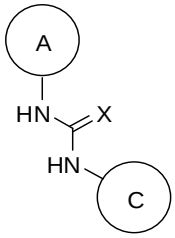
Claims

1. A compound having the Formula **I**:

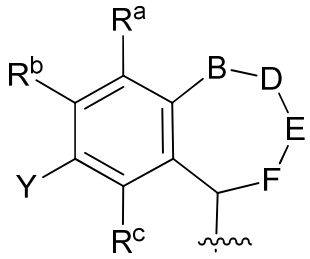


I

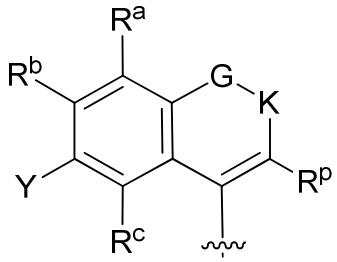
or stereoisomers, tautomers, or pharmaceutically acceptable salts, or solvates thereof, wherein:

X is O or S;

Ring A is formula A-1 or A-2



A-1



A-2

Y is H, halogen, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkyl [optionally substituted with 1-5 fluoros], cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-6C)alkoxy [optionally substituted with 1-5 fluoros], CN, aminocarbonyl or (1-4C alkoxy)carbonyl;

R^a, R^b and R^c are independently selected from H, halogen, (1-3C)alkyl, (1-3C)alkoxy and CN;

B is NR^1, O, a bond, CR^dR^e, S or SO_2;

D is NR^1, O, a bond, CR^fR^g, S or SO_2;

E is NR^1, O, a bond, or CR^hR^i, S or SO_2;

F is CR^jR^k;

provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms and zero or only one of B, D or E is NR^1, O, S or SO_2;

G is CR^mR^n;

K is NR^1;

R^1 is (1-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], (1-6C)alkylC(=O)- or (1-6C alkoxy)C=O-;

R^d, R^e, R^f, R^g, R^h, R^i, R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

or one of a pair of R^d and R^e, or R^f and R^g, or R^h and R^i, or R^j and R^k, together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidinyl ring,

or one of a pair of R^d and R^e, or R^f and R^g, or R^h and R^i, or R^j and R^k form an oxo group,

and wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom;

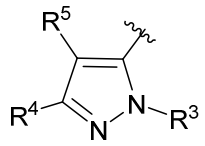
R^m is H, (1-3C)alkyl [optionally substituted with 1-5 fluoros], cyclopropyl or cyclobutyl, and

R^n is H or (1-3C)alkyl [optionally substituted with 1-5 fluoros], or

R^m and R^n together form an oxo group;

R^p is H, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], or (2-6C)cyanoalkyl;

Ring C is formula **C-1**



C-1 ;

R^3 is (1-6C)alkyl, hydroxy(1-6C)alkyl, Ar^2, $hetCyc^1$, (3-7C)cycloalkyl, or $hetAr^2$;

Ar^2 is phenyl optionally substituted with one or more groups independently selected from halogen and (1-6C)alkyl;

$hetCyc^1$ is a 5-6-membered saturated or partially unsaturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

$hetAr^2$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

R^4 is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3C)alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, $hetAr^3$(1-6C)alkyl, Ar^3(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(1-6C)alkoxy, $hetCyc^2$(1-6C)alkoxy, $hetAr^3$(1-6C)alkoxy, Ar^3(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], $hetAr^4$, $hetAr^4$-O-, Ar^4, $hetCyc^2(O)CH_2$-, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, $hetCyc^2C(=O)$(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, $hetCyc^2C(=O)O$-, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, $hetCyc^3$, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, $hetAr^5$ or $hetCyc^4$-O-;

hetCyc^2 is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with 1-2 groups independently selected from (1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, and (1-6C)acyl;

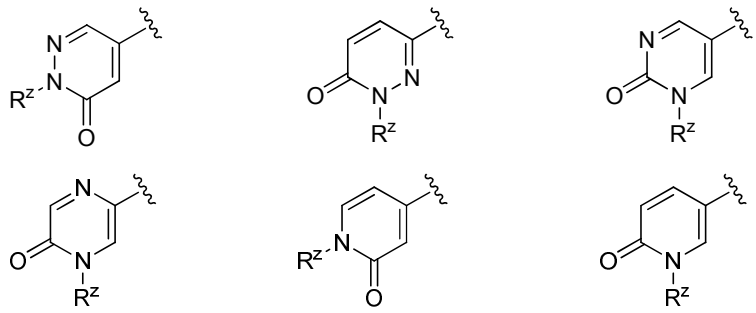
hetCyc^3 is a 4-7 membered heterocycle having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from F, CN, (1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)acyl-, (1-6C)alkylsulfonyl, trifluoromethylsulfonyl and (1-4C alkoxy)carbonyl;

hetAr^3 is a 5-membered heteroaryl ring having 1-3 ring atoms independently selected from N, O and S and optionally substituted with (1-6C)alkyl;

Ar^3 is phenyl optionally substituted with (1-4C)alkoxy;

hetAr^4 is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, S and O and optionally substituted with one or more substituents independently selected from (1-6C)alkyl, halogen, CN, hydroxy(1-6C)alkyl, trifluoro(1-6C)alkyl, difluoro(1-6C)alkyl, fluoro(1-6C)alkyl, (3-6C)cycloalkyl, (3-6C cycloalkyl)CH_2- (3-6C cycloalkyl)C(=O)-, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, (1-6C)alkylsulfonyl, NH_2, (1-6C alkyl)amino, di(1-6C alkyl)amino, (1-3C trifluoroalkoxy), fluoro(1-6C alkyl)amino, difluoro(1-6C alkyl)amino, trifluoro(1-6C alkyl)amino, and (3-4C cycloalkyl)amino;

hetAr^5 is a group selected from the structures:



where R^z is (3-4C)cycloalkyl or (1-3C)alkyl (optionally substituted with 1-3 fluoros), wherein each of said hetAr^5 groups is optionally further substituted with one or more groups independently selected from F and (1-3C)alkyl optionally substituted with 1-3 fluoros;

hetCyc^4 is a 7-8 membered bridged heterocycle having a ring nitrogen atom and optionally substituted with one or more groups independently selected from (1-6C)alkyl and halogen;

Ar^4 is phenyl optionally substituted with one or more groups independently selected from (1-6C)alkyl, halogen, CN, CF_3, CF_3O-, (1-6C)alkoxy, (1-6Calkyl)OC(=O)-, aminocarbonyl, (1-6C)alkylthio, hydroxy(1-6C)alkyl, (1-6C alkyl)SO_2-, HOC(=O)- and (1-3C alkoxy)(1-3C alkyl)OC(=O)-; and

R^5 is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy); or

R^4 and R^5 together with the atoms to which they are attached form 5-6 membered saturated, partially unsaturated or unsaturated heterocyclic ring having a ring heteroatom selected from N, O or S, wherein said heterocyclic ring is optionally substituted with one or two substituents independently selected from (1-6C alkyl)C(=O)O-, (1-6C)acyl, (1-6C)alkyl and oxo, and said sulfur ring atom is optionally oxidized to S(=O) or SO_2.

2. A compound according to claim 1, wherein X is O.

3. A compound according to any one of claims 1-2, wherein zero to four of R^d, R^e, R^f, R^g, R^h, R^i, R^j and R^k are independently H, OH, (1-6C)alkyl [optionally substituted with one to five fluoros], (3-6C)cycloalkyl [optionally substituted with one to five fluoros], (1-3C alkoxy)(2-6C)alkyl [optionally substituted with one to five fluoros], hydroxy(2-6C)alkyl [optionally substituted with one to five fluoros], (2-6C)cyanoalkyl, (1-6C)alkoxy [optionally substituted with one to five fluoros], or (1-3C alkoxy)(2-6C)alkoxy [optionally substituted with one to five fluoros],

or one of a pair of R^d and R^e, or R^f and R^g, or R^h and R^i, or R^j and R^k, together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidinyl ring, or one of a pair of R^d and R^e, or R^f and R^g, or R^h and R^i, or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

4. A compound according to claim 3, wherein zero to two of R^d, R^e, R^f, R^g, R^h, R^i, R^j and R^k are independently OH, methyl, methoxy, $CH_3OCH_2CH_2O$-, or cyclopropyl,

or one of a pair of R^d and R^e, or R^f and R^g, or R^h and R^i, or R^j and R^k, together with the carbon atom to which they are attached form a (3-6C)cycloalkyl, oxetanyl or azetidinyl ring, or one of a pair of R^d and R^e, or R^f and R^g, or R^h and R^i, or R^j and R^k form an oxo group, and the remainder are hydrogen, wherein only one of R^d and R^e can be OH and neither is OH if B is connected to a heteroatom, and only one of R^f and R^g can be OH and neither is OH if D is connected to a heteroatom, and only one of R^h and R^i can be OH and neither is OH if E is connected to a heteroatom, and only one of R^j and R^k can be OH and neither is OH if F is connected to a heteroatom.

5. A compound according to any one of claims 1-4, wherein Ring A is A-1.

6. A compound according to claim 5, wherein B is a bond or CR^dR^e, D is a bond or CR^fR^g, E is a bond or CR^hR^i, and F is CR^jR^k, provided that the ring formed by B, D, E, and F together with the atoms to which they are attached contains at least five atoms.

7. A compound according to any of claims 1-6, wherein Y is H, halogen or (1-3C alkoxy)(1-6C)alkyl.

8. A compound according to any of claims 1-7, wherein R^a, R^b and R^c are independently selected from halogen, (1-3C)alkyl, (1-3C)alkoxy and CN.

9. A compound according to any one of claims 1-8, wherein:

R^4 is OH, (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluro(2-6C)alkyl, pentafluro(2-6C)alkyl, cyano(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(2-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, amino(1-6C)alkyl, aminocarbonyl(1-6C)alkyl, (1-3C)alkylsulfonamido(1-6C)alkyl, sulfamido(1-6C)alkyl, hydroxycarbonyl(1-6C)alkyl, $hetAr^3$(1-6C)alkyl, Ar^3(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, difluoro(1-6C)alkoxy, trifluoro(1-6C)alkoxy, tetrafluoro(2-6C)alkoxy, pentafluoro(2-6C)alkoxy cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, amino(2-6C)alkoxy, hydroxyl-carbonyl(1-6C)alkoxy, $hetCyc^2$(1-6C)alkoxy, $hetAr^3$(1-6C)alkoxy, Ar^3(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl [optionally substituted with F, OH, (1-6C alkyl), (1-6C) alkoxy, or (1-3C alkoxy)(1-6C)alkyl], $hetAr^4$, $hetAr^4$-O-, Ar^4, $hetCyc^2(O)CH_2$-, (1-4C alkoxycarbonyl)(1-6C)alkoxy, hydroxycarbonyl(1-6C)alkoxy, aminocarbonyl(1-6C)alkoxy, $hetCyc^2C(=O)$(1-6C)alkoxy, hydroxy(1-3C alkoxy)(1-

6C)alkoxy, hydroxytrifluoro(1-6C)alkoxy, (1-3C)alkylsulfonamido(1-6C)alkoxy, (1-3C)alkylamido(1-6C)alkoxy, di(1-3C alkyl)amino-carboxy, $hetCyc^2C(=O)O$-, hydroxydifluoro(1-6C)alkyl, (1-4C alkylcarboxy)(1-6C)alkyl, (1-6C)alkoxycarbonyl, hydroxylcarbonyl, aminocarbonyl, (1-3C alkoxy)aminocarbonyl, $hetCyc^3$, halogen, CN, trifluoromethylsulfonyl, N-(1-3C alkyl)oxadiazolonyl, or $hetAr^5$;

and

R^5 is (1-6C)alkyl, monofluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, tetrafluoro(2-6C)alkyl, pentafluoro(2-6C)alkyl, halogen, CN, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-3C alkoxy)(1-4C)alkyl, (1-4C alkyl)OC(=O)-, (1-6C)alkylthio, (3-4C)cycloalkyl, amino, aminocarbonyl, trifluoro(1-3C alkyl)amido, or phenyl (optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy).

10. A compound according to claim 9, wherein R^4 is selected from (1-6C)alkoxy, $hetAr^4$ and $hetAr^5$.

11. A compound according to claim 10, wherein R^4 is $hetAr^4$ or $hetAr^5$.

12. A compound according to any one of claims 1-11, wherein R^5 is selected from halogen, CN, (1-6C)alkyl, (1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-6C)alkylthio, or phenyl optionally substituted with one or more groups independently selected from halogen, (1-6C)alkyl and (1-6C)alkoxy.

13. A compound according to claim 12, wherein R^5 is (1-6C)alkyl.

14. A compound according to any one of claims 1-13, wherein R^3 is selected from Ar^2 and (1-6C)alkyl.

15. A compound according to claim 14, wherein R^3 is Ar^2.

16. A compound according to claim 9, where R^4 is selected from H, (1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C)alkyl, cyano(1-6C)alkyl, (1-3C alkoxy)(1-6C)alkyl, (1-6C)alkoxy, monofluoro(1-6C)alkoxy, cyano(1-6C)alkoxy, hydroxy(1-6C)alkoxy, dihydroxy(2-6C)alkoxy, $hetCyc^2$(1-6C)alkoxy, Ar^3(1-6C)alkoxy, (1-4C alkoxy)(1-6C)alkoxy, (1-3C alkylsulfonyl)(1-6C)alkoxy, (3-6C)cycloalkyl, $hetAr^4$, $hetAr^4$-O-, Ar^4, and $hetAr^5$.

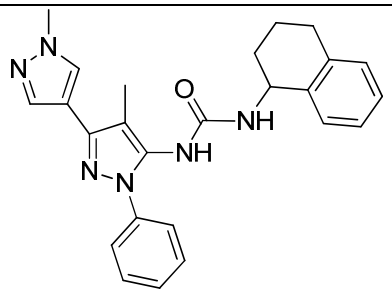
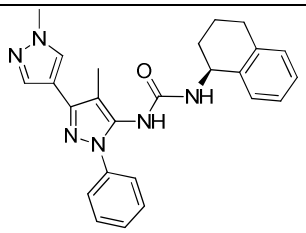
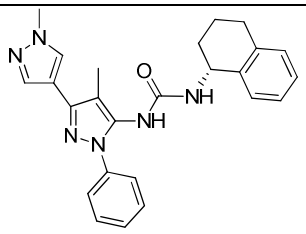
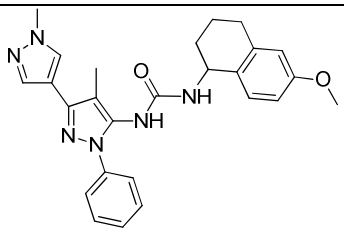
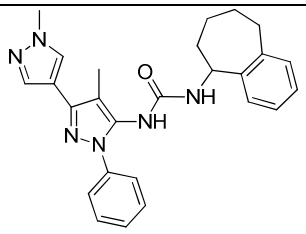
17. A compound according to claim 16, wherein R^4 is $hetCyc^2$(1-6C)alkoxy.

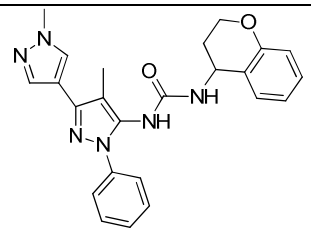
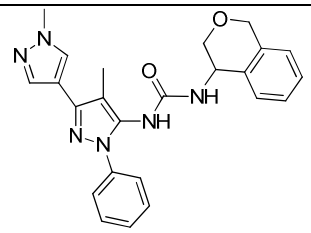
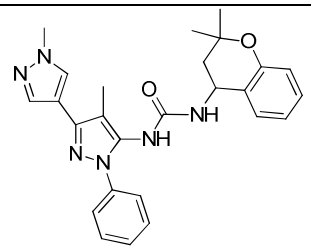
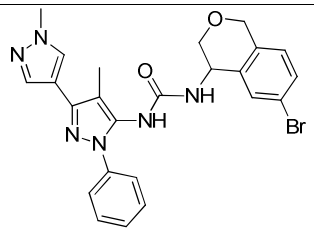
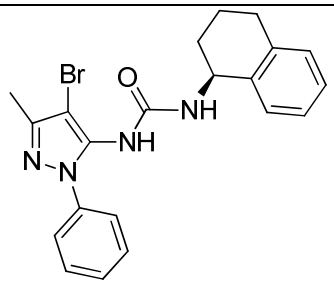
18. A compound according to claim 17, wherein R^5 is (1-6C)alkyl.

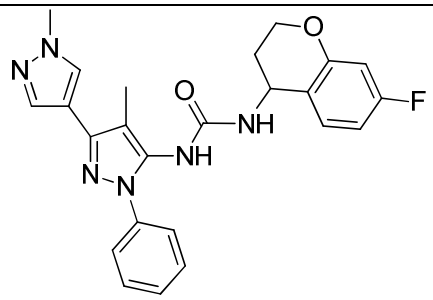
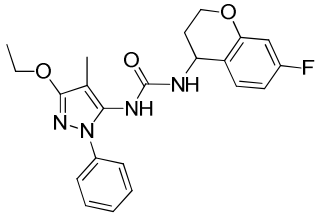
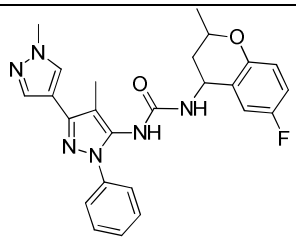
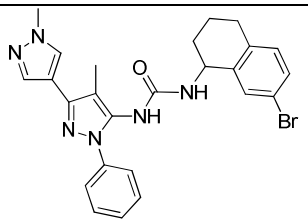
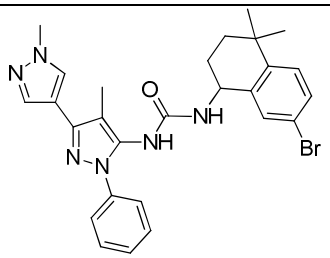
19. A compound according to claim 18, wherein R^3 is Ar^2.

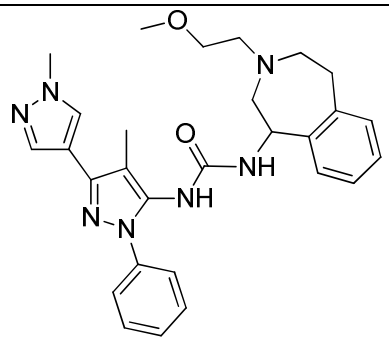
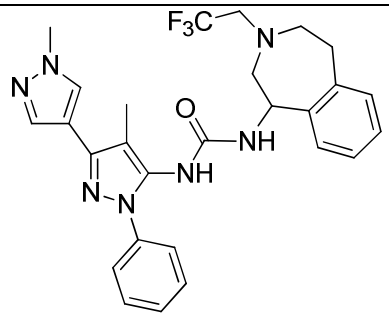
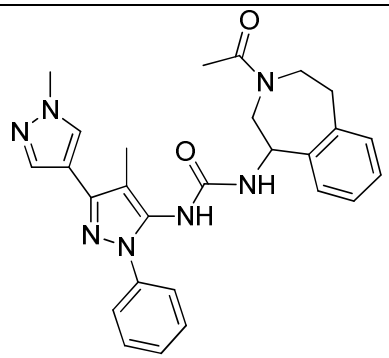
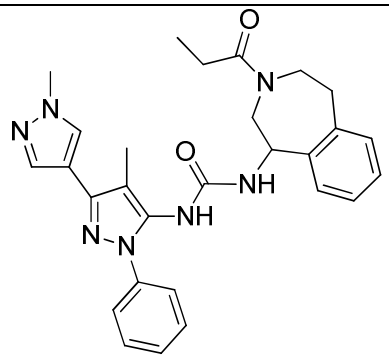
20. A compound according to claim 19, wherein Y is H.

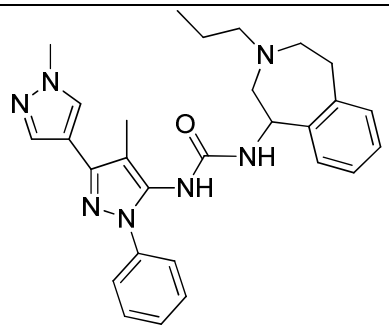
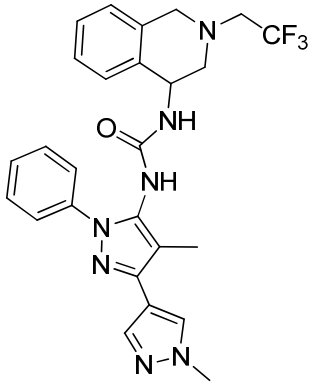
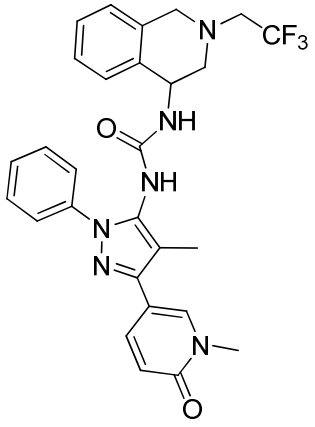
21. A compound according to claim 1, selected from

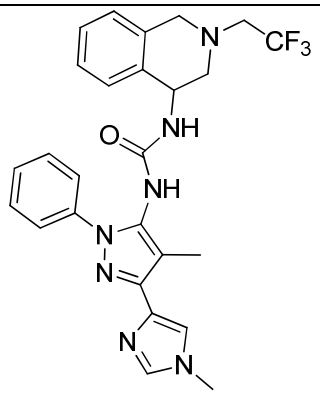
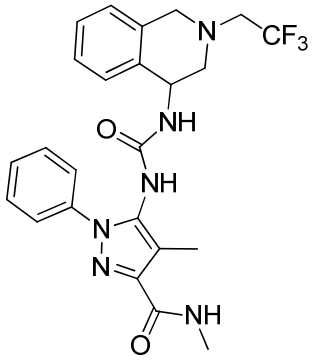
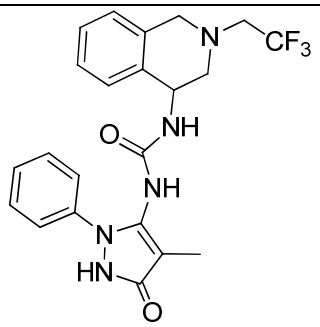
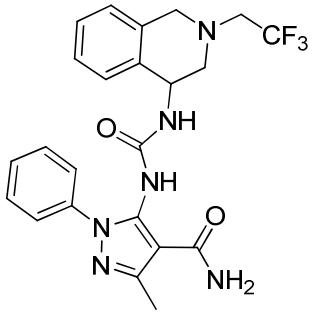
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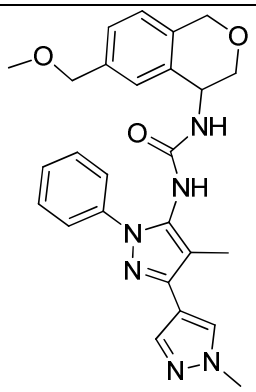
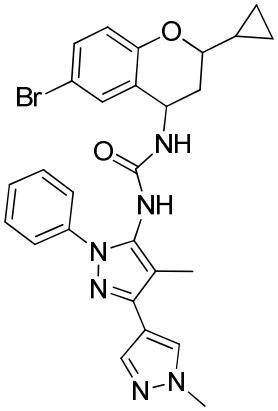
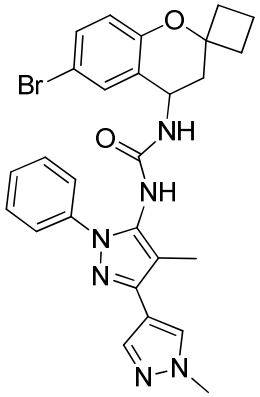
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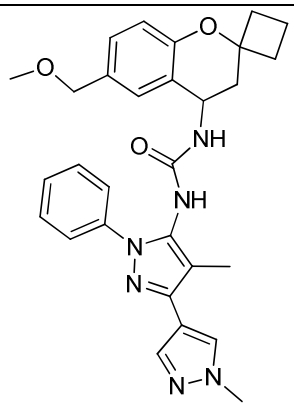
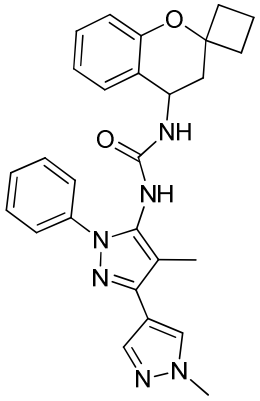
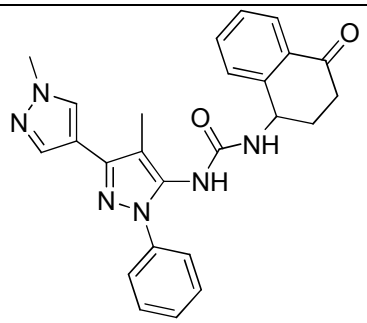
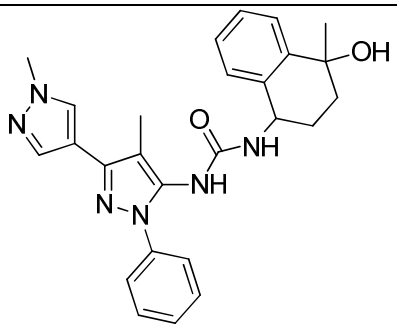
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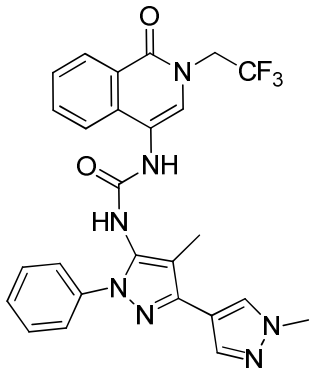
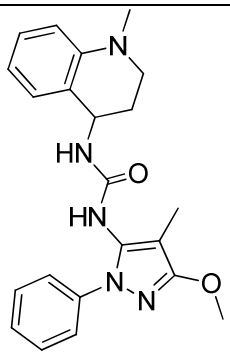
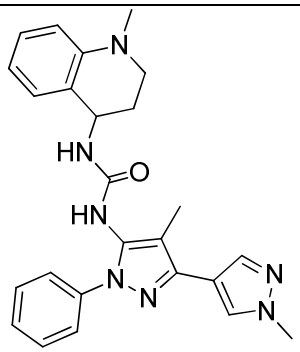
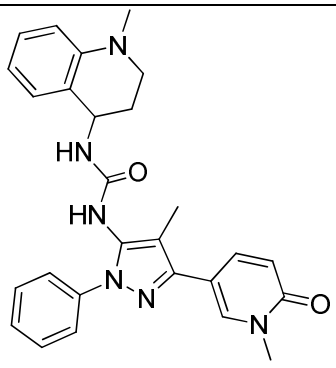
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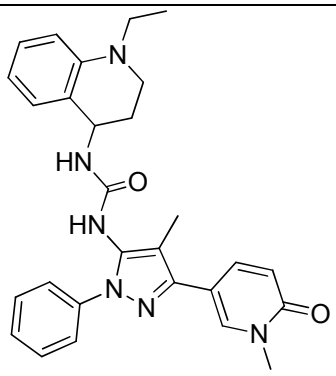
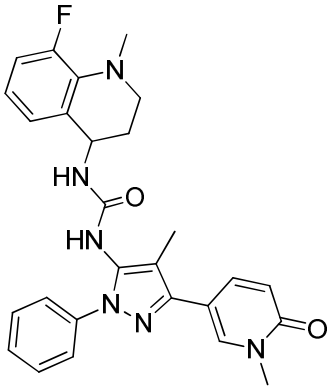
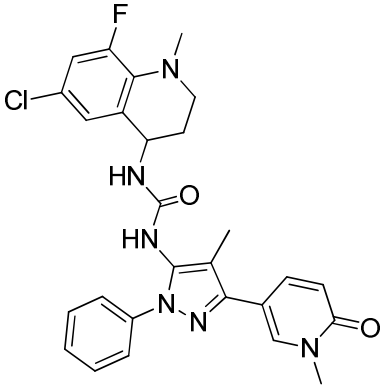
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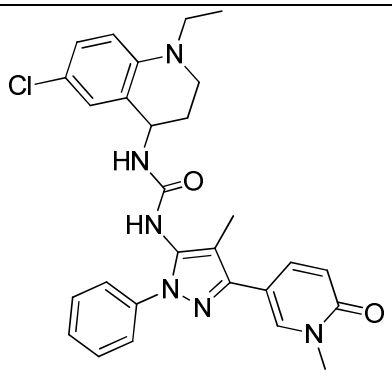
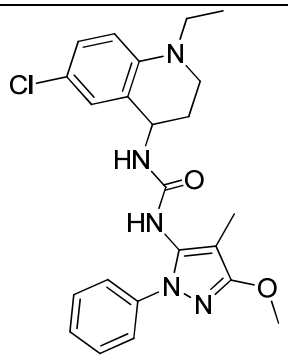
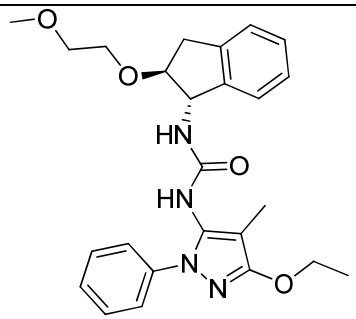
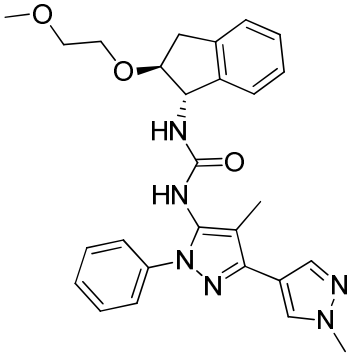
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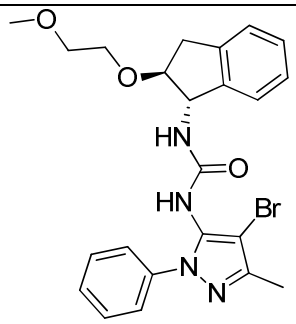
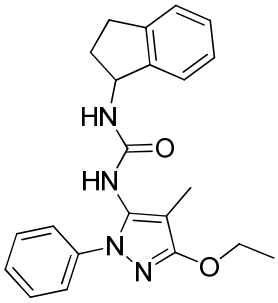
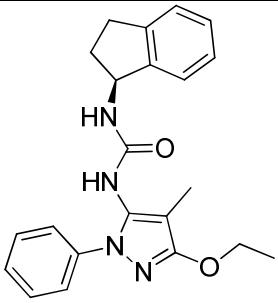
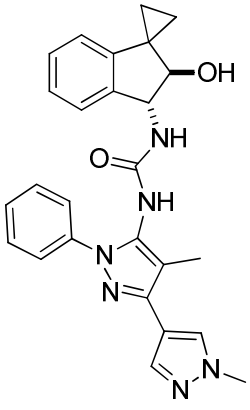
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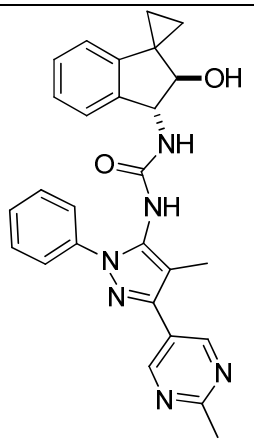
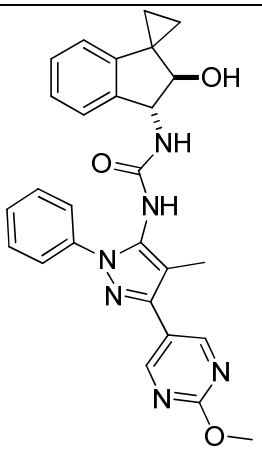
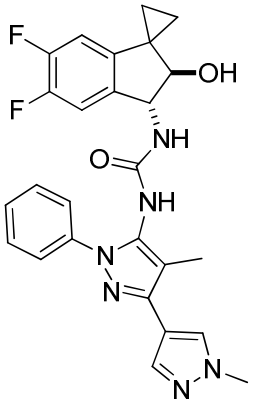
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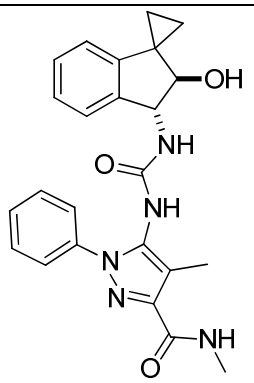
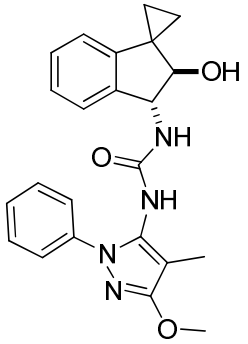
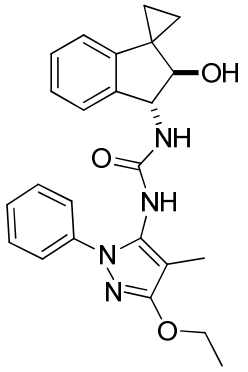
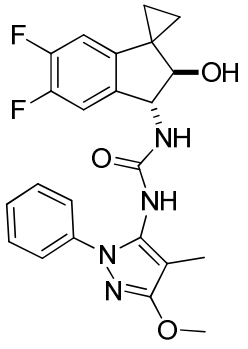
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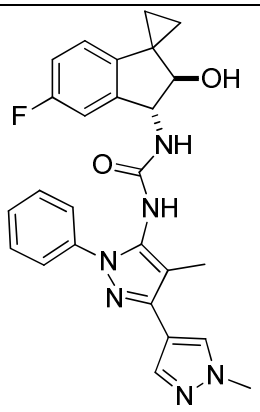
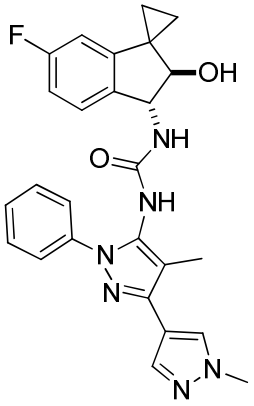
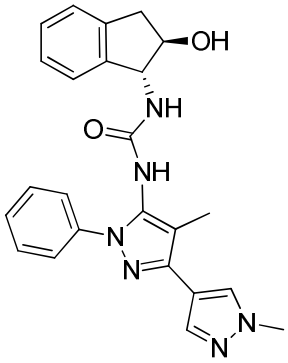
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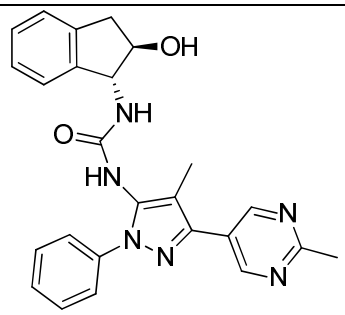
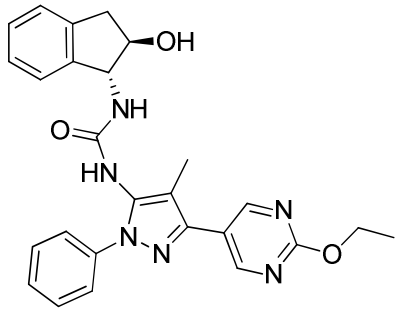
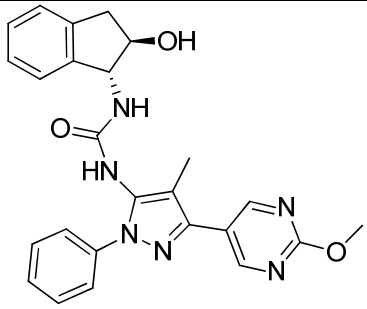
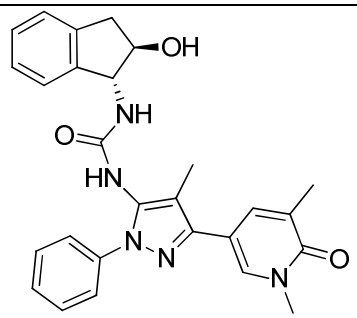
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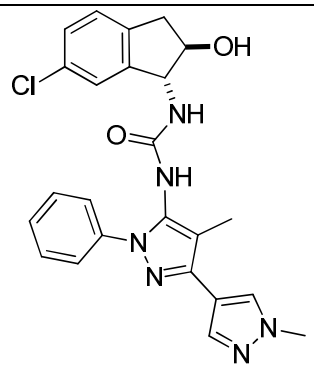
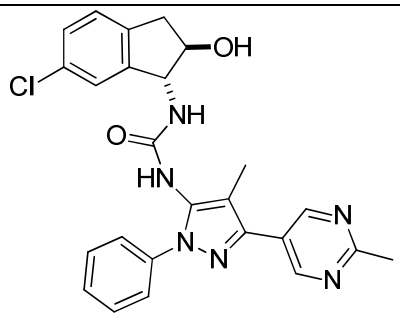
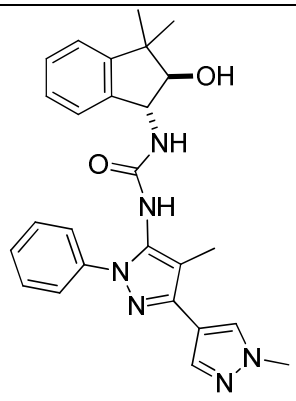
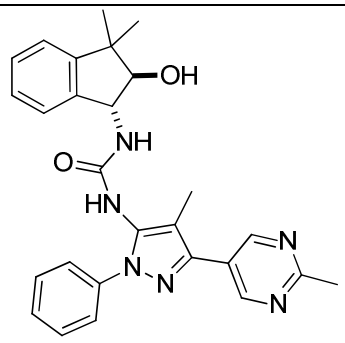
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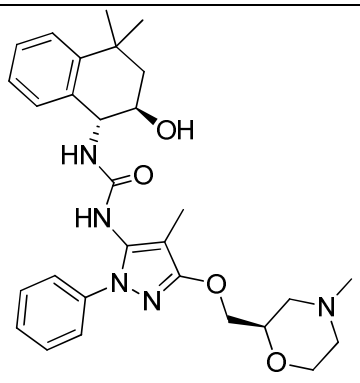
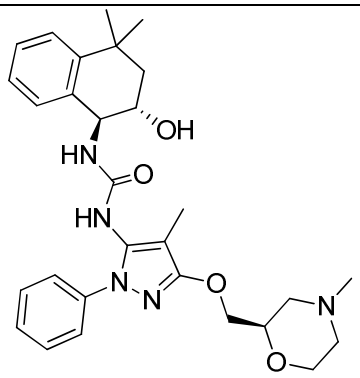
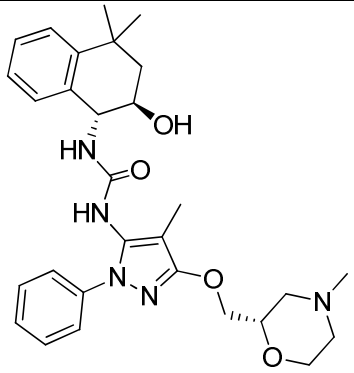
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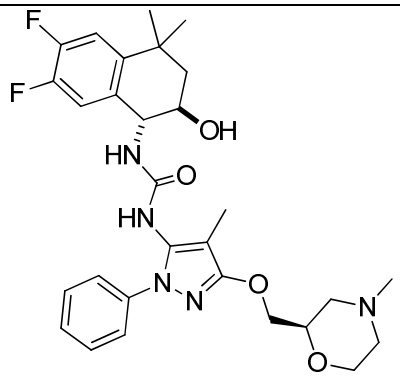
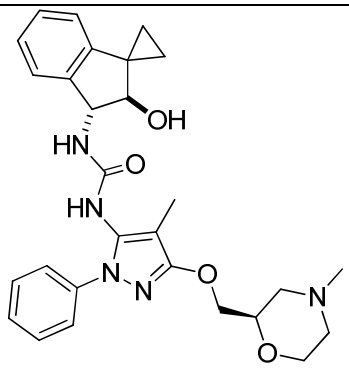
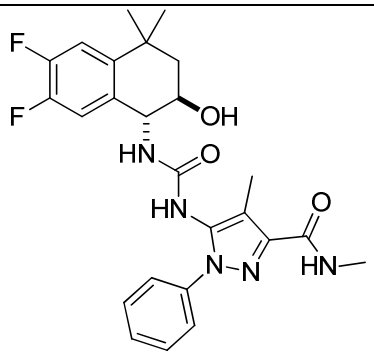
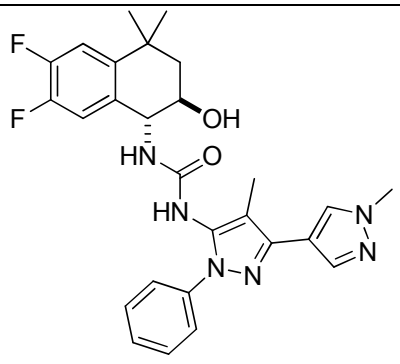
Ex. #	Structure
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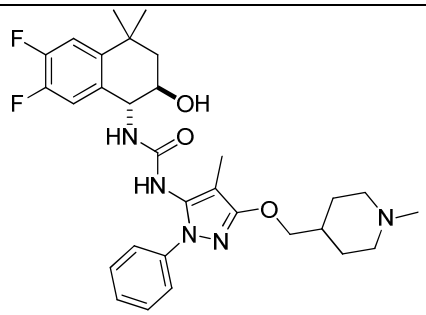
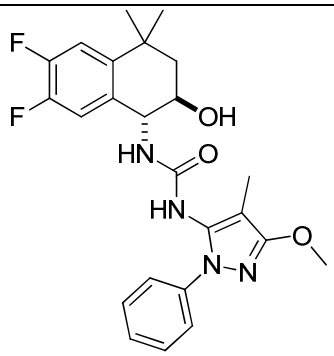
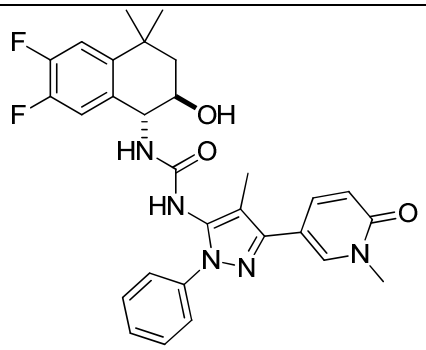
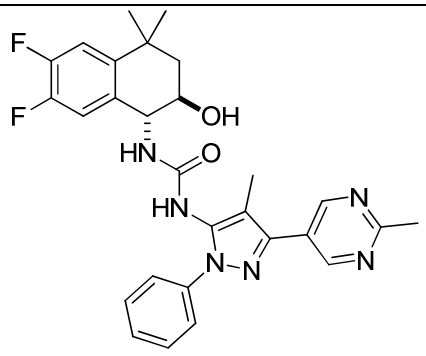
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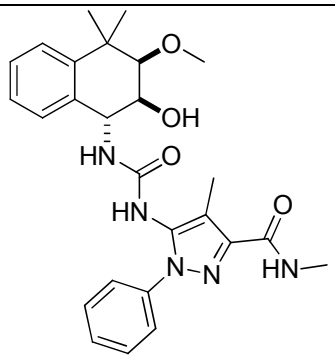
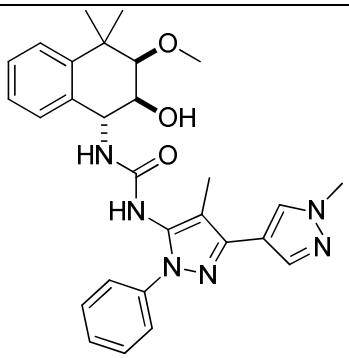
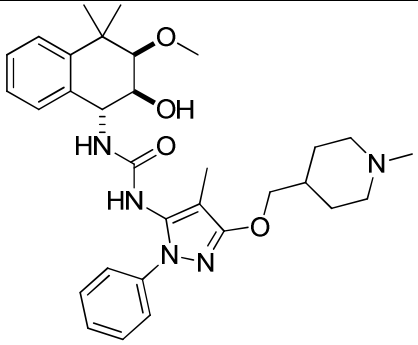
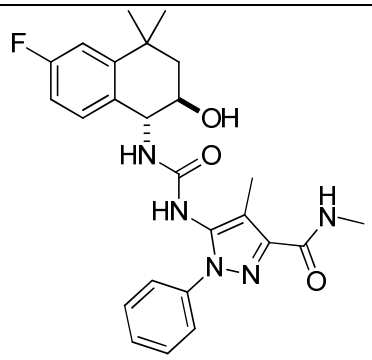
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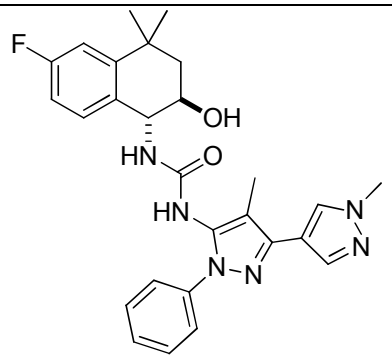
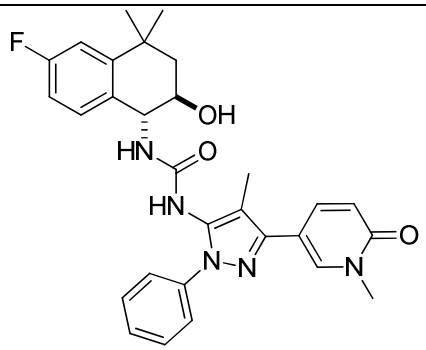
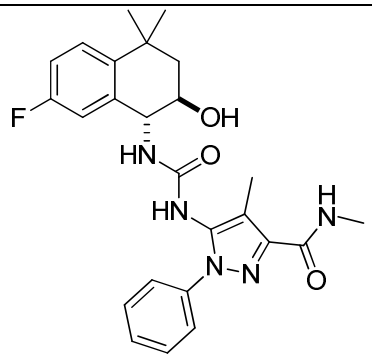
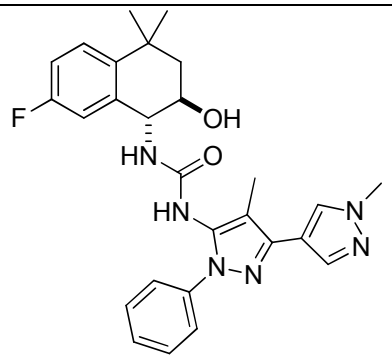
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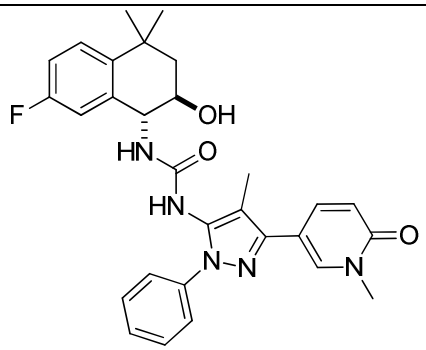
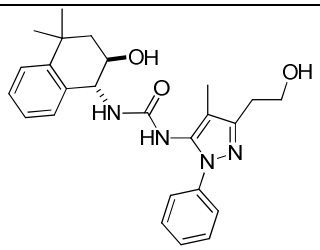
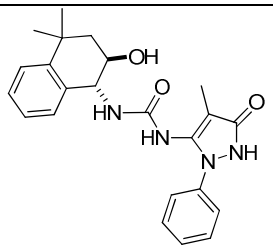
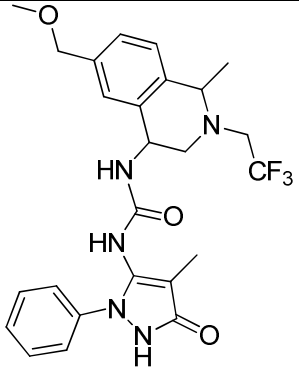
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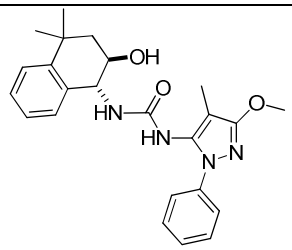
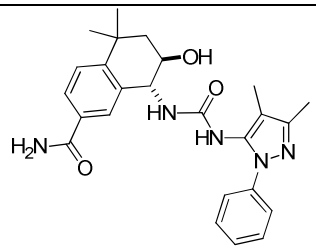
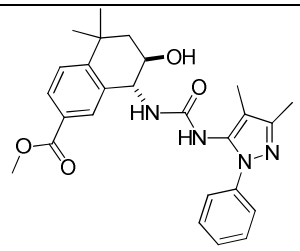
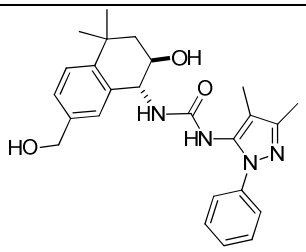
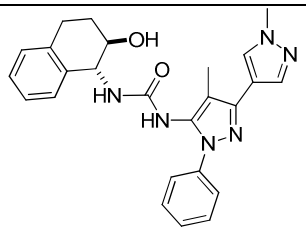
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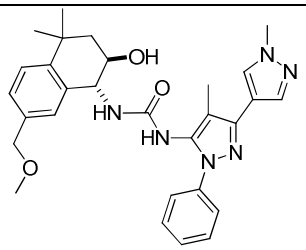
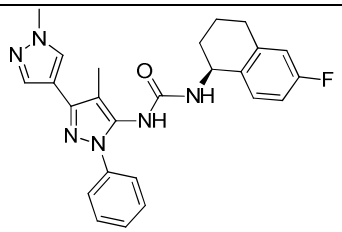
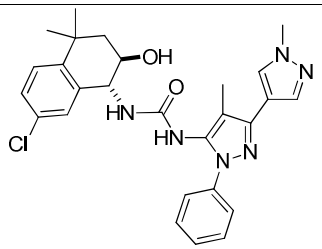
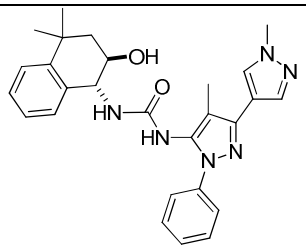
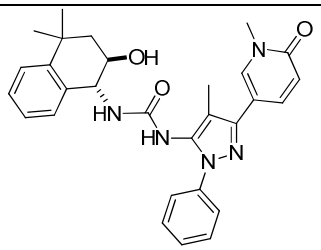
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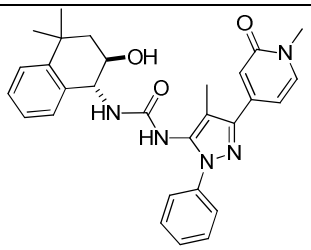
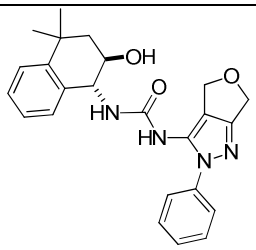
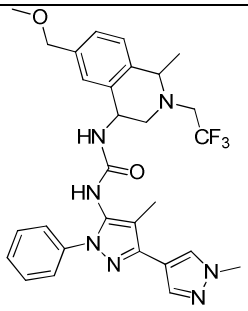
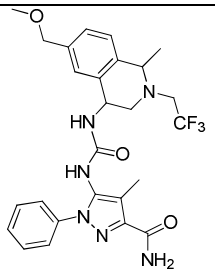
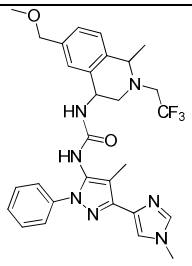
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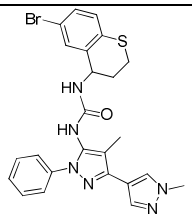
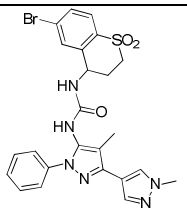
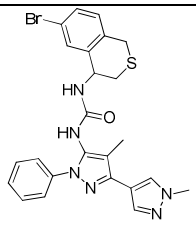
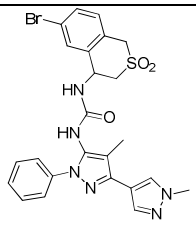
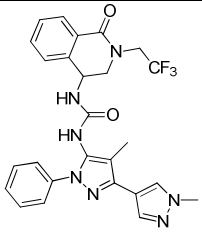
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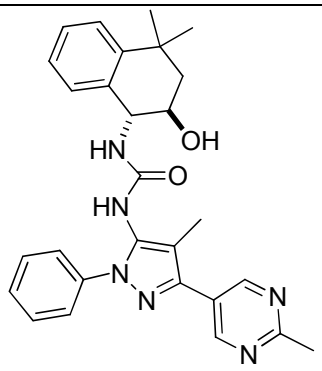
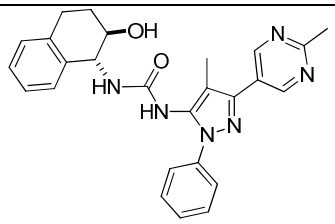
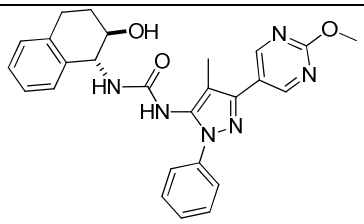
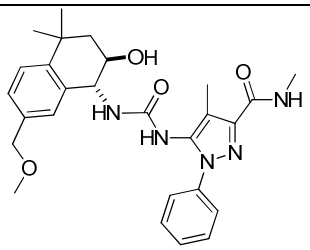
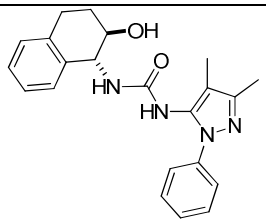
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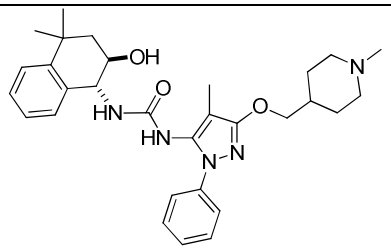
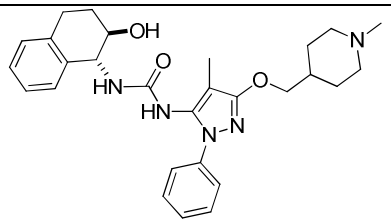
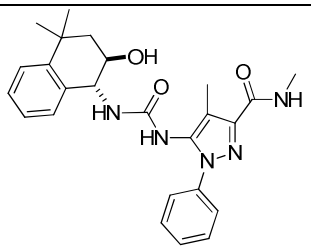
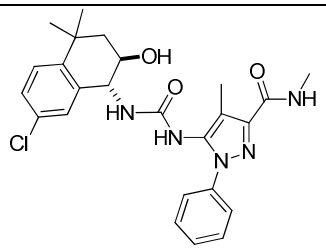
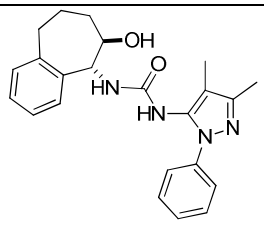
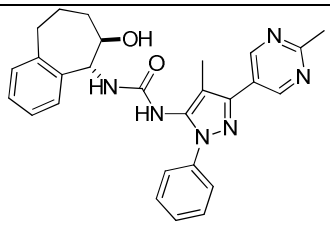
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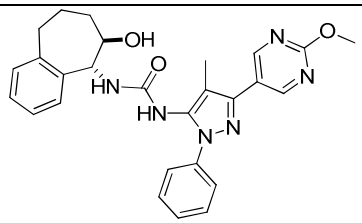
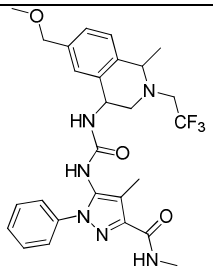
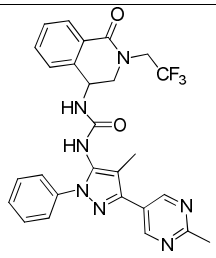
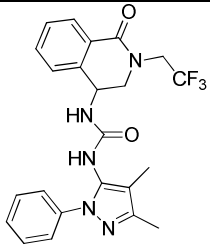
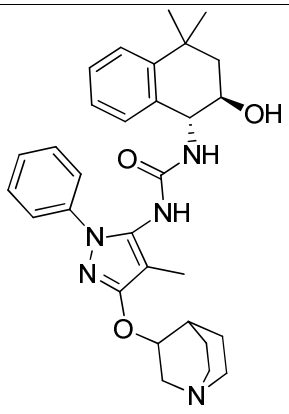
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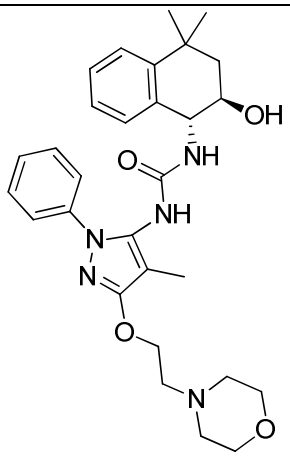
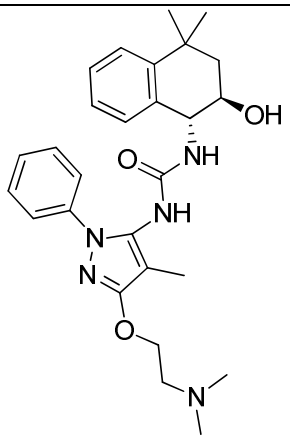
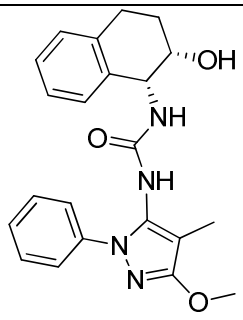
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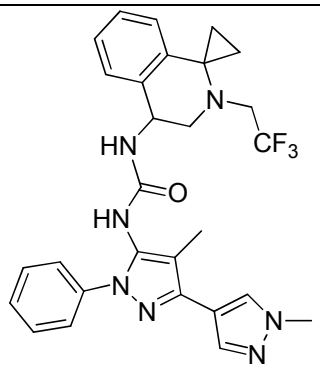
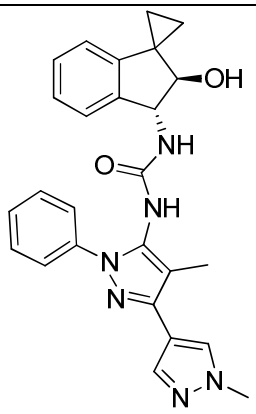
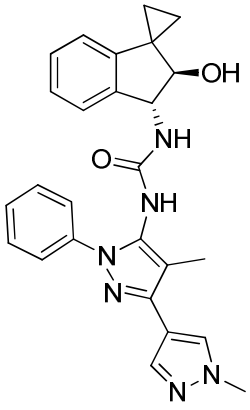
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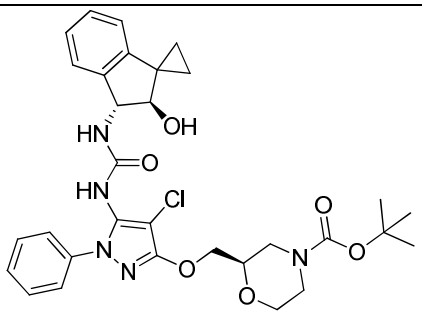
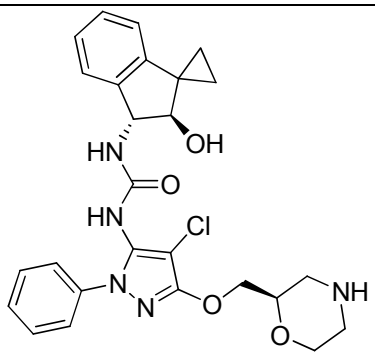
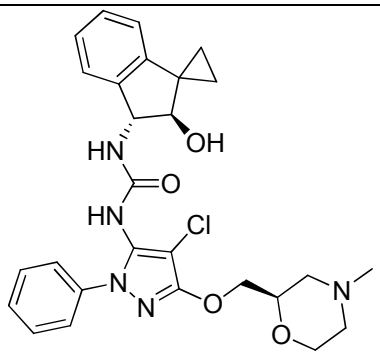
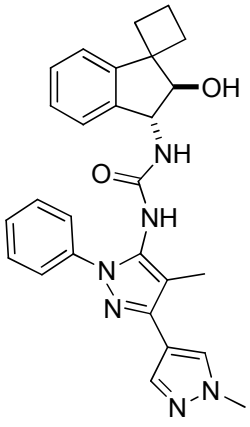
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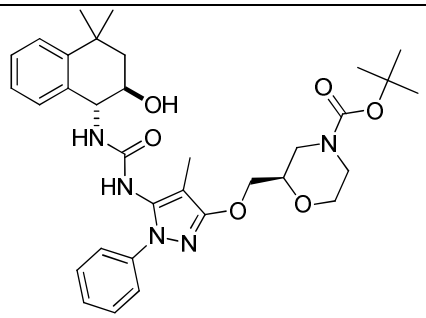
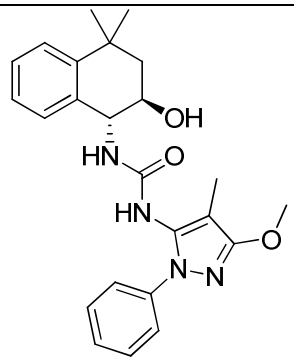
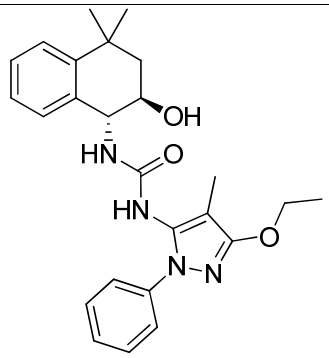
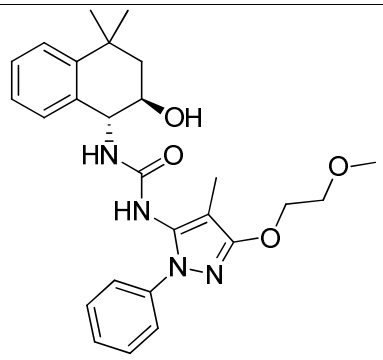
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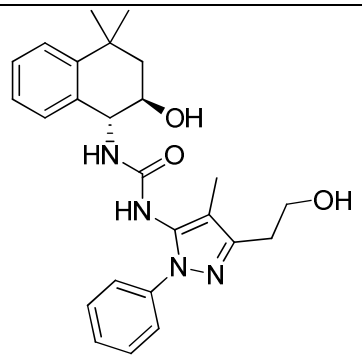
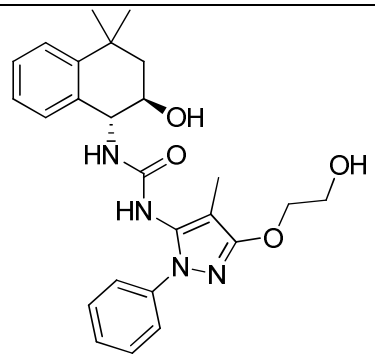
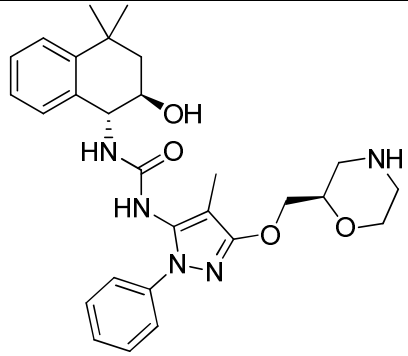
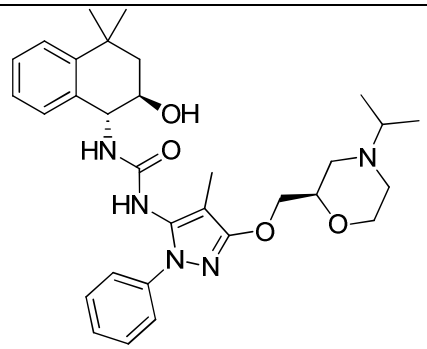
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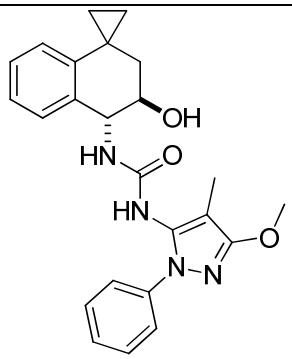
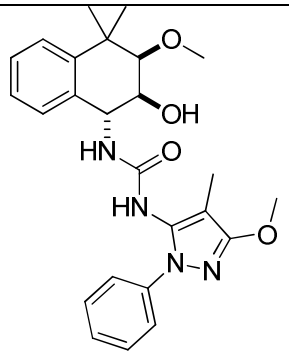
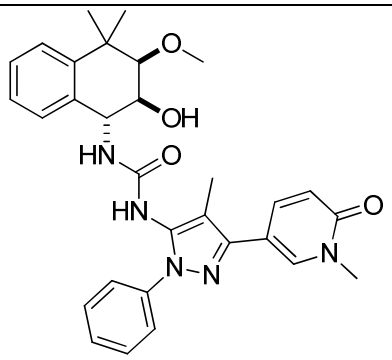
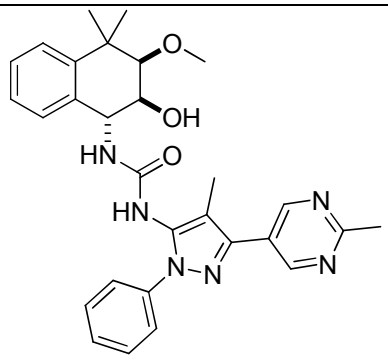
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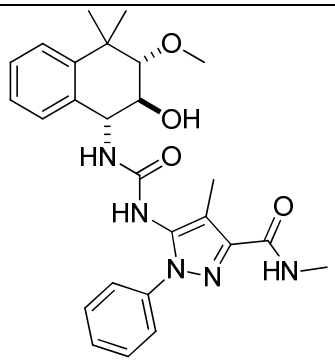
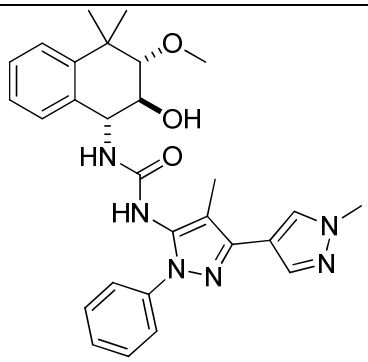
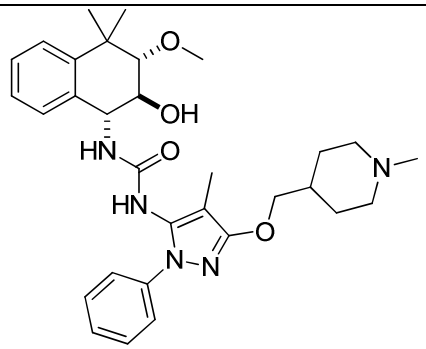
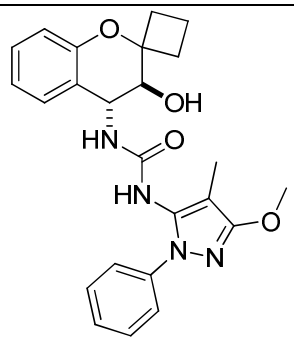
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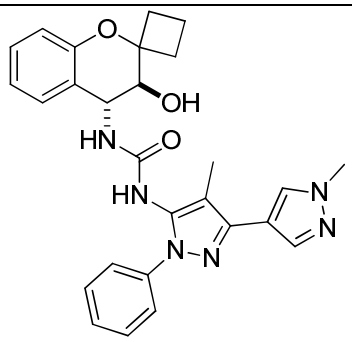
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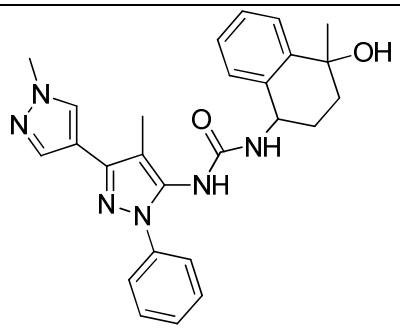
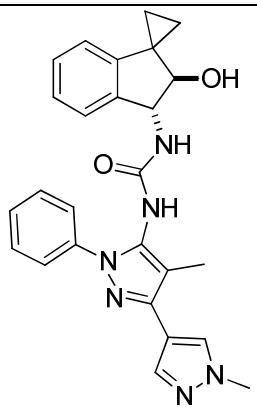
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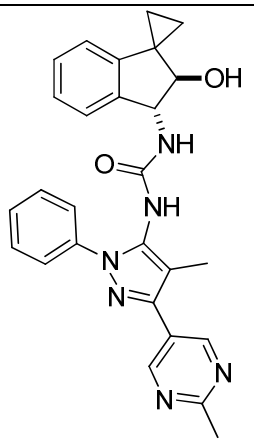
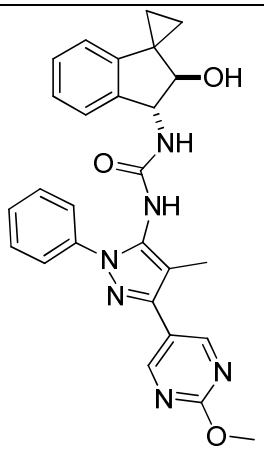
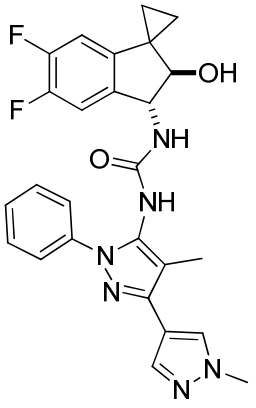
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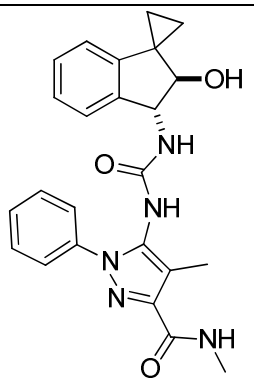
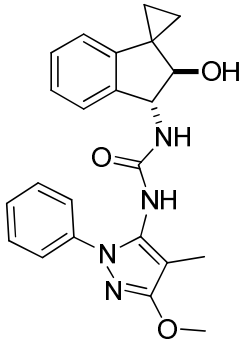
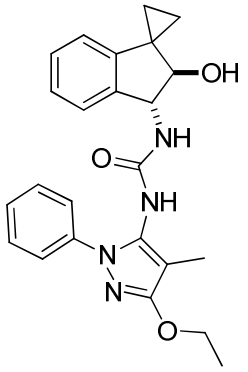
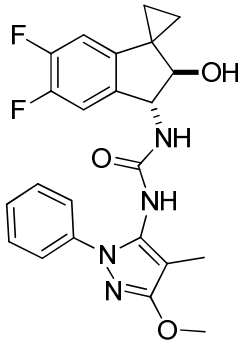
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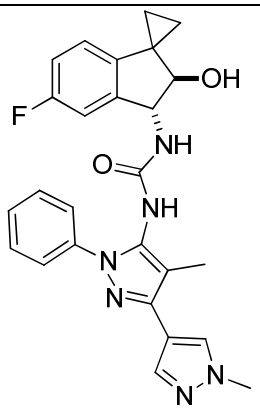
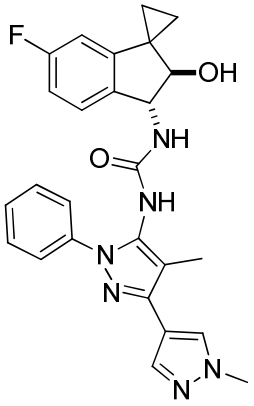
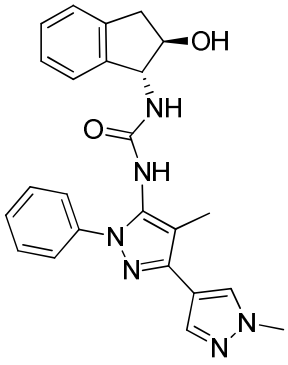
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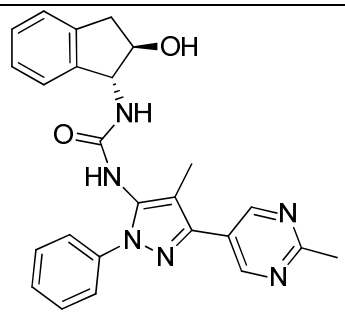
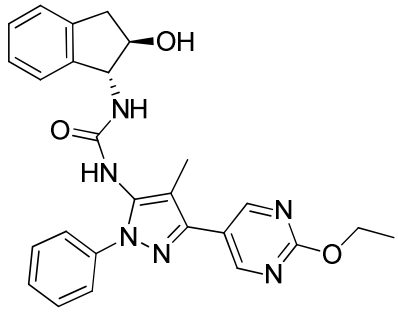
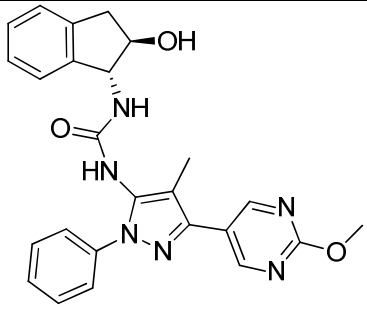
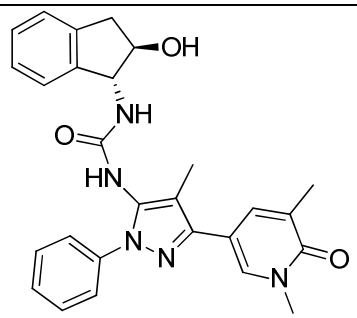
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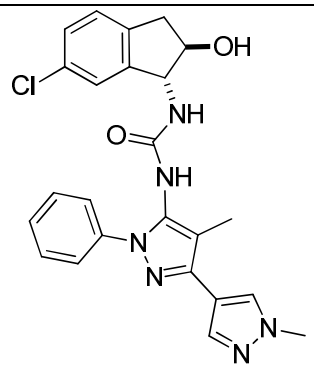
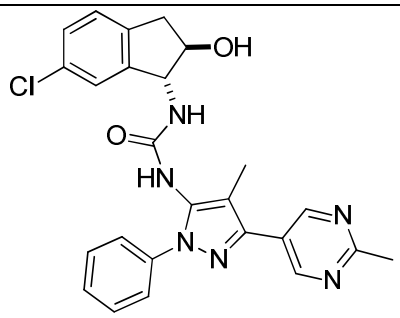
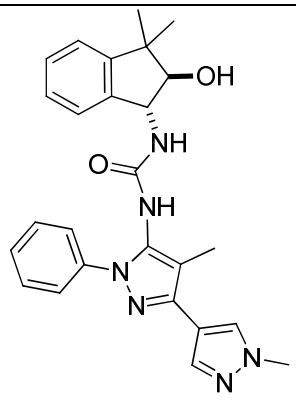
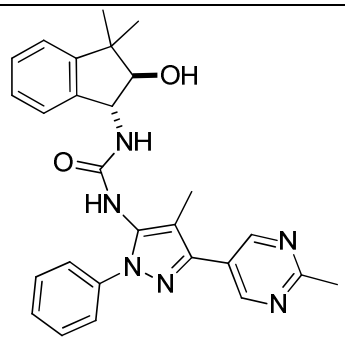
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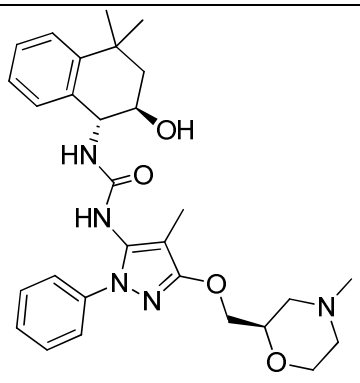
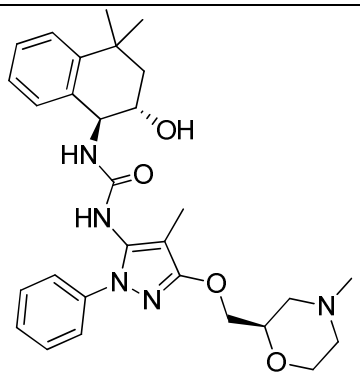
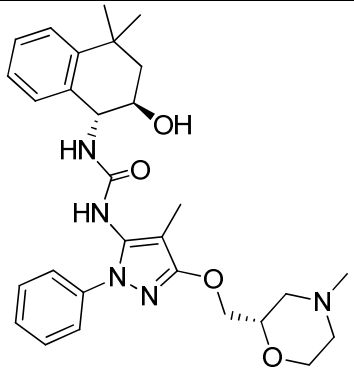
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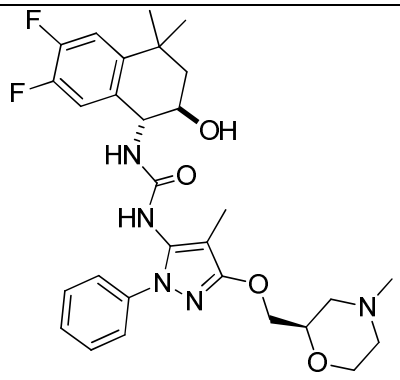
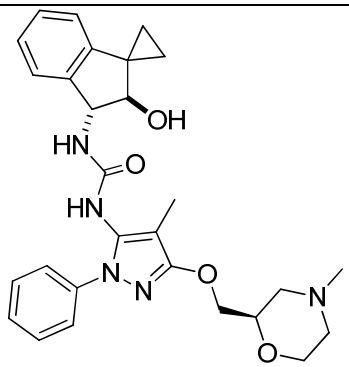
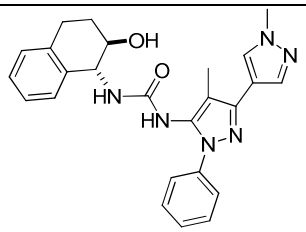
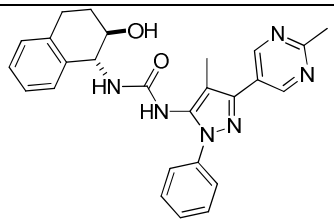
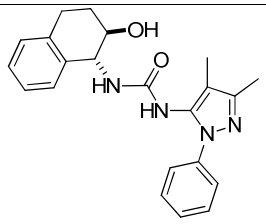
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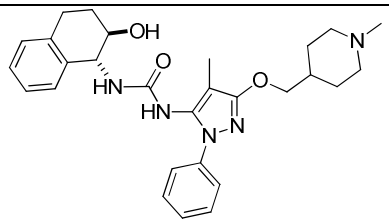
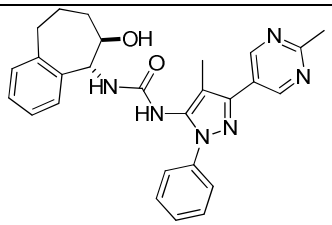
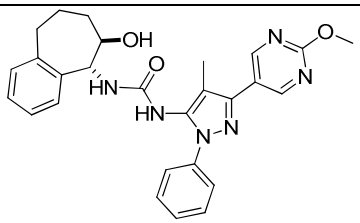
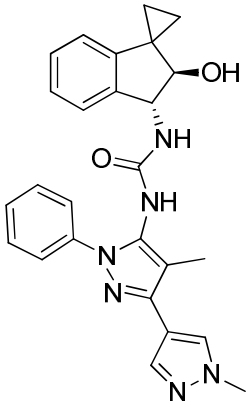
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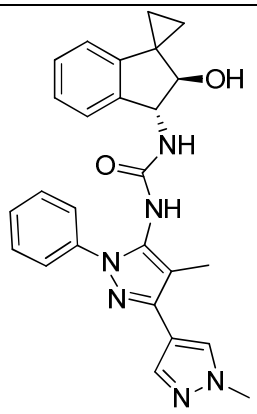
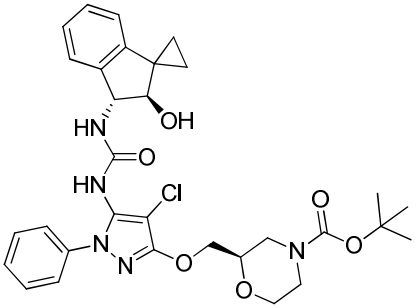
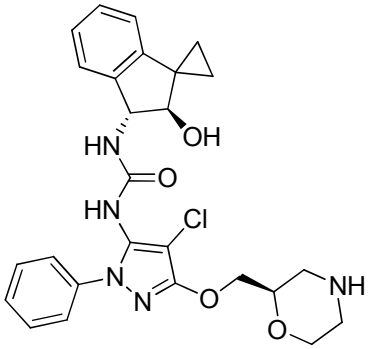
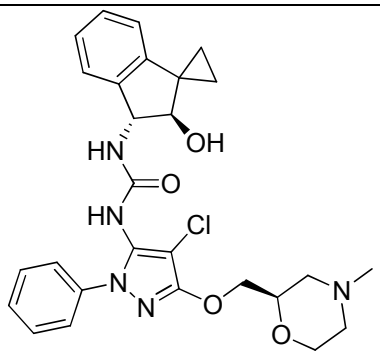
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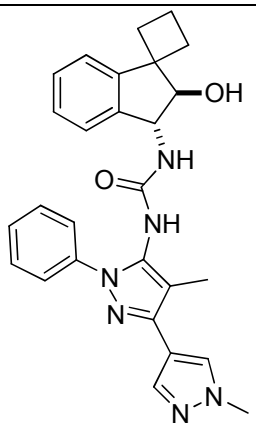
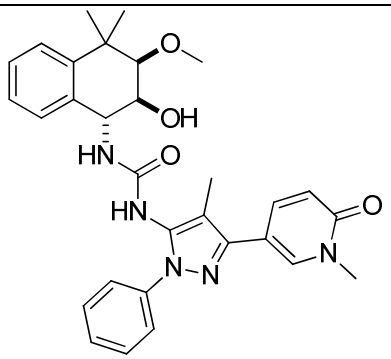
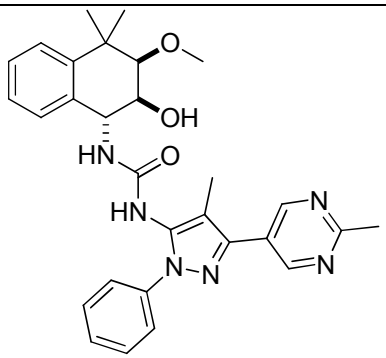
Ex. #	Structure
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73	

Ex. #	Structure
74	
75	
76	

Ex. #	Structure
77	
78	
101	
118	
121	

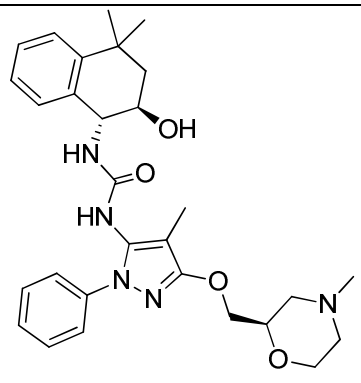
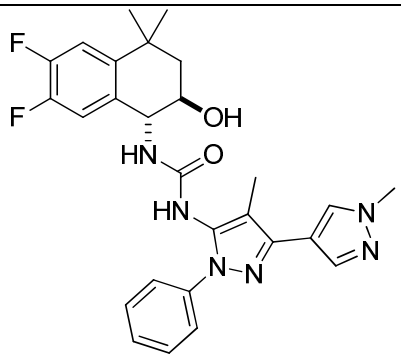
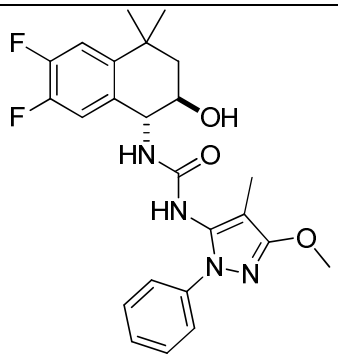
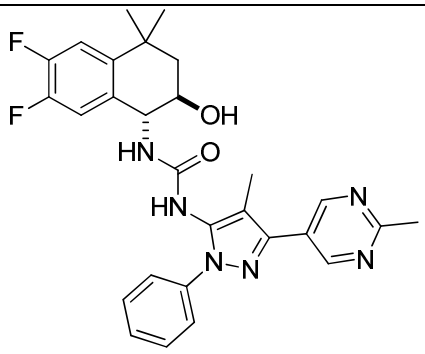
Ex. #	Structure
123	
127	
128	
137	

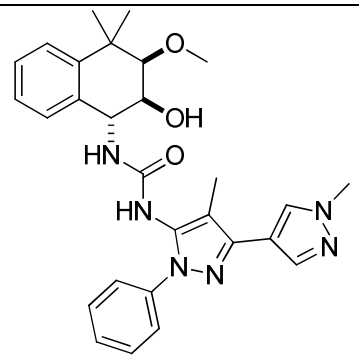
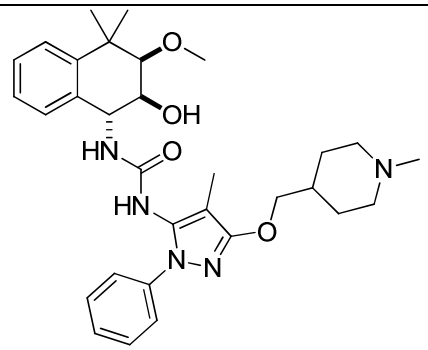
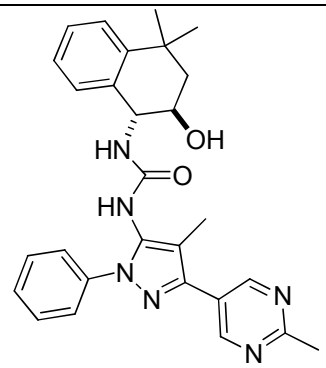
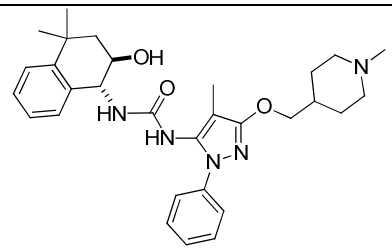
Ex. #	Structure
138	
139	
140	
141	

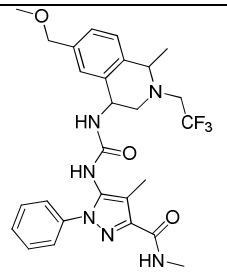
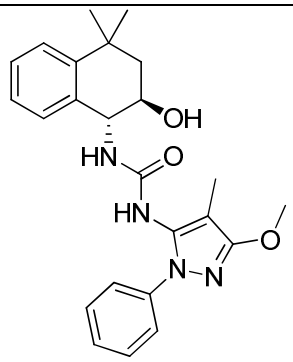
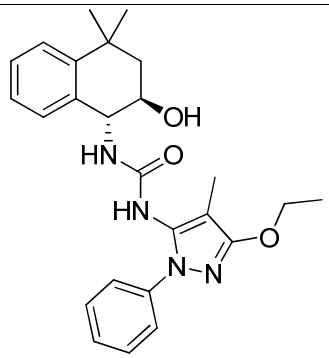
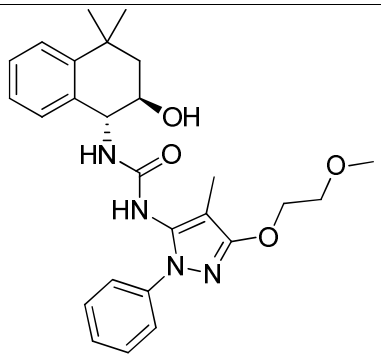
Ex. #	Structure
142	
154	
155	

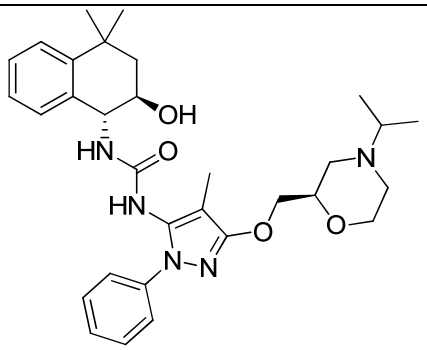
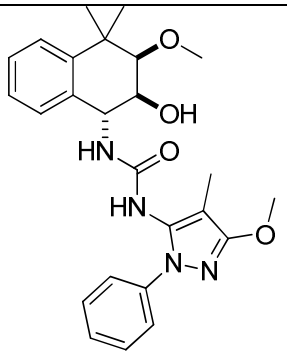
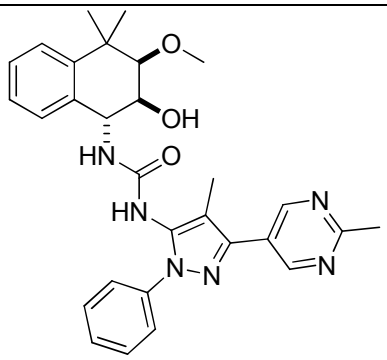
23. A compound of claim 21, selected from:

Ex. #	Structure

Ex. #	Structure
74	
80	
82	
84	

Ex. #	Structure
86	
87	
117	
122	

Ex. #	Structure
129	
144	
146	
147	

Ex. #	Structure
151	
153	
155	

24. A pharmaceutical composition, which comprises a compound of Formula **I** as defined in any one of claims 1 to 23 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable diluent or carrier.

25. A compound of Formula **I** as defined in any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 24, for use in therapy.

26. A compound of Formula **I** as defined in any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 24, for use in the treatment of pain, cancer, inflammation/inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis and pelvic pain syndrome.

27. The compound or pharmaceutical composition of claim 26, for use in the treatment of pain.

28. The compound or pharmaceutical composition for use as defined in claim 27, wherein the pain is chronic pain.

29. The compound or pharmaceutical composition for use as defined in claim 27, wherein the pain is acute pain.

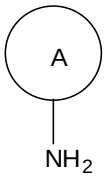
30. The compound or pharmaceutical composition for use as defined in claim 27, wherein the pain is inflammatory pain, neuropathic pain, pain associated with cancer, pain associated with surgery or pain associated with bone fracture.

31. The compound or pharmaceutical composition for use as defined in claim 26, wherein said cancer is a cancer having a dysregulation of TrkA.

32. A compound of Formula **I** as defined in any one of claims 1 to 23, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for treating pain, cancer, inflammation/inflammatory diseases, neurodegenerative diseases, certain infectious diseases, Sjogren's syndrome, endometriosis, diabetic peripheral neuropathy, prostatitis and pelvic pain syndrome.

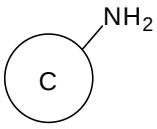
33. A process for the preparation of a compound of claim 1, which comprises:

(a) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **II**



II

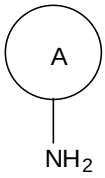
with a corresponding compound having the formula **III**



III

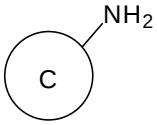
in the presence carbonyldiimidazole or triphosgene and a base; or

(b) for a compound of Formula **I** where X is S, coupling a corresponding compound having the formula **II**



II

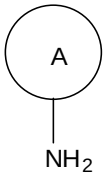
with a corresponding compound having the formula **III**



III

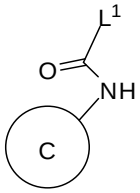
in the presence di(1H-imidazol-2-yl)methanethione and a base; or

(c) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **II**



II

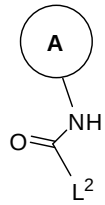
with a corresponding compound having the formula **IV**



IV

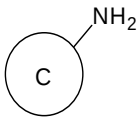
where L^1 is a leaving group, in the presence of a base; or

(d) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **V**



V

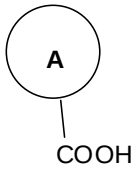
where L^2 is a leaving group, with a corresponding compound having the formula **III**



III

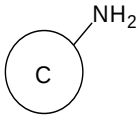
in the presence of a base; or

(e) for a compound of Formula **I** where X is O, activating a corresponding compound having the formula **VI**



VI

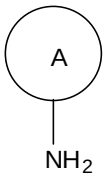
with diphenylphosphoryl azide followed by coupling the activated intermediate with a corresponding compound having the formula **III**



III

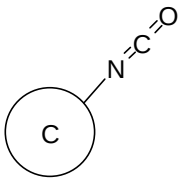
in the presence a base; or

(f) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **II**



II

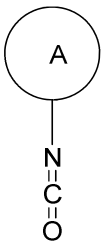
with a corresponding compound having the formula **VII**



VII

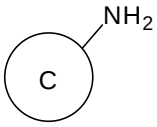
in the presence of a base; or

(g) for a compound of Formula **I** where X is O, coupling a corresponding compound having the formula **VIII**



VIII

with a corresponding compound having the formula **III**



III

in the presence of a base; and

optionally removing protecting groups and optionally preparing a pharmaceutically acceptable salt thereof.