compounds for treating diseases influenced by the inhibition of kinase activity of Mnk1 and/or Mnk2, including, for example, the compounds disclosed in WO 2014/044691 and the various patent documents cited therein and the 4-(dihydropyridinon-3-yl)amino-5-methylthieno[2,3,-d]pyrimidines disclosed by Yu *et al., European Journal ofMed. Chem.,* 95: 116-126, 2015.

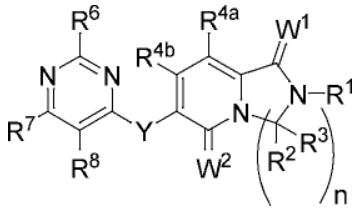
[0009] Accordingly, while advances have been made in this field there remains a significant need in the art for compounds that specifically inhibit Mnk kinase activity, particularly with regard to Mnk's role in regulation of cancer pathways, as well as for associated composition and methods. The present invention may fulfill this need and may provide further related advantages.

SUMMARY

[0009a] Aspects of the invention are defined in the independent claims. Some optional features of the invention are defined in the dependent claims.

[0010] The present disclosure provides compounds that inhibit or modulate the activity of Mnk, as well as stereoisomers, tautomers and pharmaceutically acceptable salts of such compounds as candidate therapeutic agents. The present disclosure also provides compositions containing such compounds and associated methods for treating conditions that would benefit from Mnk inhibition, such as cancer.

[0011] As disclosed herein there are compounds that conform to Formula I as well as to a stereoisomer, tautomer or pharmaceutically acceptable salt of such compounds.

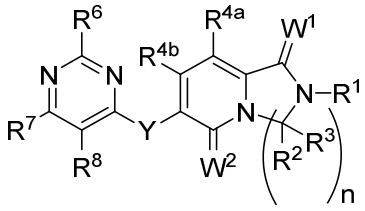


(I)

[0012] For Formula I compounds, R^1, R^2, R^3, R^{4a}, R^{4b}, R^6, R^7, R^8, W^1, W^2, Y and "n" are as defined below.

CLAIMS

1. A compound according to Formula (I):



(I)

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

W^1 and W^2 are independently O, S or N-OR', where R' is lower alkyl;

Y is $–N(R^5)–$, -O-, -S-, -C(O)-, -S=O, $-S(O)_2-$, or $–CHR^9–$;

R^1 is hydrogen, lower alkyl, cycloalkyl or heterocyclyl wherein any lower alkyl, cycloalkyl or heterocyclyl is optionally substituted with 1, 2 or 3 J groups;

n is 1, 2 or 3;

R^2 and R^3 are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, araalkylene, heteroaryl, heteroarylalkylene, cycloalkyl, cycloalkylalkylene, heterocyclyl, or heterocyclylalkylene, wherein any alkyl, aryl, araalkylene, heteroaryl, heteroarylalkylene, cycloalkyl, cycloalkylalkylene, heterocyclyl, or heterocyclylalkylene, is optionally substituted with 1, 2 or 3 J groups;

or R^2 and R^3 taken together with the carbon atom to which they are attached form a cycloalkyl or heterocyclyl, wherein any cycloalkyl or heterocyclyl is optionally substituted with 1, 2 or 3 J groups;

R^{4a} and R^{4b} are each independently hydrogen, halogen, hydroxyl, thiol, hydroxyalkylene, cyano, alkyl, alkoxy, acyl, thioalkyl, alkenyl, alkynyl, cycloalkyl, aryl, or heterocyclyl;

R^5 is hydrogen, cyano, or lower alkyl;

or R^5 and R^8 taken together with the atoms to which they are attached form a fused heterocyclyl optionally substituted with 1, 2 or 3 J groups;

R^6, R^7 and R^8 are each independently hydrogen, hydroxy, halogen, cyano, amino, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkylene, cycloalkylalkenylene, alkylaminyl, alkylcarbonylaminyl, cycloalkylcarbonylaminyl, cycloalkylaminyl,

heterocyclylaminyl, heteroaryl, or heterocyclyl, and wherein any amino, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkylene, cycloalkylalkenylene, amino, alkylaminyl, alkylcarbonylaminyl, cycloalkylcarbonylaminyl, cycloalkylaminyl, heterocyclylaminyl, heteroaryl, or heterocyclyl is optionally substituted with 1, 2 or 3 J groups;

or R^7 and R^8 taken together with the atoms to which they are attached form a fused heterocyclyl or heteroaryl optionally substituted with 1, 2 or 3 J groups;

J is –SH, -SR^9, -$S(O)R^9$, -$S(O)_2R^9$, -$S(O)NH_2$, -$S(O)NR^9R^9$, -NH_2, -NR^9R^9, -COOH, -$C(O)OR^9$, -$C(O)R^9$, -$C(O)$-NH_2, -$C(O)$-NR^9R^9, hydroxy, cyano, halogen, acetyl, alkyl, lower alkyl, alkenyl, alkynyl, alkoxy, haloalkyl, thioalkyl, cyanoalkylene, alkylaminyl, NH_2-C(O)-alkylene , NR^9R^9-C(O)-alkylene, -CHR^9-C(O)-lower alkyl, -C(O)-lower alkyl, alkylcarbonylaminyl, cycloalkyl, cycloalkylalkylene, cycloalkylalkenylene, cycloalkylcarbonylaminyl, cycloalkylaminyl, -CHR^9-C(O)-cycloalkyl, -C(O)-cycloalkyl, -CHR^9-C(O)-aryl, -CHR^9-aryl, -C(O)-aryl, -CHR^9-C(O)-heterocycloalkyl, -C(O)-heterocycloalkyl, heterocyclylaminyl, or heterocyclyl; or any two J groups bound to the same carbon or hetero atom may be taken together to form oxo; and

R^9 is hydrogen, lower alkyl or -OH.

2. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 wherein n is 1 and Y is –$N(R^5)$–.

3. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 wherein W^1 and W^2 are O.

4. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 wherein R^2 and R^3 are each independently hydrogen , methyl, ethenylene, propynylene, 2-methyl-1-propenylene, benzyl, fluorobenzyl, chlorobenzyl, cyclopentyl, cyclohexyl, difluorocyclohexyl, iso-propyl, trifluoromethyl, 1,1,1-trifluoroethylene, thiophene, thiazole, methylenenitrile, chlorophenyl, fluorophenyl, fluorochlorophenyl, difluorophenyl, pyridine, methylpyridine, chloropyridine, N-methylaminomethylene, aminomethylene, 1-aminoethylene, t-butyl, methylaminomethylene, propyl, 1-hydroxyethylene, or 1,1-difluoroethylene.

5. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 4 wherein R^2 and R^3 are each independently methyl, trifluoromethyl, 1,1,1-trifluoroethylene, cyclopentyl, cyclohexyl, difluorocyclohexyl, chlorophenyl, or fluorophenyl.

6. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 wherein n is 1 and R^2 and R^3 together with the carbon atom to which they are attached forms a cycloalkyl or a heterocyclyl ring that is optionally substituted with 1, 2 or 3 J groups.

7. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 6 wherein R^2 and R^3 together with the carbon atom to which they are attached forms a cycloalkyl ring selected from the group consisting of cyclobutyl, cyclopentyl and cyclohexyl and wherein any cyclobutyl, cyclopentyl or cyclohexyl is optionally substituted with halogen, hydroxy, or trifluoromethylene groups.

8. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 6 wherein R^2 and R^3 together with the carbon atom to which they are attached forms a heterocyclyl ring that is optionally substituted with 1, 2 or 3 J groups selected from the group consisting of halogen, -CN, N-methyl amino, methyl, difluoroethylene, and methylenenitrile.

9. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 8 wherein the heterocyclyl ring is piperidine.

10. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 wherein R^7 and R^8 together with the atoms to which they are attached form a fused heteroaryl ring that is optionally substituted with 1, 2 or 3 J groups.

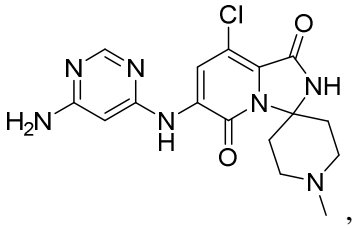
11. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 wherein R^{4a} and R^{4b} are each independently hydrogen, halogen, or alkyl.

12. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 wherein R^5 is hydrogen.

13. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 wherein R^6 and R^8 are hydrogen and R^7 is hydroxy, halogen, cyano, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl cycloalkylalkylene, cycloalkylalkenylene, amino, alkylaminyl, alkylcarbonylaminyl, cycloalkylcarbonylaminyl, cycloalkylaminyl, heterocyclylaminyl, heteroaryl, or heterocyclyl, and wherein any alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkylalkylene, cycloalkylalkenylene, amino, alkylaminyl, alkylcarbonylaminyl, cycloalkylcarbonylaminyl, cycloalkylaminyl, heterocyclylaminyl, heteroaryl, or heterocyclyl is optionally substituted with 1, 2 or 3 J groups.

14. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 13 wherein R^6 and R^8 are hydrogen and R^7 is amino, cycloalkylcarbonylaminyl, heterocyclylaminyl, or cycloalkylalkylene.

15. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1 selected from the group consisting of: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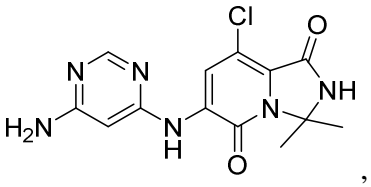
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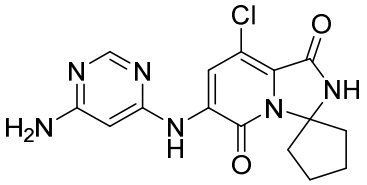
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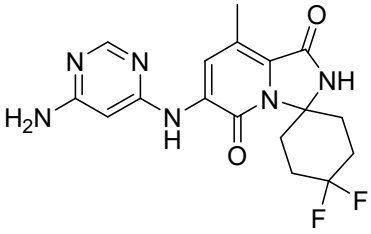
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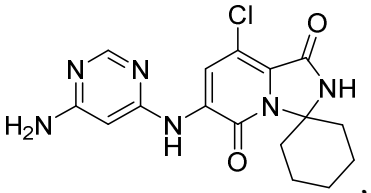
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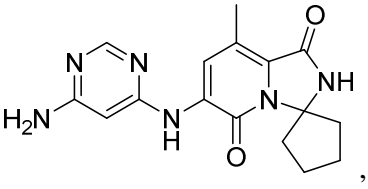
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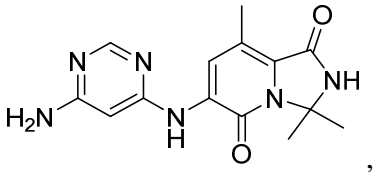
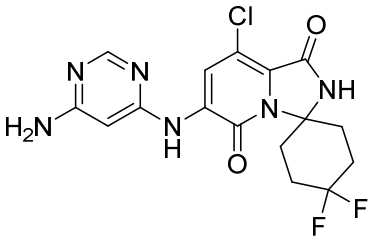
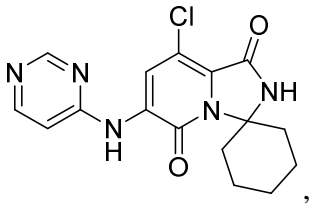
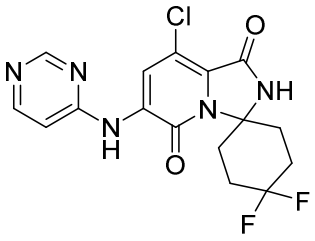
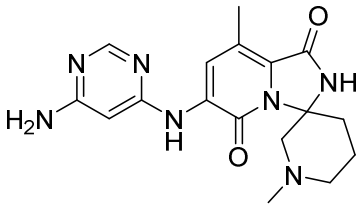
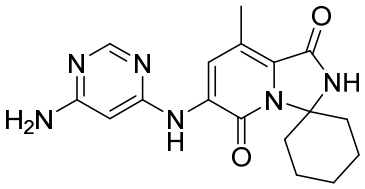
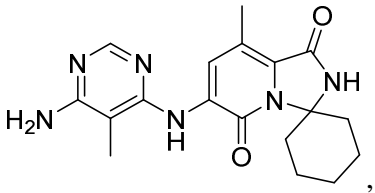
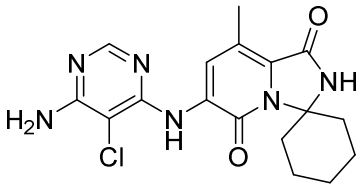
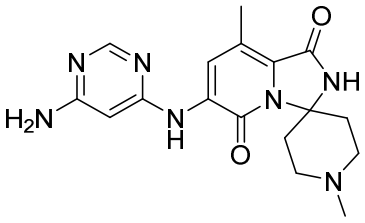
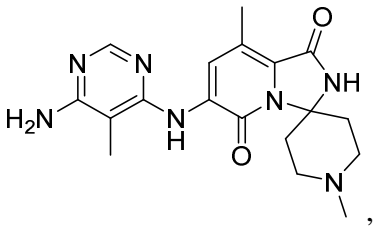
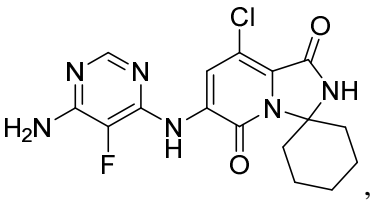
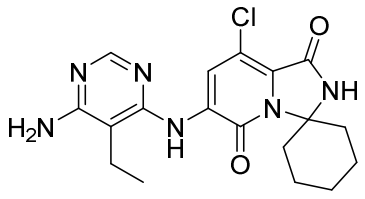
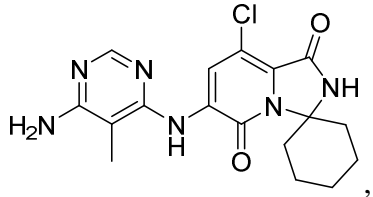
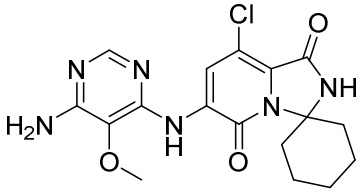
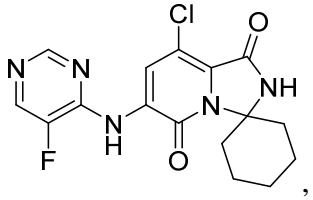
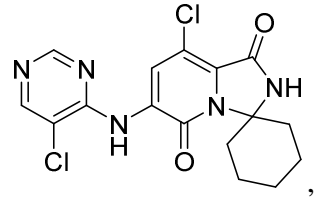
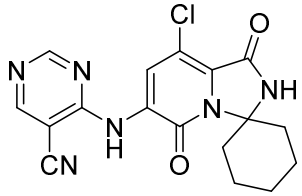
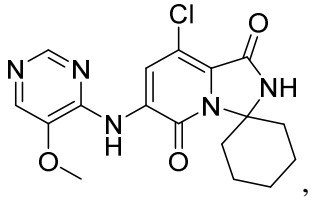
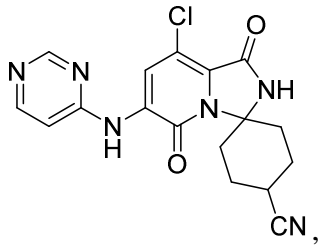
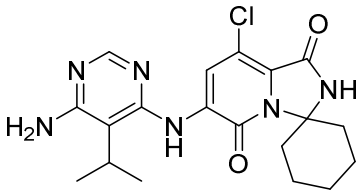
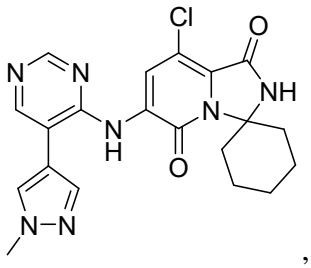
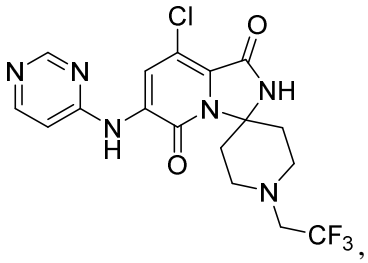
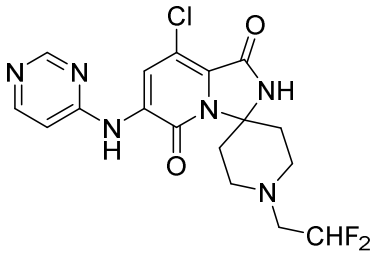
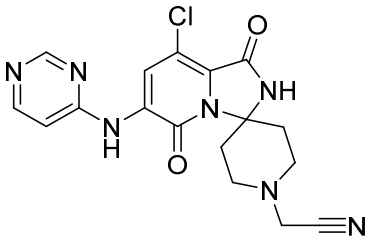
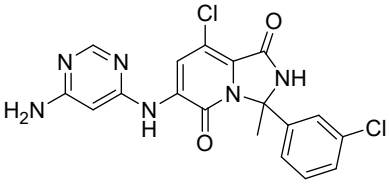
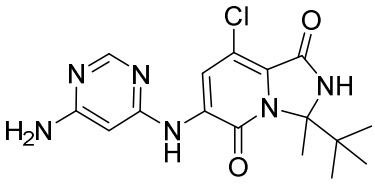
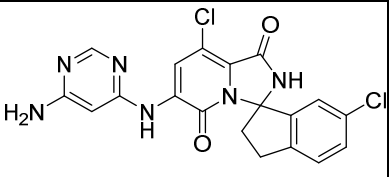
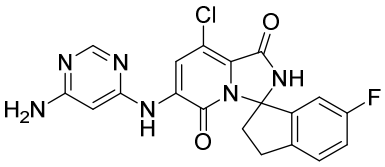
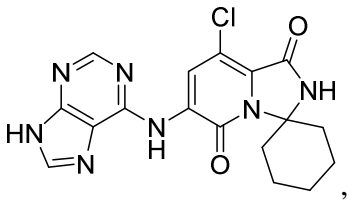
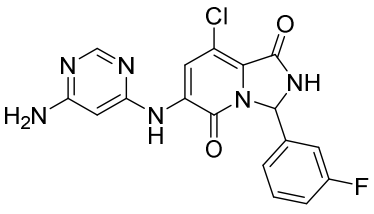
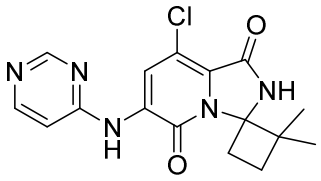
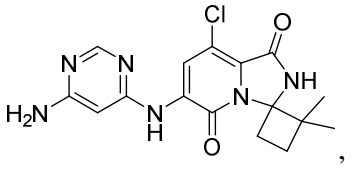
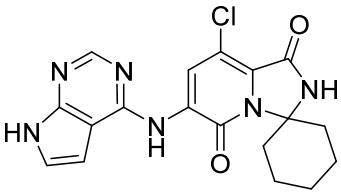
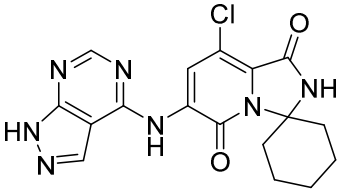
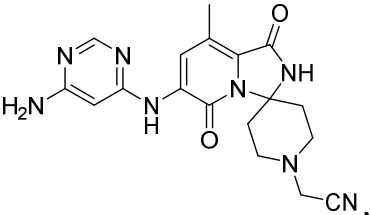
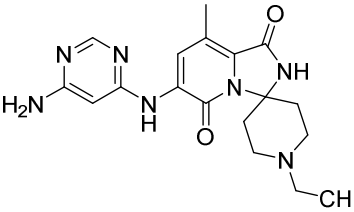
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,,
 ,	 ,	 ,
 ,	 ,	 ,

	 ,	 ,
	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
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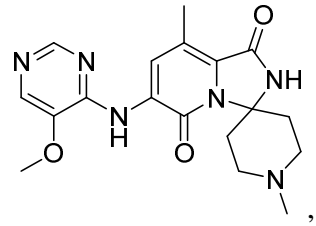
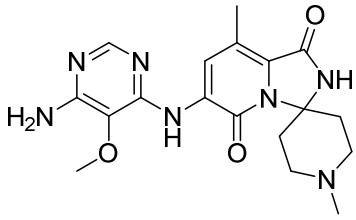
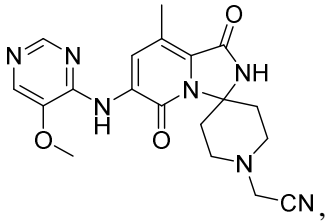
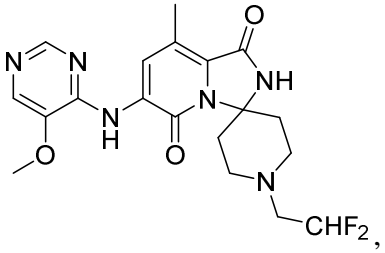
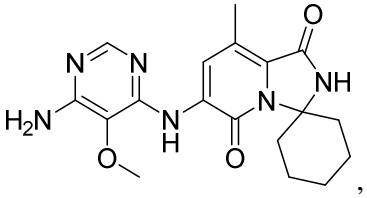
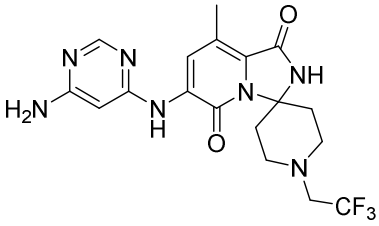
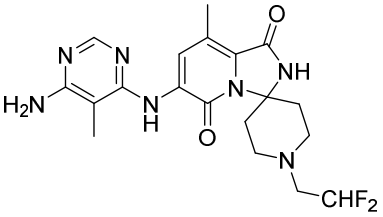
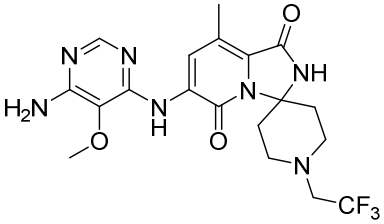
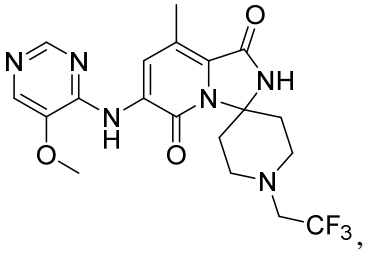
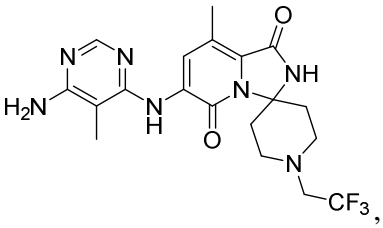
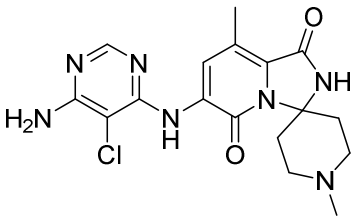
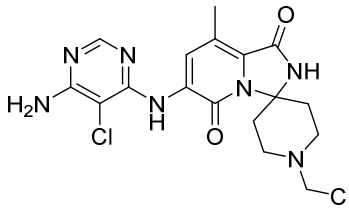
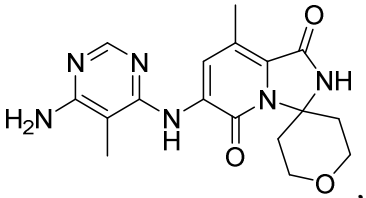
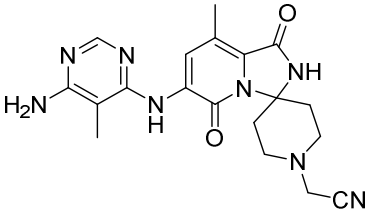
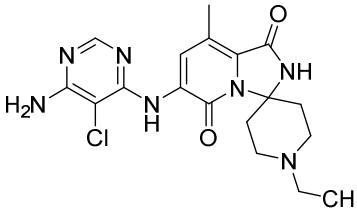
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
 ,	 ,	 ,
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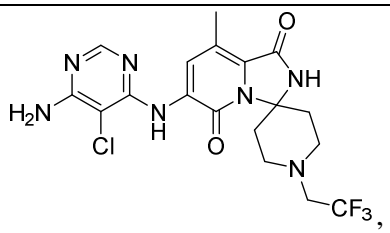
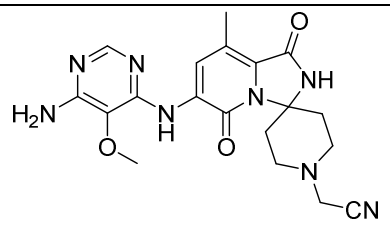
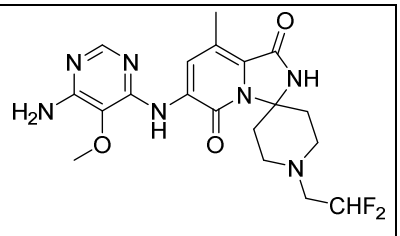
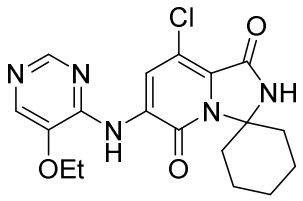
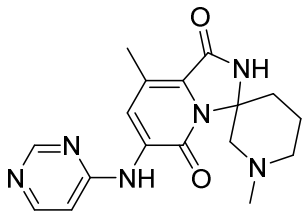
 ,	 ,	 ,
 , and	 .	

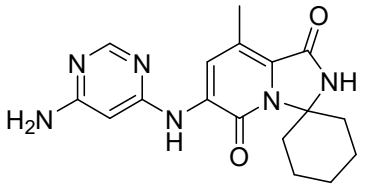
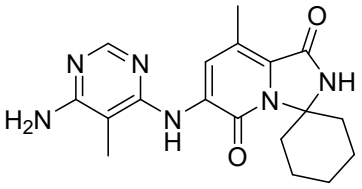
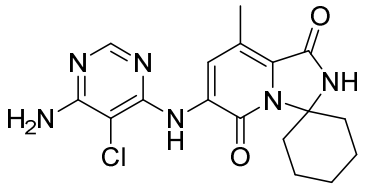
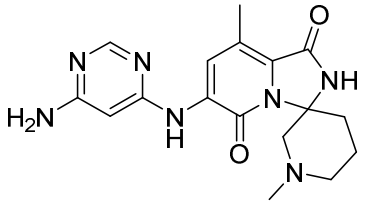
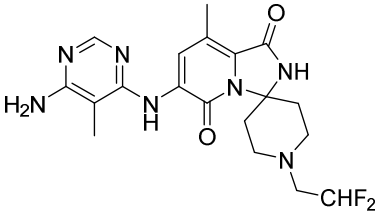
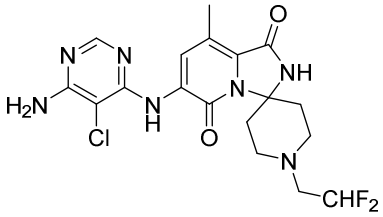
16. The compound according to claim 1, wherein the pharmaceutically acceptable salt of the Formula I compound is an organic or inorganic acid salt selected from the group consisting of acetate, mesylate, sulfate, citrate, oxalate, hydrochloride, dihydrochloride, isothionate, lactate, and laurate.

17. A pharmaceutical composition comprising (i) a therapeutically effective amount of at least one compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 1; (ii) in combination with a pharmaceutically acceptable carrier, diluent or excipient.

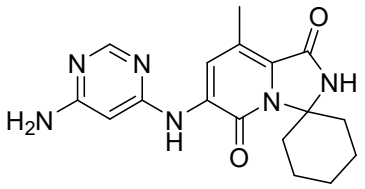
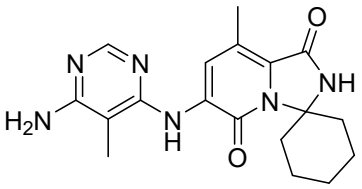
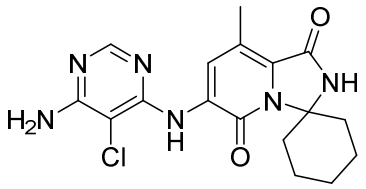
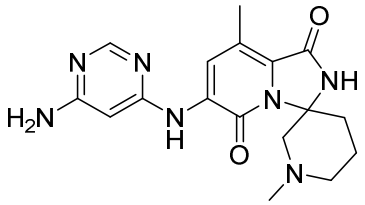
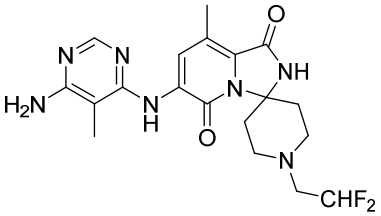
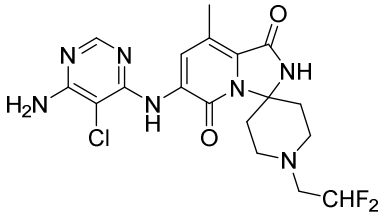
18. The compound of claim 16, wherein the pharmaceutically acceptable salt of the Formula I compound is selected from the group consisting of mesylate, sulfate and hydrochloride.

19. The compound according to claim 18, wherein the pharmaceutically acceptable salt of the Formula I compound is hydrochloride.

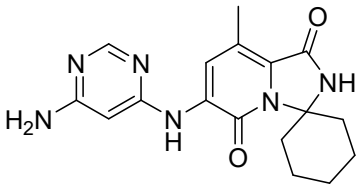
20. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 15 selected from

 ,	 ,	 ,
 ,	 , and	 .

21. The pharmaceutical composition according to claim 17 wherein the compound is selected from

 ,	 ,	 ,
 ,	 , and	 .

22. A compound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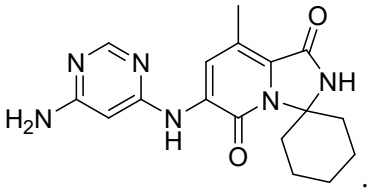
or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof.

23. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 22 wherein the pharmaceutically acceptable salt is selected from the group consisting of mesylate, sulfate and hydrochloride.

24. The compound or a stereoisomer, tautomer or pharmaceutically acceptable salt thereof according to claim 23 wherein the pharmaceutically acceptable salt is hydrochloride.

25. A compound



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