyl, (alkyl)amino, (cycloalkyl)amino, (heterocycloalkyl)amino, (aryl)amino, and (heteroaryl)amino, any of which is optionally substituted with one or more R^5;

each R^5 is independently chosen from halo, cyano, amido, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, $P(O)(CH_3)_2$, SO_2CH_3, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with one or more alkyl;

two R^5, together with the intervening atoms, optionally combine to form a cycloalkyl or heterocycloalkyl;

R^{6a}, R^{6b}, and R^{6c} are independently chosen from H, halo, alkyl, cyano, alkoxy, hydroxy, haloalkyl, and haloalkoxy; and

each R^7 is independently chosen from alkyl, cyano, halo, and hydroxy.

21. The compound as recited in claim 20, wherein X is -CH_2-.

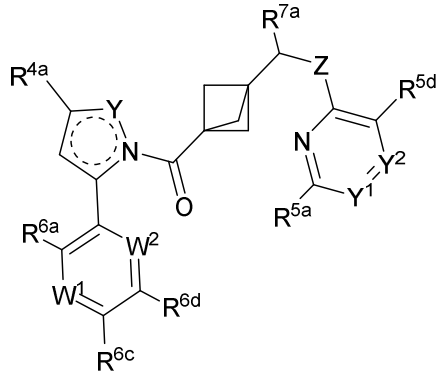
22. The compound as recited in claim 21, wherein W is C(R^{6a}).

23. The compound as recited in claim 22, wherein R^{6a}, R^{6b}, and R^{6c} are independently chosen from H, fluoro, methyl, cyano, and methoxy.

24. The compound as recited in claim 23, wherein R^{6a}, R^{6b}, and R^{6c} are independently chosen from H and fluoro.

25. The compound as recited in any one of claims 16–25, wherein R^2 is chosen from aryl, heteroaryl, (aryl)oxy, and (heteroaryl)oxy.

26. The compound as recited in claim 1, having structural Formula (VII):



(VII)

or a salt thereof, wherein:

W^1 is chosen from $C(R^{6b})$ and N;

W^2 is chosen from $C(R^{6e})$ and N;

Y is chosen from NH and N;

Y and the intervening carbons and nitrogen combine to form a pyrazoline;

Y^1 is chosen from $C(R^{5b})$ and N;

Y^2 is chosen from $C(R^{5c})$ and N;

Z is chosen from O, NH, and $N(CH_3)$;

R^{1c} and R^{1d}, together with the intervening carbon and nitrogen, combine to form a 5-membered heterocycloalkyl which is optionally substituted with one R^4;

R^{2a} and R^{2b} are independently chosen from H, hydroxy, cyano, halo, and alkyl,

or R^{2a} and R^{2b} combine to form alkylene or heteroalkylene, either of which is optionally substituted with 1 or 2 R^5;

R^{4a} is chosen from H, halo, cyano, and hydroxy;

R^{5a}, R^{5b}, R^{5c}, and R^{5d} are independently chosen from H, halo, cyano, amido, alkyl, alkoxy, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, $P(O)(CH_3)_2$, SO_2CH_3, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with alkyl;

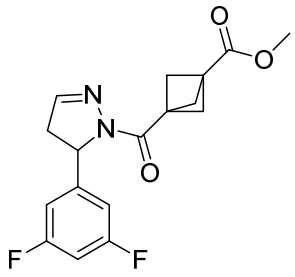
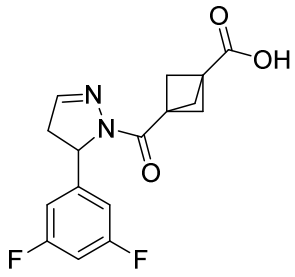
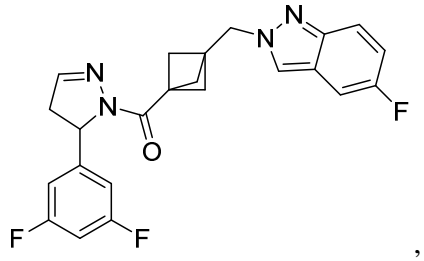
R^{6a}, R^{6b}, R^{6c}, R^{6d}, and R^{6e} are independently chosen from H, halo, alkyl, cycloalkyl, cyano, alkoxy, hydroxy, haloalkyl, hydroxyalkyl, and haloalkoxy; and

R^{7a} is chosen from H, alkyl, cyano, halo, and hydroxy.

27. The compound as recited in claim 26, wherein R^{5a}, R^{5b}, R^{5c}, and R^{5d} are independently chosen from H, halo, cyano, $CONH_2$, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, cyano$C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}}$

$_{6}$alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkyl, haloC_{1-6}alkyl, $P(O)(CH_3)_2$, SO_2CH_3, and 5- to 7-membered heteroaryl optionally substituted with methyl.

28. The compound as recited in claim 27, wherein at least one of R^{5a} and R^{5d} is H.
29. The compound as recited in any one of claims 26–28, wherein R^{6a}, R^{6b}, R^{6c}, R^{6d}, and R^{6e} are independently chosen from H, halo, methyl, cyclopropyl, cyano, and hydroxymethyl.
30. The compound as recited in claim 29, wherein at least one of R^{6a}, R^{6c}, and R^{6d} is H.
31. The compound as recited in any one of claims 26–30, wherein exactly one of Y^1 and Y^2 is N.
32. The compound as recited in any one of claims 26–31, wherein at most one of W^1 and W^2 is N.
33. The compound as recited in claim 32, wherein W^1 is chosen from CH and CF.
34. The compound as recited in claim 33, wherein W^2 is chosen from CH and CF.
35. The compound as recited in claim 1, chosen from:


, 
, 
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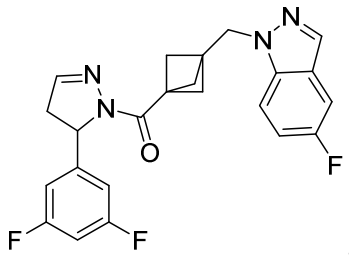
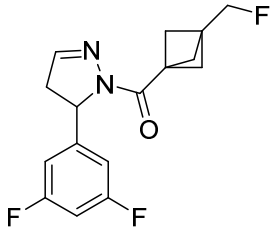
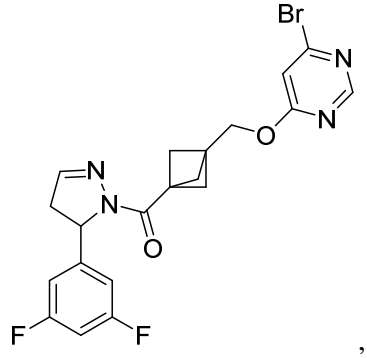

, 
, 
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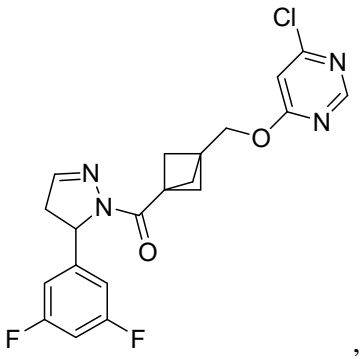
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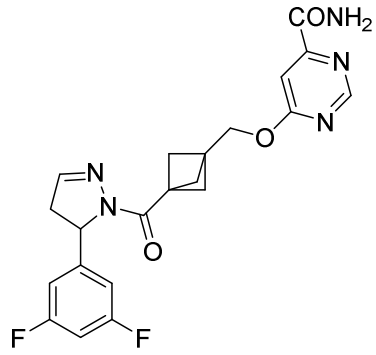
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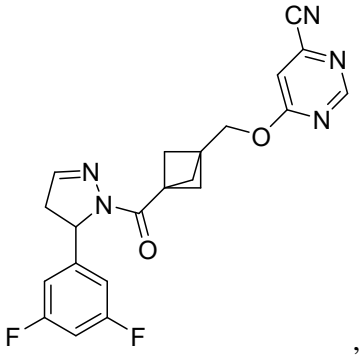
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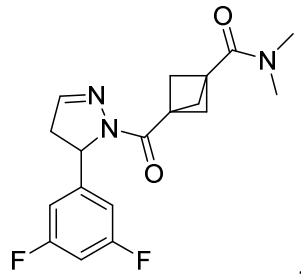
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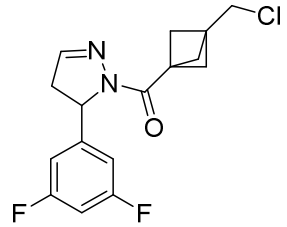
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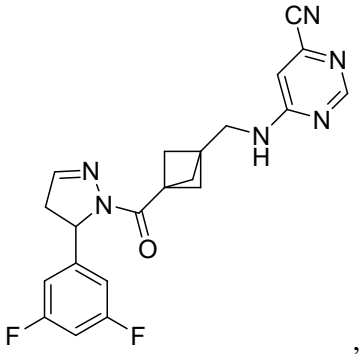
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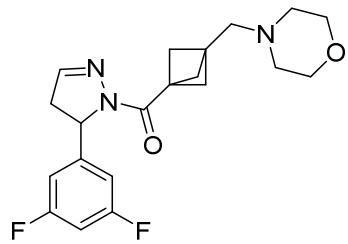
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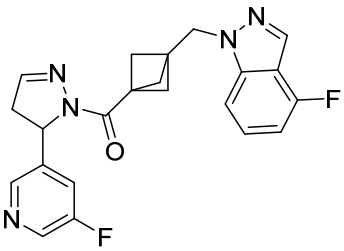
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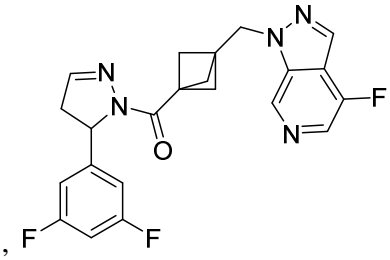
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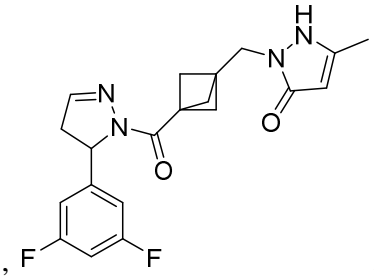
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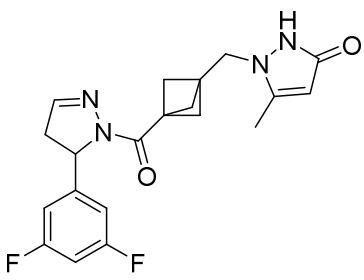
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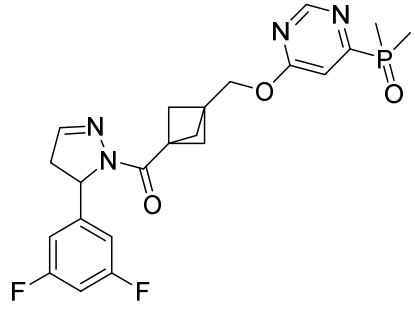
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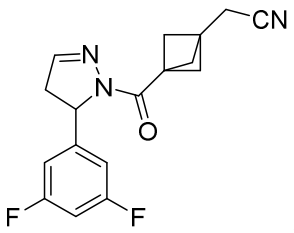
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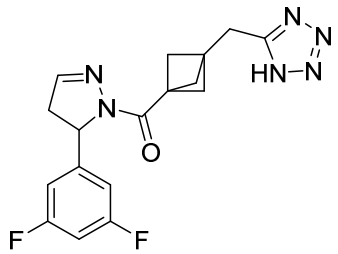
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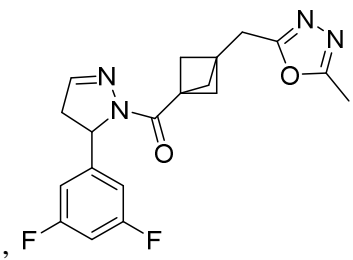
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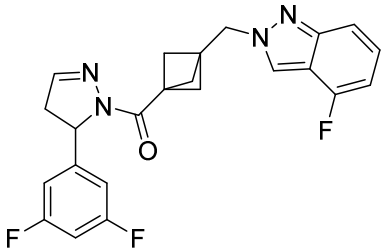
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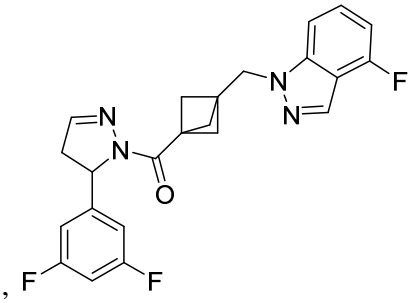
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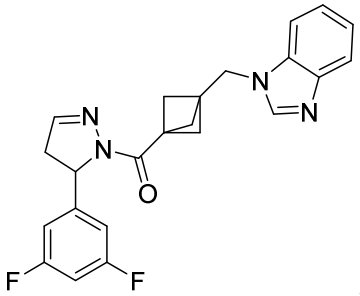
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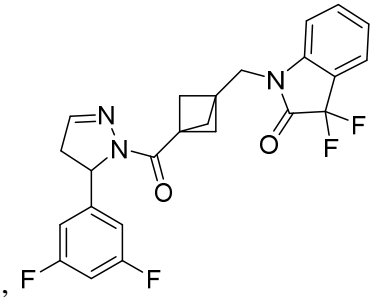
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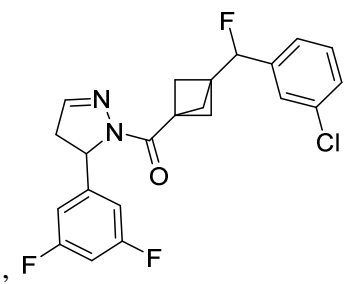

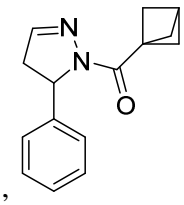
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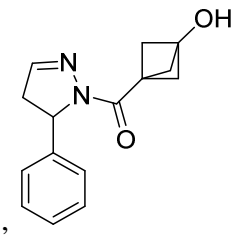
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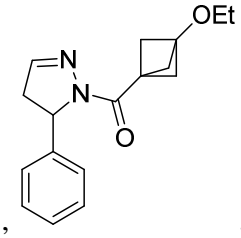
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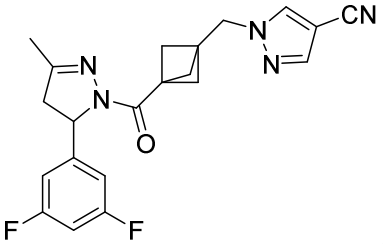
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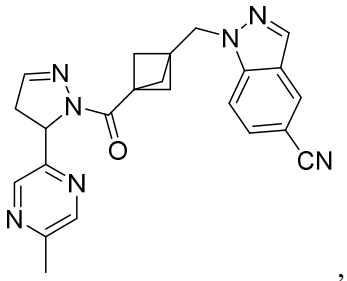
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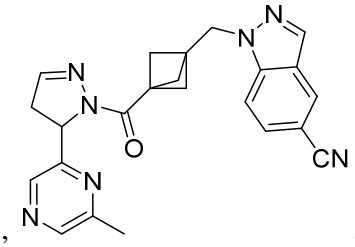
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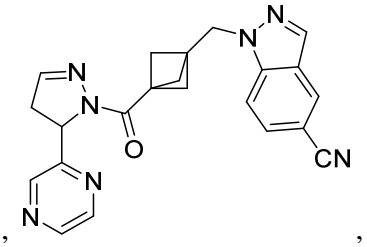
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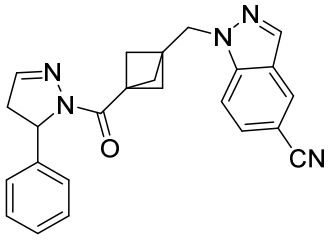
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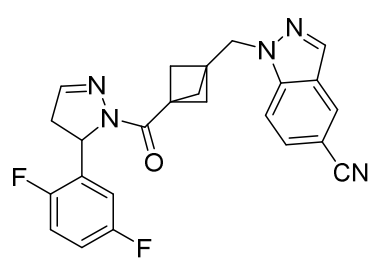
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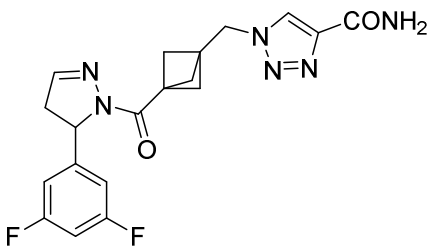
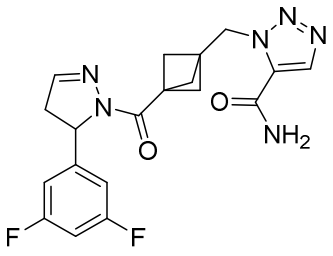

, 
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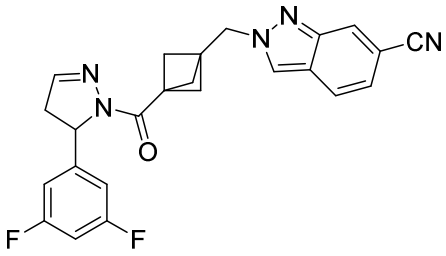
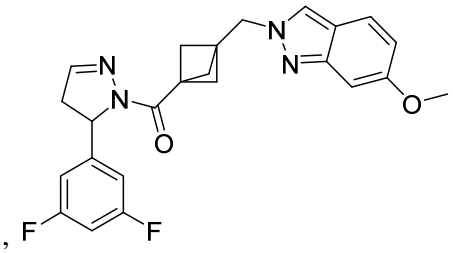

, 
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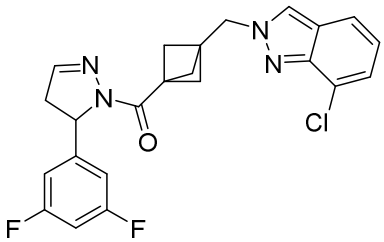
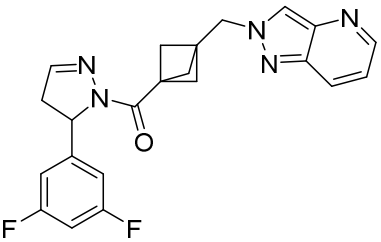

, 
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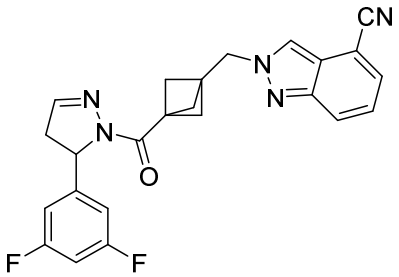
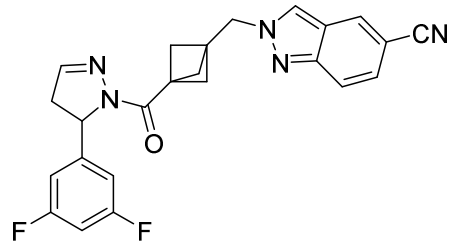

, 
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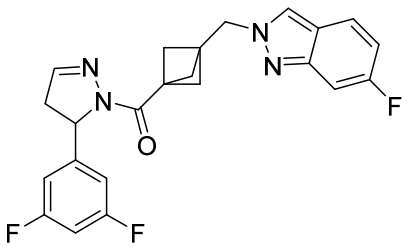
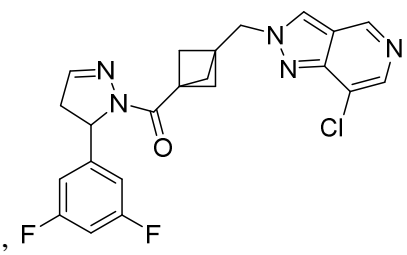

, 
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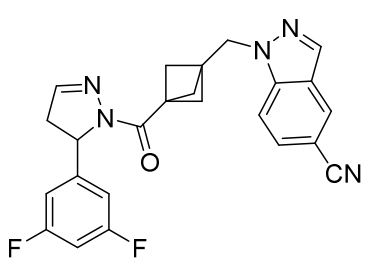
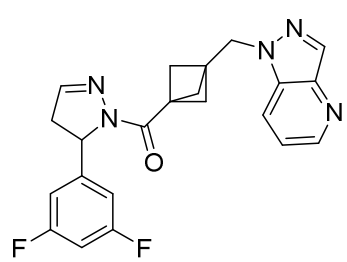
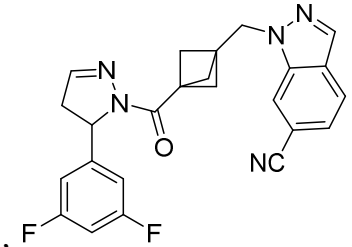

, 
, 
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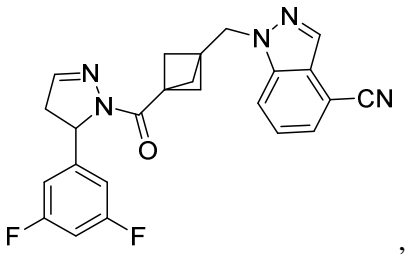
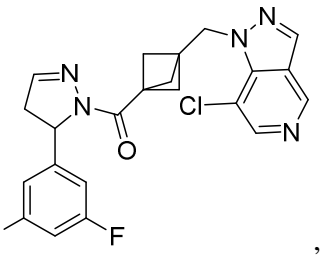
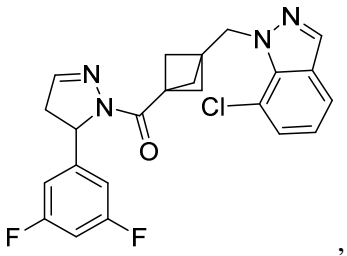
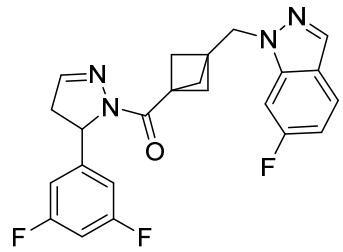
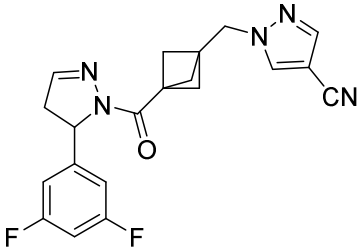
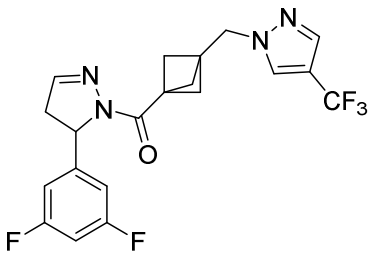
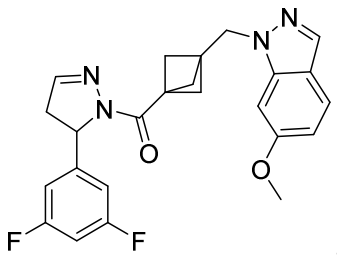
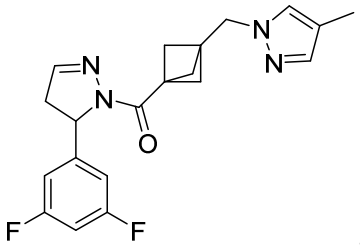
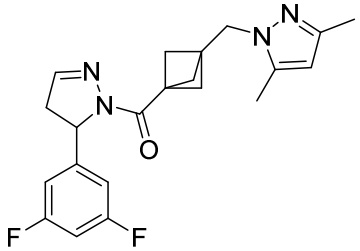
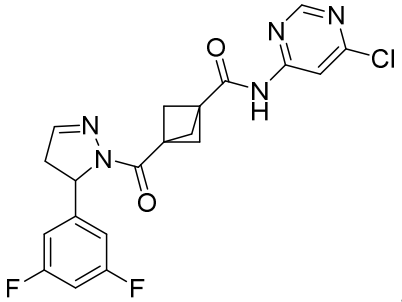
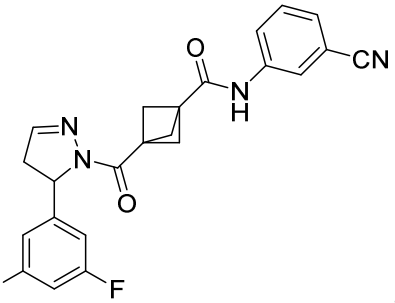
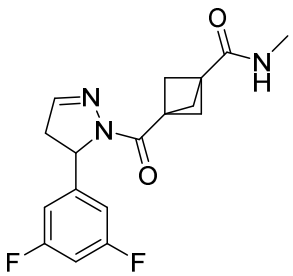
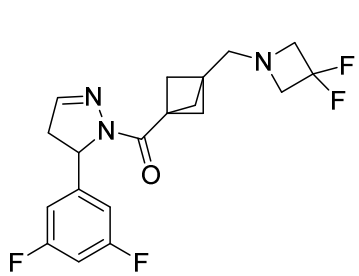
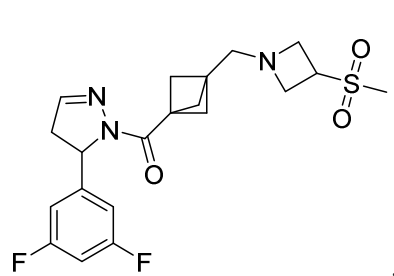

, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
, 
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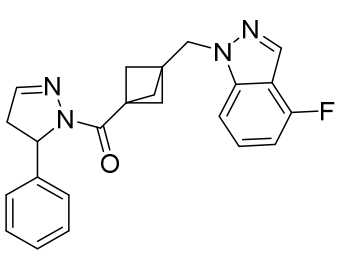
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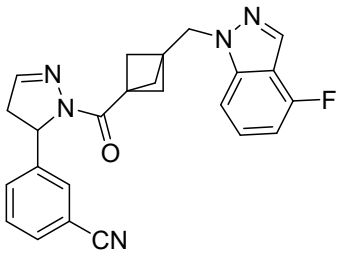
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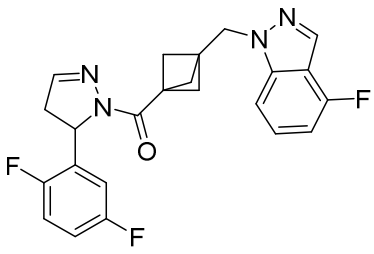
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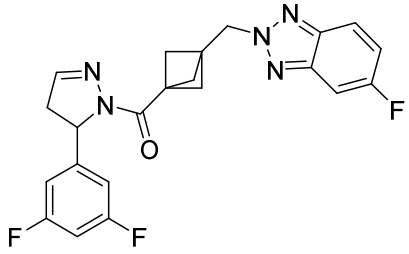
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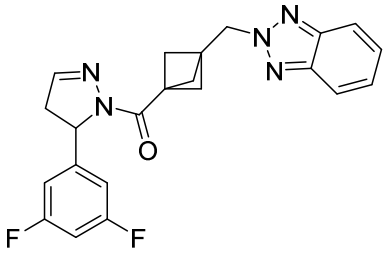
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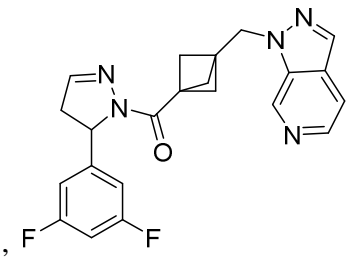
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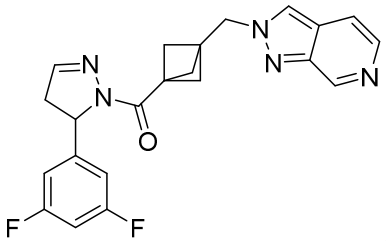
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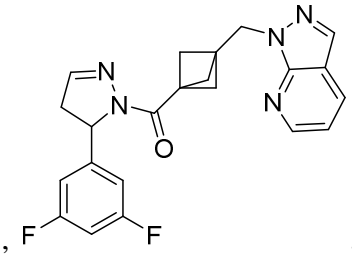
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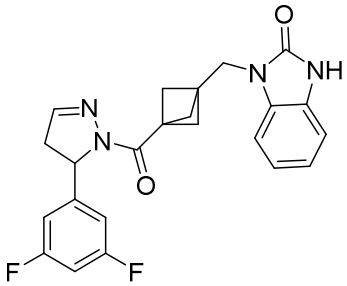
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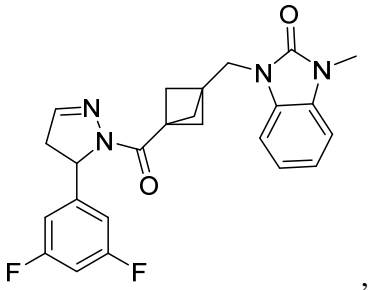
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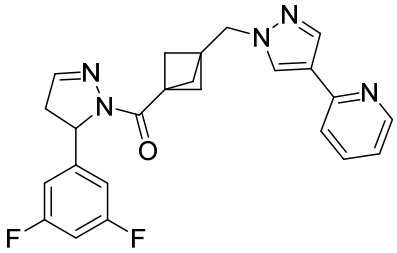
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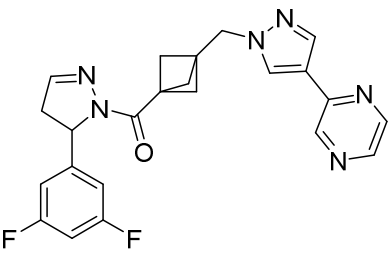
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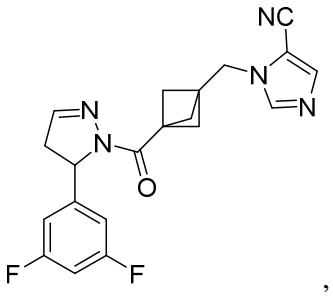
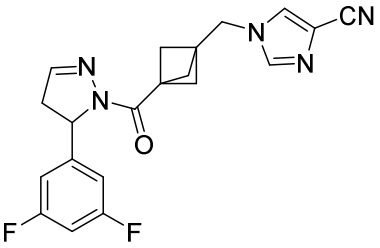
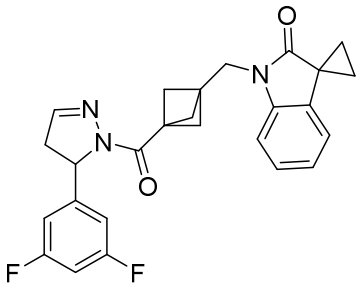
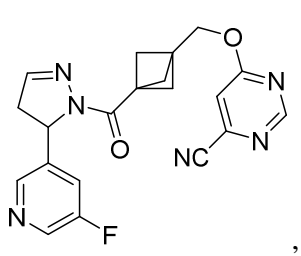
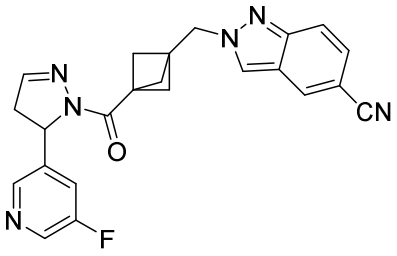
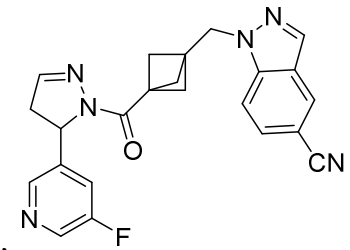
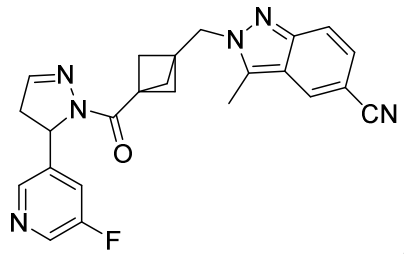
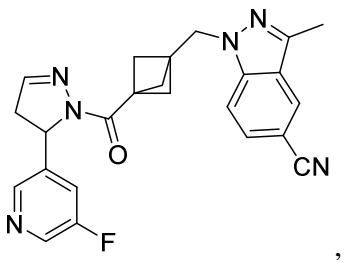
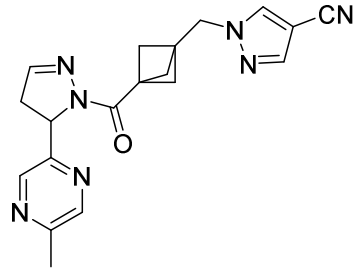
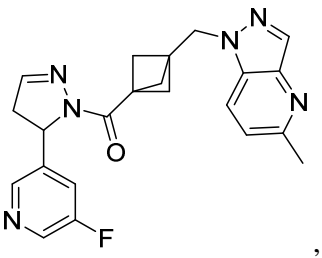
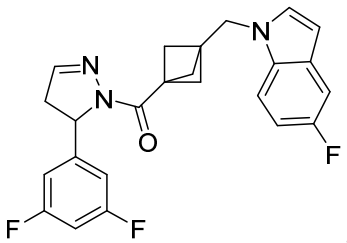
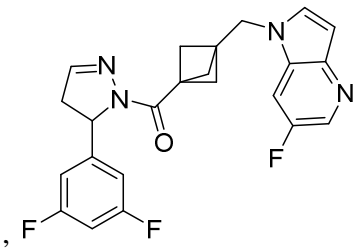
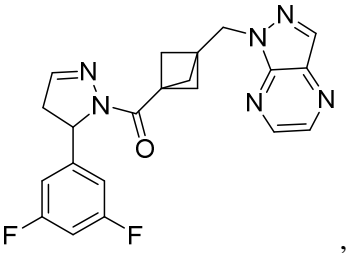
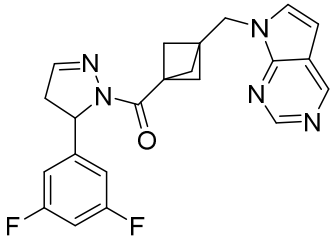
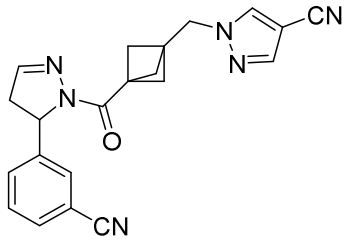
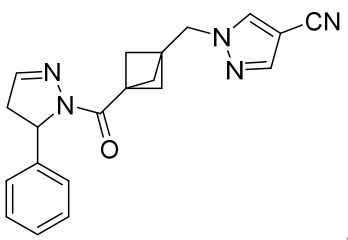

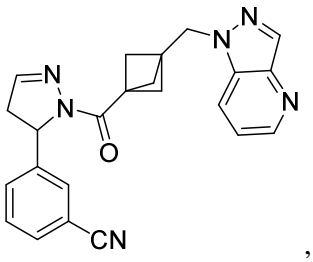
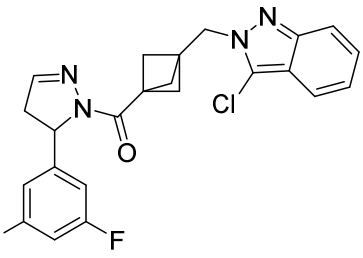
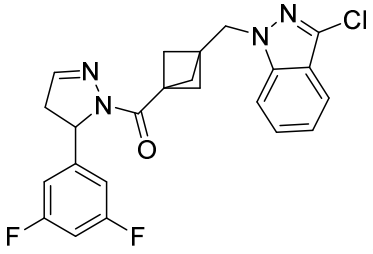
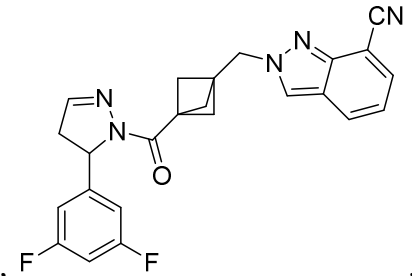
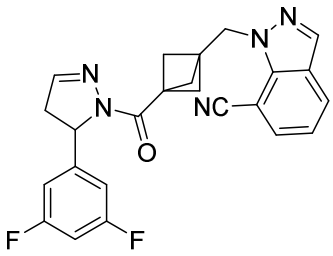
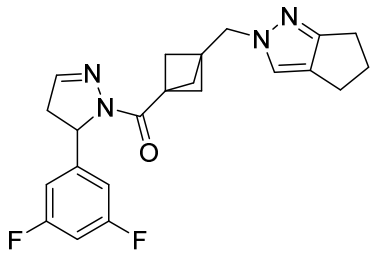
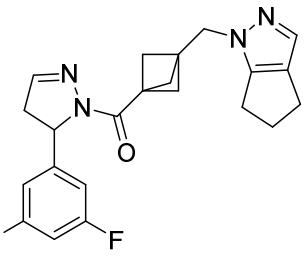
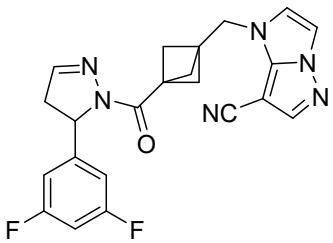
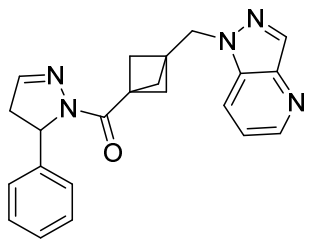
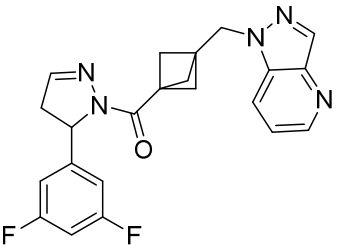
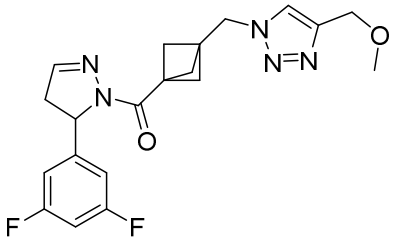
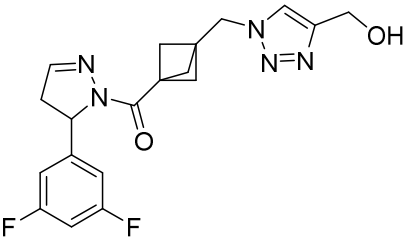
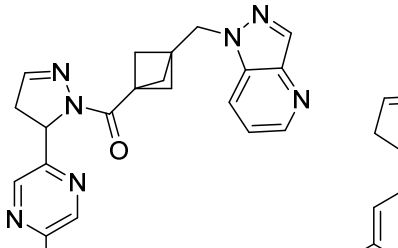
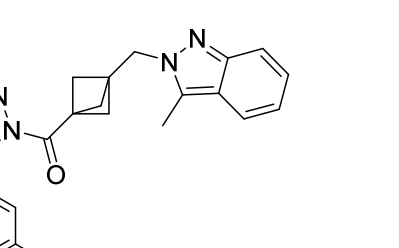

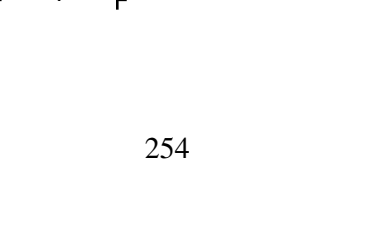

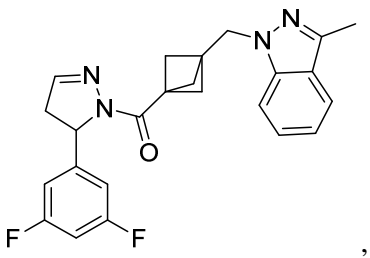
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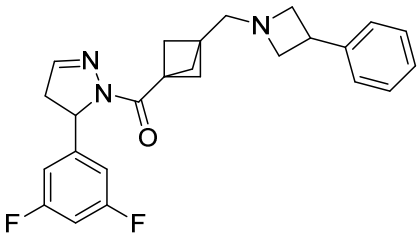
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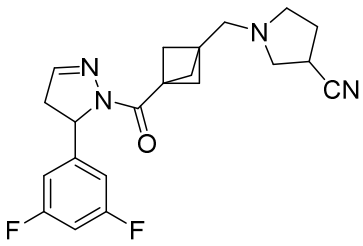
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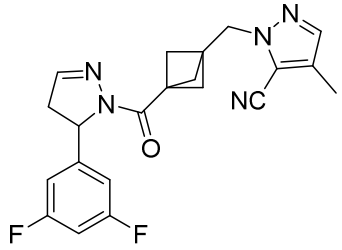
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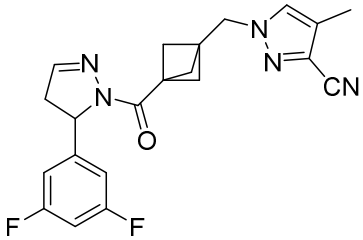
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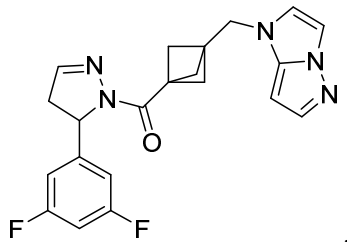
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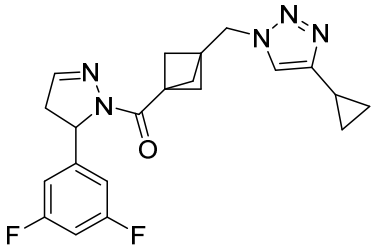
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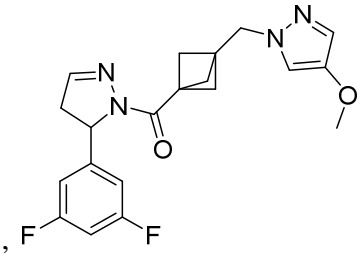
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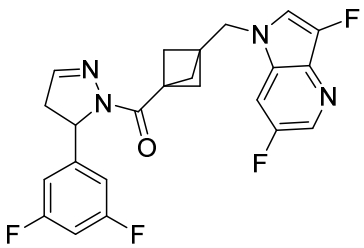
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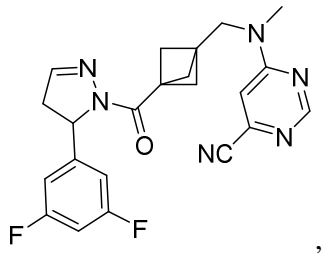
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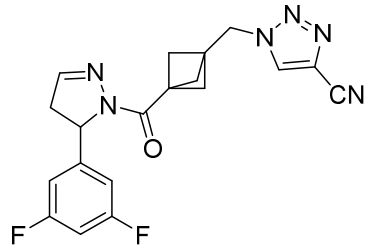
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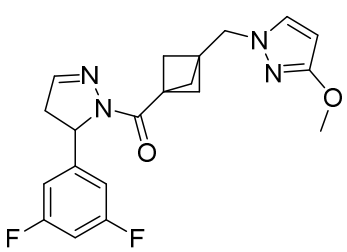
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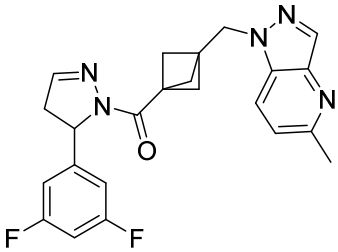
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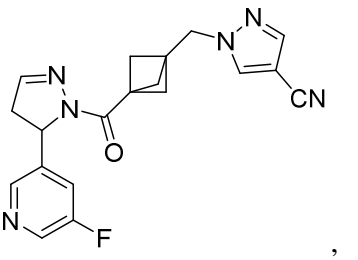
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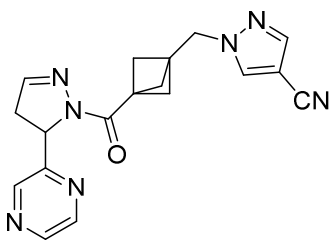
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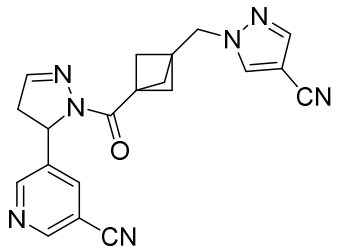
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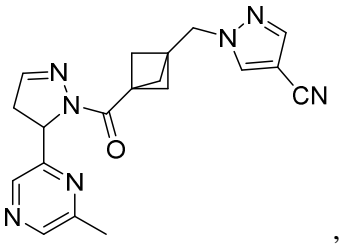
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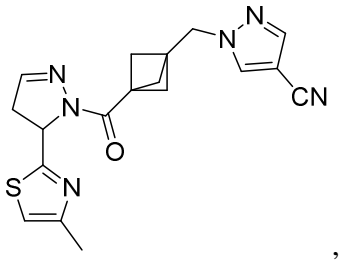
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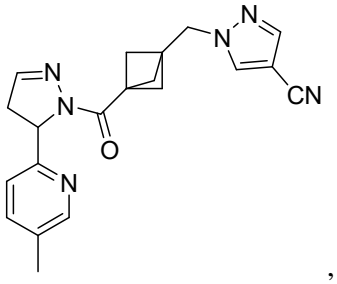
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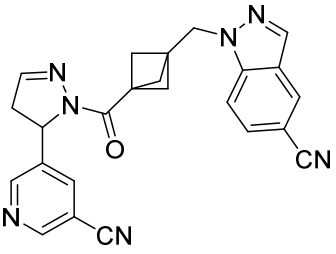
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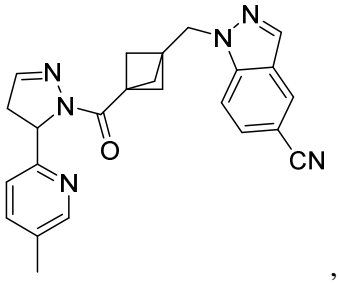
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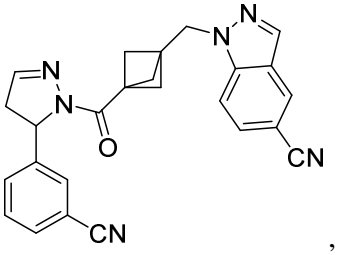
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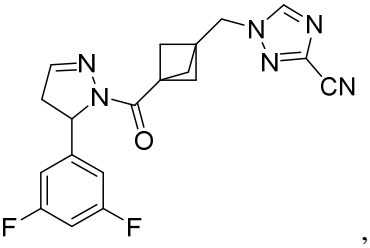
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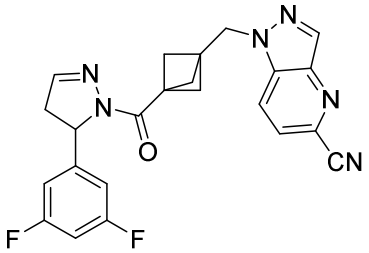
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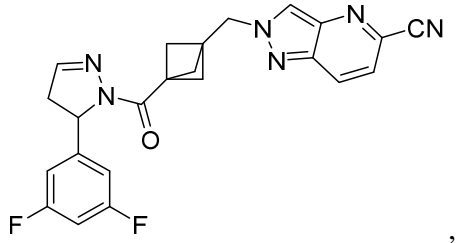
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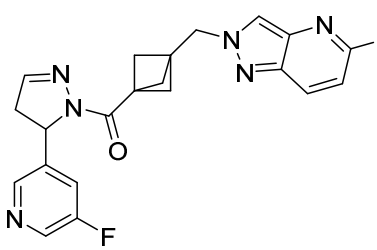
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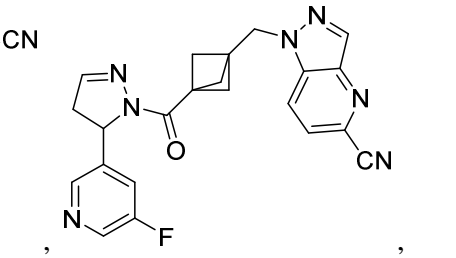
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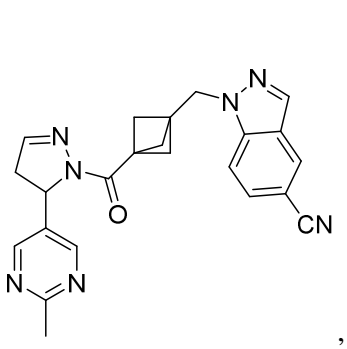
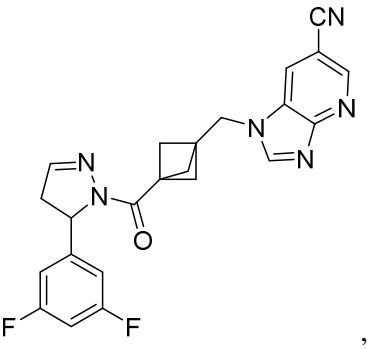
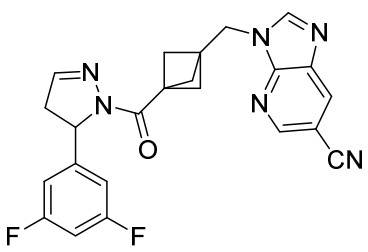
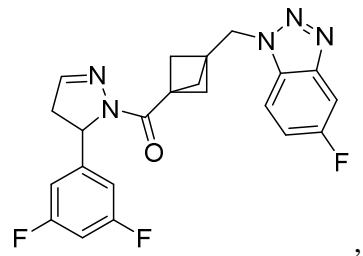
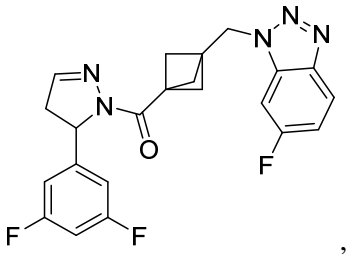
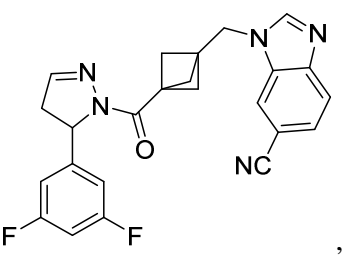
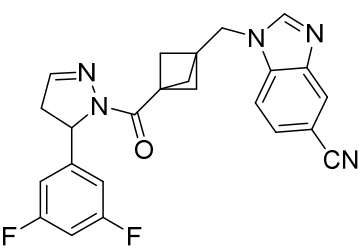
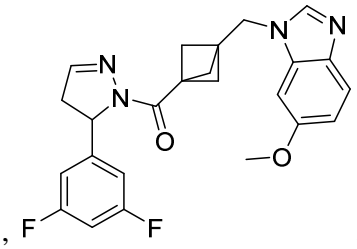
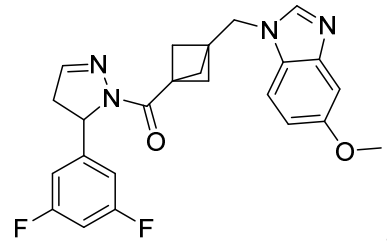
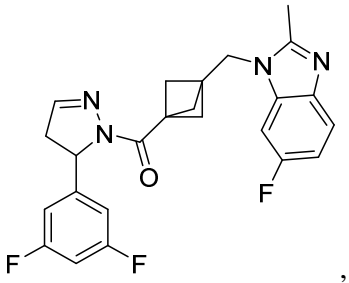
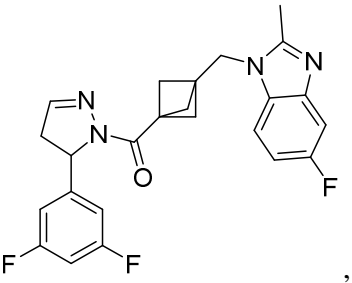
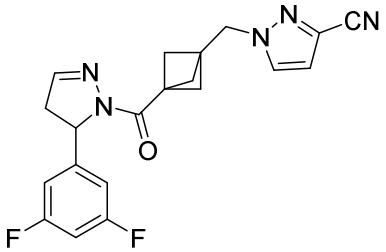
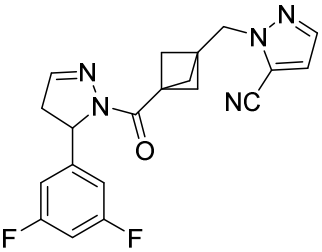

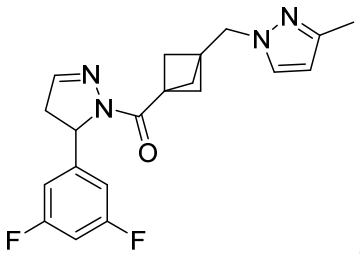
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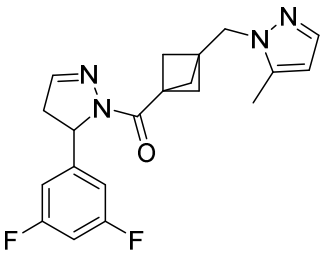
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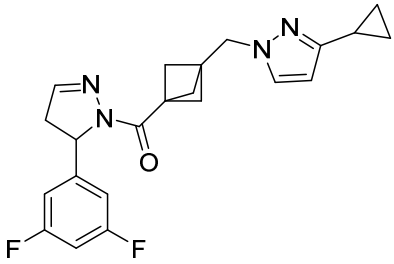
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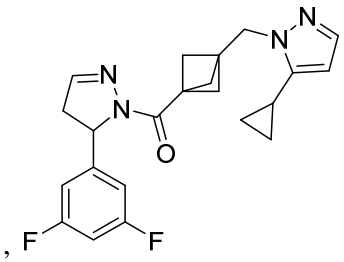
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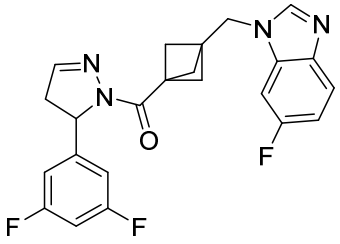
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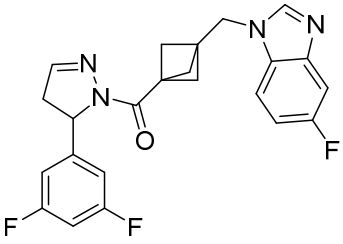
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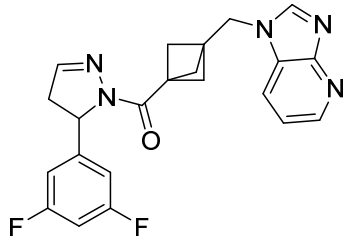
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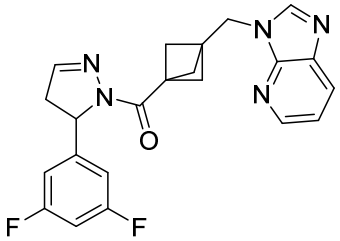
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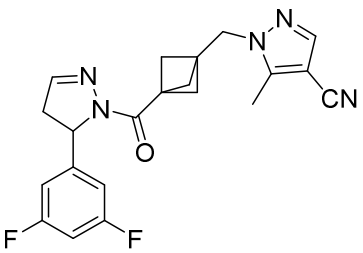
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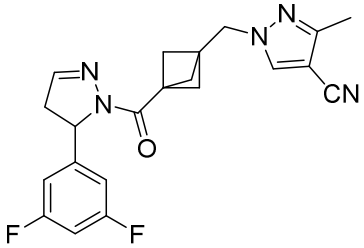
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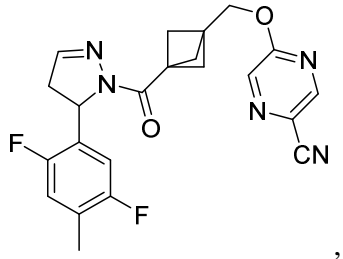
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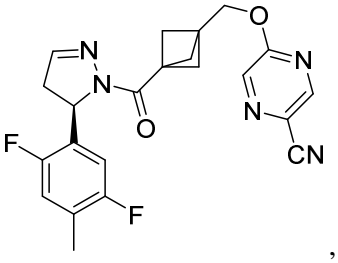
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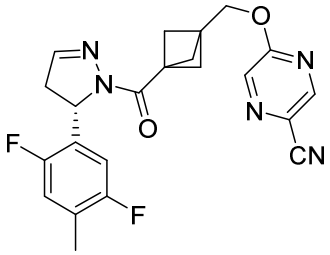
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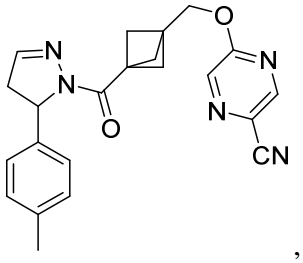
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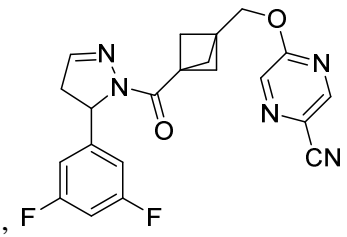
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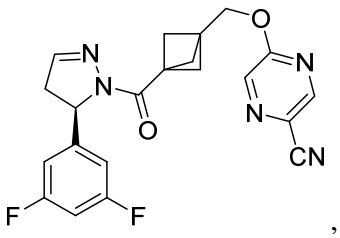
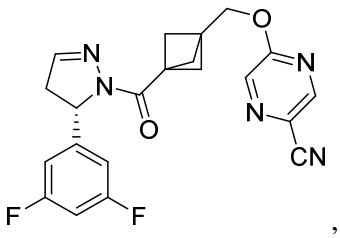
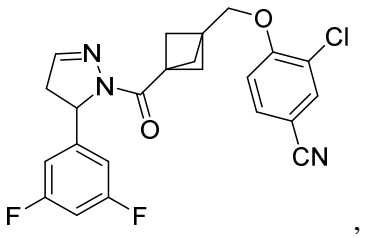
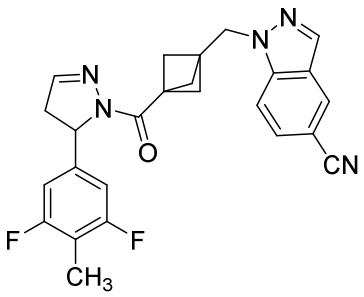
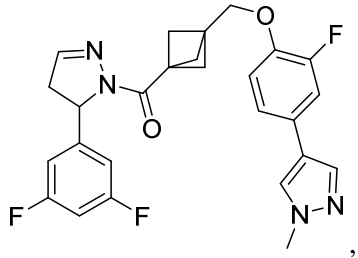
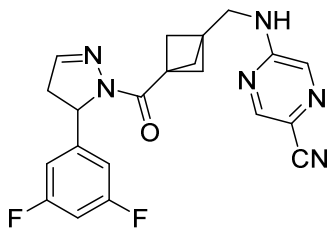
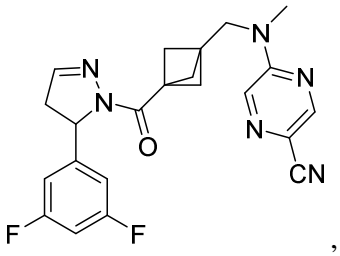
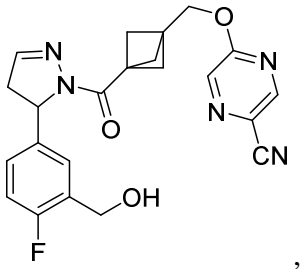
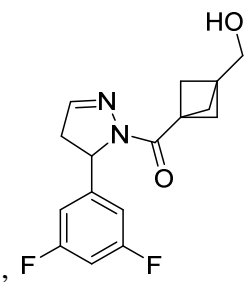
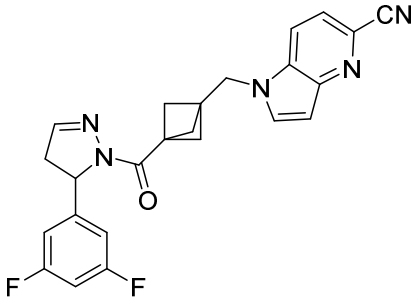
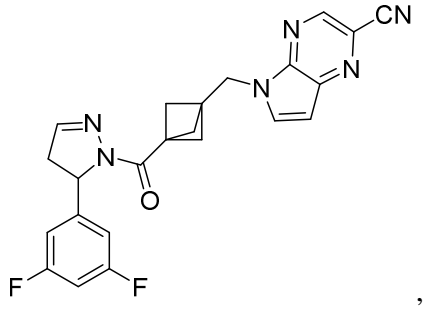
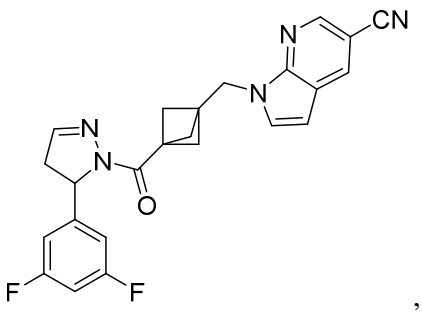
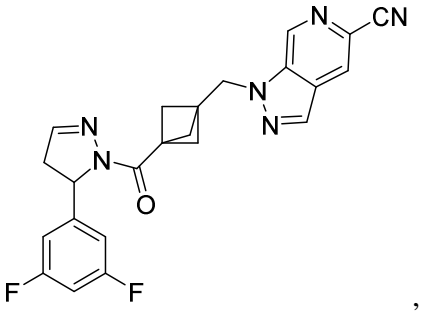
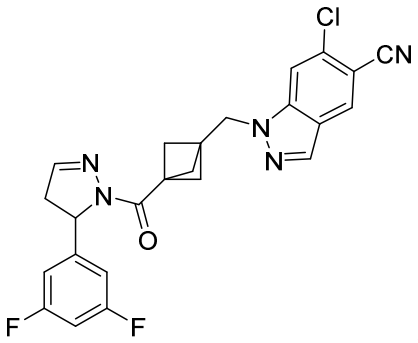
 ,  ,  ,

 ,  ,  ,

 ,  ,  ,

 ,  ,

 ,  ,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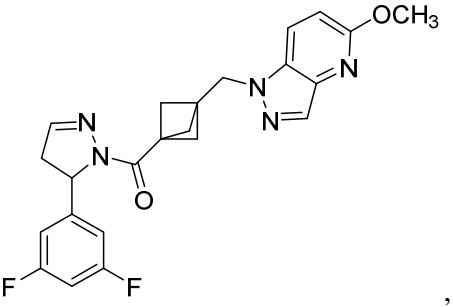
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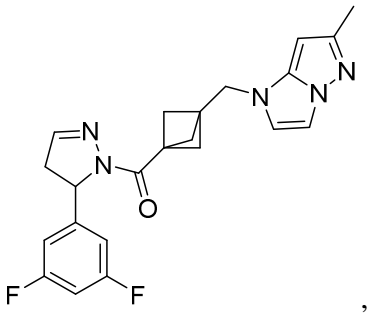
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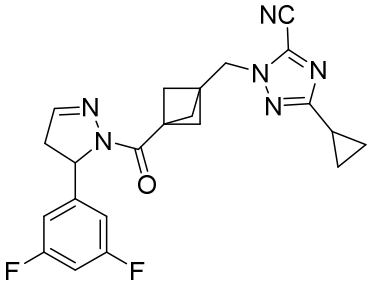
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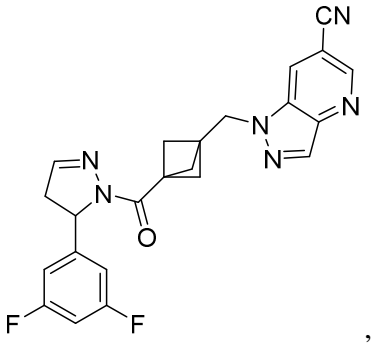
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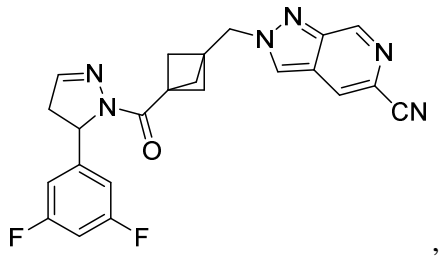
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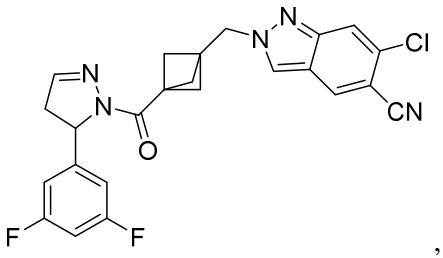
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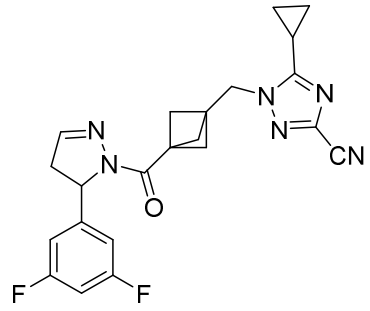
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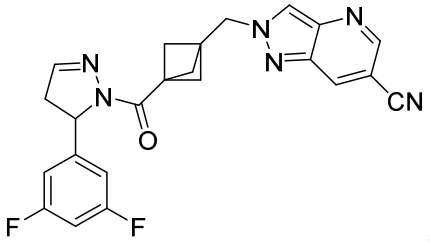
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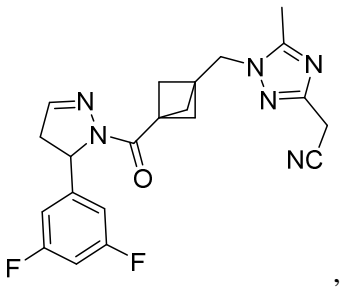
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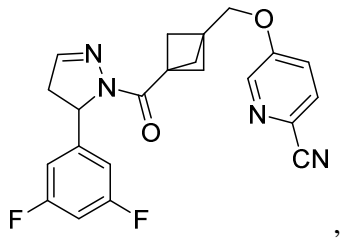
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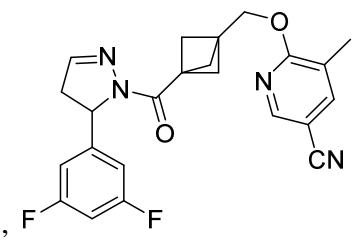
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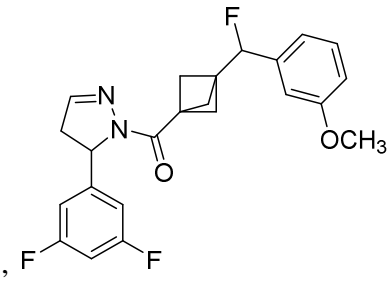
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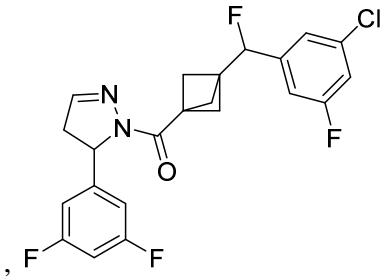
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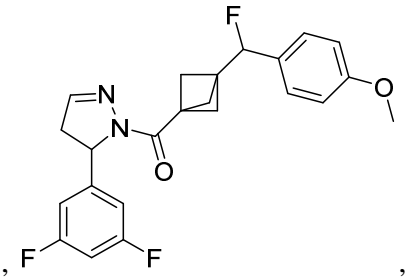
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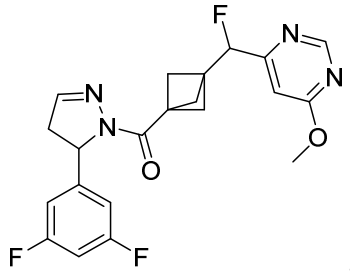
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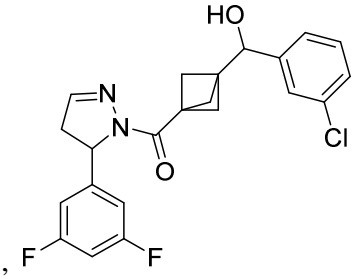
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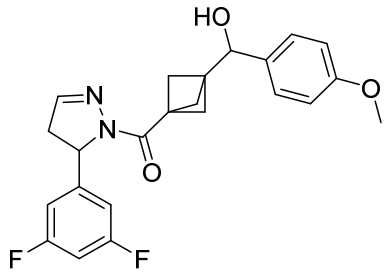
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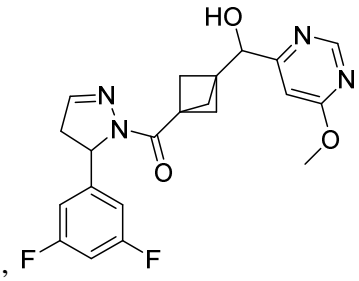
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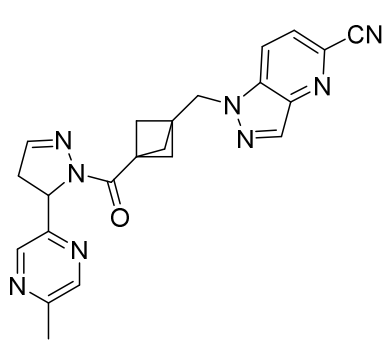
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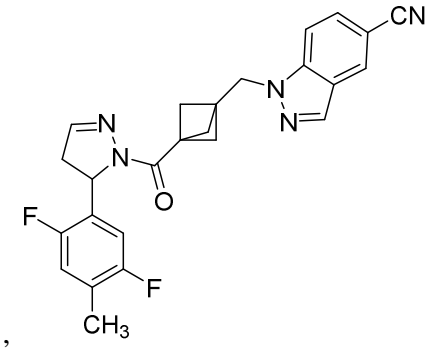
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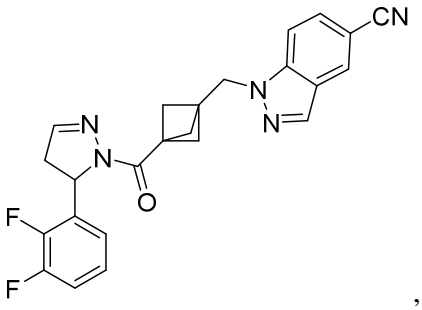
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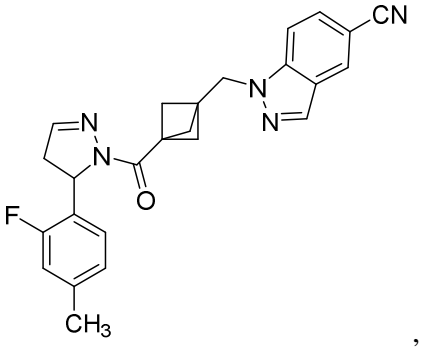
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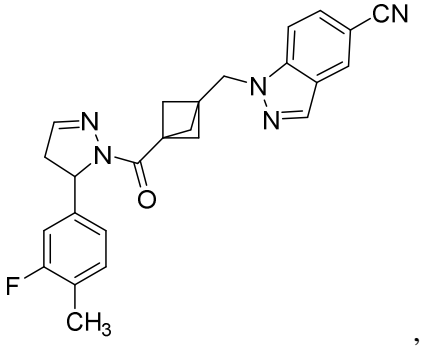
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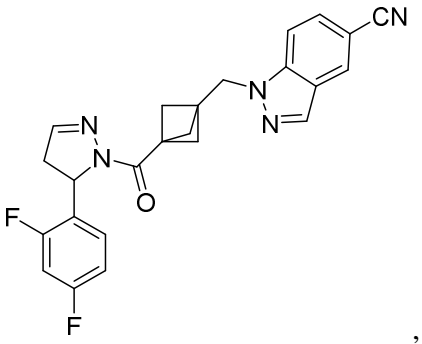
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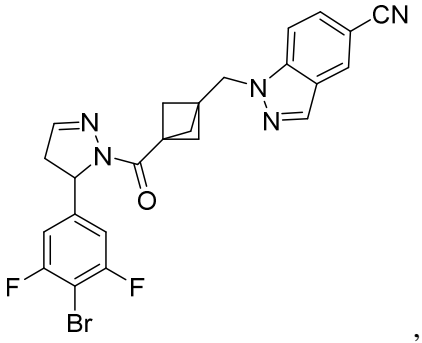
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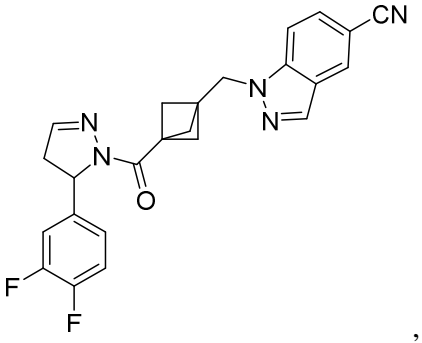
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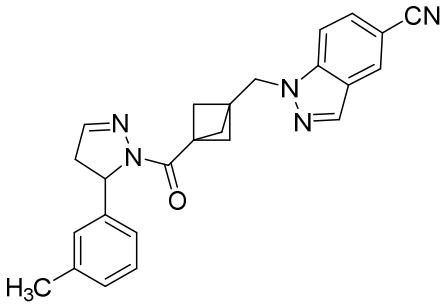
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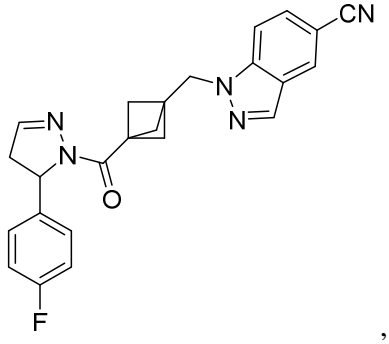
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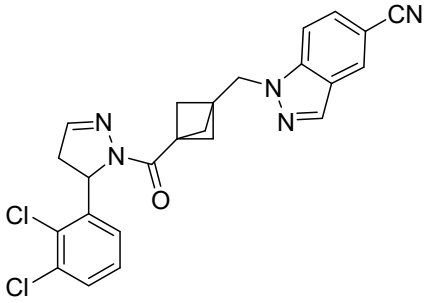
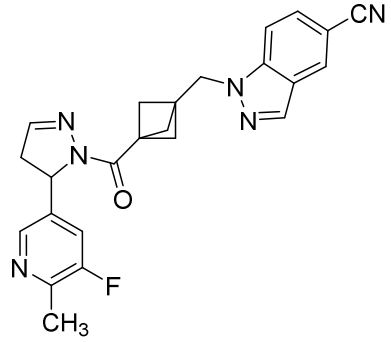
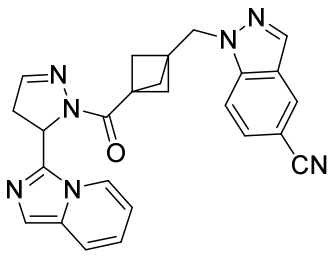
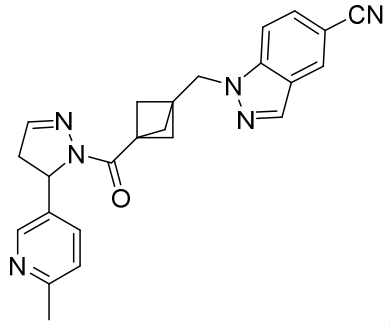
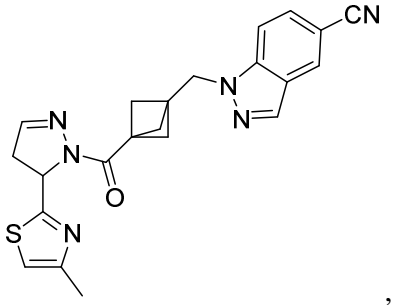
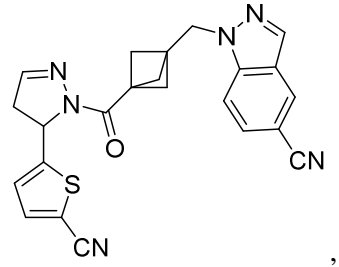
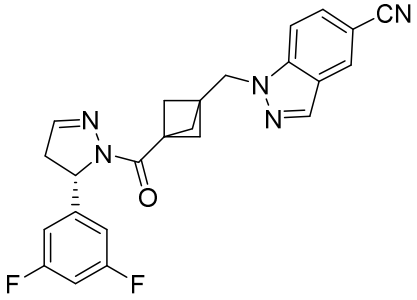
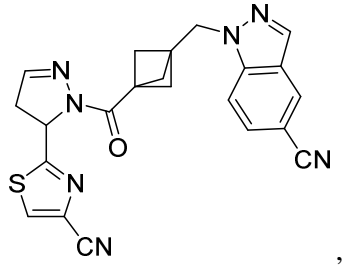
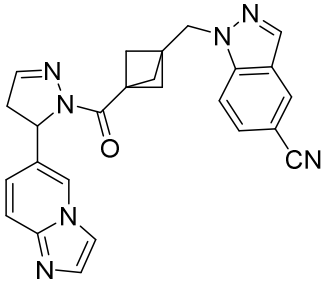
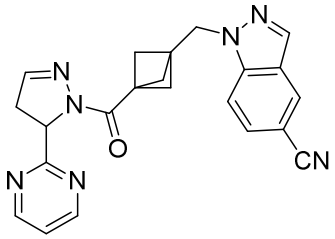
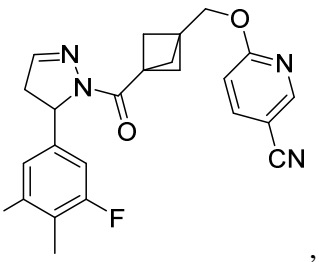

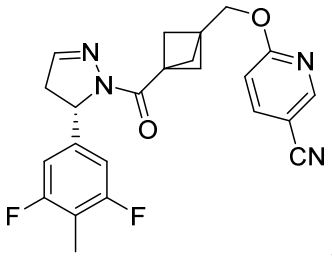
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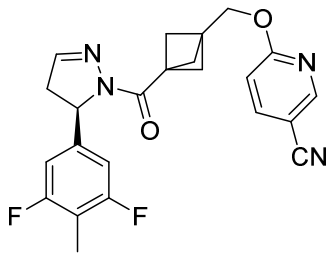
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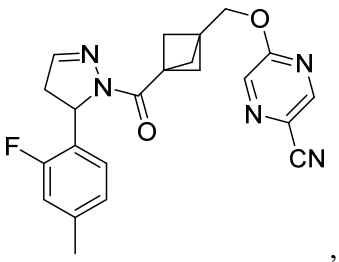
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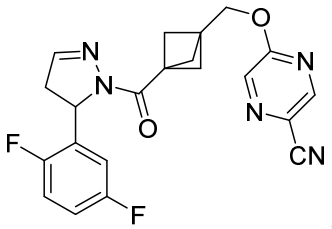
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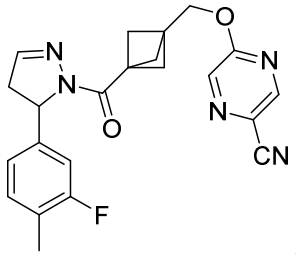
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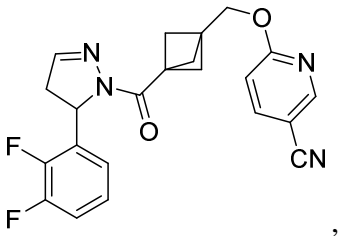
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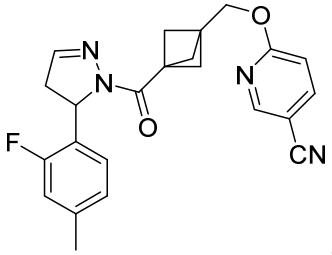
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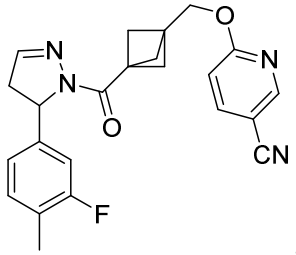
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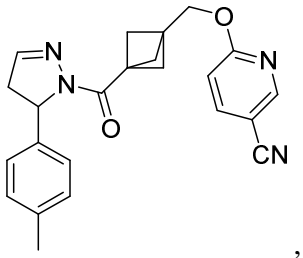
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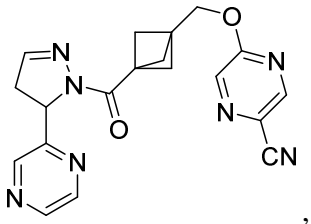
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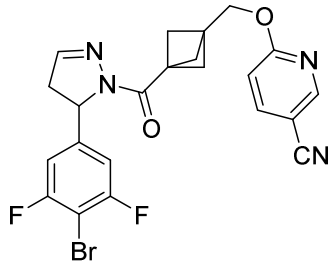
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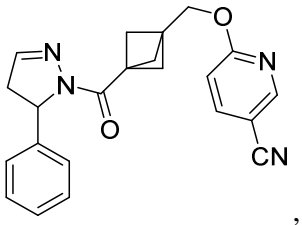
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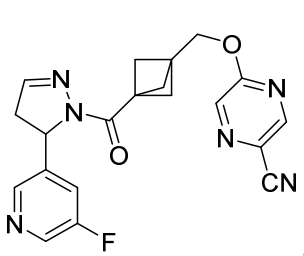
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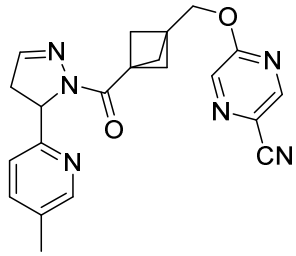
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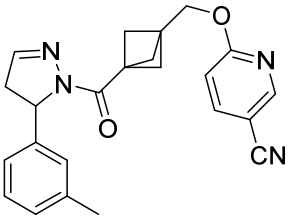
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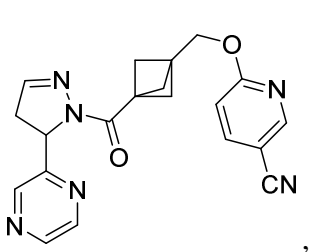
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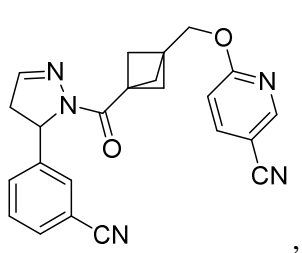
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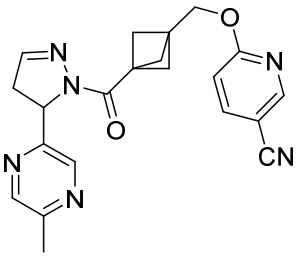
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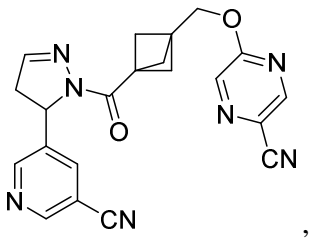
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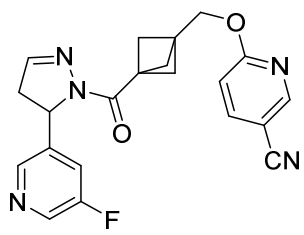
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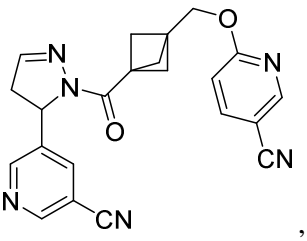
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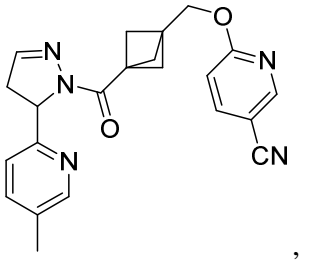
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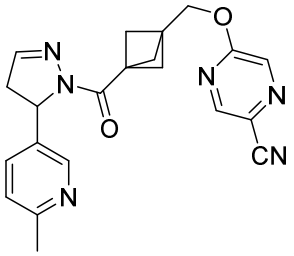
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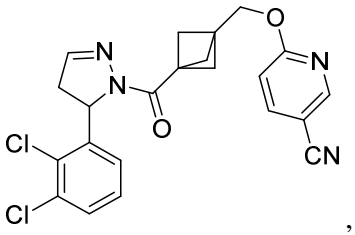
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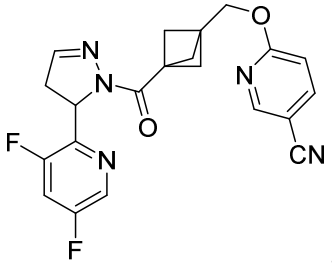
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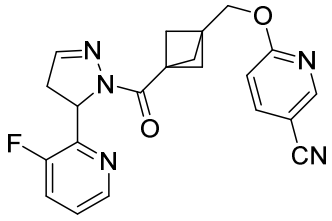
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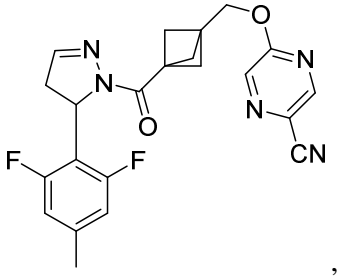
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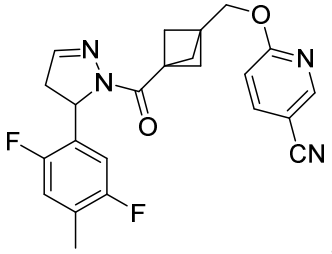
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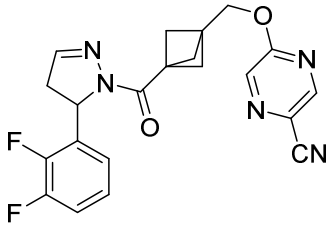
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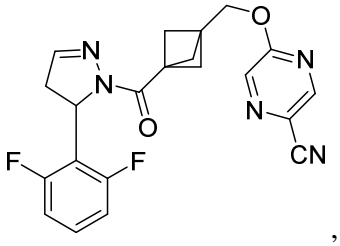
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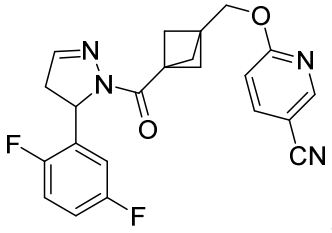
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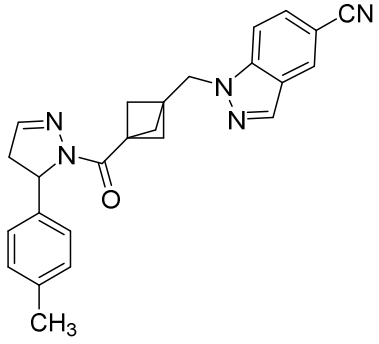
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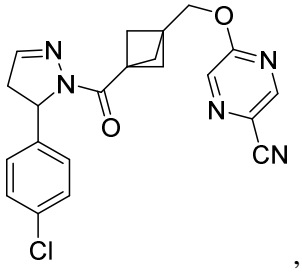
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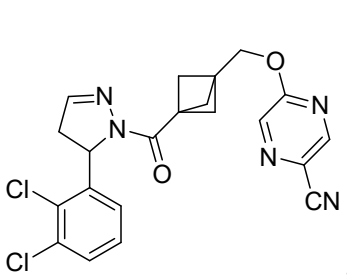
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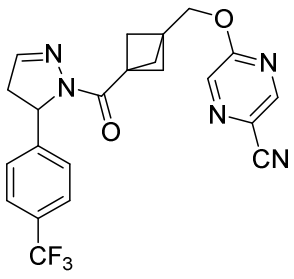
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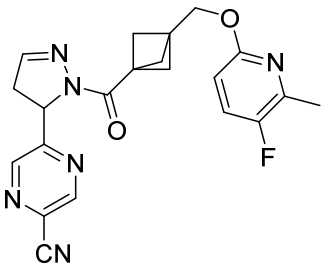
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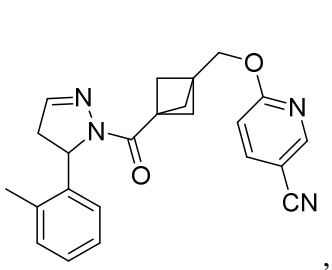
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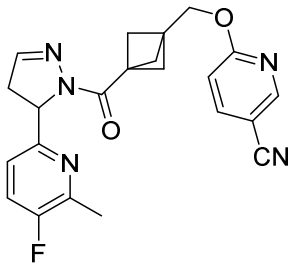
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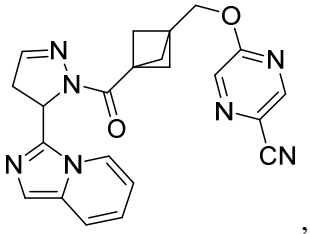
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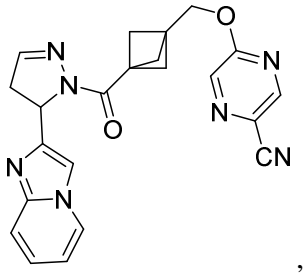
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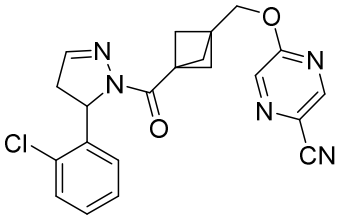
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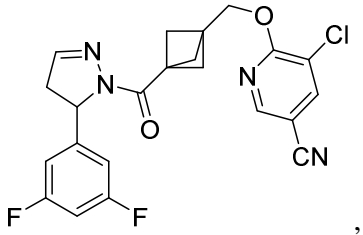
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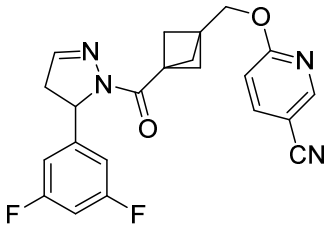
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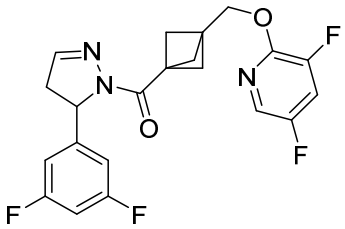
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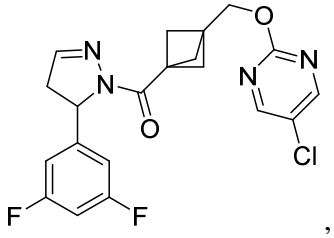
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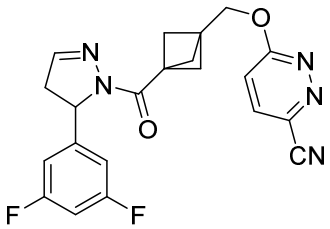
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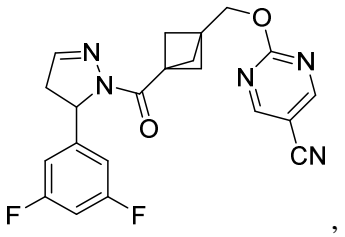
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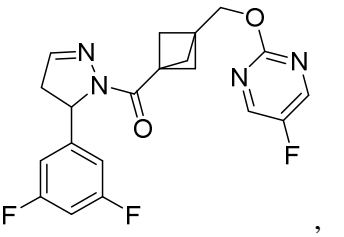
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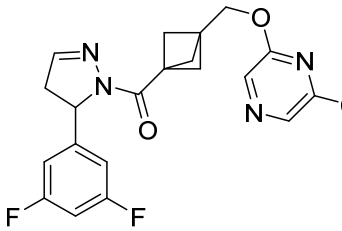
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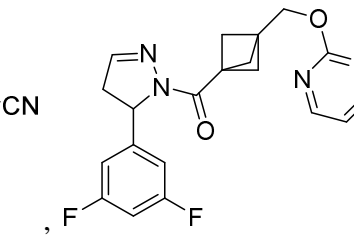
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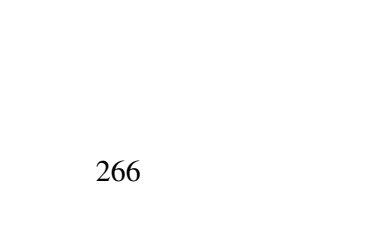
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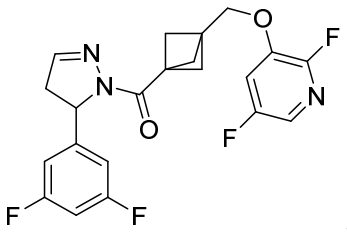
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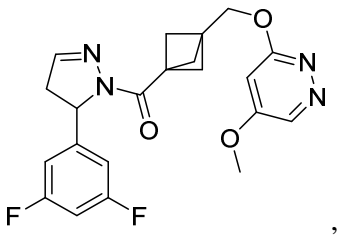
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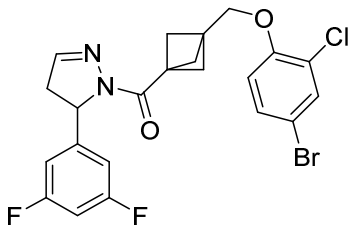
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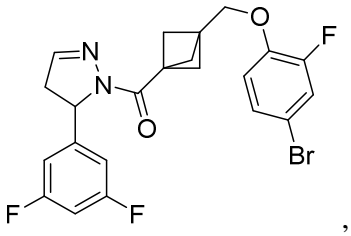
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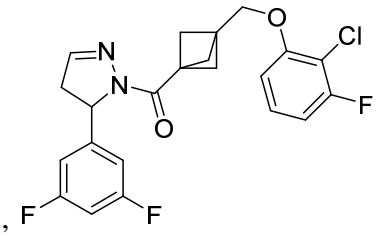
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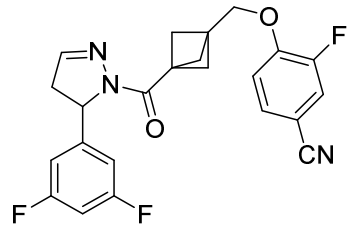
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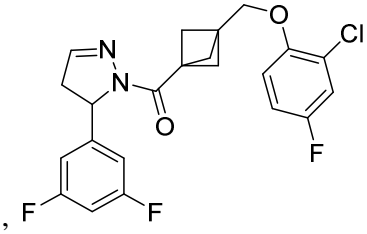
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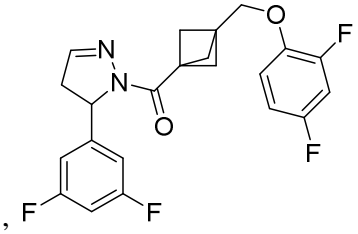
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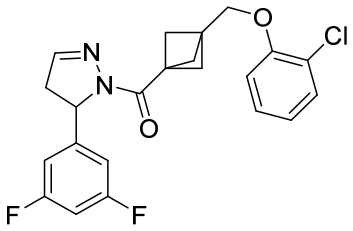
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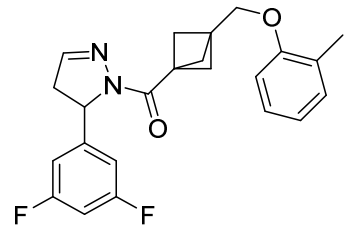
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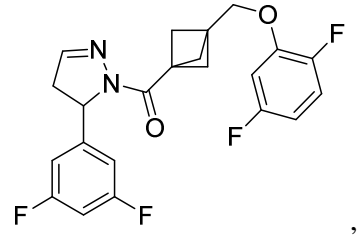
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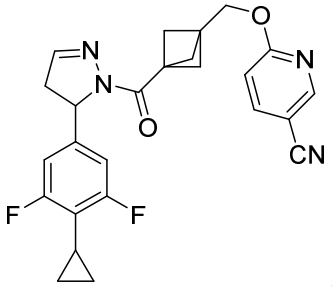
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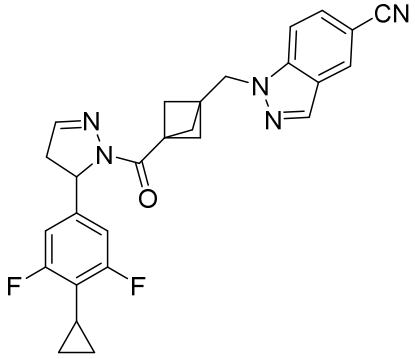
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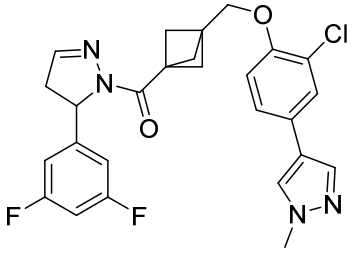
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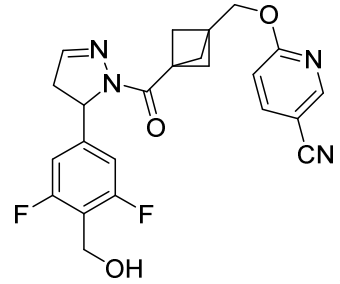
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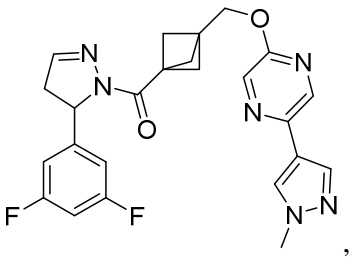
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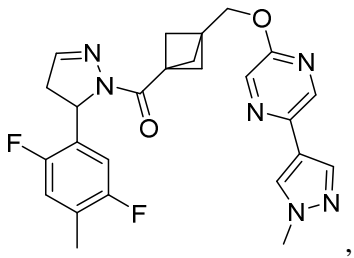
and  , or a salt thereof.

36. A compound as recited in any one of claims 1 – 35 for use as a medicament.
37. A compound as recited in any one of claims 1 – 35 for use in the manufacture of a medicament for the prevention or treatment of a disease ameliorated by the inhibition of RIPK1.
38. A compound as recited in any one of claims 1 – 35 for use in the treatment of a disease mediated by RIPK1.
39. The compound as recited in claim 38, wherein said disease is a neurological disease.
40. The compound as recited in claim 39, wherein said neurological disease is accompanied by an inflammatory component of cellular stress.
41. The compound as recited in claim 40, wherein said neurological disease is chosen from multiple sclerosis, Neimanm-Pick disease, Alzheimers disease, Parkinson's disease, amyotrophic lateral sclerosis, Lewy body dementia, frontotemporal dementia, and glutamine expansion diseases such as Huntington's disease, Kennedy's disease, and spinocerebellar ataxia.
42. The compound as recited in claim 38, wherein said disease is a neuropathy.
43. The compound as recited in claim 42, wherein said neuropathy is chosen from diabetic neuropathy and chemotherapy induced neuropathy.
44. The compound as recited in claim 38, wherein said disease is a retinal disease.
45. The compound as recited in claim 44, wherein said retinal disease is chosen from macular degeneration and retinitis.
46. The compound as recited in claim 38, wherein said disease is an auto-immune disorder.
47. The compound as recited in claim 46, wherein said auto-immune disorder is chosen from ulcerative colitis, rheumatoid arthritis, psoriasis, lupus, and inflammatory bowel disease.
48. The compound as recited in claim 38, wherein said disease is an inflammatory disease.
49. The compound as recited in claim 48, wherein said inflammatory disease is in one or more organs chosen from lung, heart, kidney, and liver.
50. The compound as recited in claim 38, wherein said disease is cancer.

51. The compound as recited in claim 50, wherein the cancer is treated by promoting an appropriate immune response to the tumor.
52. The compound as recited in claim 51, wherein the appropriate response to the tumor comprises, or results in, one or more of the following:
    - an increase in the number or activity, or degree of tumor infiltration, of cytotoxic T-lymphocytes and/or natural killer cells;
    - an increase in the number or activity of M1 macrophages in the tumor microenvironment and/or a decrease in the in the number or activity of M2 macrophages in the tumor microenvironment;
    - a decrease in the number or activity of regulatory T cells; and
    - a decrease in the number or activity of myeloid-derived suppressor cells.
    - a decrease in the number or activity of myeloid-derived suppressor cells.
53. A compound as recited in any one of claims 1 – 35 for use in the treatment of an injury to the CNS.
54. The compound as recited in claim 53, wherein said injury is chosen from traumatic brain injury and stroke.
55. A pharmaceutical composition comprising a compound as recited in claim 1 together with a pharmaceutically acceptable carrier.