METHODS OF TREATING MIGRAINE WITH MNK INHIBITORS

BACKGROUND

Technical Field

The present disclosure describes compounds and methods useful as mitogen activated protein kinase-interacting kinase ("MNK") inhibitors, useful for the treatment of migraines and related conditions.

Description of the Related Art

Migraines are experienced by approximately 35 million people in the U.S. alone every year. 45% of women and 18% of men will experience migraines at some point in their lives. Not only are migraines painful, they can seriously disupt the ability of migraine sufferers to perform even the most basic functions of life. Worse still, migraines are most typical in people ages 35-45, which are often prime wage-earning and child-raising years, allowing migraines to often affect much more than just individual well-being.

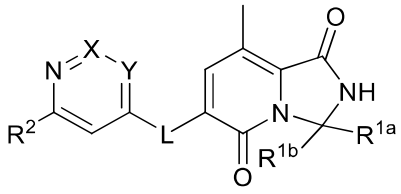
The causes of migraines are still not well-understood and, although treatments have certainly improved in recent years, many common therapies have serious side-effects or simply don't work for many migraine sufferers.

Accordingly, there is a need to develop compounds that are effective for treating migraine. Embodiments of the present disclosure fulfill this need and provide further related advantages.

BRIEF SUMMARY

In brief, the present disclosure provide compounds useful for the treatment of migraines, including pharmaceutically acceptable salts, stereoisomers, tautomers, and prodrugs thereof.

In one aspect, the present disclosure refers to use of a compound having the following Structure (II):



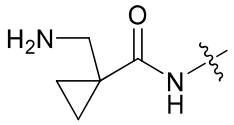
(II)

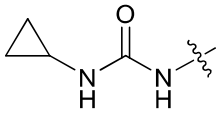
or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment, prevention, or mitigation of a migraine or symptoms related to a migraine, wherein

R^{1a} is C_1-C_6 alkyl or aryl;

R^{1b} is C_1-C_6 alkyl or aryl,

or R^{1a} and R^{1b}, together with the carbon to which they are both attached, join to form cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl;

R^2 is $–NHR^{3a}$, $–NHC(=O)R^{3b}$, $–NHC(=S)R^{3b}$, $–C(=O)R^{3c}$, 

, or 

;

R^{3a} is hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl, each of which is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, C_3-C_6 cycloalkyl, $-NHS(O)_2CH_3$, heterocyclyl, $-C(=O)OH$, $-C(=O)N(R^{3d})R^{3d}$, or $-N(R^{3d})R^{3d}$;

R^{3b} is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or heterocyclyl each of which is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halo, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-NHS(O)_2CH_3$, $-N(R^{3d})R^{3d}$, heterocyclyl, $-C(=O)OH$, $-C(=O)N(R^{3d})R^{3d}$, $-NHC(=O)CH_3$, $-CH_2C(=O)OH$,

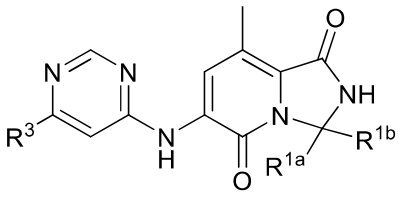
R^{3c} is $-N(R^{3d})R^{3d}$ or heterocyclyl;

R^{3d} is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

L is –NH– or $–CH_2NH–$; and

X is N and Y is CH or X is CH and Y is N.

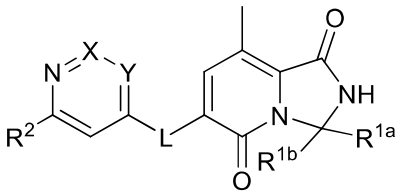
In one example, the compounds have the following Structure (I):



(I)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein each of R^{1a}, R^{1b}, and R^3 are as defined herein.

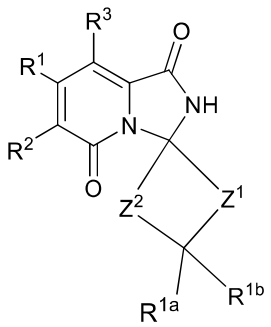
In another example, the compounds have the following Structure (II):



(II)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein, R^{1a}, R^{1b}, R^2, X, Y, and L are as defined herein.

In still another example, the compounds have the following Structure (III):



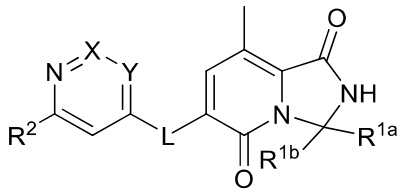
(III)

or a pharmaceutically acceptable salt, hydrate, isotopic isomer, solvate, complex, stereoisomer, tautomer, or prodrug thereof, wherein, R^{1a}, R^{1b}, R^1, R^2, R^3, Z^1, and Z^2 are as defined herein.

In still another example, the compounds have the following Stucture (IX):

CLAIMS

1. Use of a compound having the following Structure (II):



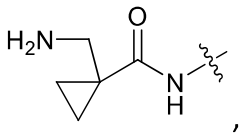
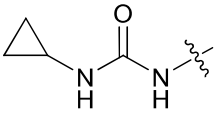
(II)

or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, in the manufacture of a medicament for the treatment, prevention, or mitigation of a migraine or symptoms related to a migraine, wherein

R^{1a} is C_1-C_6 alkyl or aryl;

R^{1b} is C_1-C_6 alkyl or aryl,

or R^{1a} and R^{1b}, together with the carbon to which they are both attached, join to form cycloalkyl, cycloalkenyl, heterocyclyl, aryl, or heteroaryl;

R^2 is $–NHR^{3a}$, $–NHC(=O)R^{3b}$, $–NHC(=S)R^{3b}$, $–C(=O)R^{3c}$, , or ;

R^{3a} is hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl, each of which is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, C_3-C_6 cycloalkyl, $-NHS(O)_2CH_3$, heterocyclyl, $-C(=O)OH$, $-C(=O)N(R^{3d})R^{3d}$, or $-N(R^{3d})R^{3d}$;

R^{3b} is C_1-C_6 alkyl, C_3-C_6 cycloalkyl, or heterocyclyl each of which is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, halo, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $-NHS(O)_2CH_3$, $-N(R^{3d})R^{3d}$, heterocyclyl, $-C(=O)OH$, $-C(=O)N(R^{3d})R^{3d}$, $-NHC(=O)CH_3$, $-CH_2C(=O)OH$,

R^{3c} is -N(R^{3d})R^{3d} or heterocyclyl;

R^{3d} is, at each occurrence, independently hydrogen, C_1-C_6 alkyl, or C_3-C_6 cycloalkyl;

L is –NH– or –CH_2NH–; and

X is N and Y is CH or X is CH and Y is N.

2. The use of claim 1, wherein R^{1a} is C_1-C_6 alkyl.

3. The use of any one of claims 1-2, wherein R^{1a} is methyl.

4. The use of claim 1, wherein R^{1a} is aryl.

5. The use of claim 1, wherein R^{1a} is phenyl.

6. The use of any one of claims 1-5, wherein R^{1b} is C_1-C_6 alkyl.

7. The use of any one of claims 1-6, wherein R^{1b} is methyl.

8. The use of claim 1, wherein R^{1a} and R^{1b}, together with the carbon to which they are both attached, join to form cycloalkyl.

9. The use of claim 8, wherein the cycloalkyl is cyclopentyl or cyclohexyl.

10. The use of claim 1, wherein R^{1a} and R^{1b}, together with the carbon to which they are both attached, join to form cycloalkenyl.

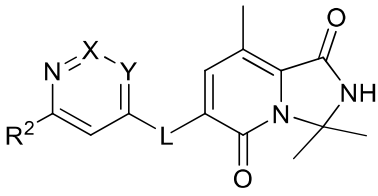
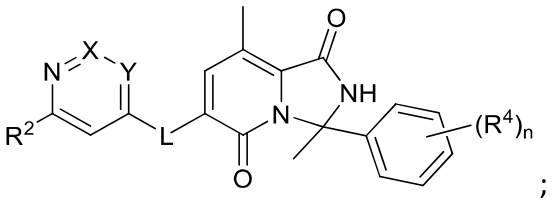
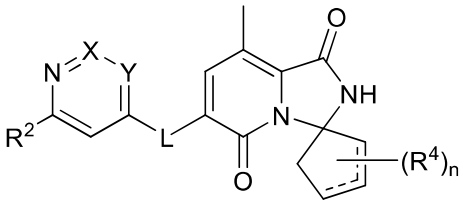
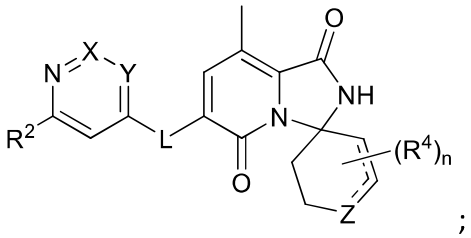
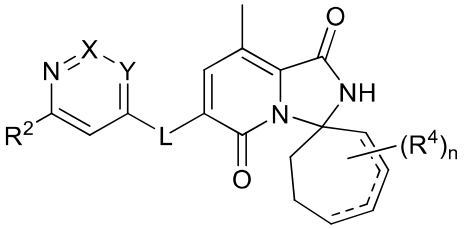
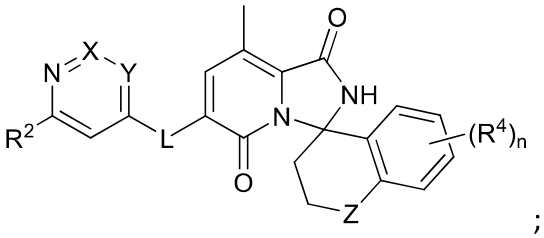
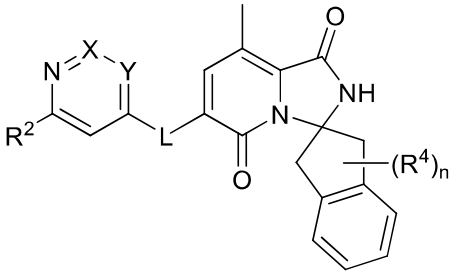
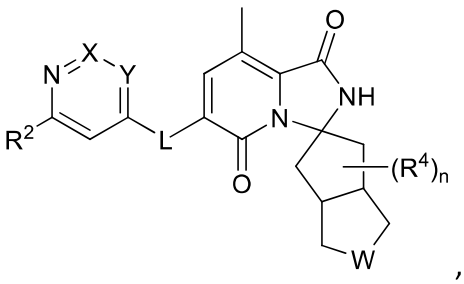
11. The use of claim 10, wherein the cycloalkenyl is cyclopentenyl, cyclohexenyl, or cycloheptenyl.

12. The use of claim 1, wherein R^{1a} and R^{1b}, together with the carbon to which they are both attached, join to form heterocyclyl.

13. The use of claim 12, wherein R^{1a} and R^{1b}, together with the carbon to which they are both attached, join to form aryl.

14. The use of claim 1, wherein R^{1a} and R^{1b}, together with the carbon to which they are both attached, join to form heteroaryl.

15. The use of any one of claims 1-14, wherein the compound has one of the following structures:


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or

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or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, wherein

---- indicates a double or single bond;

R^4 is, at each occurrence, independently C_1-C_6 alkyl, C_3-C_6 cycloalkyl, halo, haloalkyl, hydroxyl, -$NHS(O)_2CH_3$, or -C(O)OH,

or two R^4, together with the carbon to which they are both attached, join to form a cycloalkyl;

W is N or O;

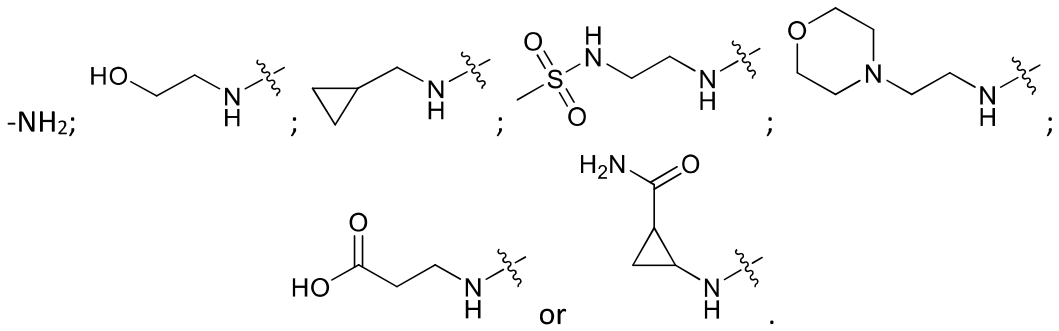
Z is C or O; and

n is 0, 1, 2, 3, or 4.

16. The use of claim 15, wherein n is 0, 1, or 2.

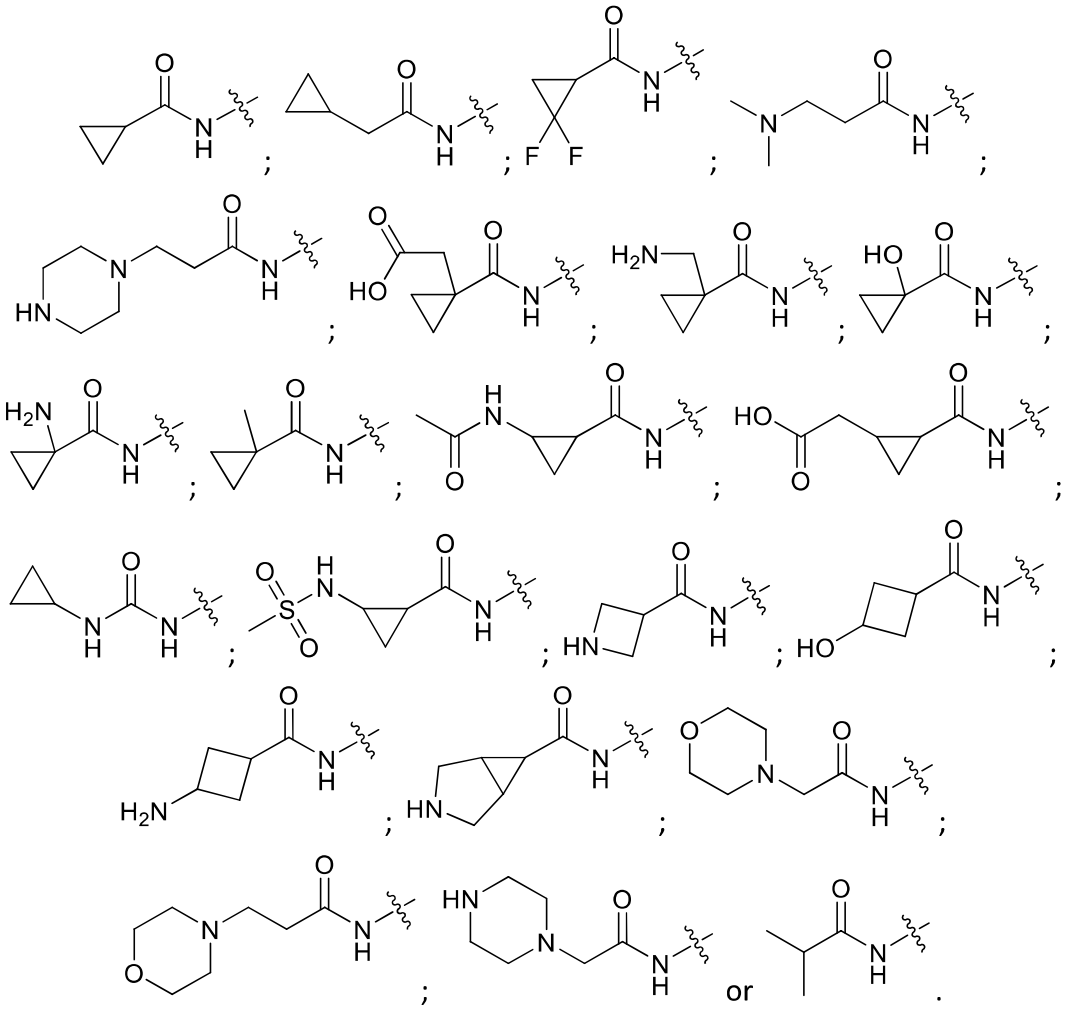
17. The use of any one of claims 1-16, wherein R^2 is $–NHR^{3a}$.

18. The use of any one of claims 1-17, wherein R^2 has one of the following structures:



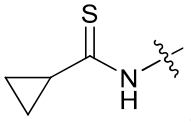
19. The use of any one of claims 1-16, wherein R^2 is $–NHC(=O)R^{3b}$.

20. The use of claim 19, wherein R^2 has one of the following structures:



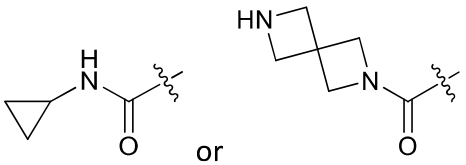
21. The use of any one of claims 1-16, wherein R^2 is –NHC(=S)R^{3b}.

22. The use of claim 21, wherein R^2 has the following structure:

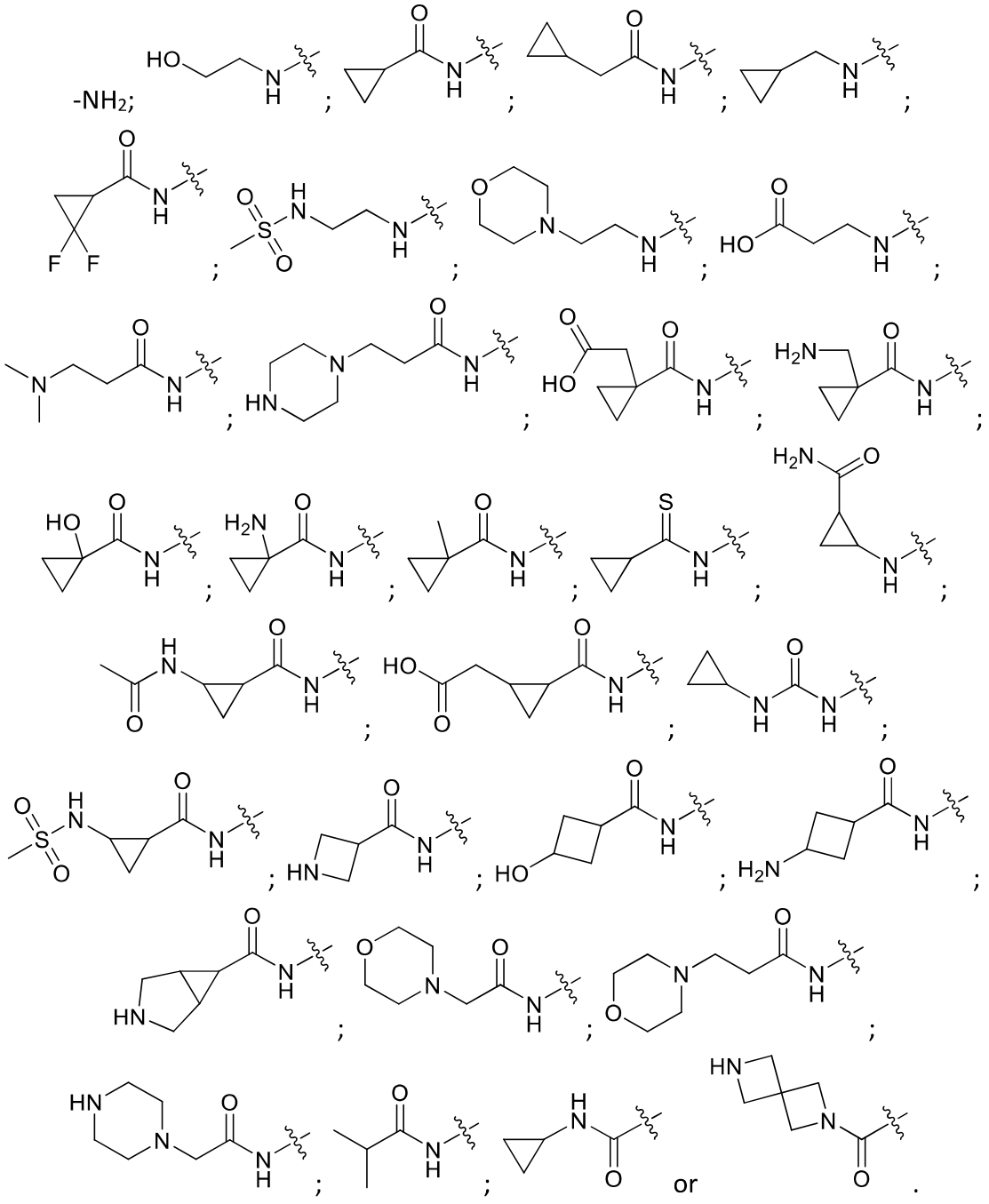


23. The use of any one of claims 1-16, wherein R^2 is –C(=O)R^{3c}.

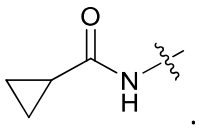
24. The use of claim 23, wherein R^2 has one of the following structures:



25. The use of any one of claims 1-24, wherein R^2 has one of the following structures:



26. The use of any one of claims 1-16, wherein R^2 has one of the following structures:

-NH_2 or .

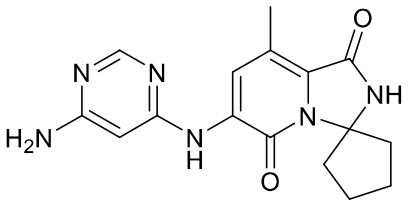
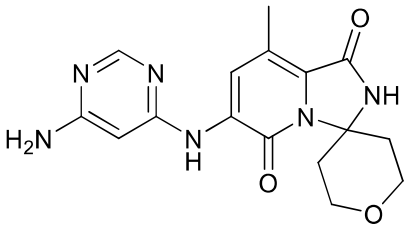
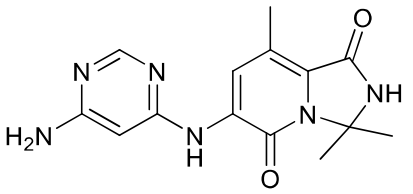
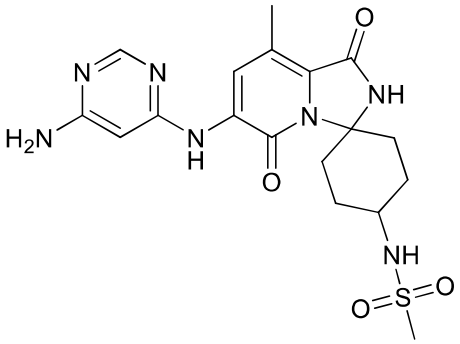
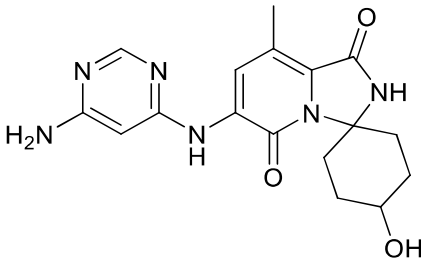
27. The use of any one of claims 1-26, wherein X is CH and Y is N.

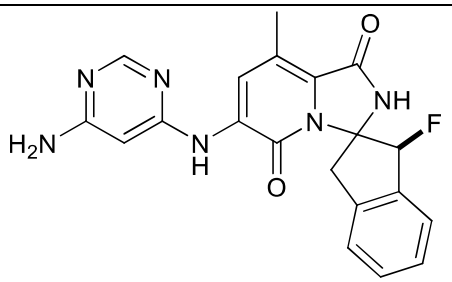
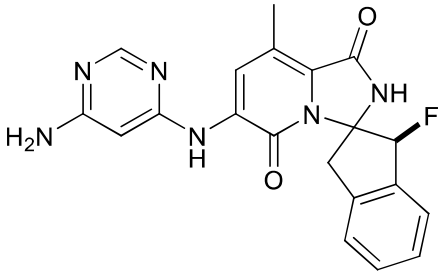
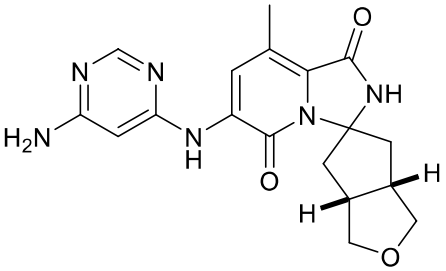
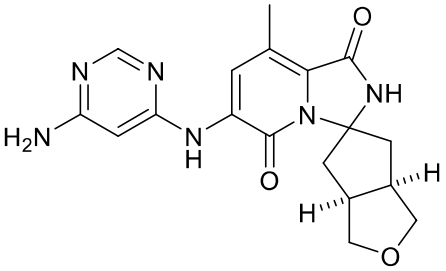
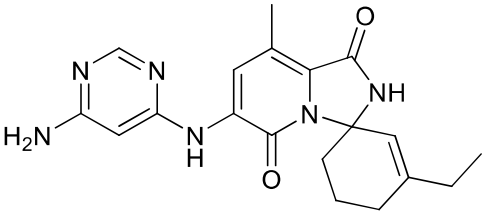
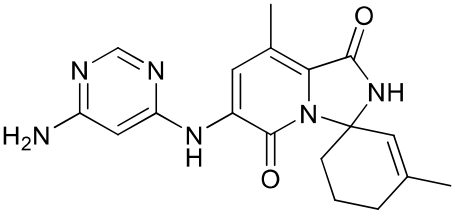
28. The use of any one of claims 1-26, wherein X is N and Y is CH.

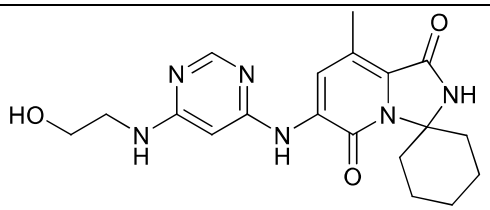
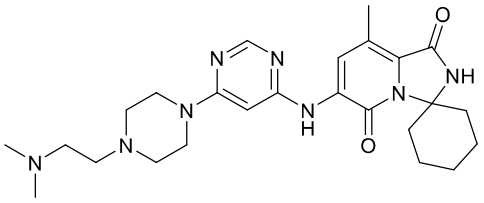
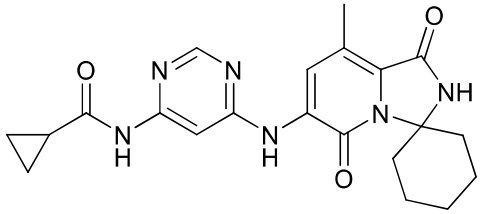
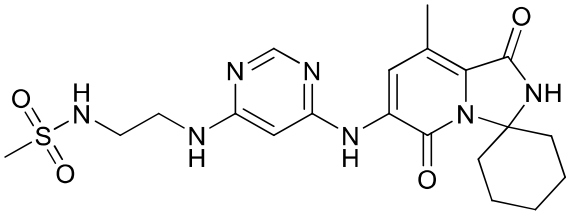
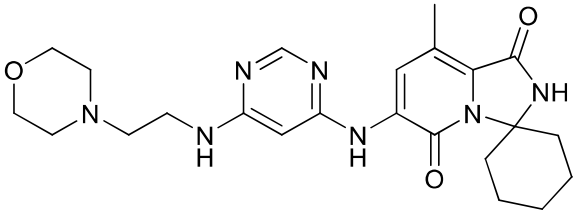
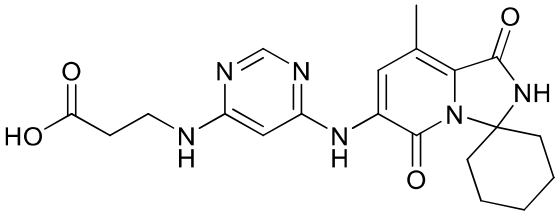
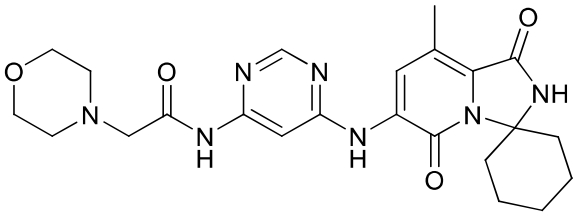
29. The use of any one of claims 1-26, wherein L is –NH–.

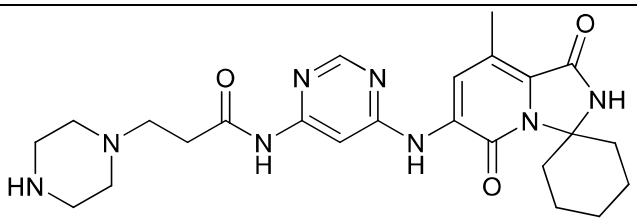
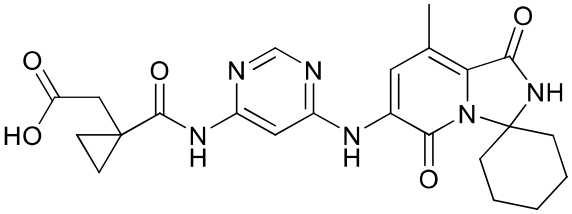
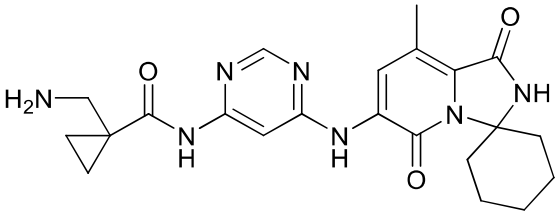
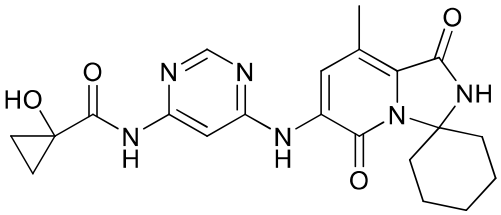
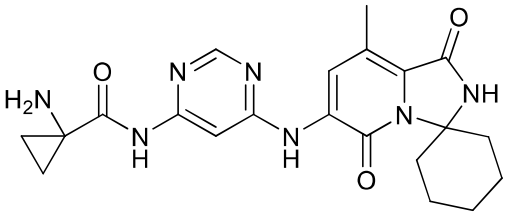
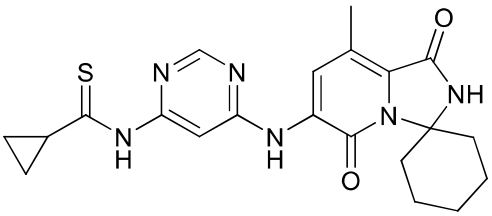
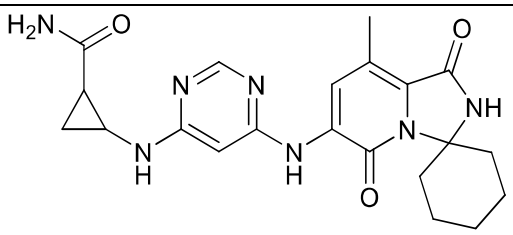
30. The use of any one of claims 1-26, wherein L is –CH_2NH–.

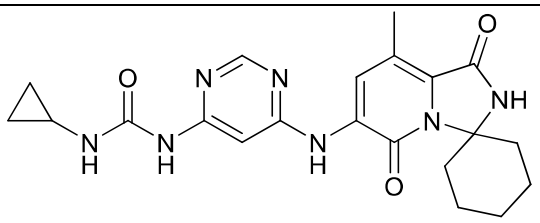
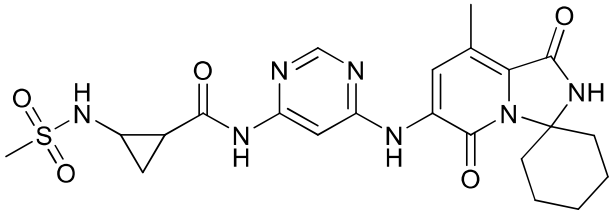
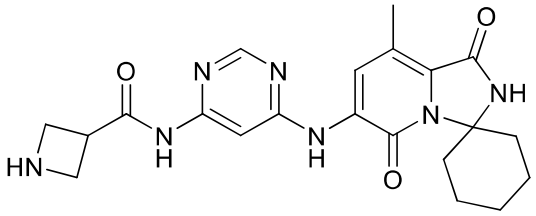
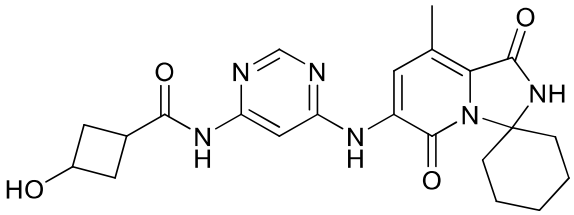
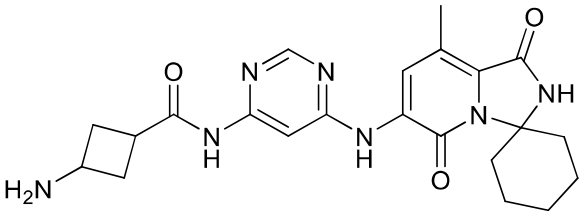
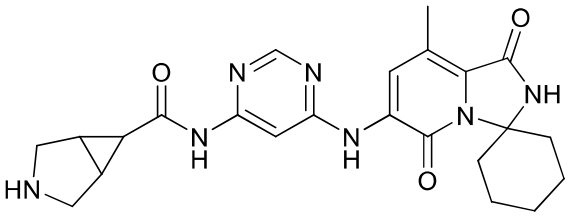
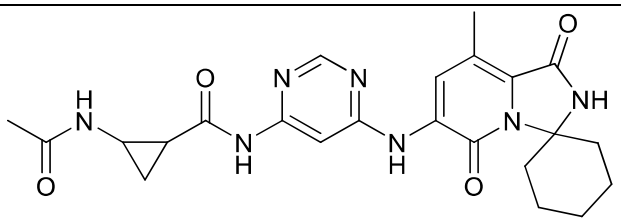
31. The use of any one of claims 1-30, wherein the compound comprises one of the structures as shown hereafter:

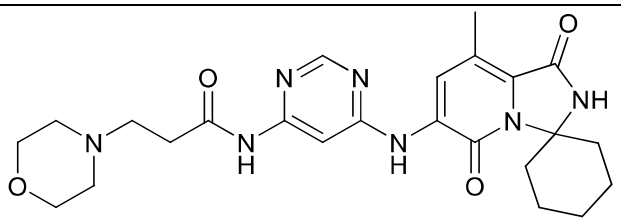
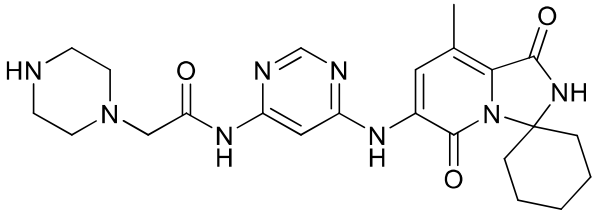
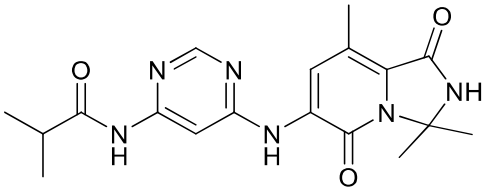
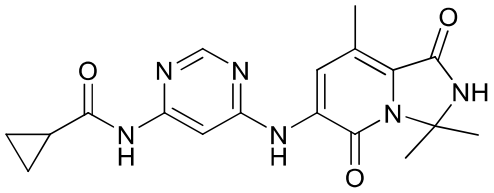
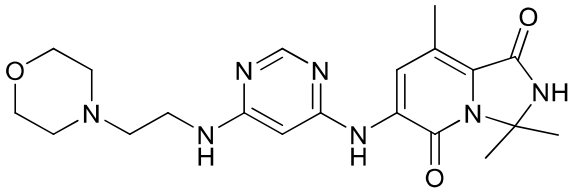
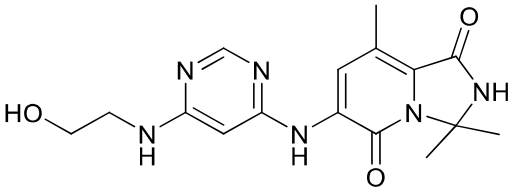
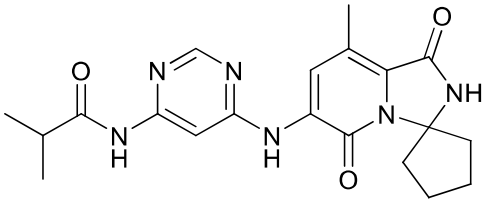
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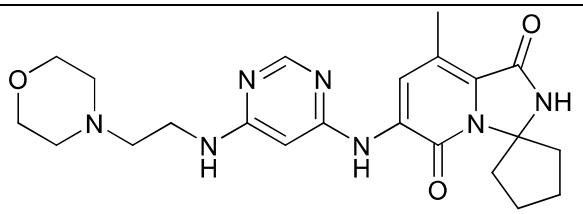
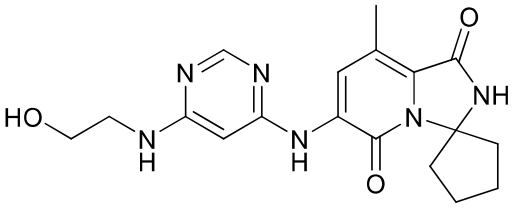
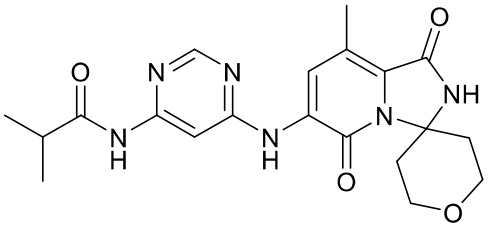
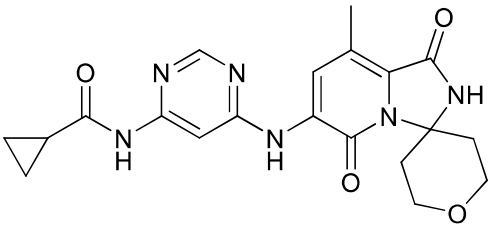
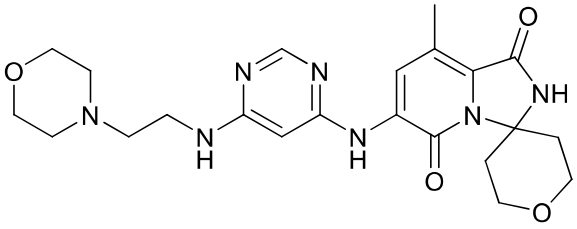
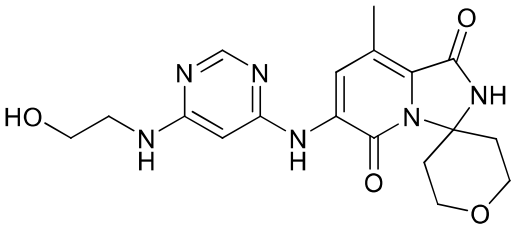
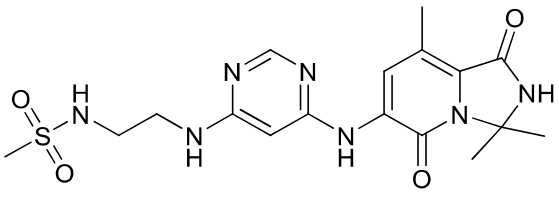
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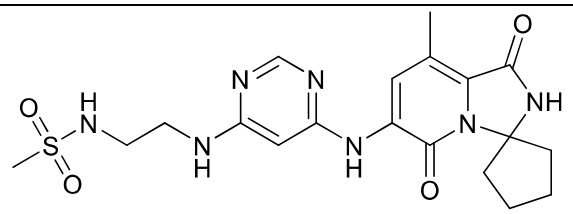
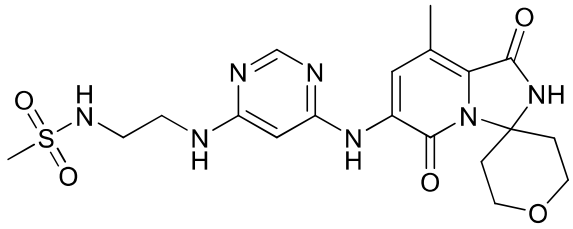
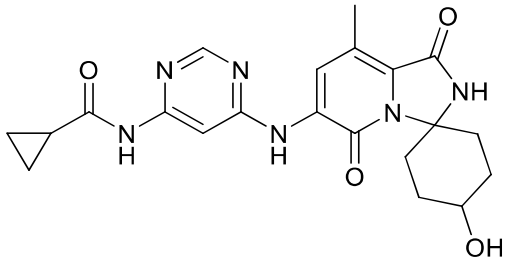
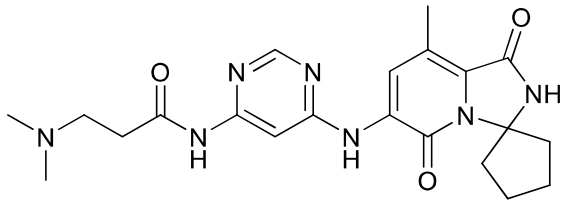
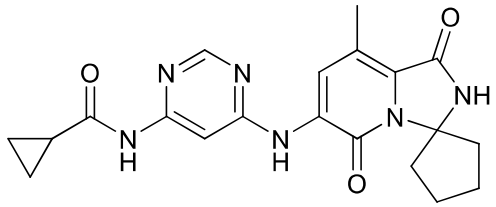
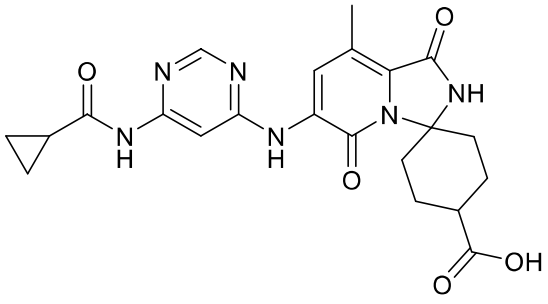
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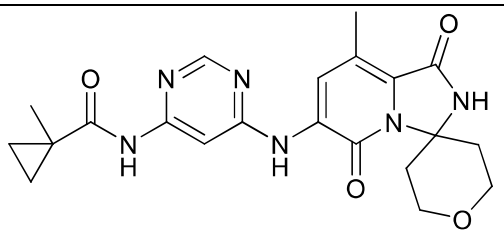
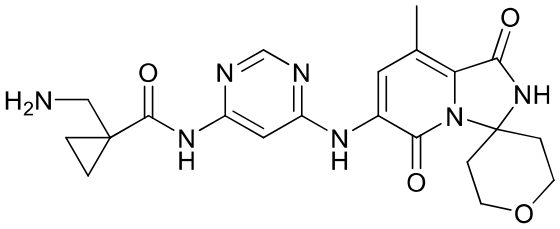
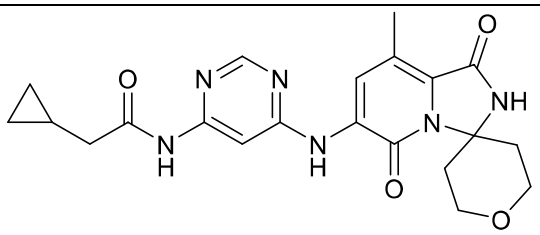
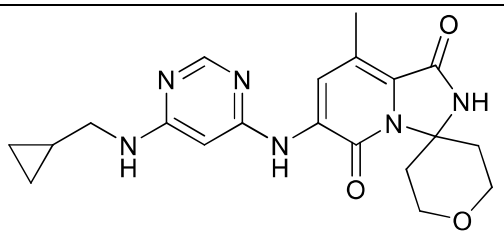
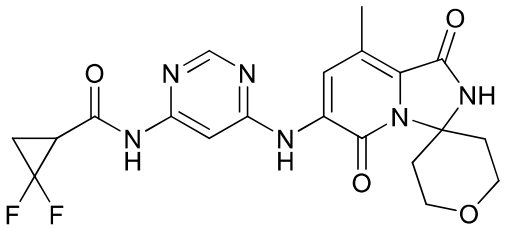
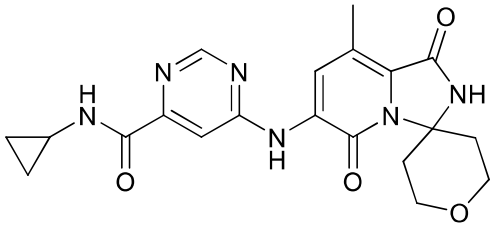
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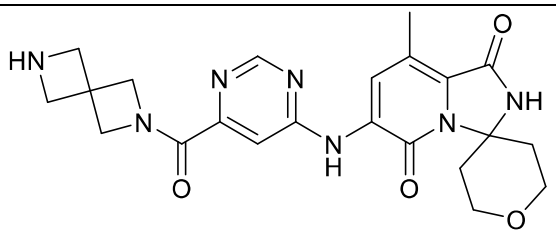
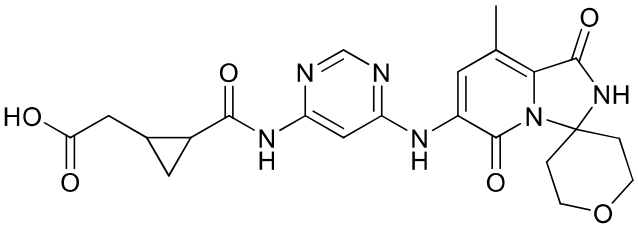
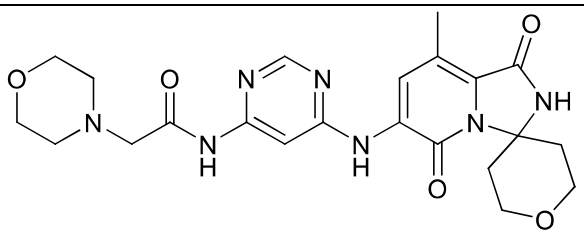
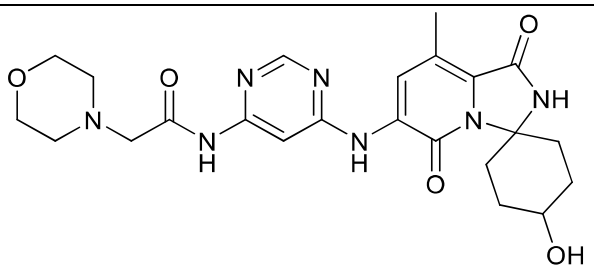
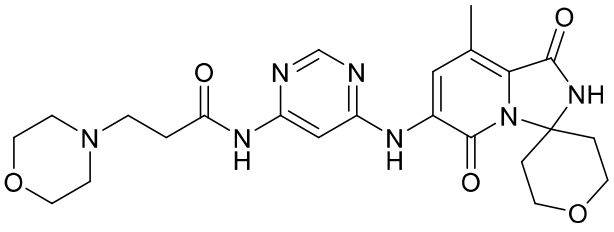
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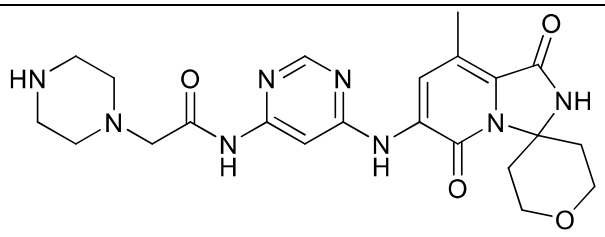
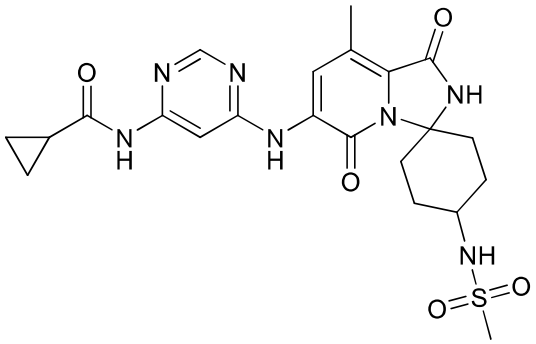
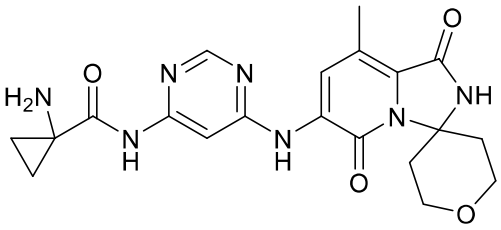
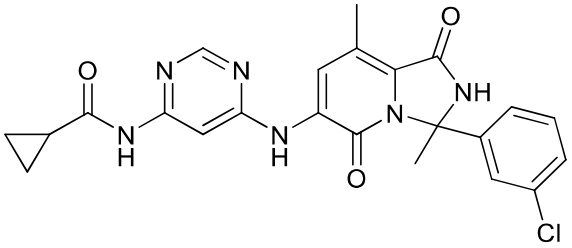
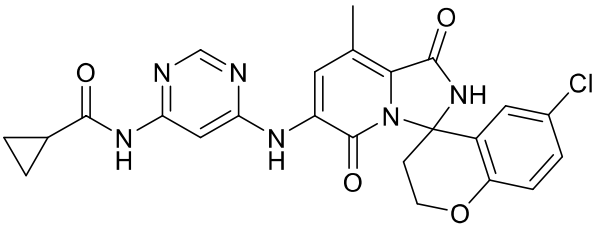
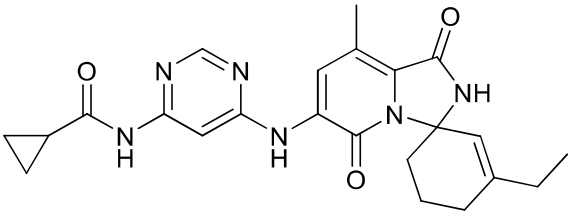
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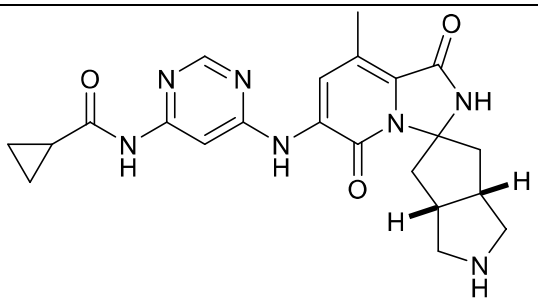
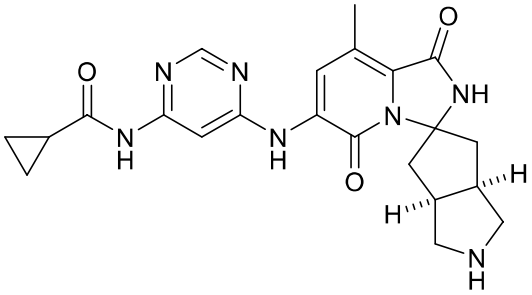
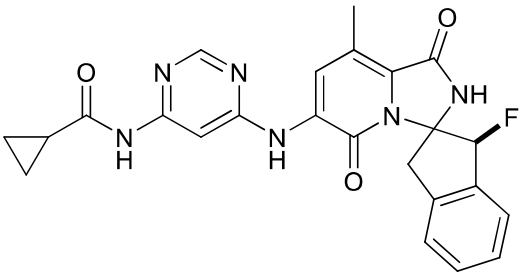
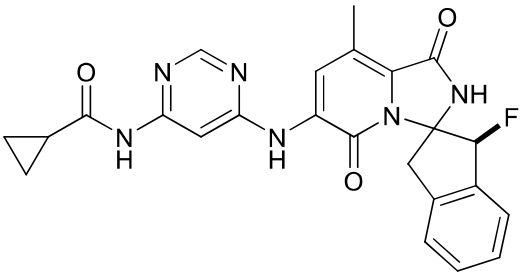
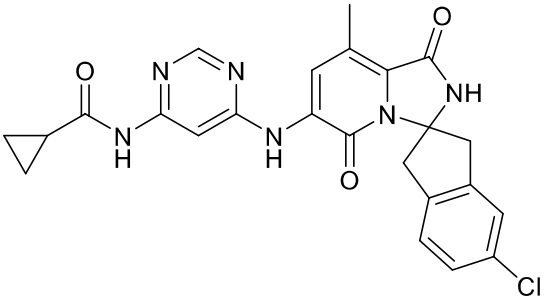
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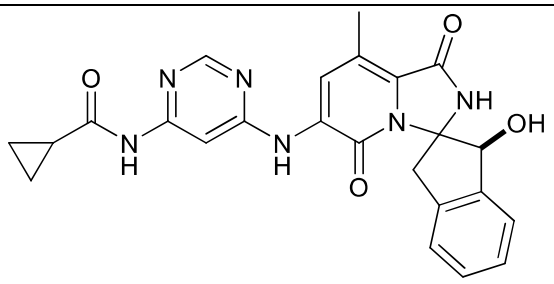
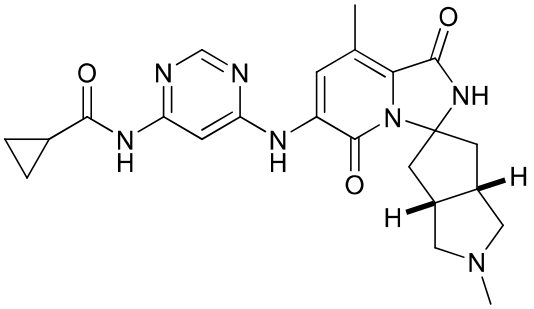
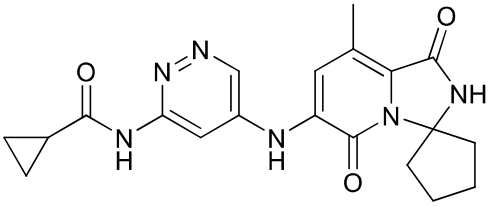
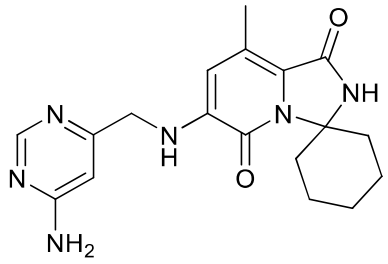
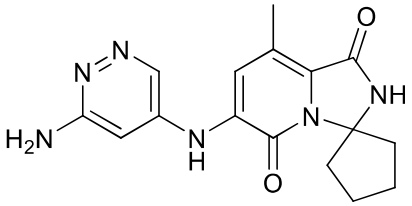
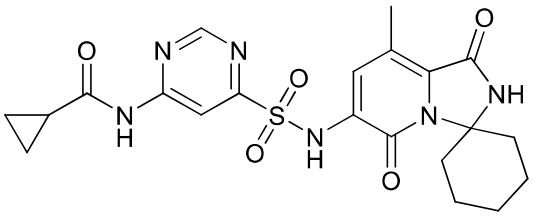
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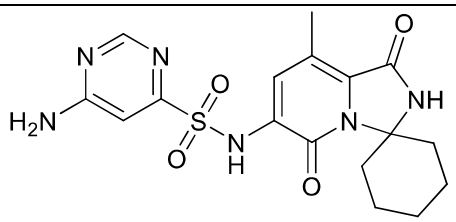
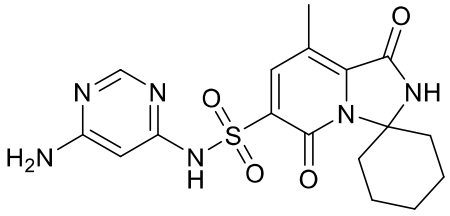
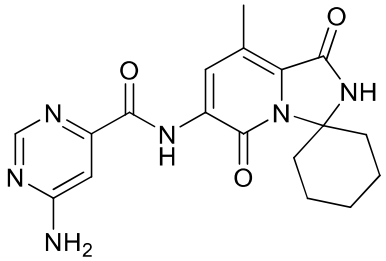
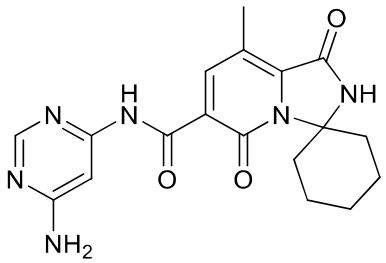
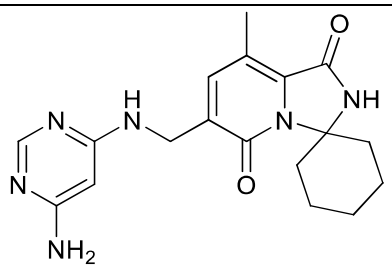
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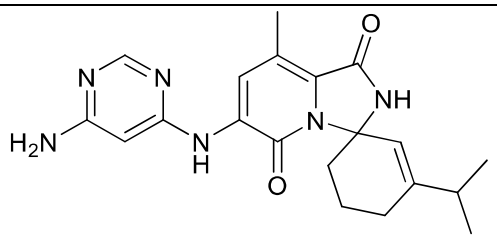
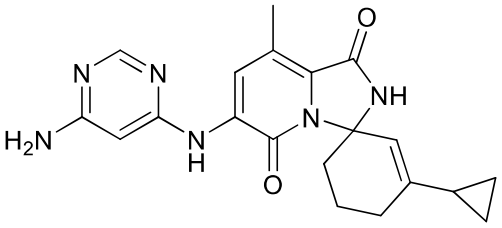
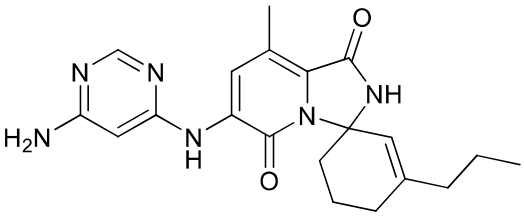
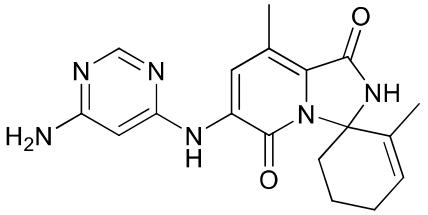
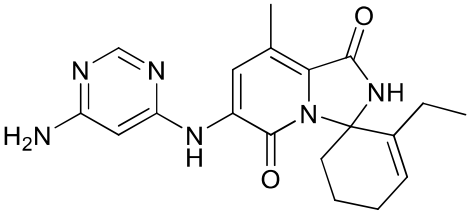
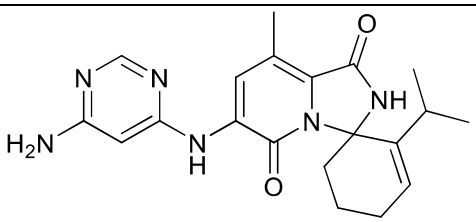
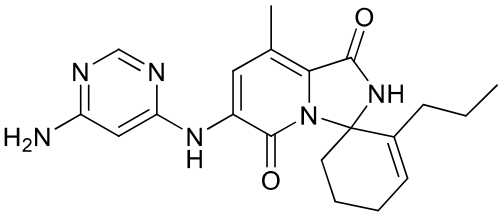
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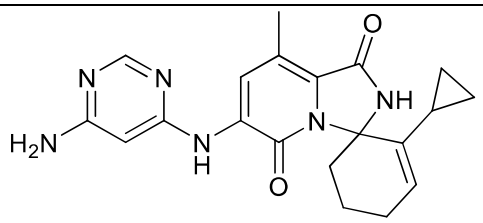
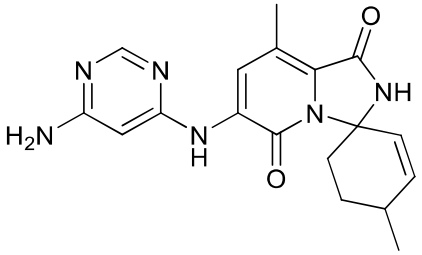
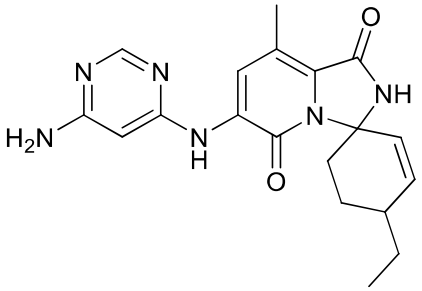
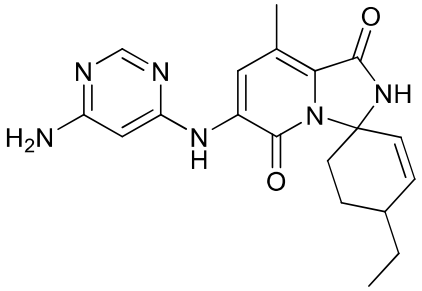
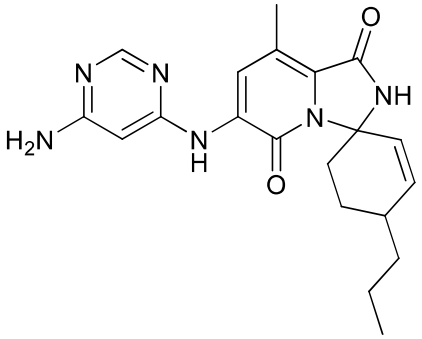
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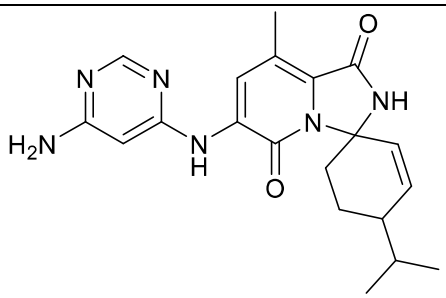
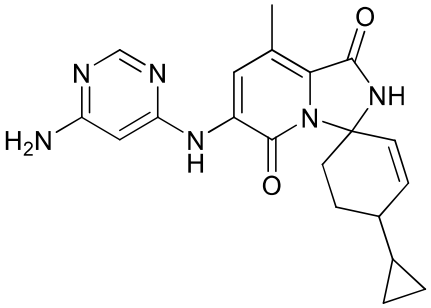
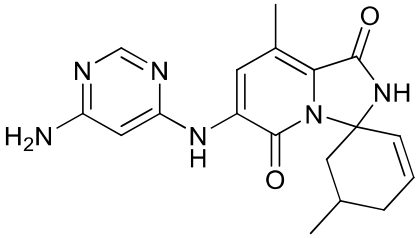
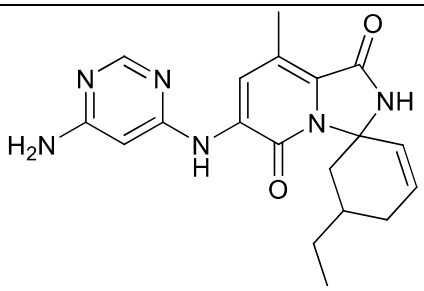
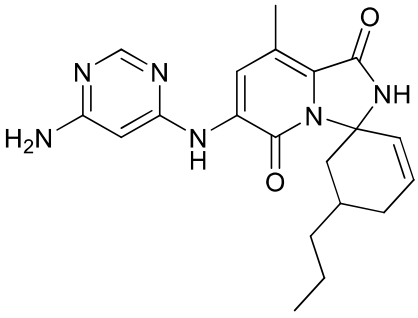
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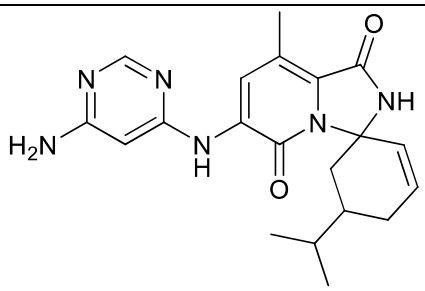
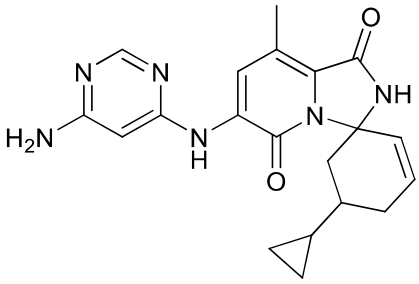
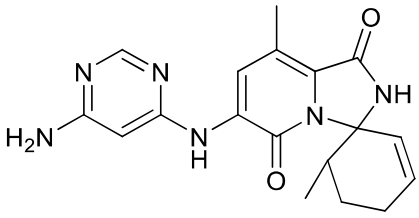
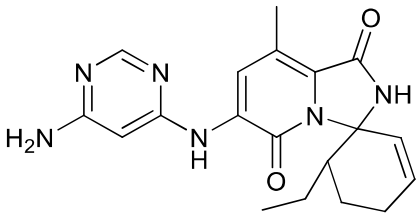
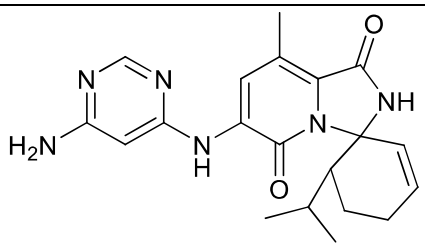
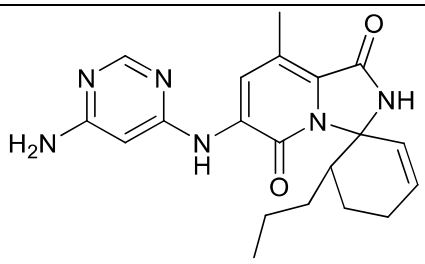
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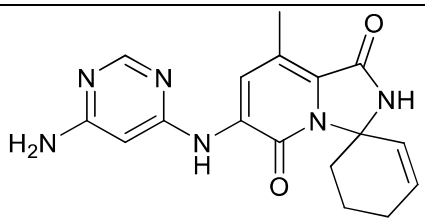
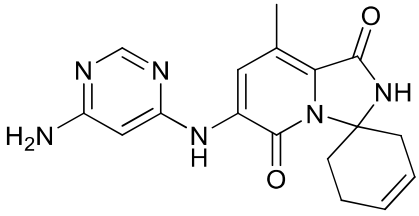
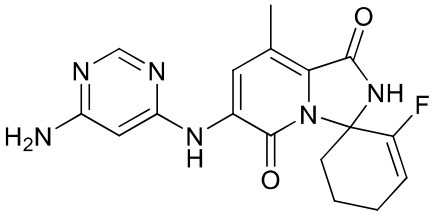
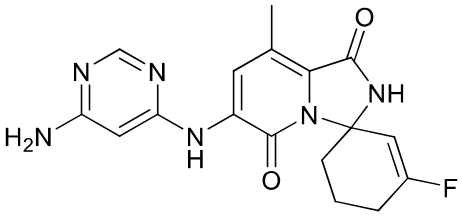
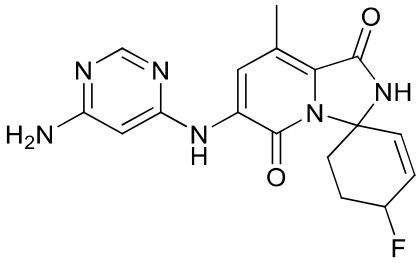
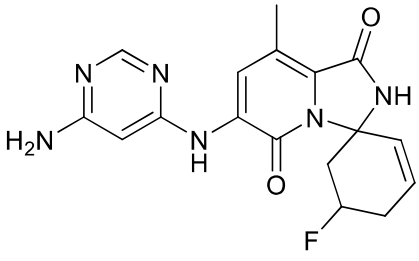
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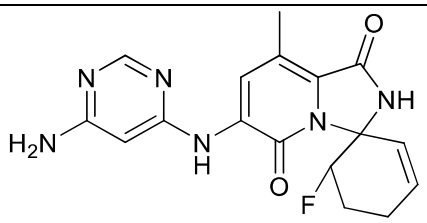
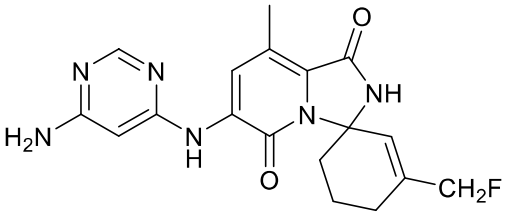
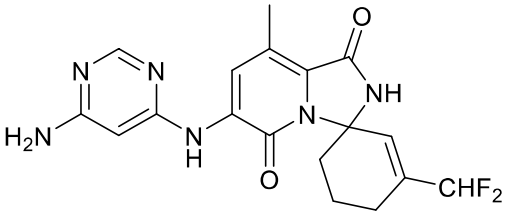
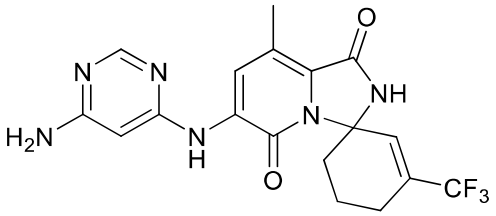
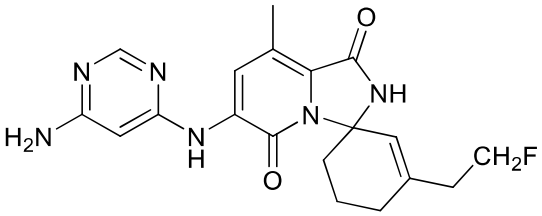
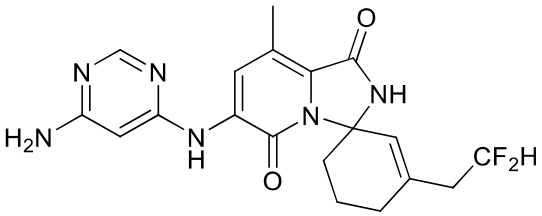
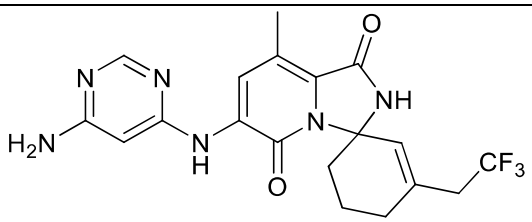
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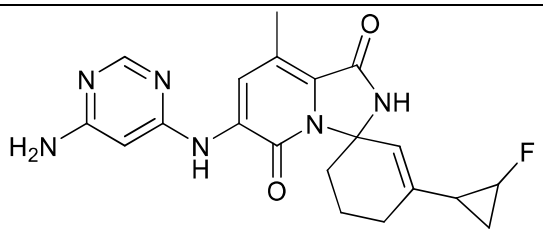
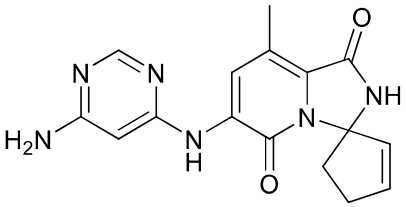
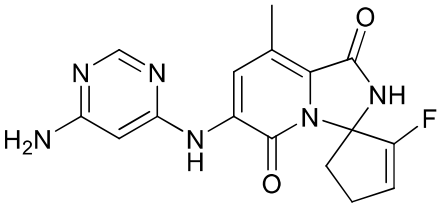
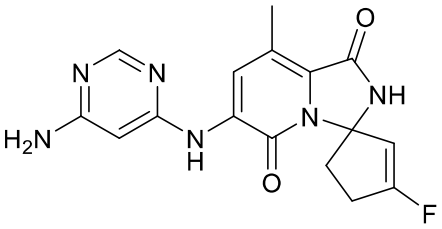
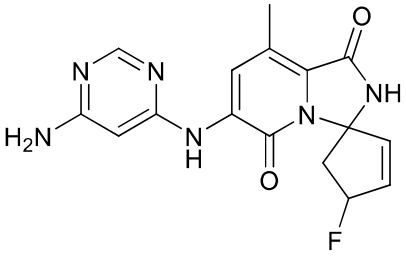
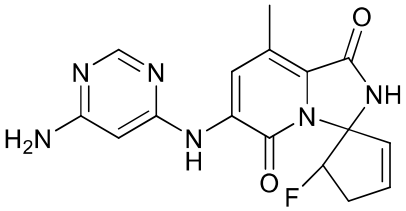
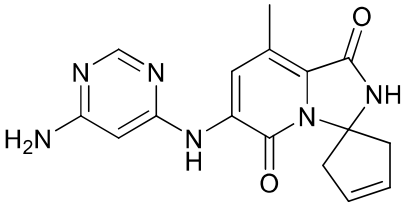
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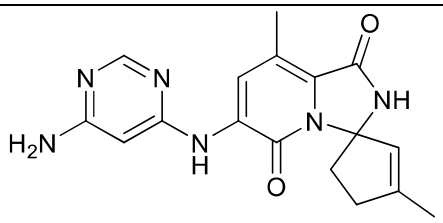
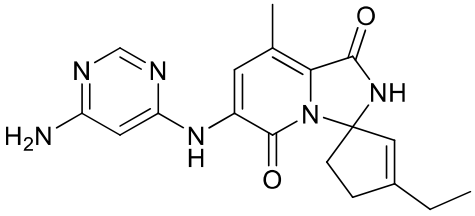
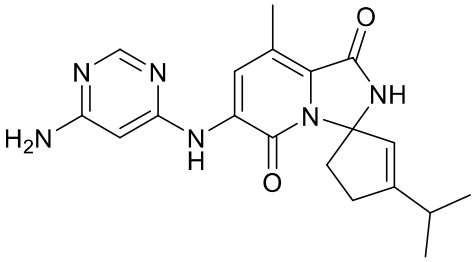
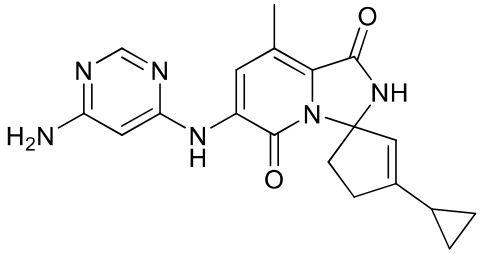
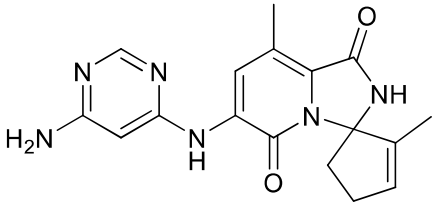
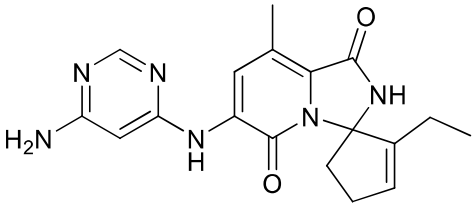
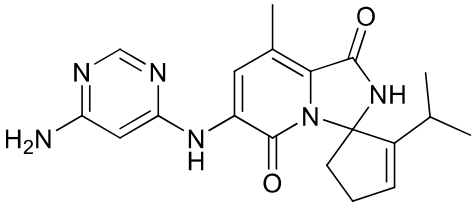
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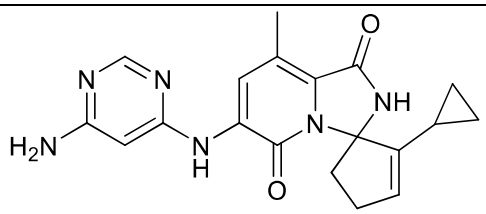
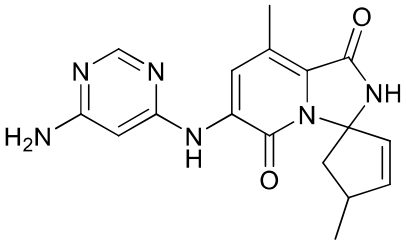
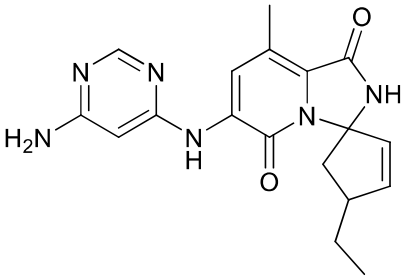
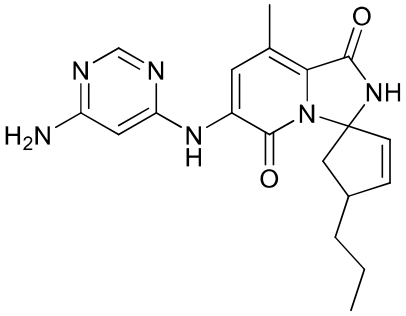
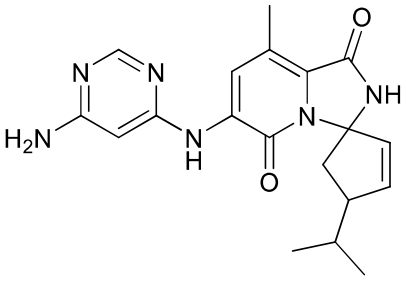
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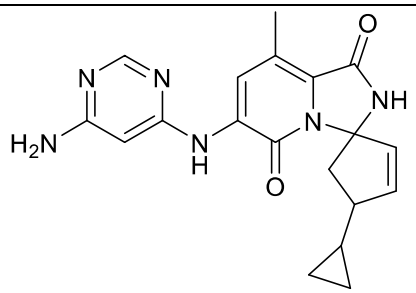
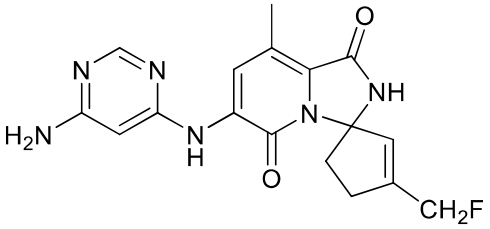
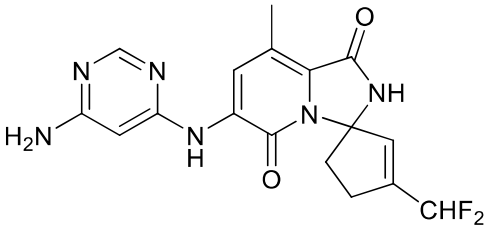
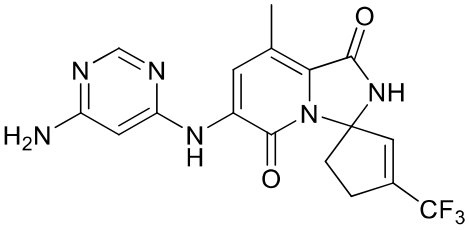
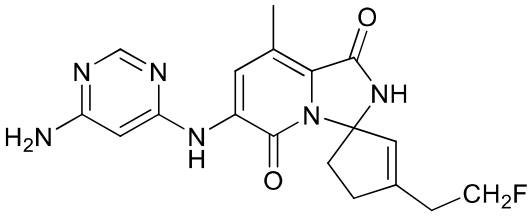
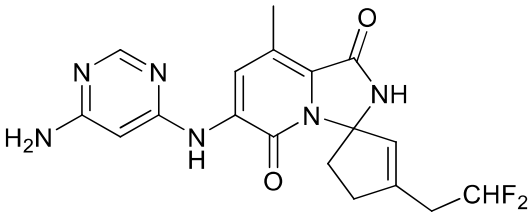
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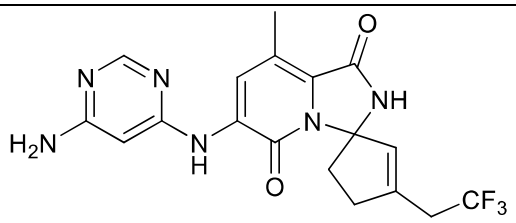
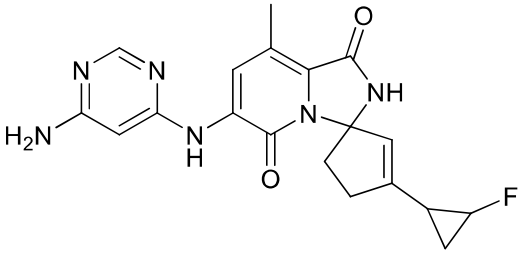
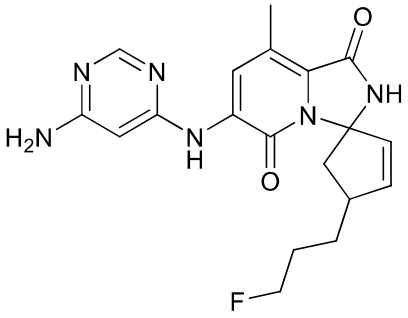
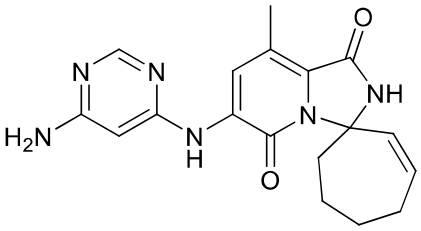
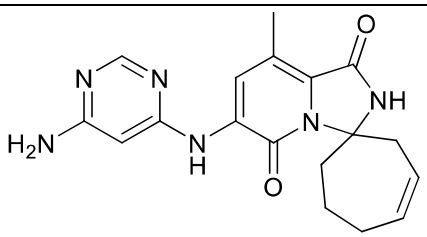
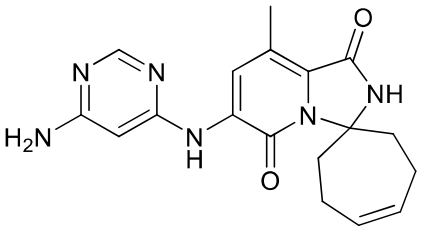
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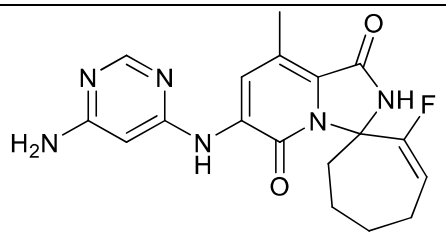
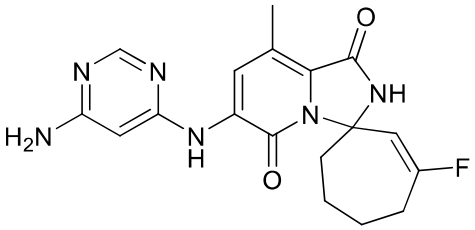
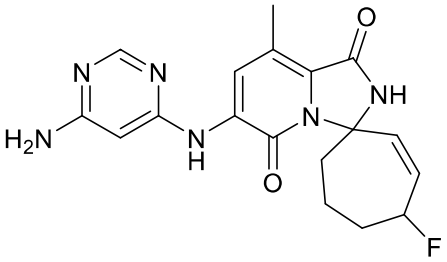
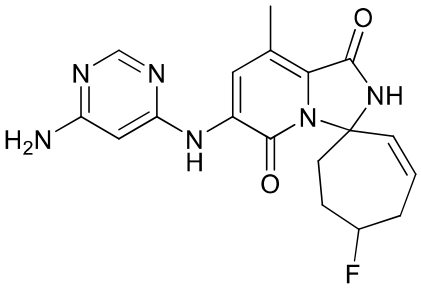
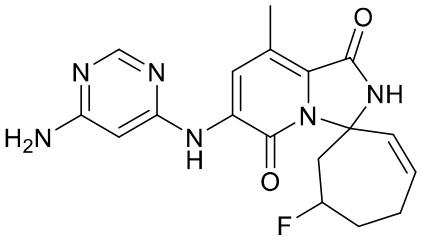
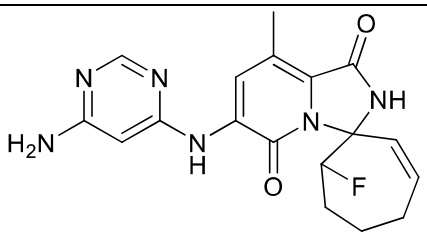
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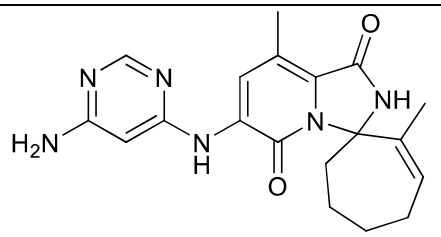
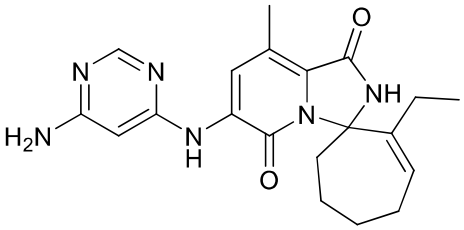
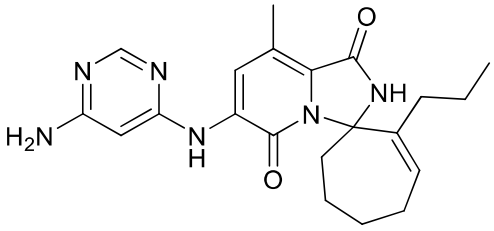
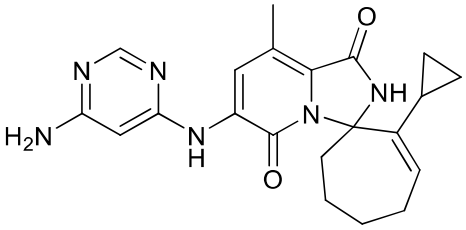
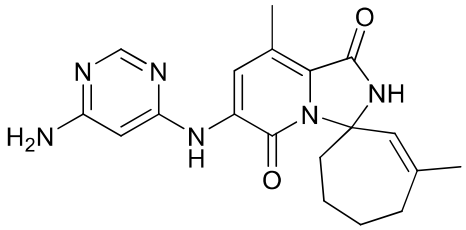
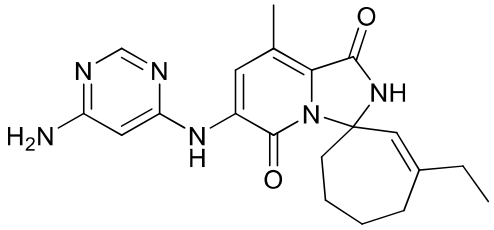
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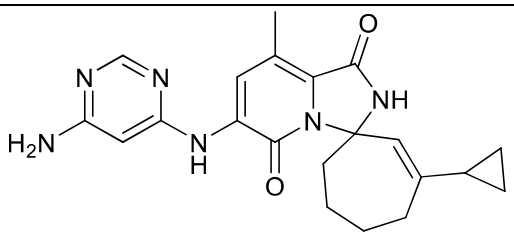
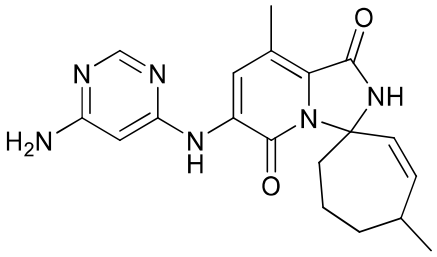
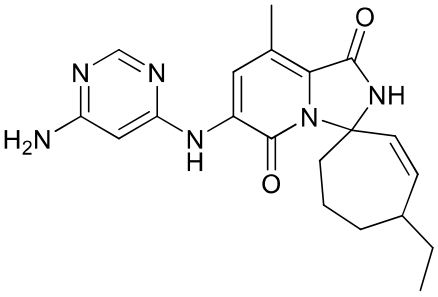
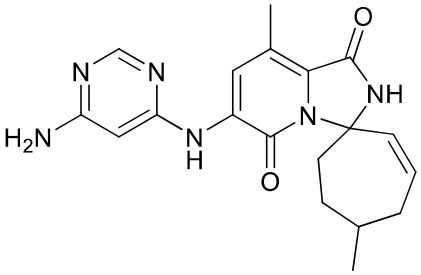
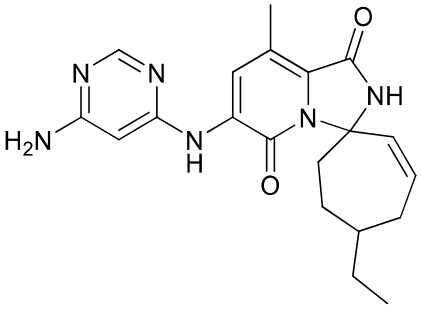
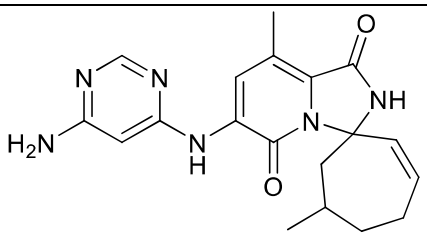
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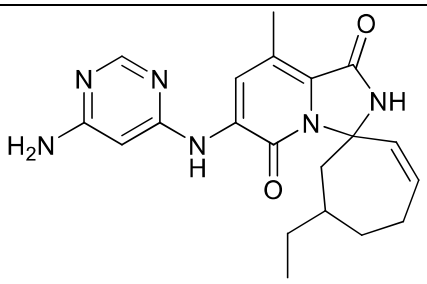
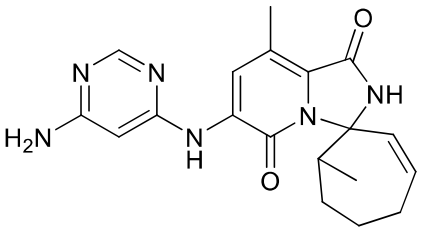
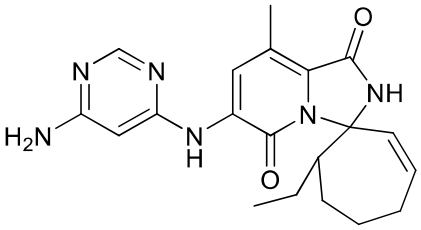
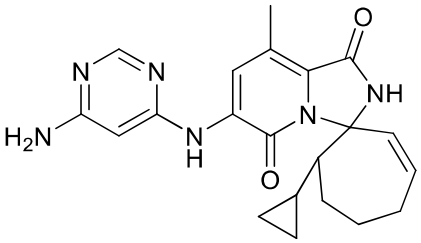
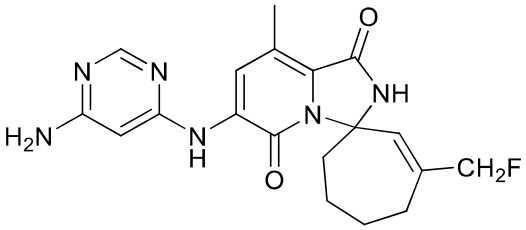
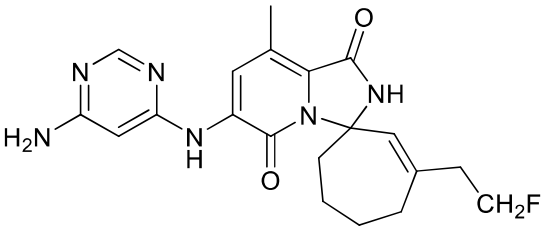
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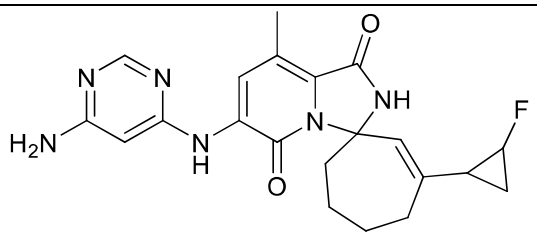
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, or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof.