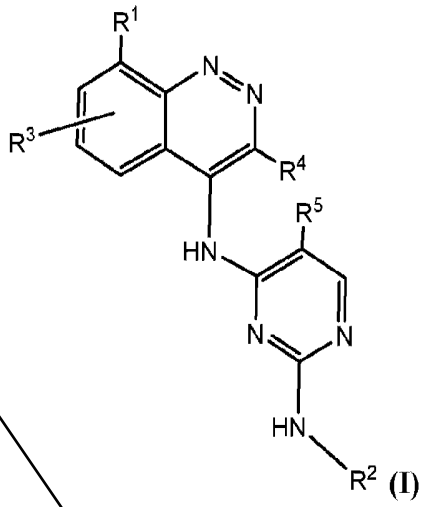
CLAIMS

What is claimed is:

1. A compound of Formula (**I**):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a C_1-C_5 alkyl or C_3-C_5 carbocycle, or a halogen;

R^2 is an aryl of at least 6 carbon atoms or nitrogen-containing heteroaryl of at least 6 atoms, optionally substituted with one or more of:

(i) one or more halogens;

(ii) a C_1-C_6 alkyl optionally substituted with a hydroxyl or one or more halogen wherein, when selected to be an alkyl larger than C_3, the alkyl is present at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2;

(iii) a sulfonamide;

(iv) a monocylic, bicyclic, or spiro-cyclic carbocycle which is optionally substituted with a hydroxyl, one or more halogen, or one or more linear, branched, or cyclic alkyl moieties of up to 6 carbon atoms which are optionally substituted with hydroxy or one or more halogen, wherein said carbocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present and selected to be a carbocycle larger than cyclopropyl, the carbocycle is at a position on the aryl

or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2; or

(v) a monocyclic, bicyclic or spiro-cyclic heterocycle which may contain up to 3 heteroatoms which are selected independently from N and O, and which is optionally and independently substituted with one or more C_1-C_6 alkyl or C_3-C_6 carbocycle which are optionally substituted with hydroxy or one or more halogen, wherein said heterocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present, said heterocycle is at a position on the aryl of R^2 which is meta- or para- to the amino bond to said aryl;

R^3 is -H, -F or -Cl;

R^4 is -H or a halogen, or a C_1-C_3 alkyl or cyclopropyl optionally substituted with one or more -F; and

R^5 is -H or -F, or a C_1-C_3 alkyl or cyclopropyl optionally substituted with one or more -F.

2. The compound of claim 1, wherein R^1 is a C_1-C_5 alkyl or C_3-C_5 carbocycle.

3. The compound of claim 2, wherein R^1 is $-CH_3$.

4. The compound of claim 2, wherein R^1 is cyclopropyl.

5. The compound of claim 1, wherein R^1 is -Cl or -F.

6. The compound of any one of claims 1-5, wherein R^2 is a phenyl or pyridinyl optionally substituted with one or more of:

(i) one or more halogens;

(ii) a C_1-C_6 alkyl optionally substituted with a hydroxyl or one or more halogen wherein, when selected to be an alkyl larger than C_3, the alkyl is present at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2;

(iii) a sulfonamide;

(iv) a monocylic, bicyclic, or spiro-cyclic carbocycle which is optionally substituted with a hydroxyl, one or more halogen, or one or more linear, branched, or cyclic alkyl moieties of up to 6 carbon atoms which are optionally substituted with

hydroxy or one or more halogen, wherein said carbocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present and selected to be a carbocycle larger than cyclopropyl, the carbocycle is at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2; or

(v) a monocyclic, bicyclic or spiro-cyclic heterocycle which may contain up to 3 heteroatoms which are selected independently from N and O, and which is optionally and independently substituted with one or more C_1-C_6 alkyl or C_3-C_6 carbocycle which are optionally substituted with hydroxy or one or more halogen, wherein said heterocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present, said heterocycle is at a position on the aryl of R^2 which is meta- or para- to the amino bond to said aryl.

7. The compound of any one of claims 1-6, wherein R^2 is a phenyl or pyridinyl substituted with one or more of:

(i) one or more halogens;

(ii) a C_1-C_6 alkyl optionally substituted with a hydroxyl or one or more halogen wherein, when selected to be an alkyl larger than C_3, the alkyl is present at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2;

(iii) a sulfonamide;

(iv) a monocylic, bicyclic, or spiro-cyclic carbocycle which is optionally substituted with a hydroxyl, one or more halogen, or one or more linear, branched, or cyclic alkyl moieties of up to 6 carbon atoms which are optionally substituted with hydroxy or one or more halogen, wherein said carbocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present and selected to be a carbocycle larger than cyclopropyl, the carbocycle is at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2; or

(v) a monocyclic, bicyclic or spiro-cyclic heterocycle which may contain up to 3 heteroatoms which are selected independently from N and O, and which is optionally and independently substituted with one or more C_1-C_6 alkyl or C_3-C_6 carbocycle which are optionally substituted with hydroxy or one or more halogen, wherein said

heterocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present, said heterocycle is at a position on the aryl of R^2 which is meta- or para- to the amino bond to said aryl.

8. The compound of any one of claims 1-7, wherein R^2 is substituted with one or more halogens.

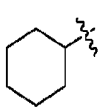
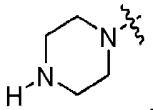
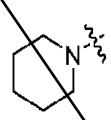
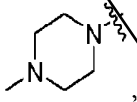
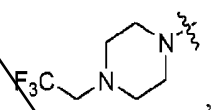
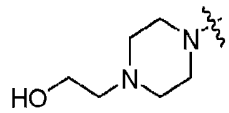
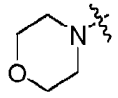
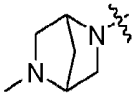
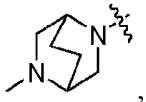
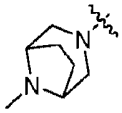
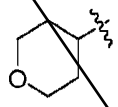
9. The compound of any one of claims 1-8, wherein R^2 is substituted with a sulfonamide.

10. The compound of any one of claims 1-9, wherein R^2 is substituted with C_1-C_6 alkyl optionally substituted with a hydroxyl or one or more halogen wherein, when selected to be an alkyl larger than C_3, the alkyl is present at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2.

11. The compound of any one of claims 1-10, wherein R^2 is substituted with a monocyclic, bicyclic, or spiro-cyclic carbocycle which is optionally substituted with a hydroxyl, one or more halogen, or one or more linear, branched, or cyclic alkyl moieties of up to 6 carbon atoms which are optionally substituted with hydroxy or one or more halogen, wherein said carbocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present and selected to be a carbocycle larger than cyclopropyl, the carbocycle is at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2.

12. The compound of any one of claims 1-10, wherein R^2 is substituted with a monocyclic, bicyclic or spiro-cyclic heterocycle which may contain up to 3 heteroatoms which are selected independently from N and O, and which is optionally and independently substituted with one or more C_1-C_6 alkyl or C_3-C_6 carbocycle which are optionally substituted with hydroxy or one or more halogen, wherein said heterocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present, said heterocycle is at a position on the aryl of R^2 which is meta- or para- to the amino bond to said aryl.

13. The compound of claim 12, wherein the heterocycle is a piperazinyl, morpholinyl, piperidinyl, diazabicyclooctanyl, diazabicycloheptanyl, or oxanyl, which is optionally and independently substituted with one or more C_1-C_6 alkyl which are optionally substituted with hydroxy or one or more halogen.

14. The compound of claim 13, wherein the heterocycle is , , , , , , , , , , or .

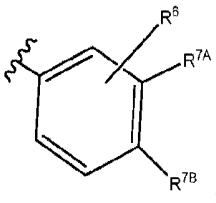
15. The compound of any one of claims 1-14, wherein the carbocycle or heterocycle attached to the aryl or heteroaryl of R^2 is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene linker.

16. The compound of claim 15, wherein the carbocycle or heterocycle attached to the aryl or heteroaryl of R^2 is attached to the aryl or heteroaryl of R^2 by a single bond.

17. The compound of any one of claims 1-16, wherein the carbocycle or heterocycle attached to the aryl or heteroaryl of R^2 is attached to the aryl or heteroaryl of R^2 at a position on R^2 which is meta- to the amino bond attached to R^2.

18. The compound of any one of claims 1-16, wherein the carbocycle or heterocycle attached to the aryl or heteroaryl of R^2 is attached to the aryl or heteroaryl of R^2 at a position on R^2 which is para- to the amino bond attached to R^2.

19. The compound of any one of claims 1-5, wherein R^2 is:

, wherein:

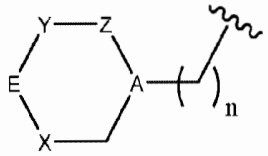
R^6 is -H, -F, -Cl, or a C_1-C_3 alkyl or cyclopropyl which is optionally and independently substituted with one or more halogen;

one of R^{7A} and R^{7B} is -H, and the other is:

(i) a halogen;

(ii) $-SO_2NR^{7F}{}_2$, wherein each R^{7F} is independently -H or a linear or branched alkyl of up to 4 carbon atoms;

(iii) a C_1-C_6 alkyl which is optionally substituted with one or more halogen; or

(iv)  , wherein:

A is >N- or >C(H)-;

E is -O-, >N(R^8), or >C(H)-R^{13};

R^8 is -H or a C_1-C_6 alkyl or C_3-C_6 carbocycle which is optionally substituted with hydroxyl or one or more halogen;

R^{13} is -H or a C_1-C_6 alkyl or C_3-C_6 carbocycle which is optionally substituted with hydroxy or one or more halogen; and

n is 0, 1, or 2, and

when E is >N(R^8), X, Y, and Z are defined as follows:

Z is $>CH_2$ and X and Y are independently $>CH_2$ or $>C(CH_3)_2$, or both X and Y are >CH- and are bonded together through a methylene or ethylene bridge; or

Y is $>CH_2$ or $>C(CH_3)_2$, and X and Z are both >CH- and are bonded together through a methylene or ethylene bridge, and

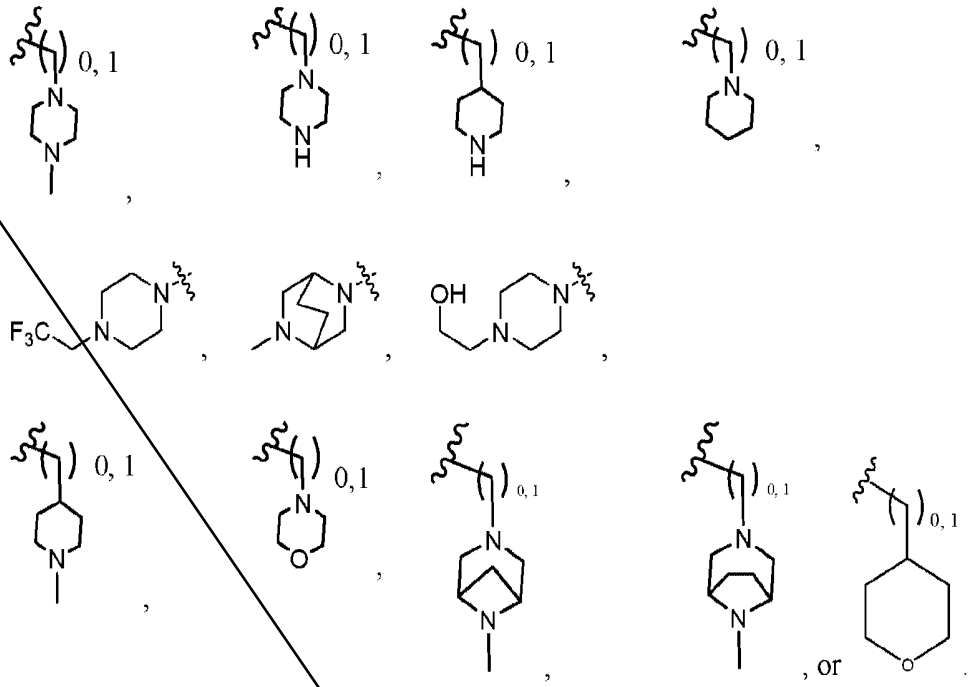
when E is -O- or >C(H)-R^{13}, X, Y, and Z are $>CH_2$.

20. The compound of claim 19, wherein R^6 is -H, -F, -Cl, $-CH_3$, or $-CF_3$.

21. The compound of claim 19 or 20, wherein n is 0 or 1.

22. The compound of claim 21, wherein n is 0.

23. The compound of any one of claims 19-22, wherein one of R^{7A} and R^{7B} is -H, and the other is:



24. The compound of any one of claims 1-23, wherein R^3 is -H.

25. The compound of any one of claims 1-23, wherein R^3 is -F or -Cl.

26. The compound of any one of claims 1-23, wherein R^3 is -F.

27. The compound of any one of claims 1-23, wherein R^3 is -Cl.

28. The compound of any one of claims 1-27, wherein R^4 is a C_1-C_3 alkyl or cyclopropyl optionally substituted with one or more -F.

29. The compound of any one of claims 1-27, wherein R^4 is halogen.

30. The compound of any one of claims 1-27, wherein R^4 is $-CF_3$.

31. The compound of any one of claims 1-27, wherein R^4 is $-CH_3$.

32. The compound of any one of claims 1-27, wherein R^4 is -H.

33. The compound of any one of claims 1-27, wherein R^4 is -Cl.

34. The compound of any one of claims 1-27, wherein R^4 is -F.

35. The compound of any one of claims 1-34, wherein R^5 is a C_1-C_3 alkyl or cyclopropyl optionally substituted with one or more -F.

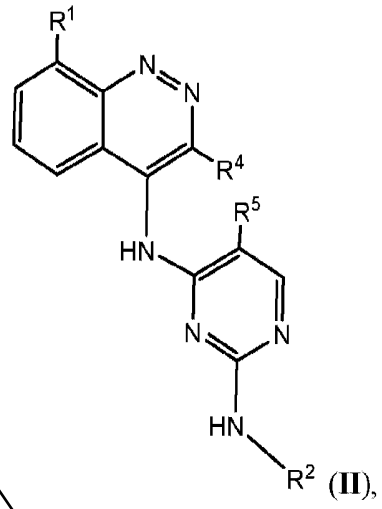
36. The compound of any one of claims 1-34, wherein R^5 is -H.

37. The compound of any one of claims 1-34, wherein R^5 is $-CH_3$.

38. The compound of any one of claims 1-34, wherein R^5 is $-CF_3$.

39. The compound of any one of claims 1-34, wherein R^5 is -F or -Cl.

40. The compound of claim 1 of Formula (**II**):

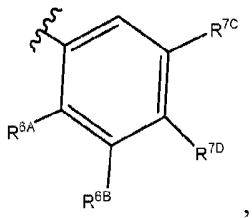


(**II**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-CH_3$ or -Cl;

R^2 is:

a)  , wherein:

one of R^{6A} and R^{6B} is -H, and the other is -H, -F, -Cl, $-CH_3$, or CF_3;

one of R^{7C} and R^{7D} is -H, and the other is:

(i) -F;

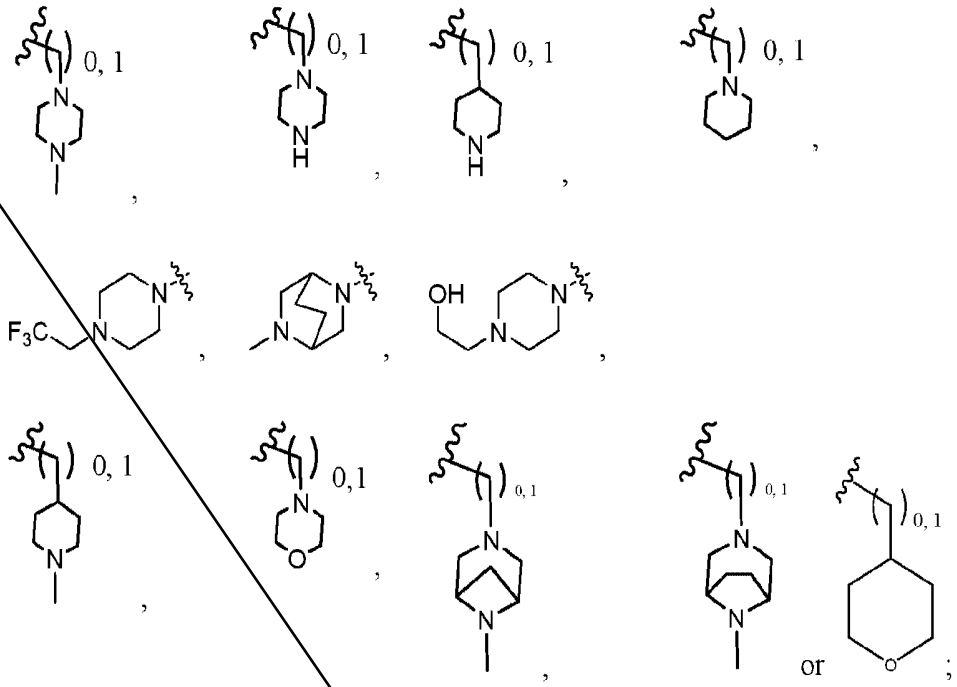
(ii) -Cl;

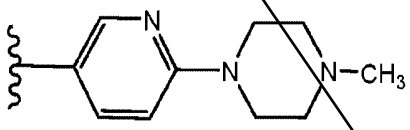
(iii) $-SO_2NH_2$;

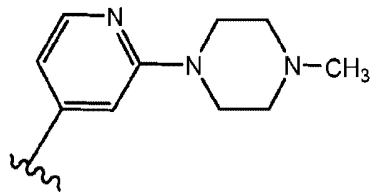
(iv) cyclohexyl;

(v) t-butyl; or

(vi)



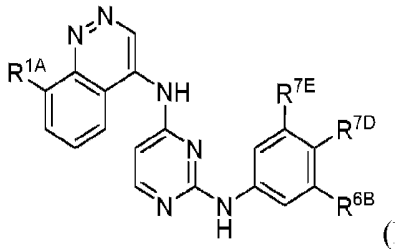
b)  ; or

c)  ;

R^4 is -H or -CH_3; and

R^5 is -H or -F.

41. The compound of claim 1 of Formula (**III**):

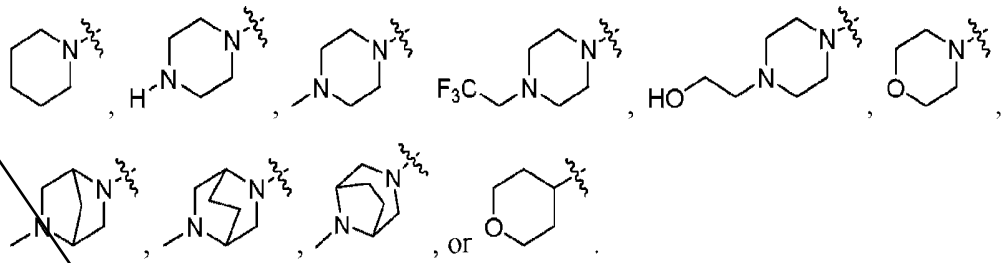
 (**III**),

or a pharmaceutically acceptable salt thereof, wherein:

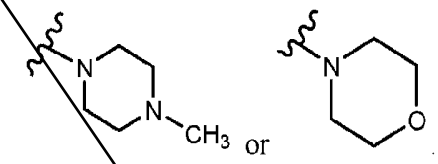
R^{1A} is methyl or cyclopropyl;

R^{6B} is -H, -F, or -Cl; and

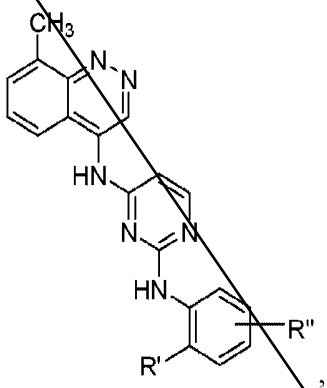
one of R^{7D} and R^{7E} is -H, and the other is a heterocycle of the formula:



42. The compound of claim 41, wherein one of R^{7D} and R^{7E} is -H, and the other is a heterocycle of the formula:

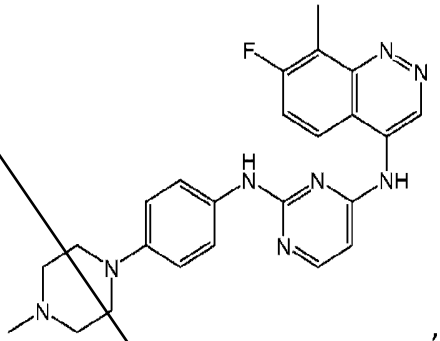


43. The compound of claim 1 having the following structure:

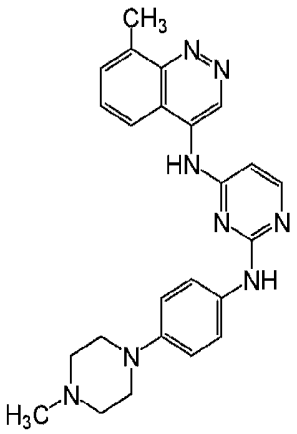


or a pharmaceutically acceptable salt thereof, wherein R' is H or F; and R" is at a position meta or para to the amino bond, and is morpholino or piperazinyl optionally *N*-substituted with $-CH_3$, $-CH_2CF_3$, or $-CH_2CH_2OH$.

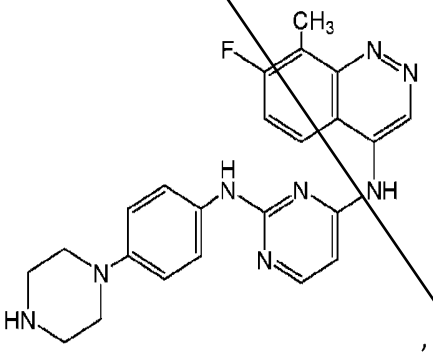
44. A compound, or a pharmaceutically acceptable salt thereof, having the structure:



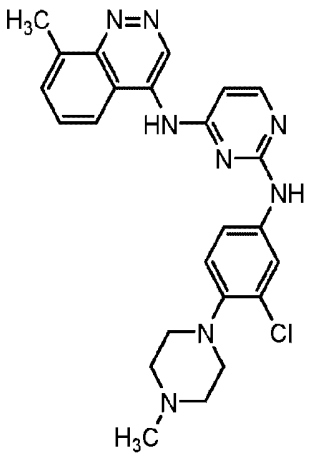
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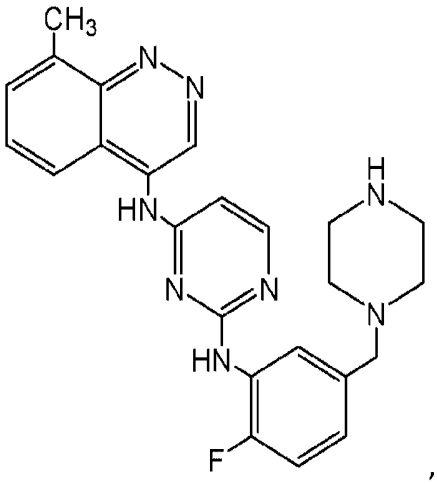
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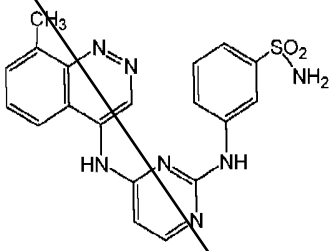
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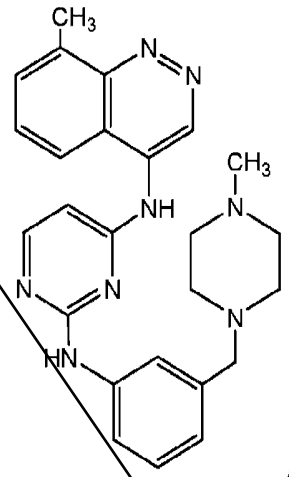
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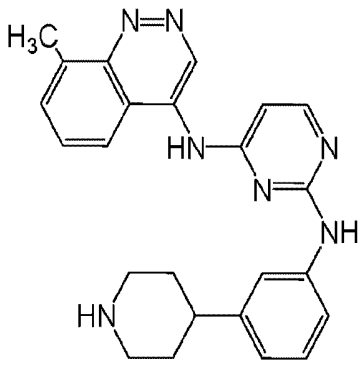
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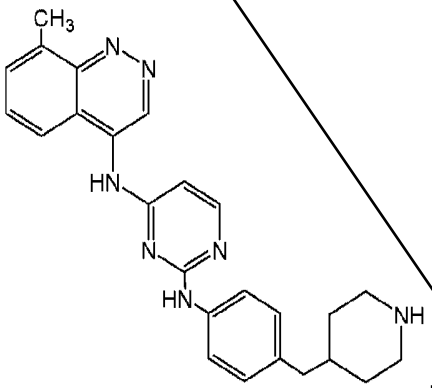
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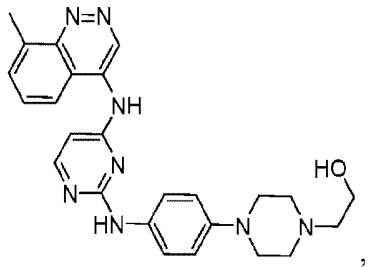
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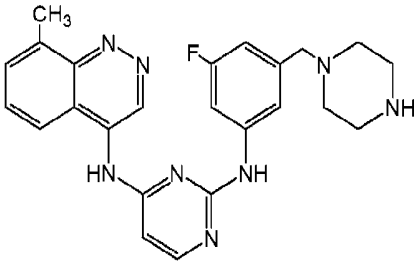
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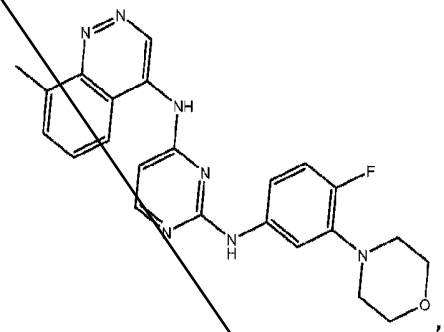
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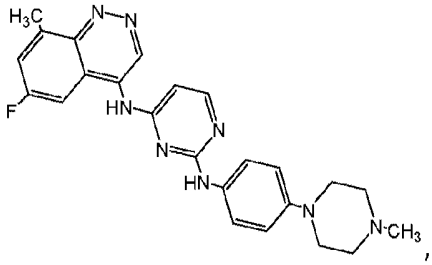
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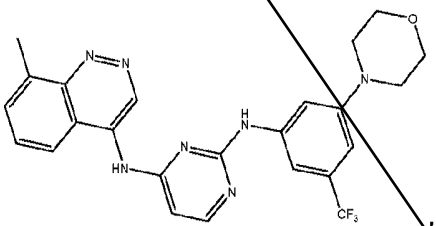
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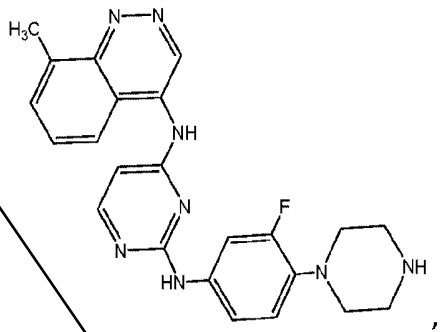
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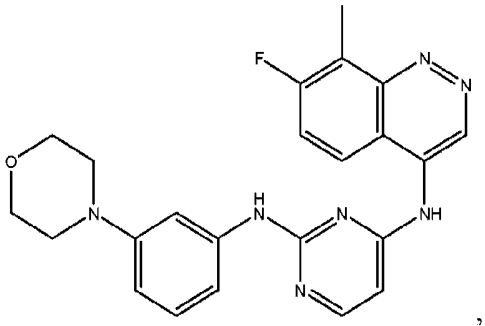
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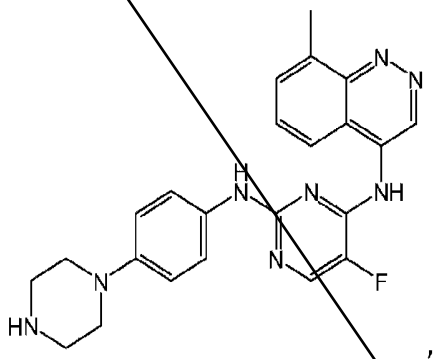
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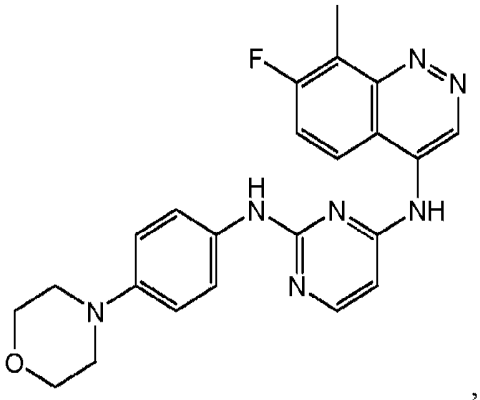
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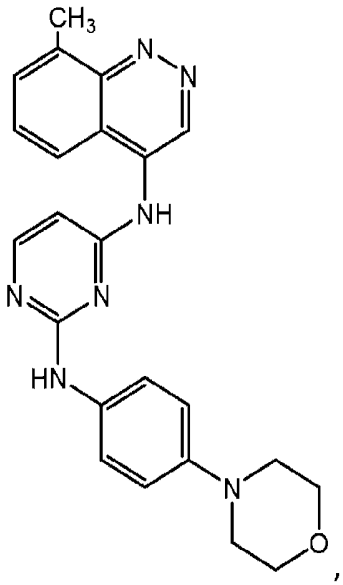
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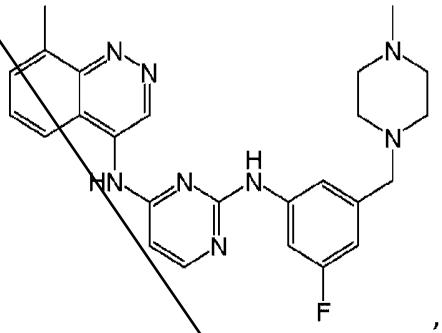
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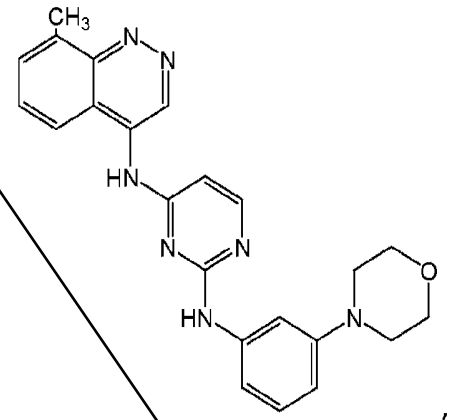
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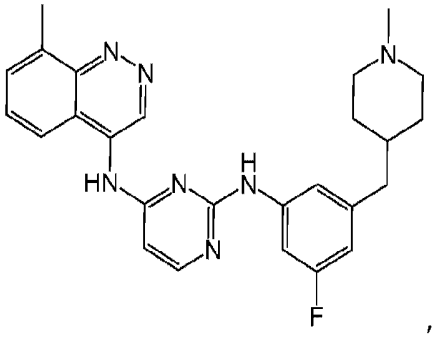
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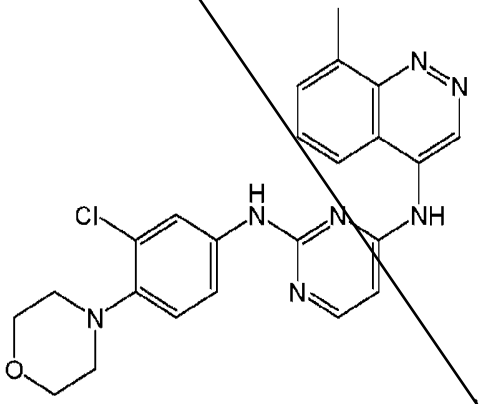
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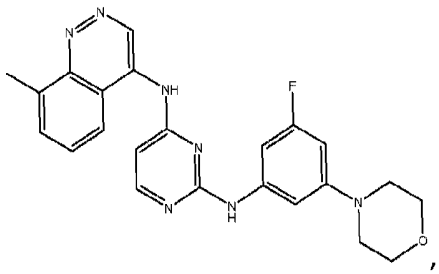
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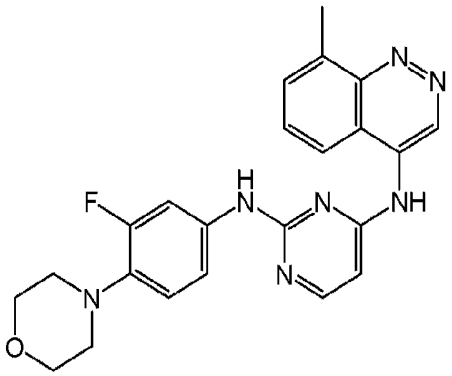
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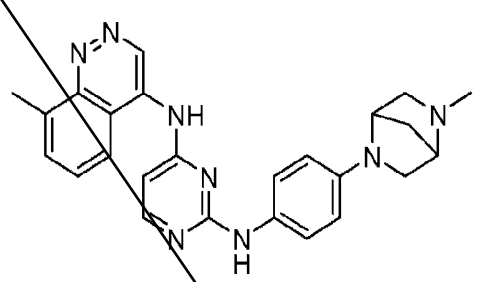
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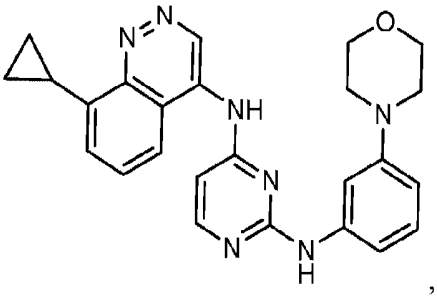
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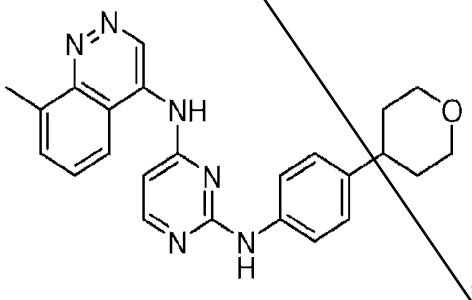
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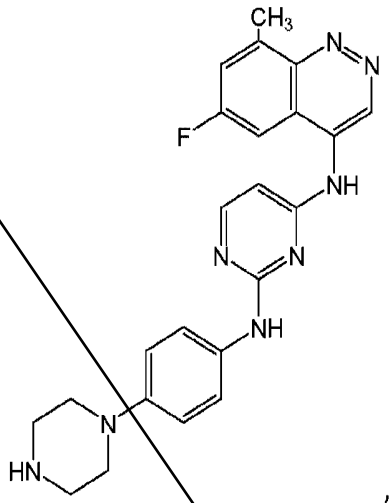
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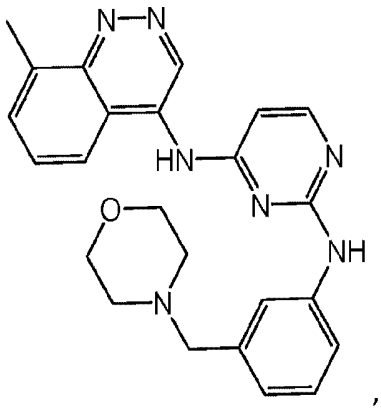


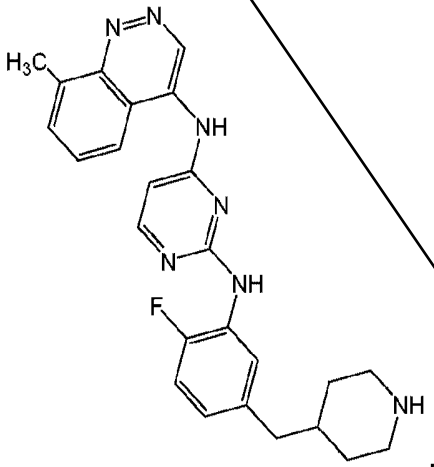
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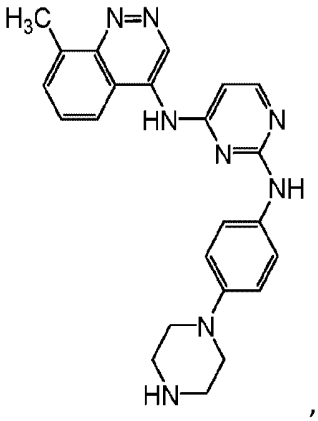


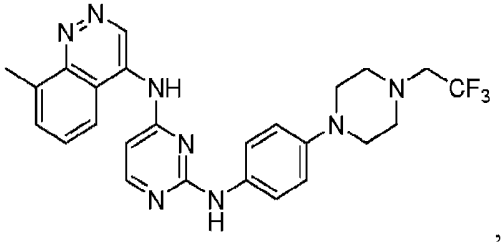
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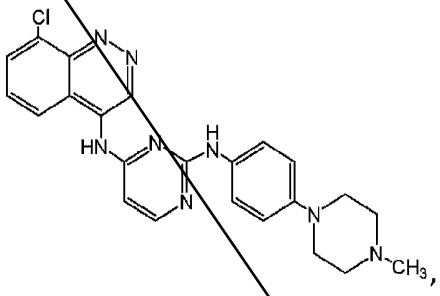


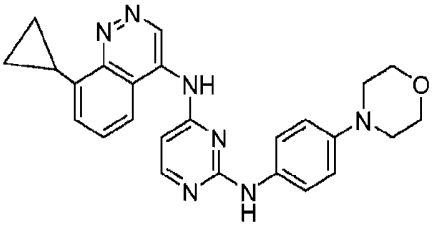


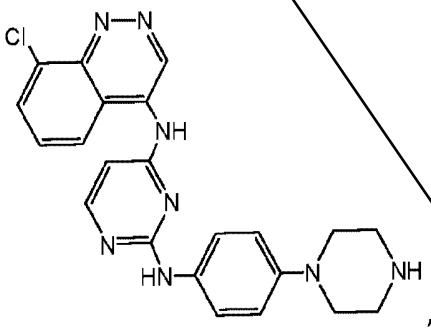


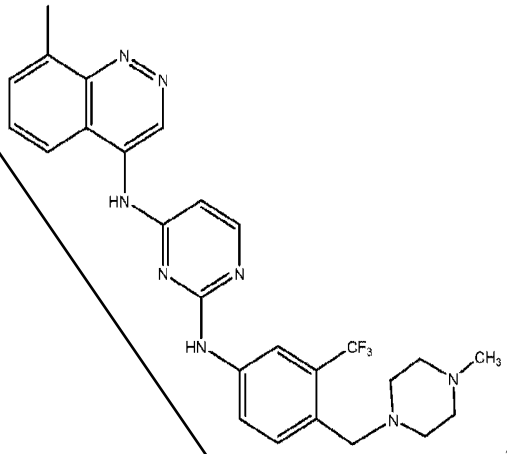




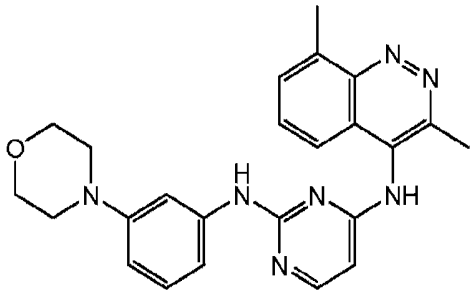




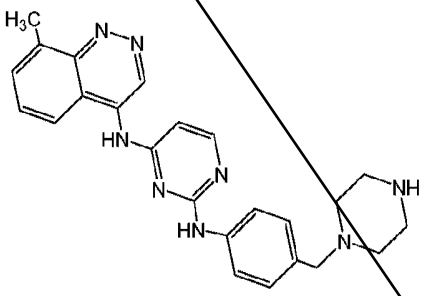




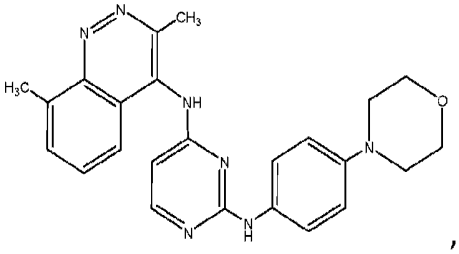
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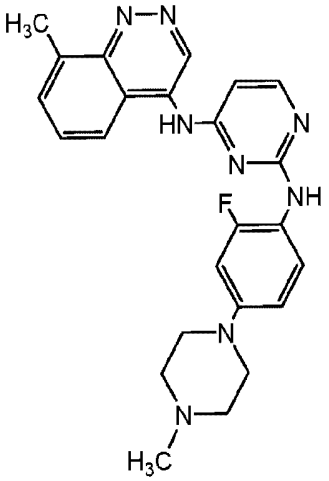
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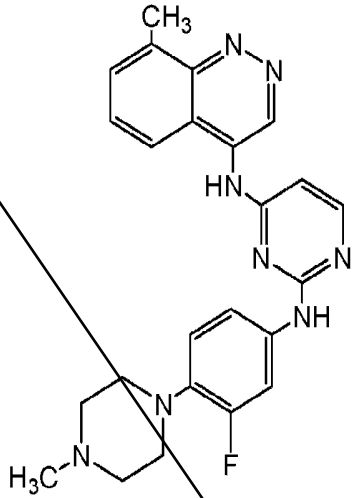
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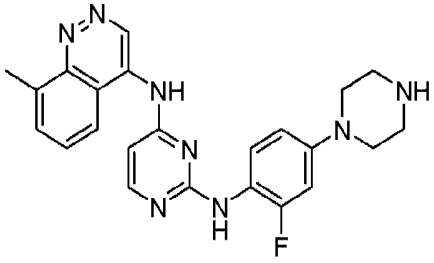
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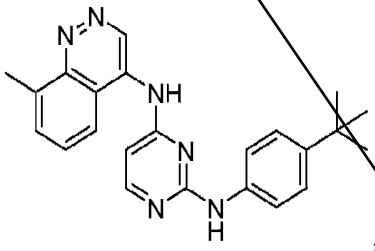
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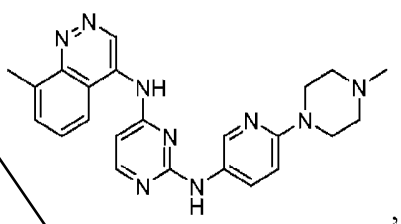
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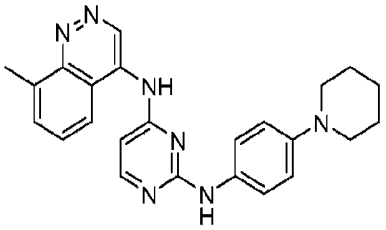
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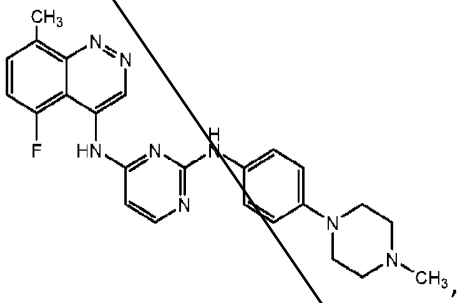
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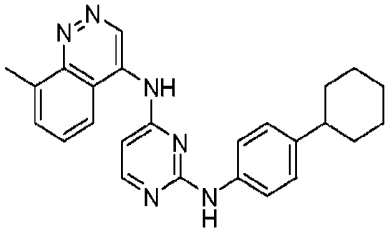
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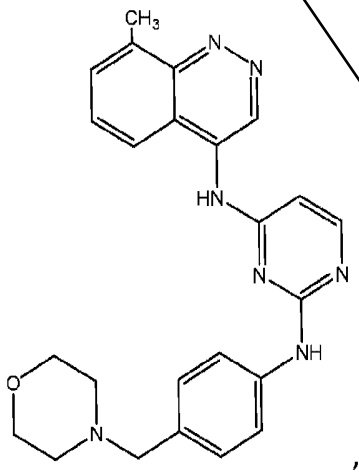
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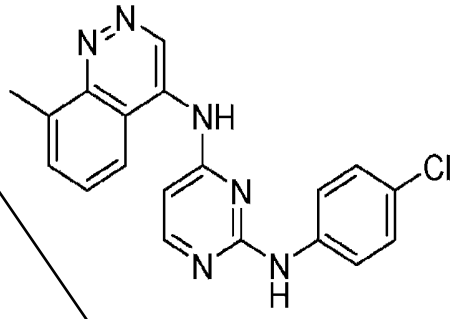
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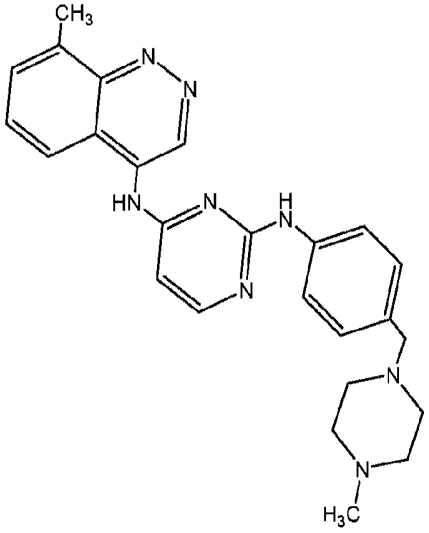
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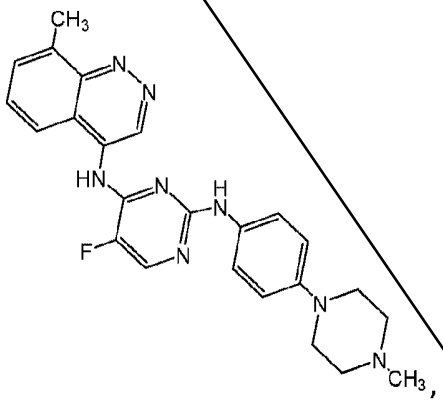
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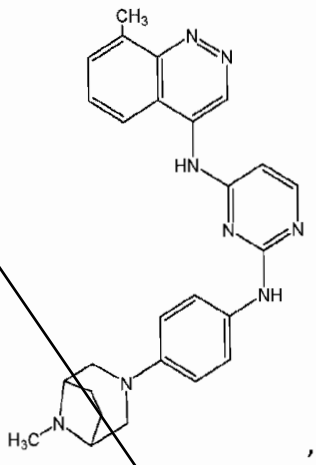
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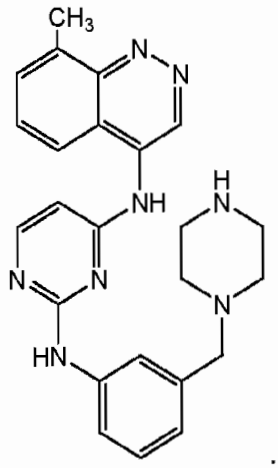
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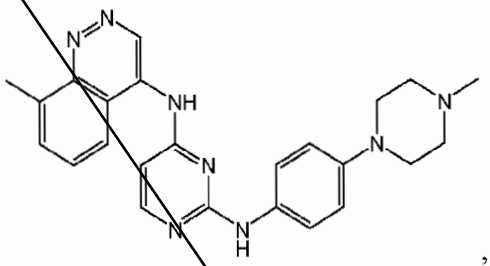


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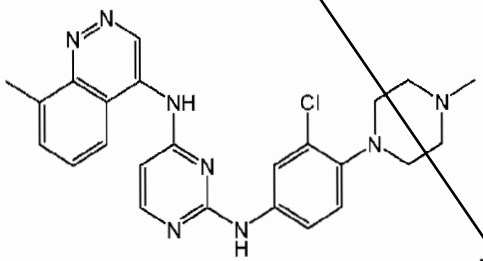
45. The compound of claim 44, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

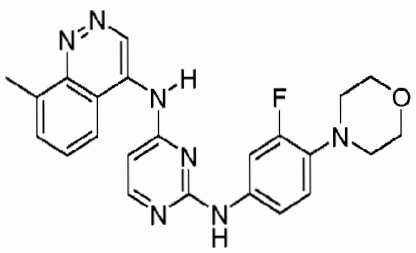
46. The compound of claim 44, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

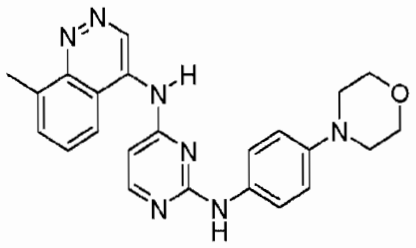
47. The compound of claim 44, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

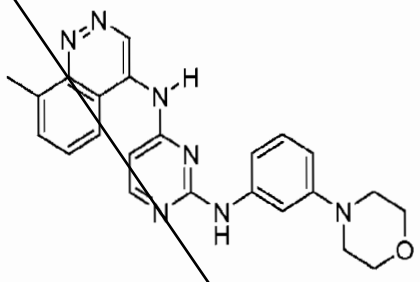
48. The compound of claim 44, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

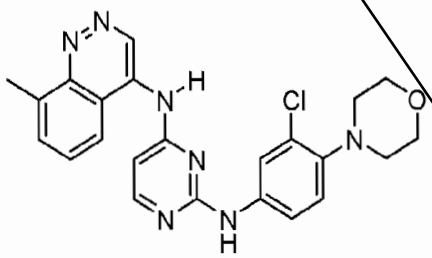
49. The compound of claim 44, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

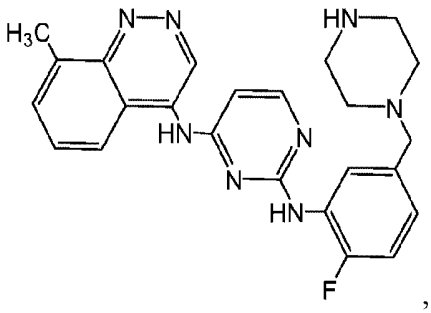
50. The compound of claim 44, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

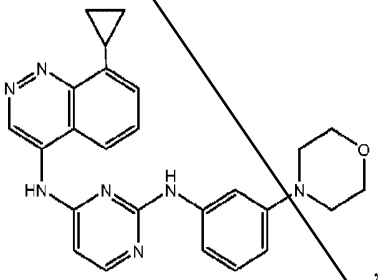
51. The compound of claim 44, wherein the compound is of the following formula:



,

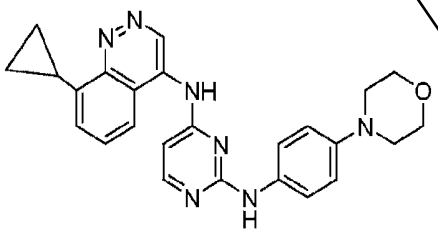
or a pharmaceutically acceptable salt thereof.

52. The compound of claim 44, wherein the compound is of the following formula:



, or a pharmaceutically acceptable salt thereof.

53. The compound of claim 44, wherein the compound is of the following formula:



, or a pharmaceutically acceptable salt thereof.

54. A pharmaceutical composition comprising a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

55. A pharmaceutical combination comprising a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54, and at least one additional therapeutic agent.

56. A method of treating a proliferative disease in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

57. The method of claim 56, wherein the proliferative disease is cancer.

58. The method of claim 57, wherein the cancer is a hematological cancer.

59. The method of claim 58, wherein the cancer is leukemia.

60. The method of claim 59, wherein the cancer is an acute leukemia.

61. The method of claim 60, wherein the acute leukemia is acute myeloid leukemia or acute lymphocytic leukemia.

62. The method of claim 59, wherein the cancer is a chronic leukemia.

63. The method of claim 62, wherein the chronic leukemia is chronic myeloid leukemia or chronic lymphocytic leukemia.

64. The method of claim 58, wherein the cancer is a lymphoma.

65. The method of claim 64, wherein the cancer is Hodgkin's lymphoma.

66. The method of claim 64, wherein the cancer is non-Hodgkin's lymphoma.

67. The method of claim 58, wherein the cancer is multiple myeloma.

68. The method of claim 57, wherein the cancer comprises a solid tumor.

69. The method of claim 57, wherein the cancer is: lung cancer, brain cancer, thyroid cancer, anaplastic astrocytoma, liver cancer, pancreatic cancer, skin cancer, melanoma, metastatic melanoma, colorectal cancer, breast cancer, prostate cancer, renal cancer, hepatocellular cancer, ovarian cancer, an HPV-associated cancer, multiple myeloma, myelodysplastic syndrome, a hematological cancer, or myelofibrosis.

70. The method of claim 57, 68 or 69, wherein the cancer is non-small cell lung cancer (NSCLC).

71. The method of claim 57, 68 or 69, wherein the cancer is neuroblastoma or glioblastoma.

72. The method of claim 57, 68 or 69, wherein the cancer is anaplastic thyroid cancer (ATC).

73. The method of claim 57, 68 or 69, wherein the cancer is colon carcinoma.

74. The method of claim 57, 68 or 69, wherein the cancer is hepatocellular carcinoma (HCC).

75. The method of claim 57, 68 or 69, wherein the cancer is pancreatic carcinoma.

76. The method of claim 57, 68 or 69, wherein the cancer is anaplastic large cell lymphoma (ALCL) or myelodysplastic syndrome.

77. The method of claim 57, 68 or 69, wherein the cancer is anaplastic astrocytoma.

78. The method of claim 57, 68 or 69, wherein the cancer is pancreatic ductal adenocarcinoma.

79. The method of claim 57 or 68, wherein the cancer is gastric cancer, breast cancer, ovarian cancer, pancreatic cancer, or mesothelioma.

80. The method of claim 57 or 68, wherein the cancer is ovarian cancer.

81. The method of claim 80, wherein the ovarian cancer is an adult granulosa cell tumor.

82. The method of claim 57, 68 or 69, wherein the cancer is an HPV-associated cancer selected from cervical cancer, oropharyngeal cancer, anal cancer, vulvar/vaginal cancer, or penile cancer.

83. A method of treating a fibrotic disease, disorder, or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

84. The method of claim 83, wherein the fibrotic disease, disorder, or condition is lung fibrosis, liver fibrosis, cardiac disease, cardiac fibrosis or restenosis, vascular fibrosis, kidney fibrosis, skin fibrosis, gastrointestinal fibrosis, bone marrow fibrosis, athrofibrosis, Dupuytren's contracture, mediastinal fibrosis, Peyronie's disease, retroperitoneal fibrosis, systemic sclerosis, autoimmune hepatitis, nonalcoholic steatohepatitis, cystic fibrosis, beta-thalassemia, actinic keratosis, hypertension, chronic kidney disease, Chagas' heart disease, dry eye, ulcer, corneal fibrosis, wet age-related macular degeneration, chronic wound, or psoriasis.

85. A method of inhibiting tumor growth in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of any

one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

86. A method of inhibiting ALK-5 activity *in vivo* or *in vitro*, the method comprising contacting ALK-5 with a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

87. The method of claim 86, wherein the inhibiting occurs *in vivo* in a subject.

88. The method of claim 86, wherein the inhibiting occurs *in vitro*.

89. A method of treating an inflammatory disease, disorder, or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

90. The method of claim 89, wherein the inflammatory disease, disorder, or condition is non-alcoholic fatty liver disease (NAFLD), alcoholic steatohepatitis (ASH), non-alcoholic steatohepatitis (NASH), primary biliary cholangitis (PBC), primary sclerosing cholangitis, autoimmune hepatitis, skin inflammation, or psoriasis.

91. The method of claim 89 or 90, wherein the inflammatory disease, disorder, or condition is an autoimmune disease, disorder, or condition.

92. The method of claim 91, wherein the autoimmune disease, disorder, or condition is osteoarthritis, rheumatoid arthritis, pain, inflammatory bowel disease, a respiratory disorder, or a skin disorder.

93. A method of treating cachexia in a subject, the method comprising administering to the subject an effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

94. A method for promoting immune infiltration in a tumor-immune microenviroment in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

95. A method for inhibiting epithelial-to-mesenchymal transition in a tumor in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

96. A method for modulating the tumor-immune microenviroment in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

97. A method for increasing tumor vasculature or blood flow to a tumor or both in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

98. A method for inhibiting metastasis of a cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

99. A method of treating a fibrotic, inflammatory or proliferative disease or condition which is susceptible to inhibition of the TGFβ signaling pathway, the method comprising administering to a subject suffering from said fibrotic, inflammatory or proliferative disease or condition a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54, in an amount effective to inhibit TGFβ signaling.

100. The method of any one of claims 56-87 and 89-99, wherein the subject is a human.

101. The method of any one of claims 56-84, 89-92, and 96-100, wherein the cancer, fibrotic disease, disorder or condition, inflammatory disease, disorder or condition, or proliferative disease, disorder or condition is driven by TGF-β signaling, or utilizes the TGF-β signaling pathway for disease progression.

102. The method of any one of claims 56-84, 89-92, and 96-101, wherein the cancer, fibrotic disease, disorder or condition, inflammatory disease, disorder or condition, or proliferative disease, disorder or condition expresses or has mutant forkhead box L2 (FOXL2) or *FOXL2*.

103. The method of any one of claims 56-84, 89-92, and 96-102, wherein the cancer, fibrotic disease, disorder or condition, inflammatory disease, disorder or condition, or proliferative disease, disorder or condition is associated with an elevated level of phosphorylated SMAD 2 (pSMAD2) or alpha smooth muscle actin (α-SMA).

104. The method of any one of claims 57-82, 96, and 99-103, wherein the cancer exhibits an excluded or desert phenotype.

105. The method of any one of claims 56-87 and 89-103, further comprising administering one or more additional therapeutic agents to the subject.

106. The method of claim 105, wherein at least one of the additional therapeutic agents is an anti-cancer agent.

107. The method of claim 106, wherein at least one of the additional therapeutic agents is taxol or abraxane, or a pharmaceutically acceptable salt thereof.

108. The method of any one of claims 105-107, wherein at least one of the additional therapeutic agents is an immune checkpoint inhibitor.

109. The method of any one of claims 105-108, wherein at least one of the additional therapeutic agents is a PD-1 or PD-L1 inhibitor.

110. The method of any one of claims 56-87 and 89-109, further comprising treating the subject with radiation therapy or surgery.

111. A method for enhancing the activity of one or more therapeutic agents for treating cancer in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-53, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 54.

112. The method of claim 111, further comprising administering the one or more therapeutic agents to the subject.

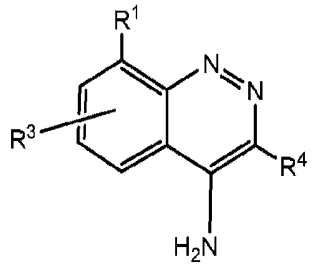
113. The method of claim 111 or 112, wherein at least one of the therapeutic agents is an anti-cancer agent.

114. The method of any one of claims 111-113, wherein at least one of the therapeutic agents is taxol or abraxane, or a pharmaceutically acceptable salt thereof.

115. The method of any one of claims 111-114, wherein at least one of the therapeutic agents is an immune checkpoint inhibitor.

116. The method of any one of claims 111-115, wherein at least one of the additional therapeutic agents is a PD-1 or PD-L1 inhibitor.

117. A compound of Formula Int-A5:



Int-A5,

or a salt thereof, wherein:

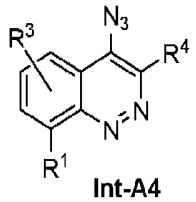
R^1 is a C_1-C_5 alkyl or C_3-C_5 carbocycle, or a halogen;

R^3 is -H, -F, or -Cl; and

R^4 is -H, a halogen, or a C_1-C_3 alkyl or cyclopropyl, optionally substituted with one or more -F.

118. A process for preparing the compound of claim 117 or a salt thereof, comprising:

(a) providing a compound of Formula IntA-4:



Int-A4, and reducing the azide functional group to an amino functional group using a palladium-catalyzed reduction,

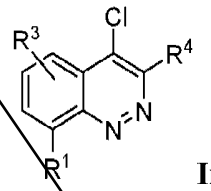
wherein:

R^1 is a C_1-C_5 alkyl or C_3-C_5 carbocycle, or a halogen;

R^3 is -H, -F, or -Cl; and

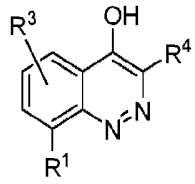
R^4 is -H, a halogen, or a C_1-C_3 alkyl or C_3 carbocycle optionally substituted with one or more -F.

119. The process of claim 118, further comprising preparing the compound of Formula Int-A4 by treating the compound of Formula Int-A3:



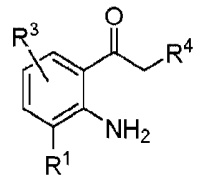
Int-A3, with sodium azide, wherein R^1, R^3 and R^4 are as defined for the compound of Formula Int-A4.

120. The process of claim 119, further comprising preparing the compound of Formula Int-A3 by treating the compound of Formula Int-A2:



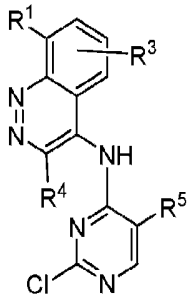
Int-A2, with phosphorousoxytrichloride, wherein R^1, R^3 and R^4 are as defined for the compound of Formula Int-A4.

121. The process of claim 120, further comprising preparing the compound Int-A2 by treating the compound of Formula Int-A1:



Int-A1, or a salt thereof, with sodium nitrite in an acid solution, wherein R^1, R^3 and R^4 are as defined for the compound of Formula Int-A4.

122. A compound of Formula Int-B2:



Int-B2,

or a salt thereof, wherein:

R^1 is a C_1-C_5 alkyl or C_3-C_5 carbocycle, or a halogen;

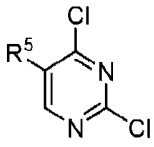
R^3 is -H, -F, or -Cl;

R^4 is -H, a halogen, or a C_1-C_3 alkyl or cyclopropyl, optionally substituted with one or more -F; and

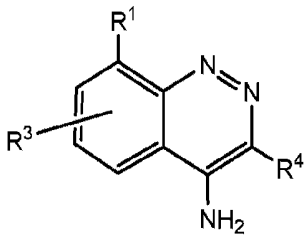
R^5 is -H, -F, or a C_1-C_3 alkyl or cyclopropyl, optionally substituted with one or more -F.

123. A process for preparing the compound of claim 122, or a salt thereof, comprising:

(a) providing a compound of Formula IntB-1:



Int-B1, and reacting it with a compound of Formula Int-A5:



Int-A5, in the presence of a palladium coupling catalyst,

wherein:

R^1 is a C_1-C_5 alkyl or C_3-C_5 carbocycle, or a halogen;

R^3 is -H, -F, or -Cl;

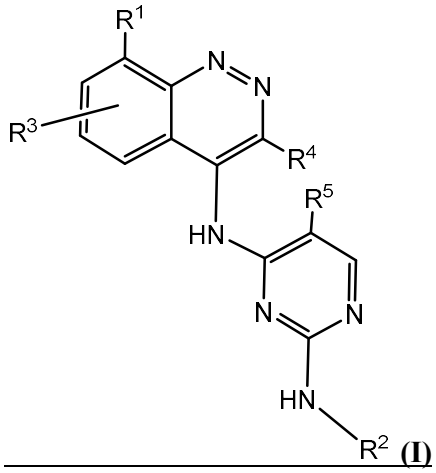
R^4 is -H, a halogen, or a C_1-C_3 alkyl or cyclopropyl, optionally substituted with one or more -F; and

R^5 is -H, -F, or a C_1-C_3 alkyl or cyclopropyl, optionally substituted with one or more -F.

CLAIMS

What is claimed is:

1. A compound of Formula (**I**):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is a C_1-C_5 alkyl, C_3-C_5 carbocycle, or a halogen;

R^2 is an aryl of at least 6 carbon atoms or nitrogen-containing heteroaryl of at least 6 atoms, optionally substituted with one or more of:

(i) one or more halogens;

(ii) a C_1-C_6 alkyl optionally substituted with a hydroxyl or one or more halogen wherein, when selected to be an alkyl larger than C_3, the alkyl is present at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2;

(iii) a sulfonamide;

(iv) a monocylic, bicyclic, or spirocyclic carbocycle which is optionally substituted with a hydroxyl, one or more halogen, or one or more linear, branched, or cyclic alkyl moieties of up to 6 carbon atoms which are optionally substituted with hydroxy or one or more halogen, wherein said carbocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present and selected to be a carbocycle larger than cyclopropyl, the carbocycle is at a position on the aryl

or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2; or

(v) a monocyclic, bicyclic or spirocyclic heterocycle which may contain up to 3 heteroatoms which are selected independently from N and O, and which is optionally and independently substituted with one or more C_1-C_6 alkyl or C_3-C_6 carbocycle which are optionally substituted with hydroxy or one or more halogen, wherein said heterocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present, said heterocycle is at a position on the aryl of R^2 which is meta- or para- to the amino bond to said aryl;

R^3 is -H, -F or -Cl;

R^4 is -H or a halogen, or a C_1-C_3 alkyl or cyclopropyl optionally substituted with one or more -F; and

R^5 is -H or -F, or a C_1-C_3 alkyl or cyclopropyl optionally substituted with one or more -F.

2. The compound of claim 1, wherein R^1 is a C_1-C_5 alkyl or C_3-C_5 carbocycle.

3. The compound of claim 1 or claim 2, wherein R^1 is -CH_3, cyclopropyl, -Cl or -F.

4. The compound of any one of claims 1-3, wherein R^2 is a phenyl or pyridinyl optionally substituted with one or more of:

(i) one or more halogens;

(ii) a C_1-C_6 alkyl optionally substituted with a hydroxyl or one or more halogen wherein, when selected to be an alkyl larger than C_3, the alkyl is present at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2;

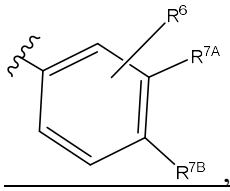
(iii) a sulfonamide;

(iv) a monocylic, bicyclic, or spirocyclic carbocycle which is optionally substituted with a hydroxyl, one or more halogen, or one or more linear, branched, or cyclic alkyl moieties of up to 6 carbon atoms which are optionally substituted with hydroxy or one or more halogen, wherein said carbocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when

present and selected to be a carbocycle larger than cyclopropyl, the carbocycle is at a position on the aryl or heteroaryl of R^2 which is meta- or para- to the amino bond to the aryl or heteroaryl of R^2; or

(v) a monocyclic, bicyclic or spirocyclic heterocycle which may contain up to 3 heteroatoms which are selected independently from N and O, and which is optionally and independently substituted with one or more C_1-C_6 alkyl or C_3-C_6 carbocycle which are optionally substituted with hydroxy or one or more halogen, wherein said heterocycle is attached to the aryl or heteroaryl of R^2 by a single bond or a methylene or ethylene linker and wherein, when present, said heterocycle is at a position on the aryl of R^2 which is meta- or para- to the amino bond to said aryl.

5. The compound of any one of claims 1-3, wherein R^2 is:



, wherein:

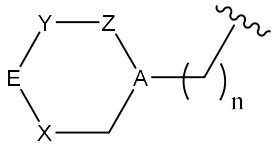
R^6 is -H, -F, -Cl, or a C_1-C_3 alkyl or cyclopropyl which is optionally and independently substituted with one or more halogen;

one of R^{7A} and R^{7B} is -H, and the other is:

(i) a halogen;

(ii) $-SO_2NR^{7F}{}_2$, wherein each R^{7F} is independently -H or a linear or branched alkyl of up to 4 carbon atoms;

(iii) a C_1-C_6 alkyl which is optionally substituted with one or more halogen; or

(iv) 

, wherein:

A is N- or C(H);

E is O, N(R^8), or C(H)(R^{13});

R^8 is -H or a C_1-C_6 alkyl or C_3-C_6 carbocycle which is optionally substituted with hydroxyl or one or more halogen;

R^{13} is -H or a C_1-C_6 alkyl or C_3-C_6 carbocycle which is optionally substituted with hydroxy or one or more halogen; and

n is 0, 1, or 2, and

when E is N(R^8), X, Y, and Z are defined as follows:

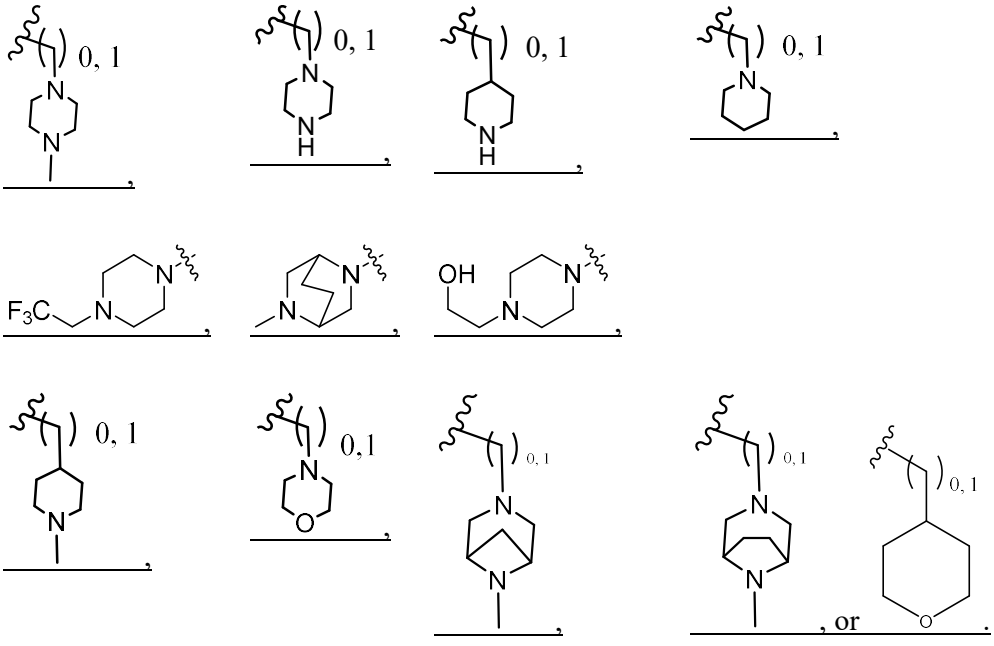
Z is $C(H)_2$ and X and Y are independently $C(H)_2$ or $C(CH_3)_2$, or both X and Y are C(H) and are bonded together through a methylene or ethylene bridge; or

Y is $C(H)_2$ or $C(CH_3)_2$, and X and Z are both C(H) and are bonded together through a methylene or ethylene bridge, and

when E is O or C(H)(R^{13}), X, Y, and Z are $C(H)_2$.

6. The compound of claim 5, wherein R^6 is -H, -F, -Cl, -CH_3, or -CF_3.

7. The compound of claim 5 or claim 6, wherein one of R^{7A} and R^{7B} is -H, and the other is:



8. The compound of any one of claims 1-7, wherein R^3 is -H.

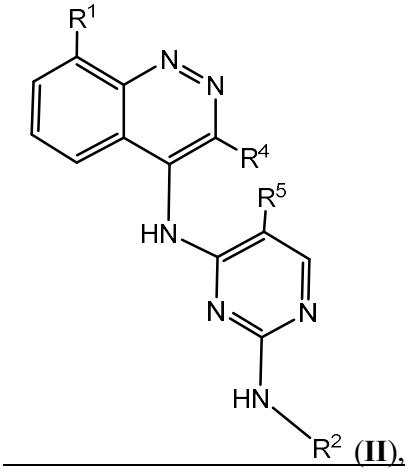
9. The compound of any one of claims 1-8, wherein R^4 is -CF_3, -CH_3, –H, –Cl, or -F.

10. The compound of claim 6, wherein R^4 is –H.

11. The compound of any one of claims 1-10, wherein R^5 is –H, $-CH_3$, $-CF_3$, or -F.

12. The compound of claim 11, wherein R^5 is –H.

13. The compound of claim 1 of Formula (**II**):

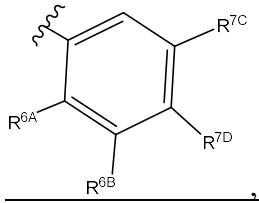


(**II**),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-CH_3$ or -Cl;

R^2 is:

a) , wherein:

one of R^{6A} and R^{6B} is -H, and the other is -H, -F, -Cl, $-CH_3$, or CF_3;

one of R^{7C} and R^{7D} is -H, and the other is:

(i) -F;

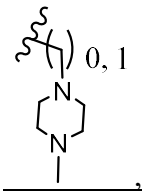
(ii) -Cl;

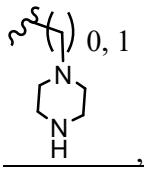
(iii) $-SO_2NH_2$;

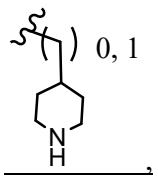
(iv) cyclohexyl;

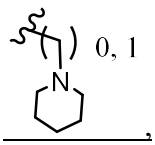
(v) t-butyl; or

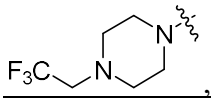
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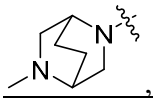
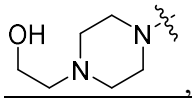


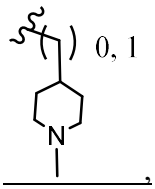
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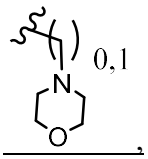
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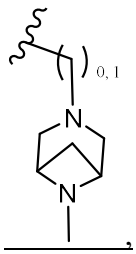
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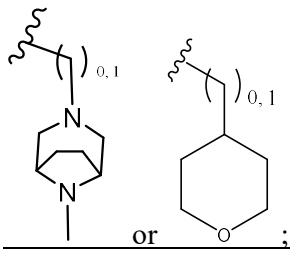
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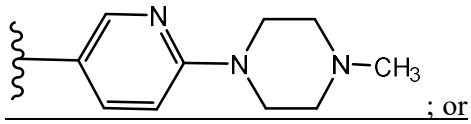
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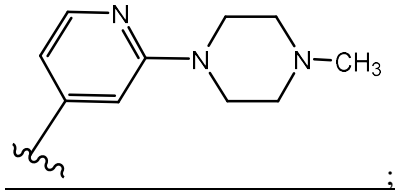
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or ;

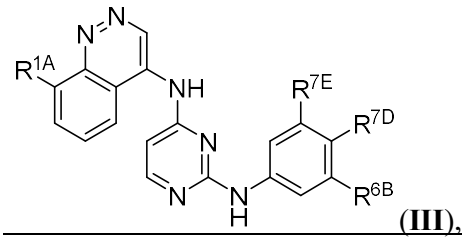
b) 
; or

c) 
;

R^4 is -H or -CH_3; and

R^5 is -H or -F.

14. The compound of claim 1 of Formula (**III**):

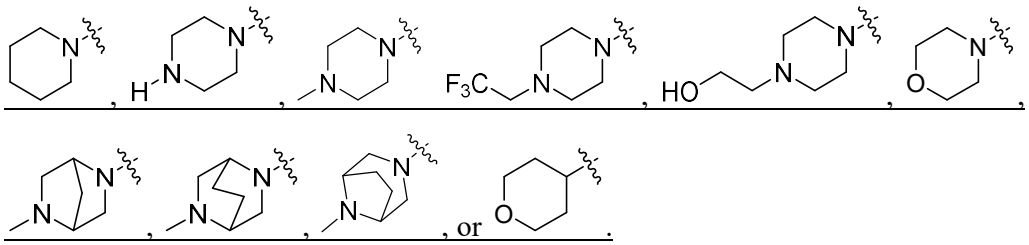

(**III**),

or a pharmaceutically acceptable salt thereof, wherein:

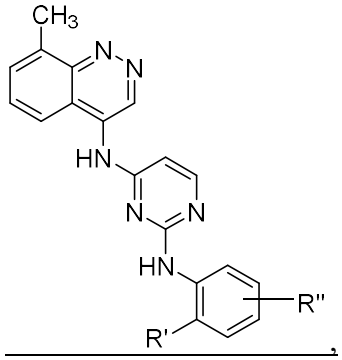
R^{1A} is methyl or cyclopropyl;

R^{6B} is -H, -F, or -Cl; and

one of R^{7D} and R^{7E} is -H, and the other is a heterocycle of the formula:

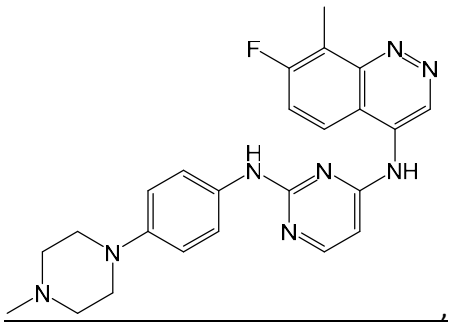


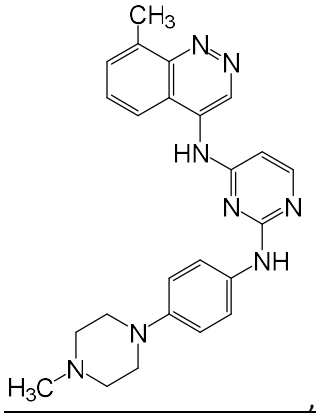
15. The compound of claim 1 having the following structure:

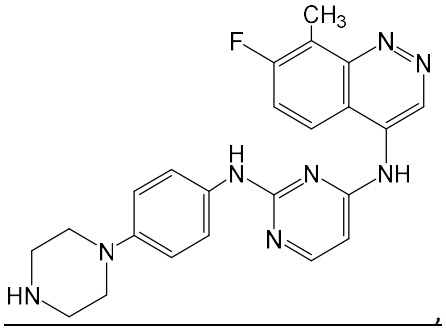


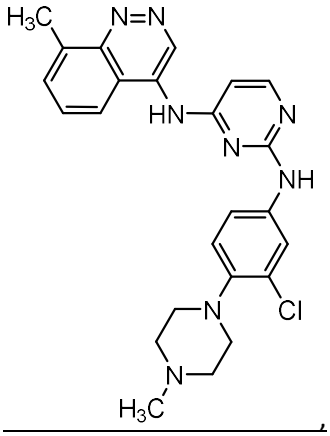
or a pharmaceutically acceptable salt thereof, wherein R' is H or F; and R" is at a position meta or para to the amino bond, and is morpholino or piperazinyl optionally *N*-substituted with $-CH_3$, $-CH_2CF_3$, or $-CH_2CH_2OH$.

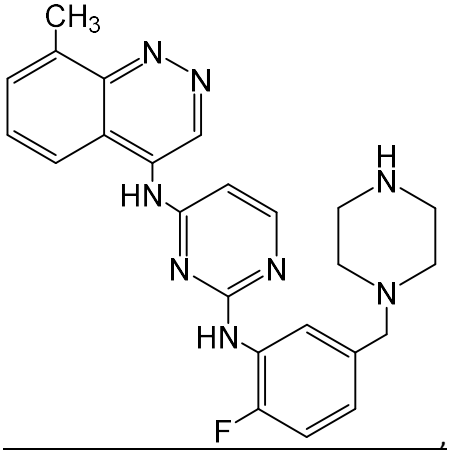
16. A compound, or a pharmaceutically acceptable salt thereof, selected from:

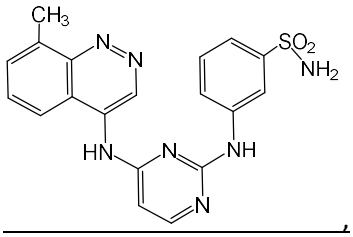


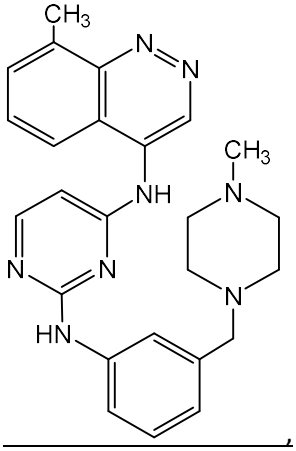


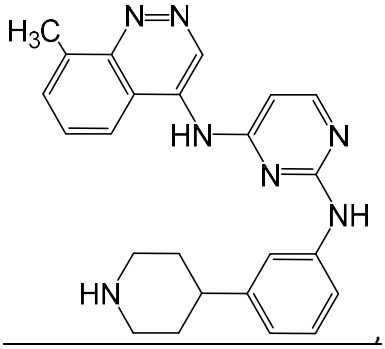


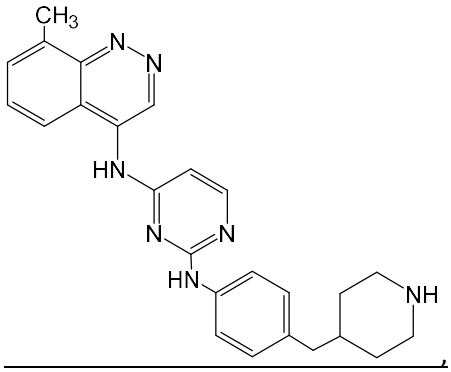


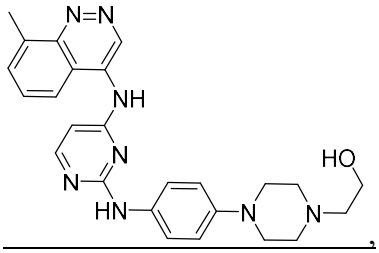


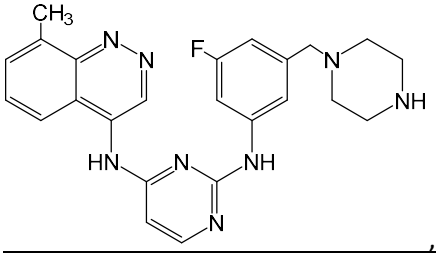


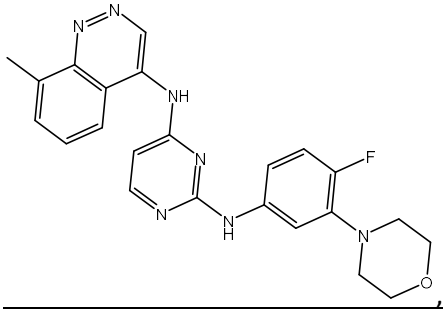


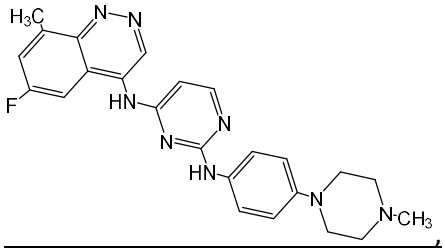


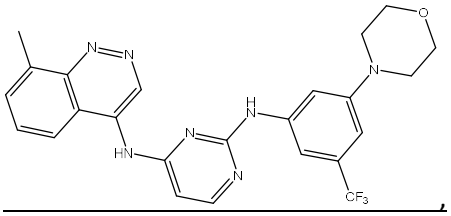


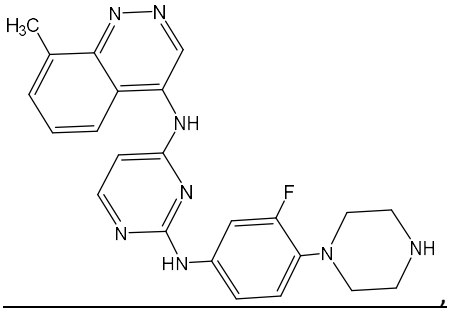


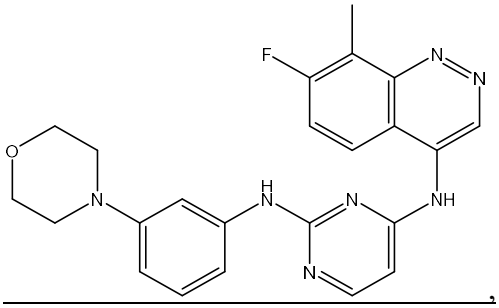


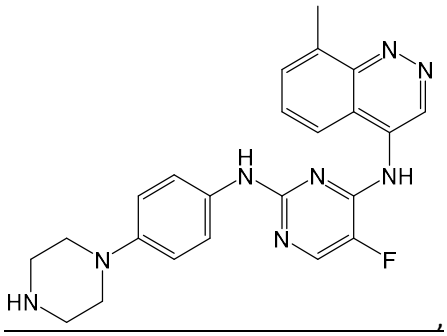


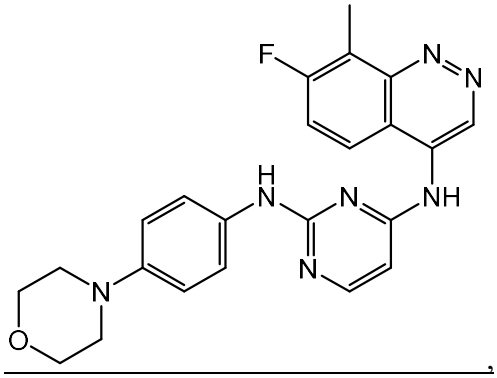


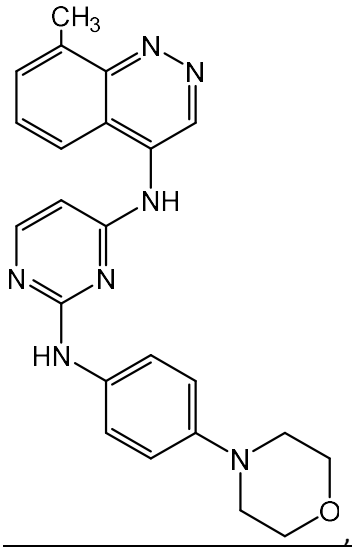


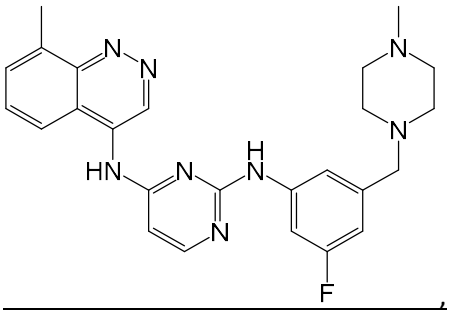


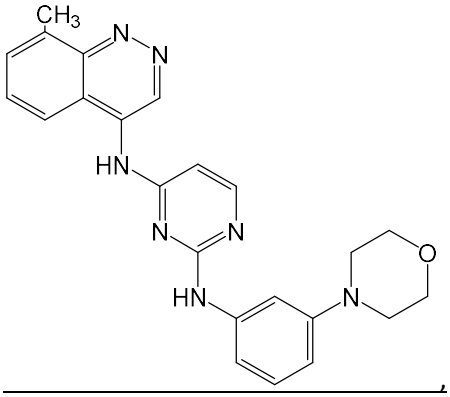


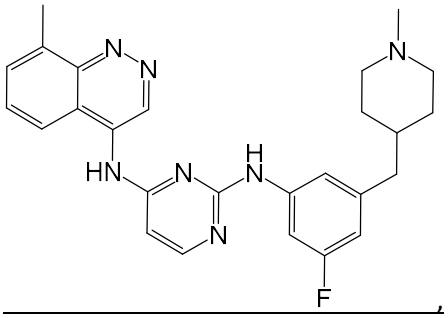


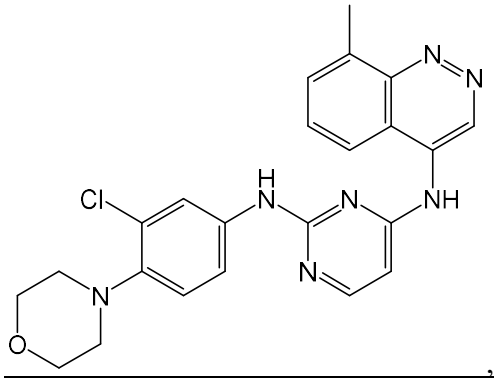


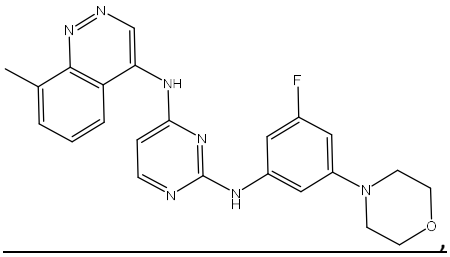


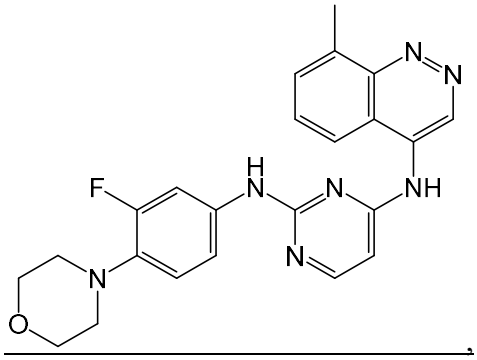


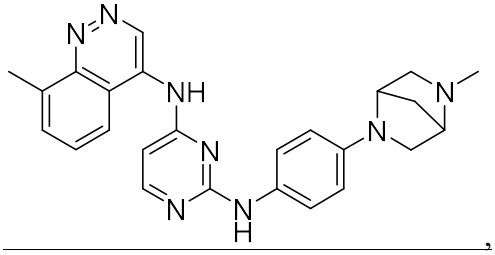


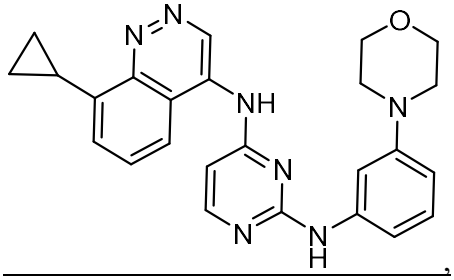


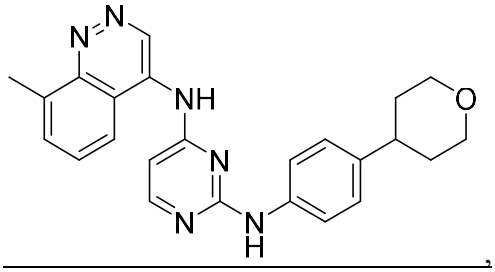


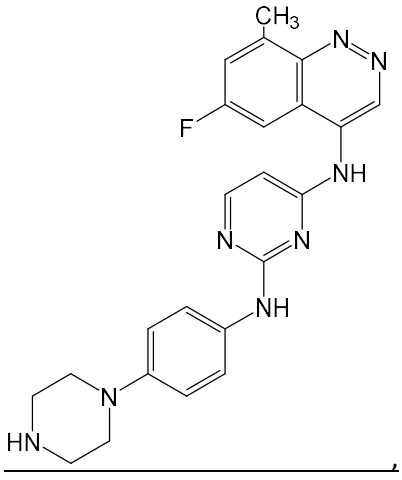


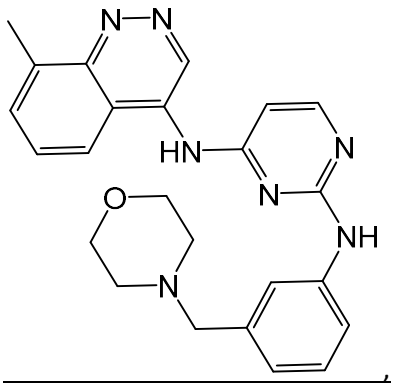


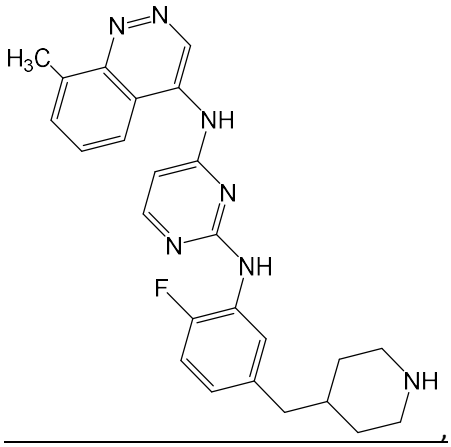


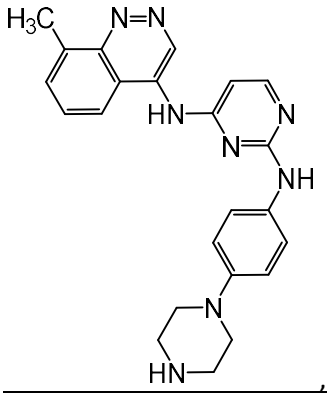


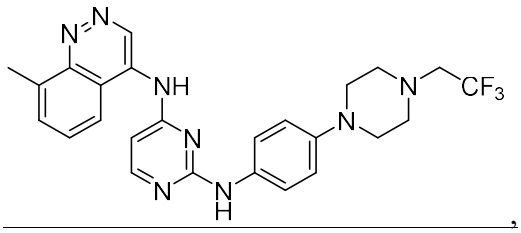


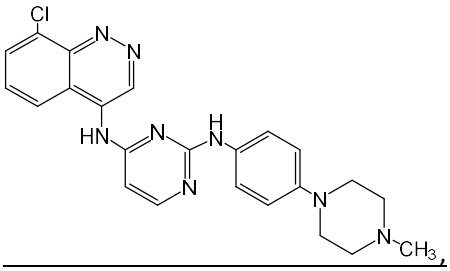


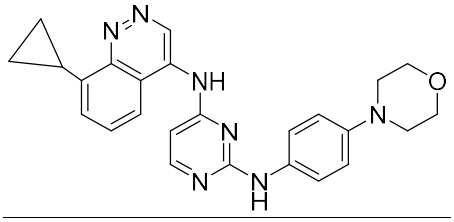


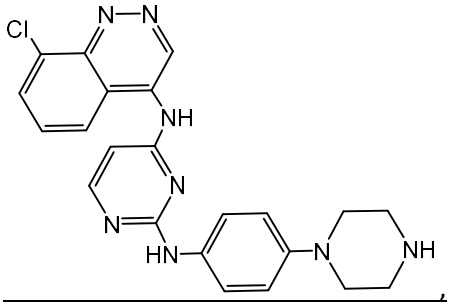


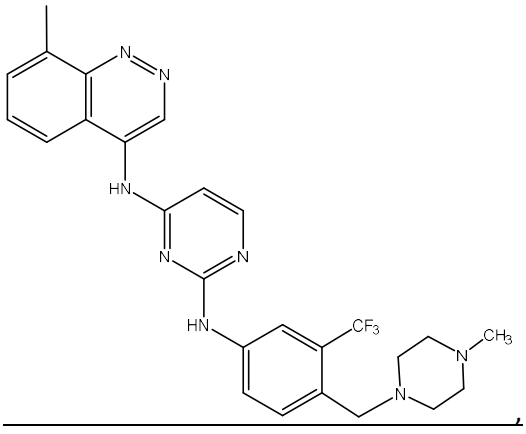


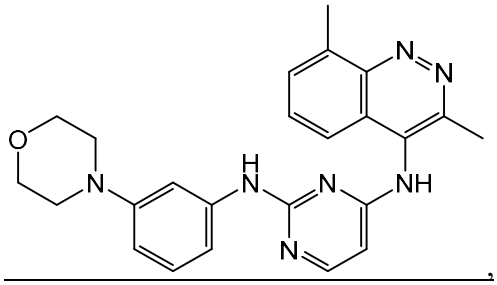


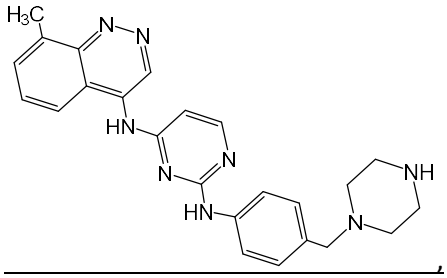


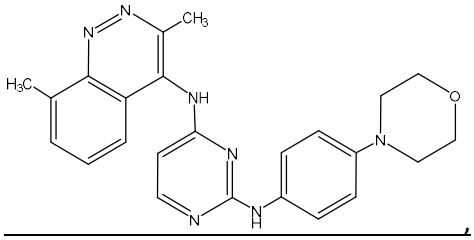


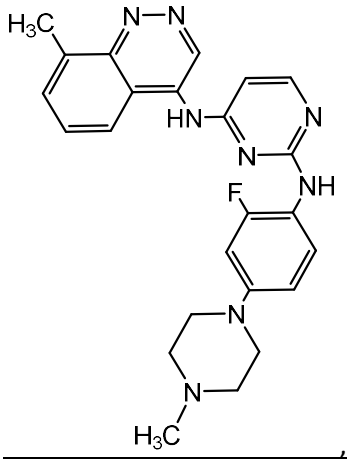


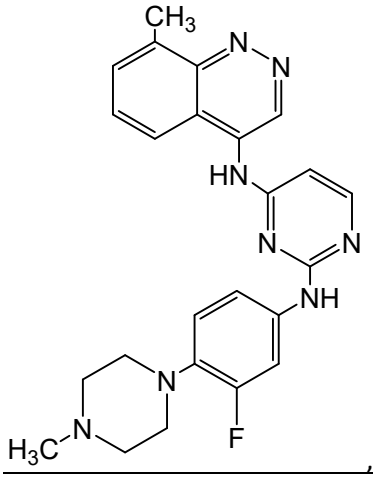


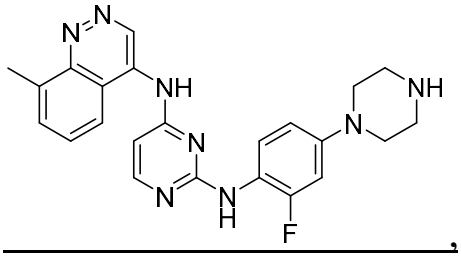


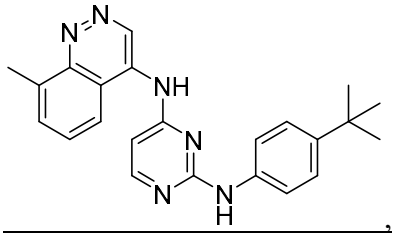


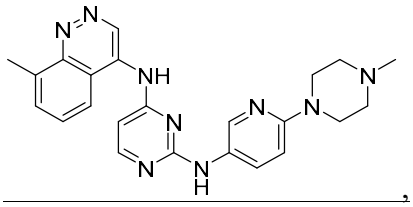


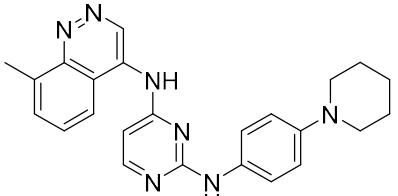


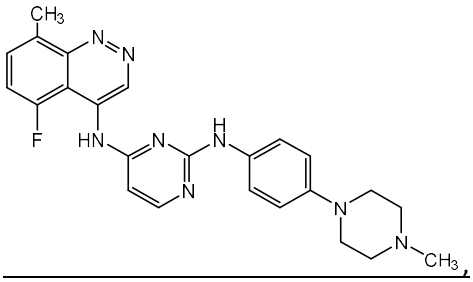


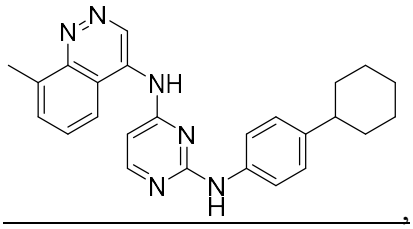


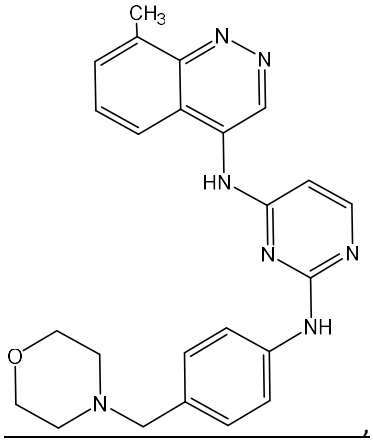


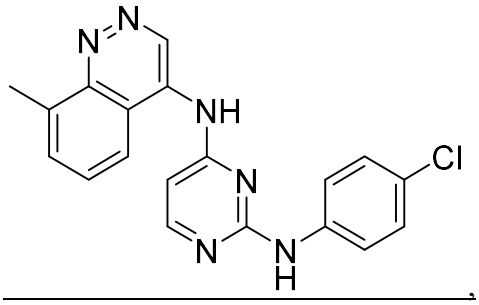


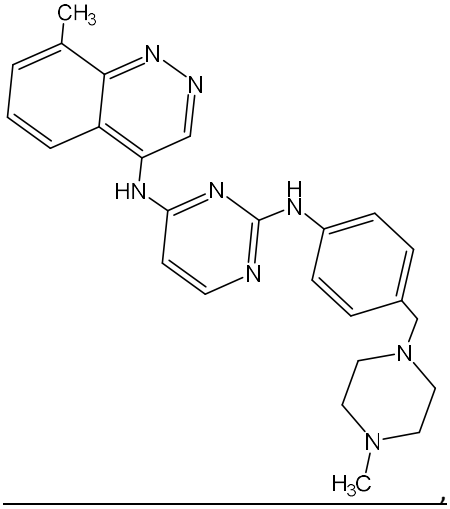


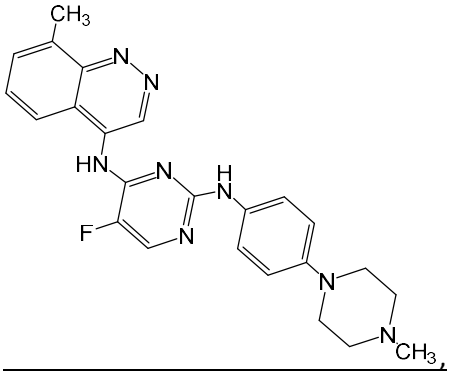


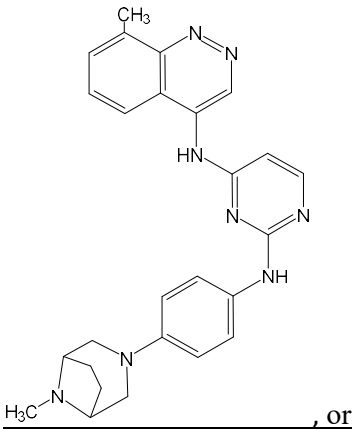




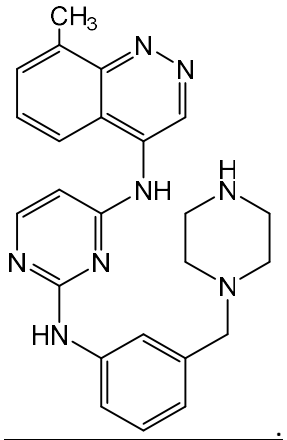






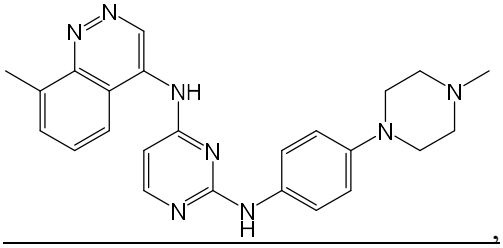


, or



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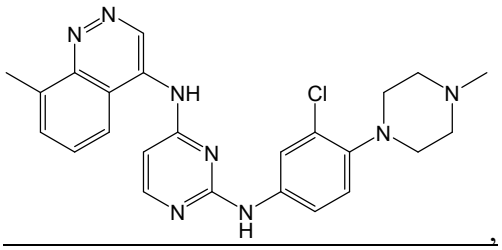
17. The compound of claim 16, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

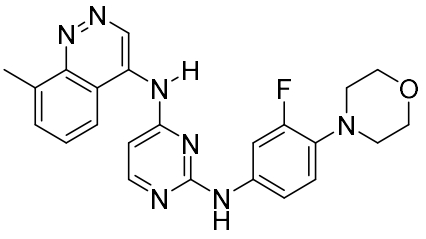
18. The compound of claim 16, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

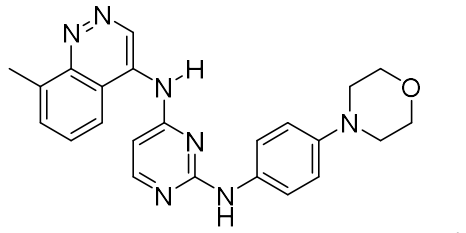
19. The compound of claim 16, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

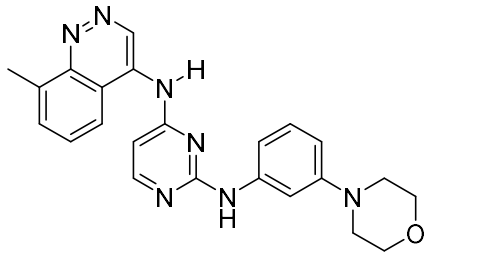
20. The compound of claim 16, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

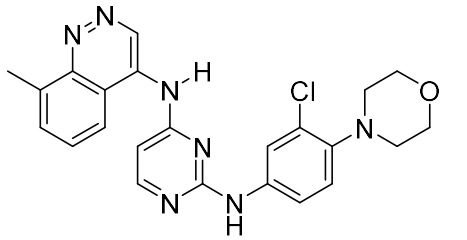
21. The compound of claim 16, wherein the compound is of the following formula:



,

or a pharmaceutically acceptable salt thereof.

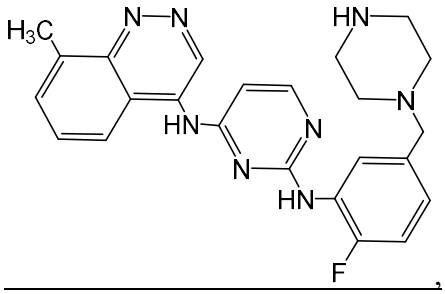
22. The compound of claim 16, wherein the compound is of the following formula:



,

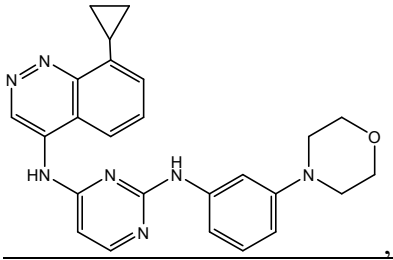
or a pharmaceutically acceptable salt thereof.

23. The compound of claim 16, wherein the compound is of the following formula:



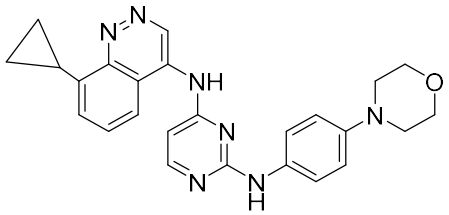
or a pharmaceutically acceptable salt thereof.

24. The compound of claim 16, wherein the compound is of the following formula:



, or a pharmaceutically acceptable salt thereof.

25. The compound of claim 16, wherein the compound is of the following formula:



, or a pharmaceutically acceptable salt thereof.

26. A pharmaceutical composition comprising a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

27. Use of a compound of any one of claims 1-25 in the manufacture of a medicament for inhibiting ALK-5 activity *in vivo* or *in vitro*.