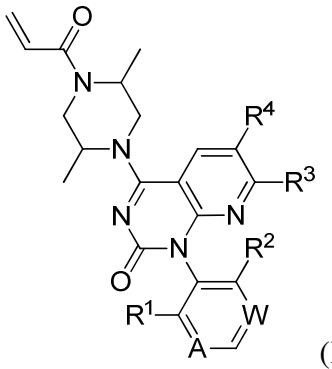
SUMMARY

[0004] In one aspect, the present disclosure refers to a compound having a structure of formula (I)



(I);

wherein

A is independently N or CH;

W is independently N or CH;

wherein one or both of A and W is N;

R^1 and R^2 are independently a branched or a linear C_{1-6}alkyl;

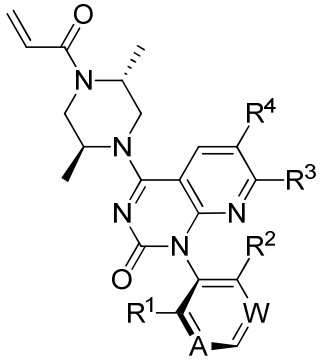
R^3 is phenyl substituted by 1 or 2 R^5 substituents;

R^5 is independently selected from one or more halo, -OH, or NH_2;

R^4 is halo; or

a stereoisomer thereof; a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof.

In one example the present disclosure comprises a compound of example 1 having a structure of formula (Ia)



(Ia); or

a pharmaceutically acceptable salt thereof.

[0005] The compound of example 1 or 2 wherein A is N.

[0006] The compound of example 1 or 2 wherein A is CH.

[0007] The compound of example 1 or 2 wherein W is N.

[0008] The compound of example 1 or 2 wherein W is CH.

[0009] The compound of any one of examples 1-6 wherein R^1 is CH_3.

[0010] The compound of any one of examples 1-6 wherein R^1 is $CH(CH_3)_2$.

[0011] The compound of any one of examples 1-8 wherein R^2 is CH_3.

[0012] The compound of any one of examples 1-8 wherein R^2 is $CH(CH_3)_2$.

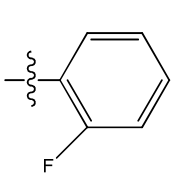
[0013] The compound of any one of examples 1-10 wherein R^5 is halo.

[0014] The compound of example 11 wherein R^5 is F.

[0015] The compound of any one of examples 1-10 wherein R^5 is -OH.

[0016] The compound of any one of examples 1-10 wherein R^5 is $-NH_2$.

[0017] The compound of any one of examples 1-10 wherein R^3 is



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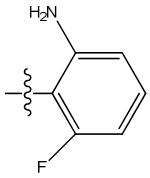
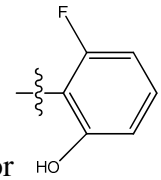


, or


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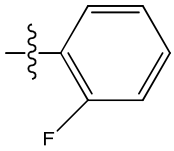
[0018] The compound of example 15 wherein R^3 is 

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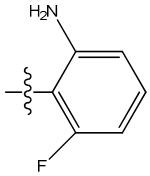
[0019] The compound of example 15 wherein R^3 is 

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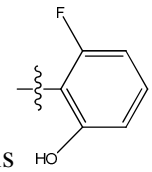
[0020] The compound of example 15 wherein R^3 is 

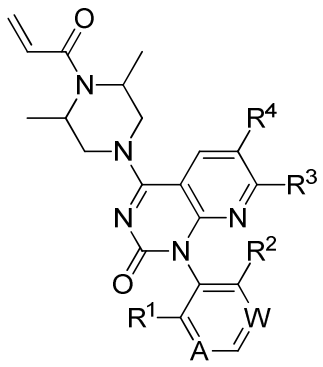
.

[0021] The compound of any one of examples 1-18 wherein R^4 is halo.

[0022] The compound of example 19 wherein R^4 is Cl.

[0023] The compound of example 19 wherein R^4 is F.

[0024] In another aspect, the present disclosure refers to a compound having a structure of formula (II)



(II)

wherein

A is independently N or CH;

W is independently N or CH;

wherein one or both A and W is N;

R^1 and R^2 are independently a branched or a linear C_{1-6}alkyl;

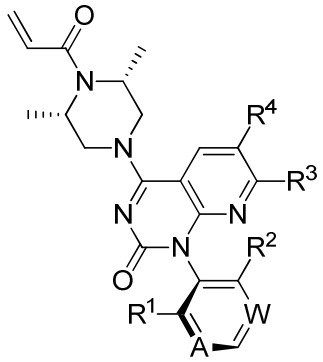
R^3 is phenyl substituted by one or two R^5 substituents;

R^5 is independently selected from one or more halo, -OH, or NH_2; and

R^4 is halo; or

or a stereoisomer thereof; a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof.

[0025] A compound of example 22 having a structure of formula (IIa)



(IIa); or

a pharmaceutically acceptable salt thereof.

[0026] The compound of example 22 or 23 wherein A is N.

[0027] The compound of example 22 or 23 wherein A is CH.

[0028] The compound of example 22 or 23 wherein W is N.

[0029] The compound of example 22 or 23 wherein W is CH.

[0030] The compound of any one of examples 22-27 wherein R^1 is CH_3.

[0031] The compound of any one of examples 22-27 wherein R^1 is $CH(CH_3)_2$.

[0032] The compound of any one of examples 22-29 wherein R^2 is CH_3.

[0033] The compound of any one of examples 22-29 wherein R^2 is $CH(CH_3)_2$.

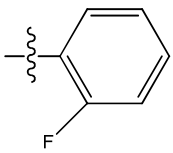
[0034] The compound of any one of examples 22-31 wherein R^5 is halo.

[0035] The compound of example 32 wherein R^5 is F.

[0036] The compound of any one of examples 22-31 wherein R^5 is -OH.

[0037] The compound of any one of examples 22-31 wherein R^5 is $-NH_2$.

[0038] The compound of any one of examples 22-31 wherein R^3 is



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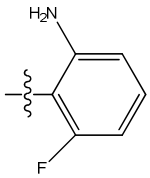

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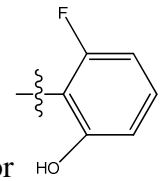

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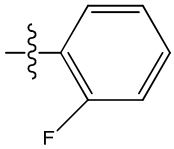
[0039] The compound of example 36 wherein R^3 is 

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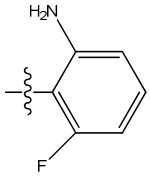
[0040] The compound of example 36 wherein R^3 is 

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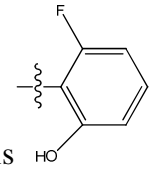
[0041] The compound of example 36 wherein R^3 is 

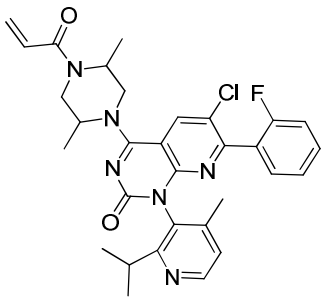
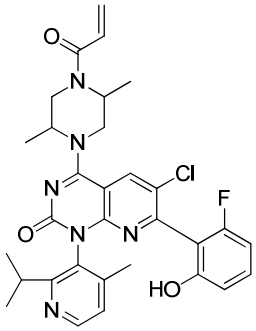
.

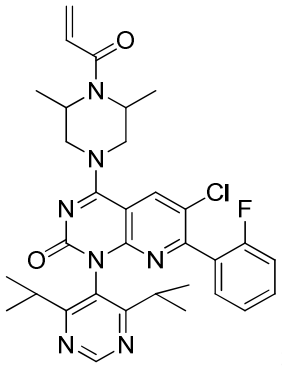
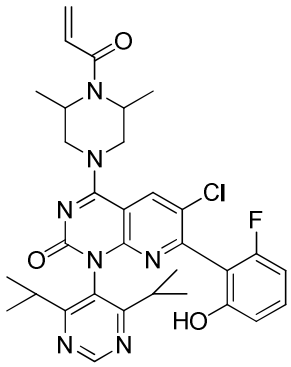
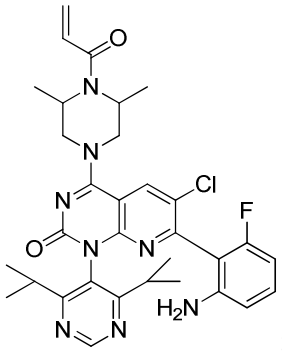
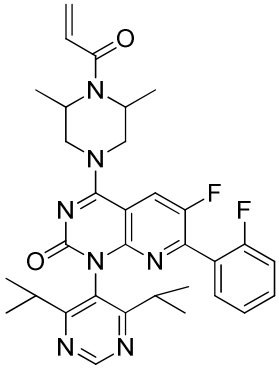
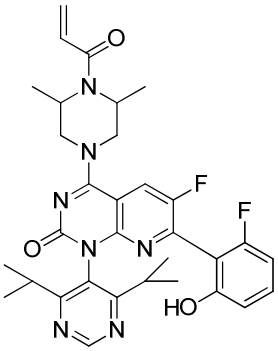
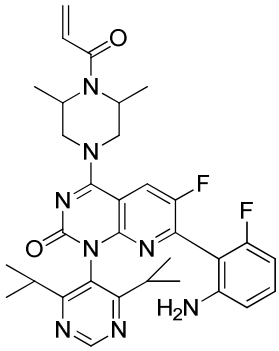
[0042] The compound of any one of examples 22-39 wherein R^4 is halo.

[0043] The compound of example 40 wherein R^4 is Cl.

[0044] The compound of example 40 wherein R^4 is F.

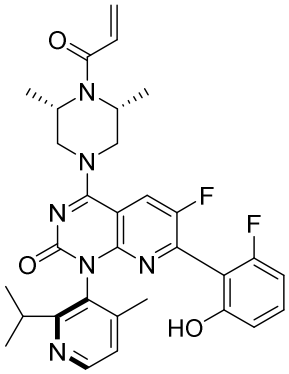
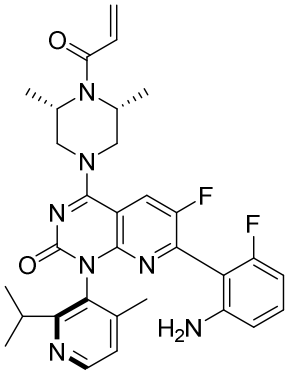
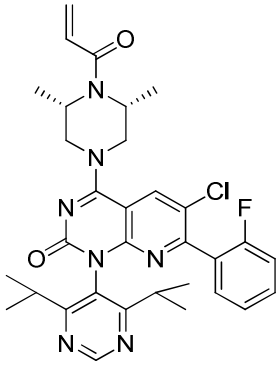
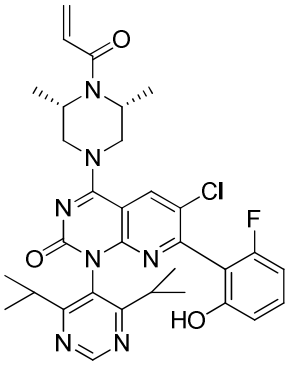
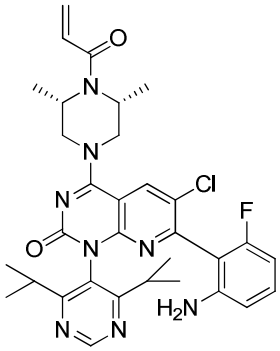
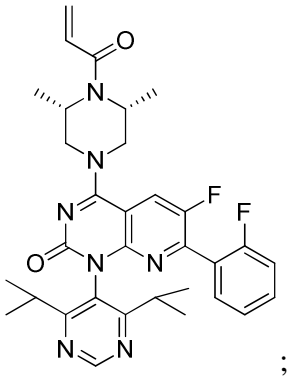
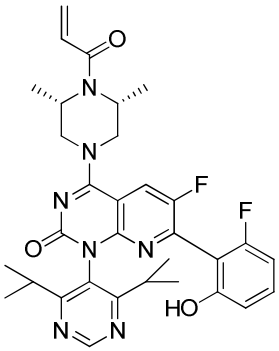
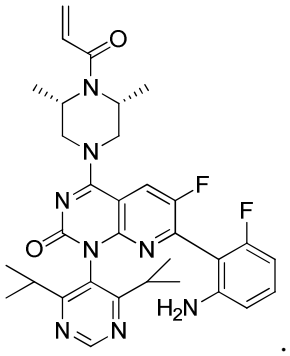
[0045] In another aspect, the present disclosure refers to a compound having a structure selected from:

 ;	 ;

 ;	 ;
 ;	 ;
 ; and	 .

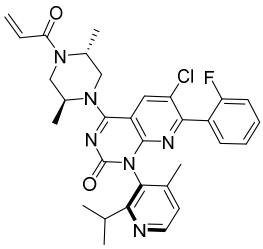
or a stereoisomer thereof; a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof.

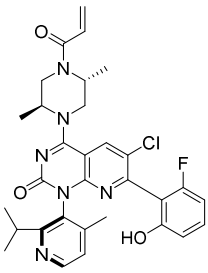
[0046] In another aspect, the present disclosure refers to a compound having a structure selected from:

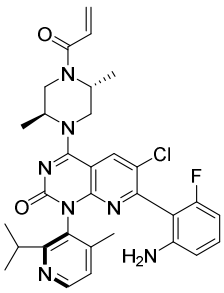
 ;	 ;
 ;	 ;
 ;	 ;
 ; and	 .

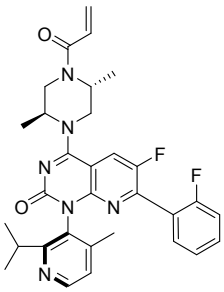
[0047] The compound of example 44 in the form of a pharmaceutically acceptable salt.

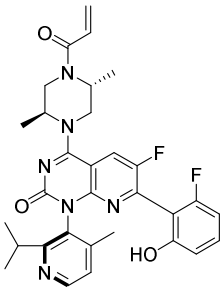
[0048] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein and a pharmaceutically acceptable excipient. In one example, the present disclosure comprises a pharmaceutical composition comprising the compound of any one of examples 1-45 and a pharmaceutically acceptable excipient.

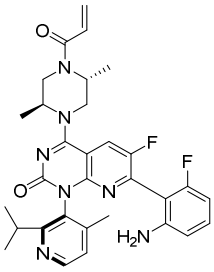
[0049] In another example, the present disclosure comprises a compound having a structure  .

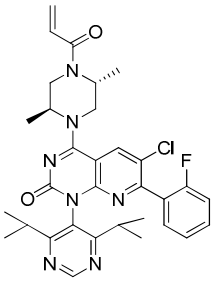
[0050] In another example, the present disclosure comprises a compound having a structure  .

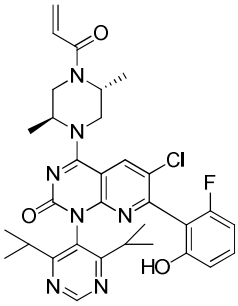
[0051] In another example, the present disclosure comprises a compound having a structure  .

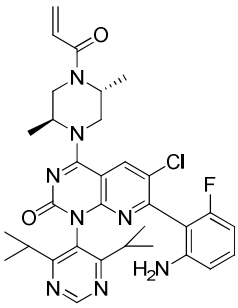
[0052] In another example, the present disclosure comprises a compound having a structure  .

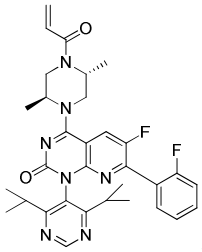
[0053] In another example, the present disclosure comprises a compound having a structure  .

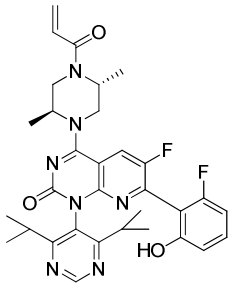
[0054] In another example, the present disclosure comprises a compound having a structure  .

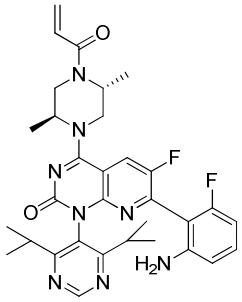
[0055] In another example, the present disclosure comprises a compound having a structure  .

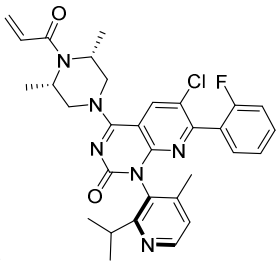
[0056] In another example, the present disclosure comprises a compound having a structure  .

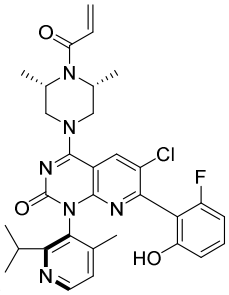
[0057] In another example, the present disclosure comprises a compound having a structure  .

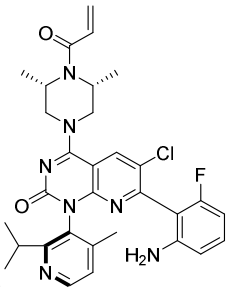
[0058] In another example, the present disclosure comprises a compound having a structure  .

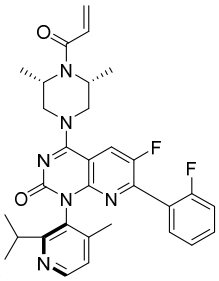
[0059] In another example, the present disclosure comprises a compound having a structure  .

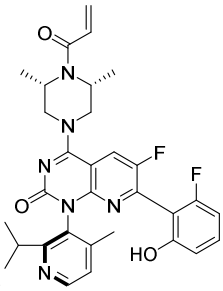
[0060] In another example, the present disclosure comprises a compound having a structure  .

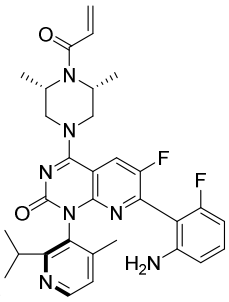
[0061] In another example, the present disclosure comprises a compound having a structure  .

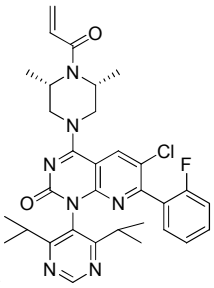
[0062] In another example, the present disclosure comprises a compound having a structure  .

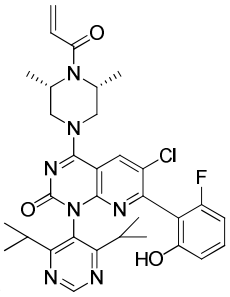
[0063] In another example, the present disclosure comprises a compound having a structure  .

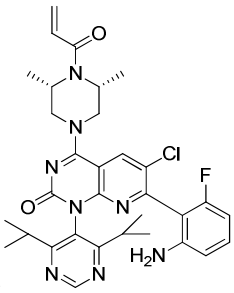
[0064] In another example, the present disclosure comprises a compound having a structure  .

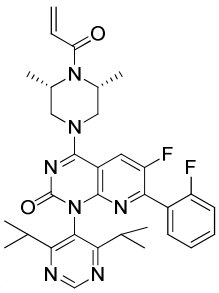
[0065] In another example, the present disclosure comprises a compound having a structure  .

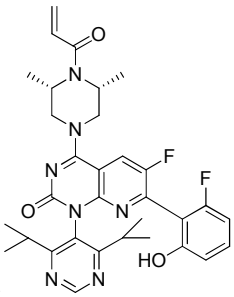
[0066] In another example, the present disclosure comprises a compound having a structure  .

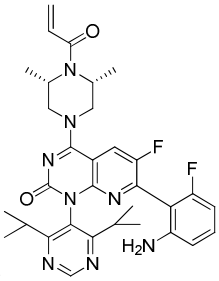
[0067] In another example, the present disclosure comprises a compound having a structure  .

[0068] In another example, the present disclosure comprises a compound having a structure  .

[0069] In another example, the present disclosure comprises a compound having a structure  .

[0070] In another example, the present disclosure comprises a compound having a structure  .

[0071] In another example, the present disclosure comprises a compound having a structure  .

[0072] In another example, the present disclosure comprises a compound having a structure  .

[0073] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein and a pharmaceutically acceptable excipient. In one example, the present disclosure comprises the compound of any one of examples 47 to 70 in the form of a pharmaceutically acceptable salt.

[0074] In another example, the present disclosure comprises a pharmaceutical composition comprising the compound of any one of examples 1-45 and 47- 71 and a pharmaceutically acceptable excipient.

[0075] In another aspect, the present disclosure refers to a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound as disclosed herein or the pharmaceutically acceptable salt thereof. In one example, the present disclosure comprises a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of examples 1-45 and 47- 71 or the composition of example 46 or 72.

[0076] In another aspect, the present disclosure refers to a use of the compound as disclosed herein or the pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a subject, wherein the cancer has a KRAS G12C mutation. In one example, the present disclosure comprises a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of examples 1-45 and 47- 71 or the composition of example 46 or 72.

[0077] The method of example 74, wherein the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

[0078] Numerous other examples of the compound of Formulas I, Ia, II and IIa are set forth herein.

[0079] Also provided are pharmaceutical compositions that include at least one pharmaceutically acceptable excipient, carrier or diluent and the compound or the pharmaceutically acceptable salt thereof, the tautomer thereof, the pharmaceutically acceptable salt of the tautomer, the stereoisomer of any of the foregoing, or the mixture thereof according to any one of the examples.

[0080] The compounds disclosed herein can be in the form of a pharmaceutically acceptable salt. The compounds provided can be formulated into a pharmaceutical formulation comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

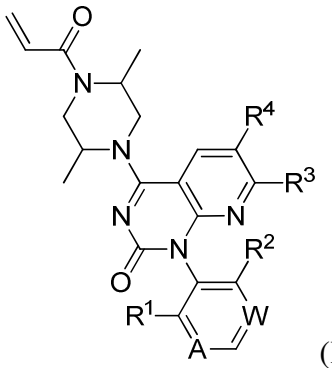
[0081] Also provided is a method of inhibiting KRAS G12C in a cell, comprising contacting the cell with a compound or composition disclosed herein. Further provided is a method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of a compound or composition disclosed herein. In some examples, the cancer is lung cancer, pancreatic cancer, or colorectal cancer.

[0082] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

CLAIMS

What is Claimed:

1. A compound having a structure of formula (I)



(I);

wherein

A is independently N or CH;

W is independently N or CH;

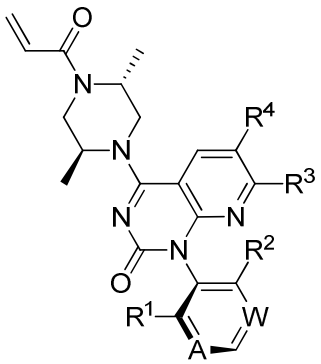
wherein one or both of A and W is N; R^1 and R^2 are independently a branched or a linear C_{1-6}alkyl; R^3 is phenyl substituted by 1 or 2 R^5 substituents;

R^5 is independently selected from one or more halo, -OH, or NH_2;

R^4 is halo; or

a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

2. The compound of claim 1 having a structure of formula (Ia)



(Ia); or

a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 wherein A is N.

4. The compound of claim 1 wherein A is CH.

5. The compound of claim 1 wherein W is N.

6. The compound of claim 1 wherein W is CH.

7. The compound of claim 1 wherein R^1 is CH_3.

8. The compound of claim 1 wherein R^1 is $CH(CH_3)_2$.

9. The compound of claim 1 wherein R^2 is CH_3.

10. The compound of claim 1 wherein R^2 is $CH(CH_3)_2$.

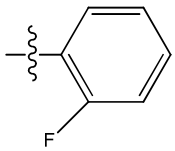
11. The compound of claim 1 wherein R^5 is halo.

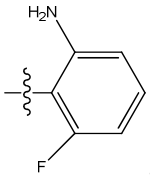
12. The compound of claim 11 wherein R^5 is F.

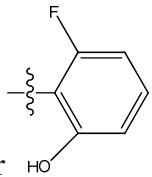
13. The compound of claim 1 wherein R^5 is -OH.

14. The compound of claim 1 wherein R^5 is $-NH_2$.

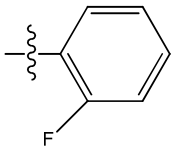
15. The compound of claim 1 wherein R^3 is



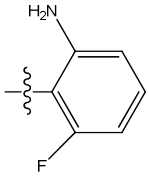
,


, or


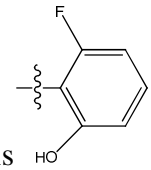
.

16. The compound of claim 15 wherein R^3 is 

.

17. The compound of claim 15 wherein R^3 is 

.

18. The compound of claim 15 wherein R^3 is 

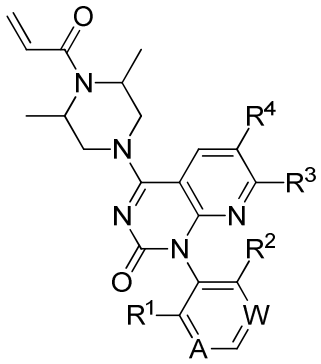
.

19. The compound of claim 1 wherein R^4 is halo.

20. The compound of claim 19 wherein R^4 is Cl.

21. The compound of claim 19 wherein R^4 is F.

22. A compound having a structure of formula (II)



(II)

wherein

A is independently N or CH;

W is independently N or CH;

wherein one or both A and W is N;

R^1 and R^2 are independently a branched or a linear C_{1-6}alkyl;

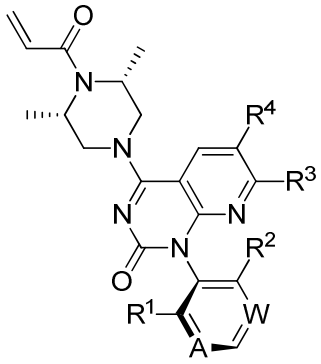
R^3 is phenyl substituted by one or two R^5 substituents;

R^5 is independently selected from one or more halo, -OH, or NH_2; and

R^4 is halo; or

or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

23. The compound of claim 22 having a structure of formula (IIa)



(IIa); or

a stereoisomer thereof; a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof.

24. The compound of claim 22 wherein A is N.

25. The compound of claim 22 wherein A is CH.

26. The compound of claim 22 wherein W is N.

27. The compound of claim 22 wherein W is CH.

28. The compound of claim 22 wherein R^1 is CH_3.

29. The compound of claim 22 wherein R^1 is $CH(CH_3)_2$.

30. The compound of claim 22 wherein R^2 is CH_3.

31. The compound of claim 22 wherein R^2 is $CH(CH_3)_2$.

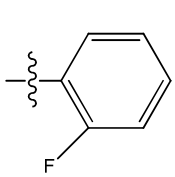
32. The compound of claim 22 wherein R^5 is halo.

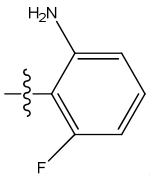
33. The compound of claim 32 wherein R^5 is F.

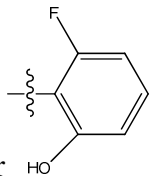
34. The compound of claim 22 wherein R^5 is -OH.

35. The compound of claim 22 wherein R^5 is $-NH_2$.

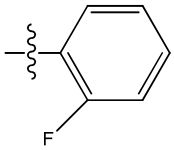
36. The compound of claim 22 wherein R^3 is



,


, or


.

37. The compound of claim 36 wherein R^3 is 

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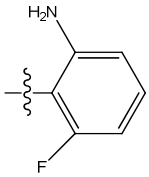
38. The compound of claim 36 wherein R^3 is 

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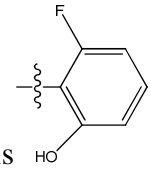
39. The compound of claim 36 wherein R^3 is 

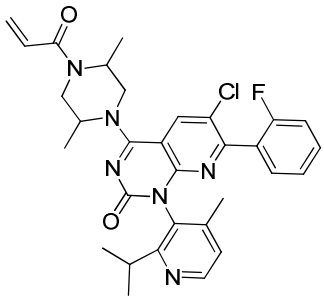
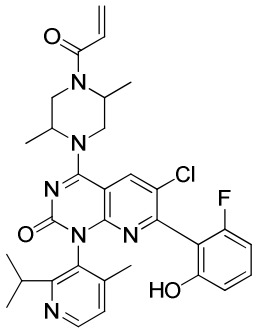
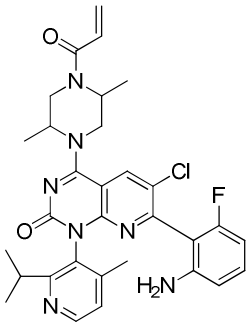
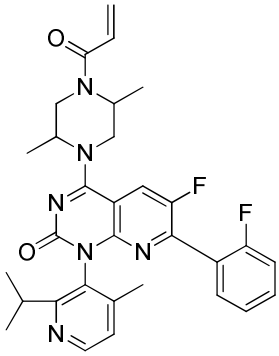
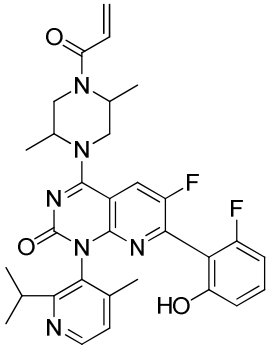
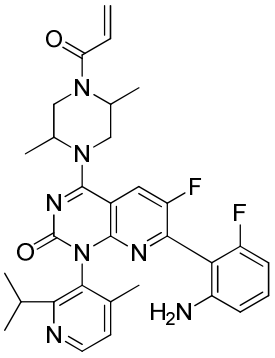
.

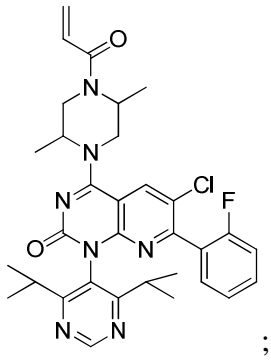
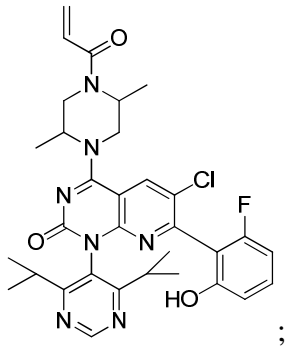
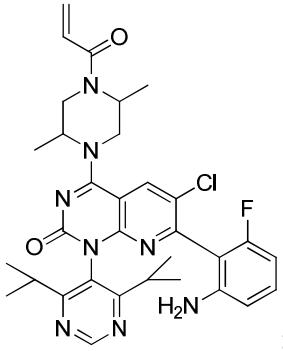
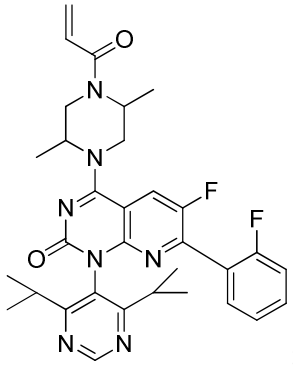
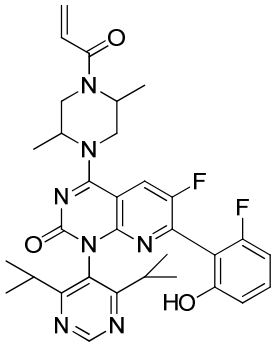
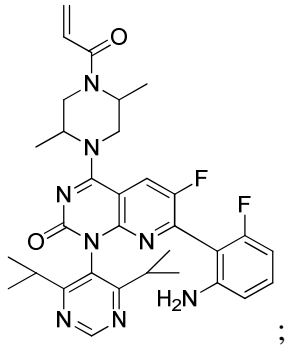
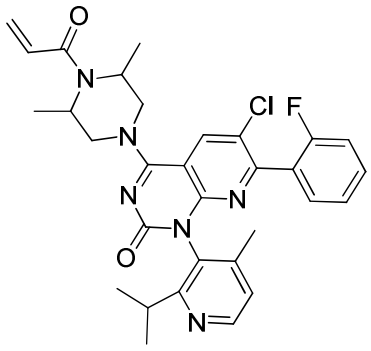
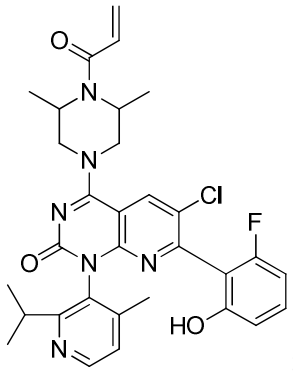
40. The compound of claim 22 wherein R^4 is halo.

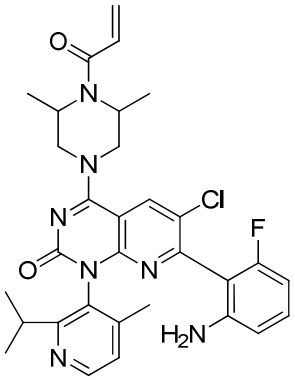
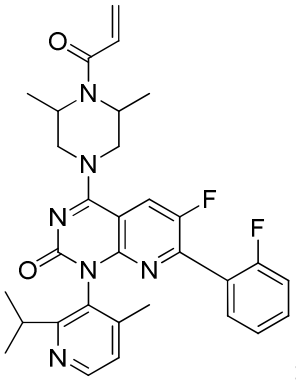
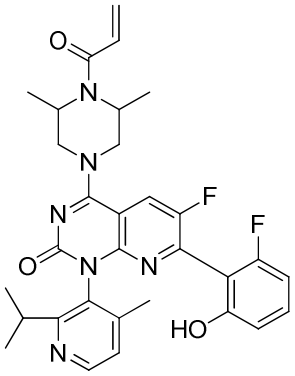
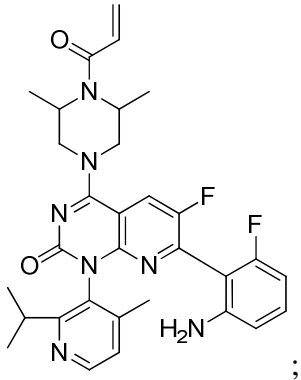
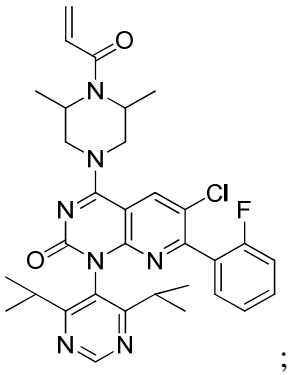
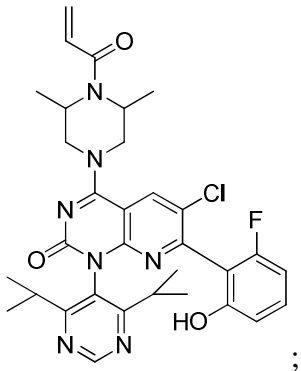
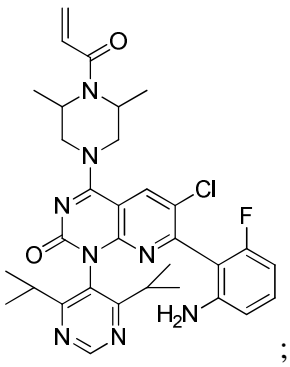
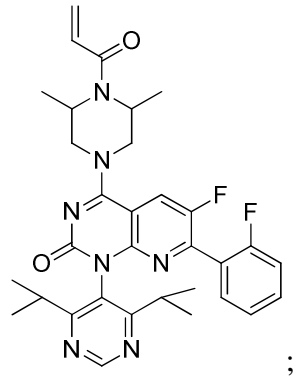
41. The compound of claim 22 wherein R^4 is Cl.

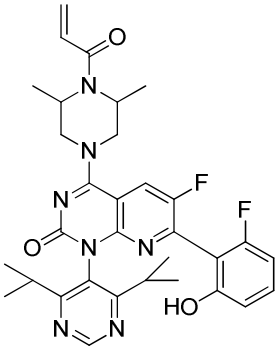
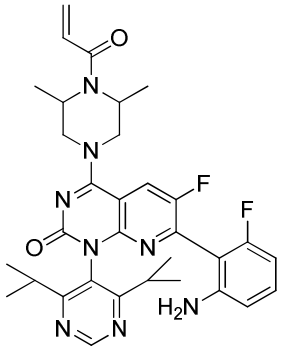
42. The compound of claim 22 wherein R^4 is F.

43. A compound having a structure selected from:

 ;	 ;
 ;	 ;
 ;	 ;

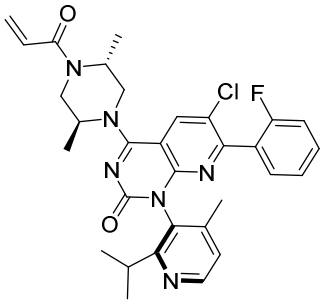
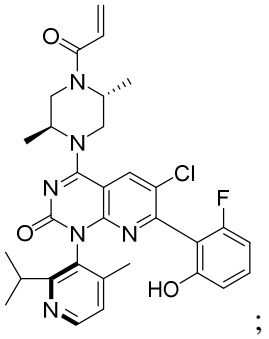
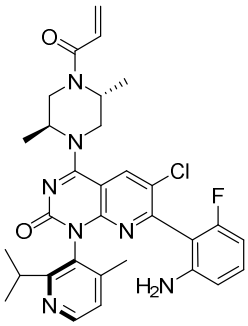
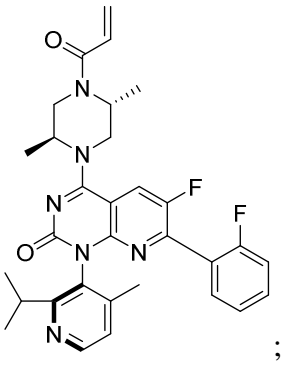
 ;	 ;
 ;	 ;
 ;	 ;
 ;	 ;

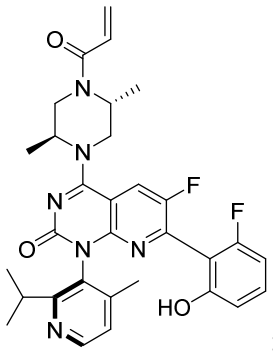
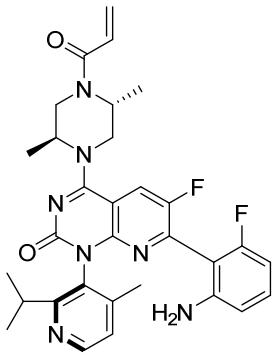
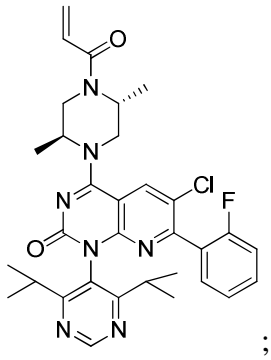
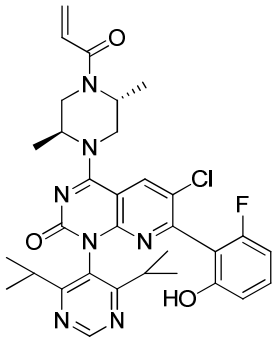
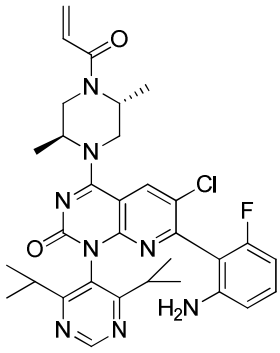
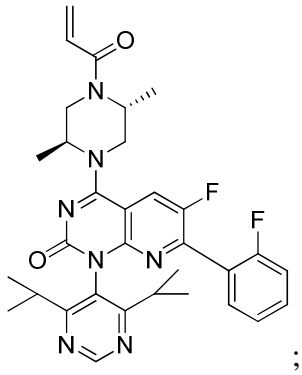
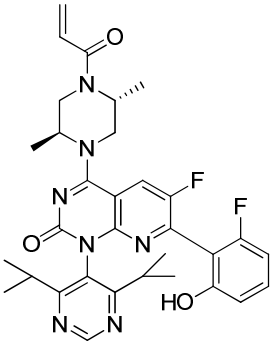
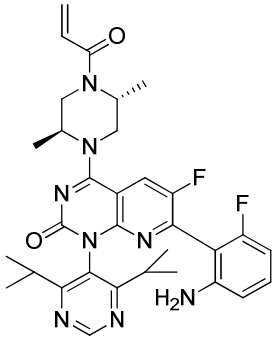
 ;	 ;
 ;	 ;
 ;	 ;
 ;	 ;

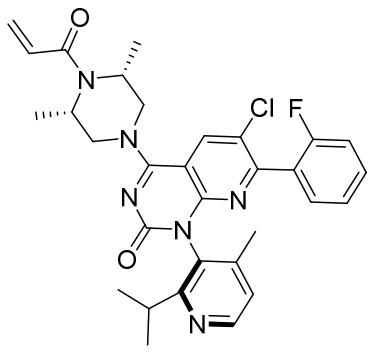
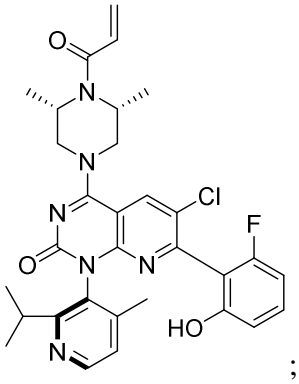
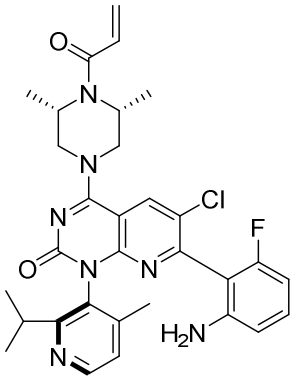
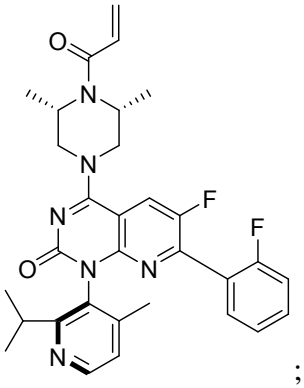
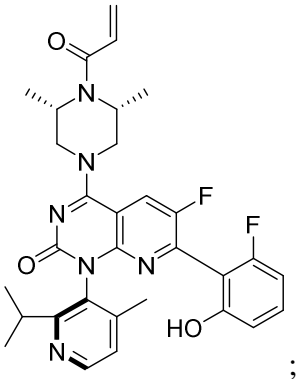
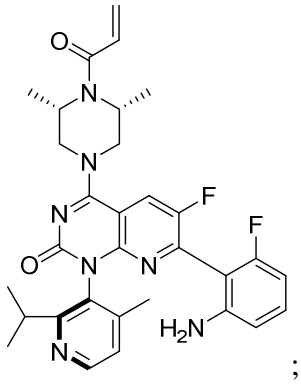
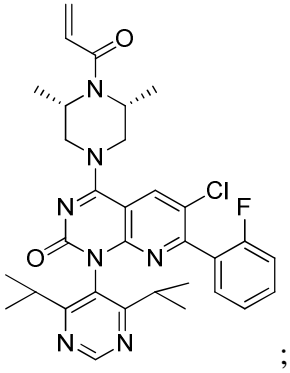
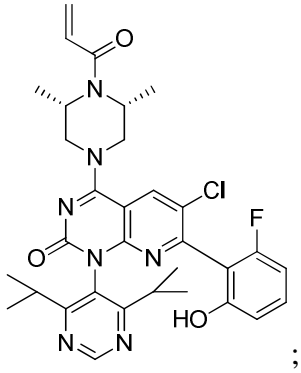
 ; and	 .

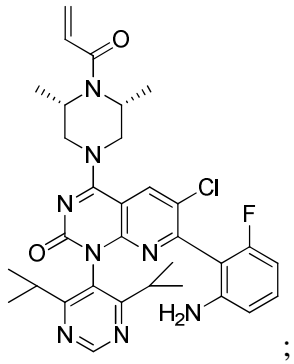
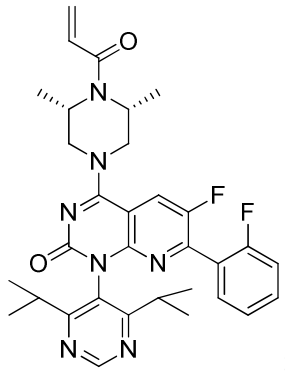
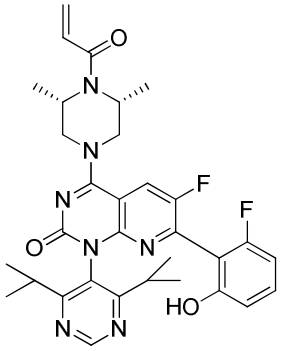
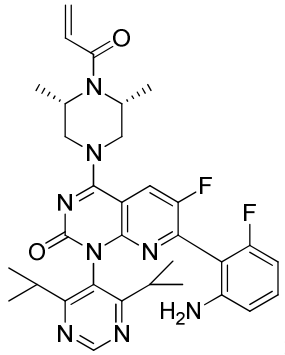
or a stereoisomer thereof, an atropisomer thereof, a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable salt of the stereoisomer thereof, or a pharmaceutically acceptable salt of the atropisomer thereof.

44. A compound having a structure selected from:

 ;	 ;
 ;	 ;

 ;	 ;
 ;	 ;
 ;	 ;
 ;	 ;

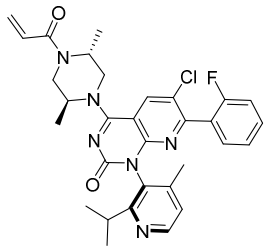
 ;	 ;
 ;	 ;
 ;	 ;
 ;	 ;

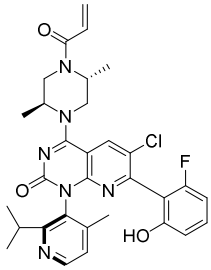
 ;	 ;
 ; and	 ;

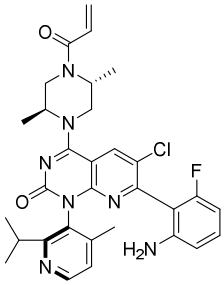
or a pharmaceutically acceptable salt.

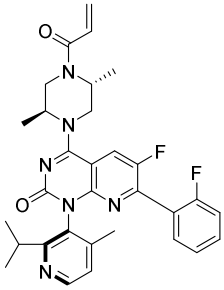
45. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable excipient.

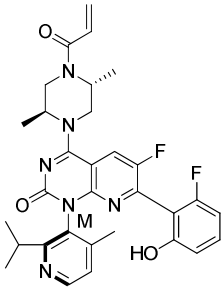
46. A pharmaceutical composition comprising the compound of claim 22 and a pharmaceutically acceptable excipient.

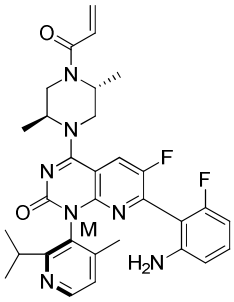
47. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

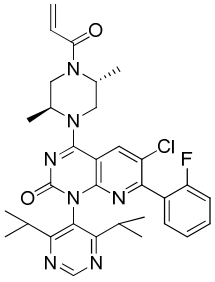
48. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

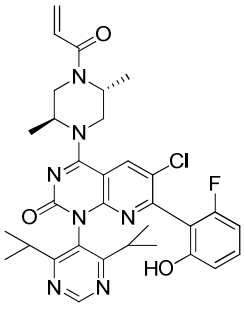
49. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

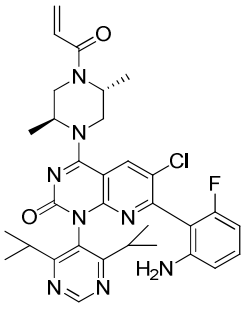
50. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

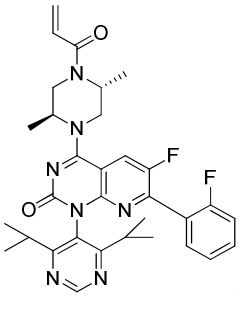
51. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

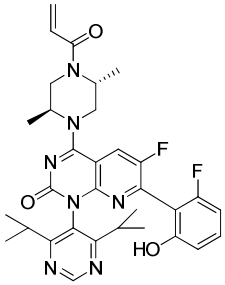
52. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

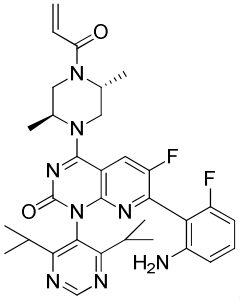
53. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

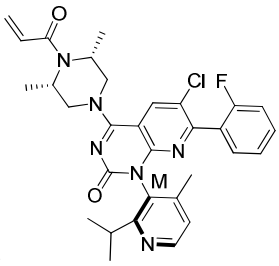
54. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

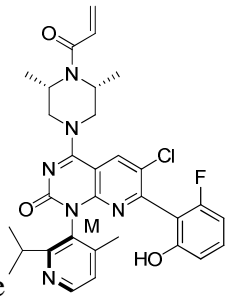
55. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

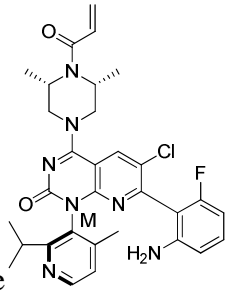
56. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

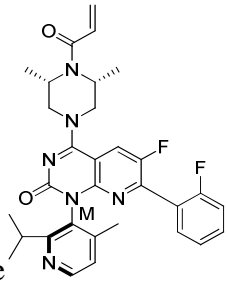
57. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

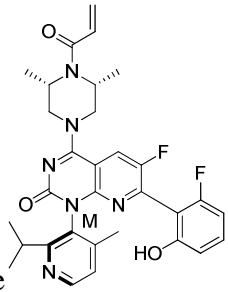
58. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

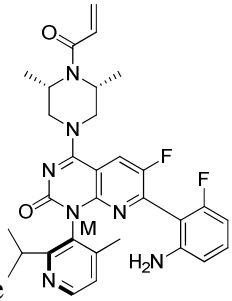
59. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

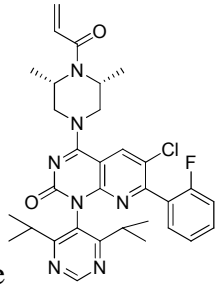
60. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

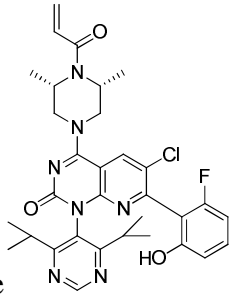
61. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

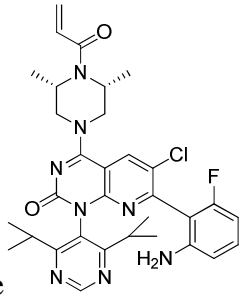
62. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

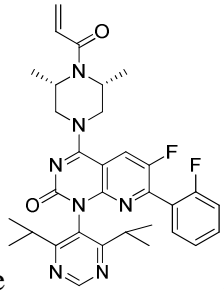
63. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

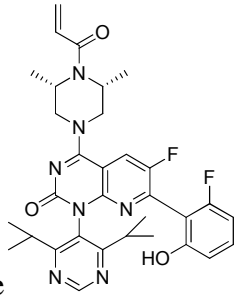
64. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

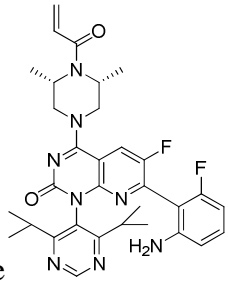
65. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

66. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

67. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

68. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

69. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

70. The compound of claim 44 having a structure  , or the pharmaceutically acceptable salt thereof.

71. A pharmaceutical composition comprising the compound of any one of claims 43, 44 or 47- 70 and a pharmaceutically acceptable excipient.

72. A method of inhibiting KRAS G12C in a cell, comprising contacting the cell with the compound of any one of claims 43, 44 or 47-70 or the pharmaceutically acceptable salt thereof.

73. Use of the compound of any one of claims 1-44 or 47-70 or the pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating cancer in a subject, wherein the cancer has a KRAS G12C mutation.

74. The use of claim 73, wherein the cancer is lung cancer, pancreatic cancer, endometrial cancer, appendix cancer, skin cancer, intraocular melanoma, or colorectal cancer.