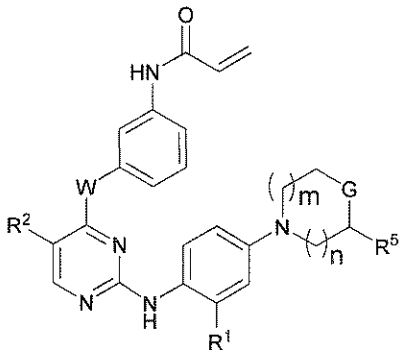
resistant patients. Moreover, T790M may also be pre-existing, there may be an independent, oncogenic role for the T790M mutation. For example, there are patients with the L858R/T790M mutation who never received gefitinib treatment. In addition, germline EGFR T790M mutations are linked with certain familial lung cancers.

[0007] Current drugs in development, including second generation covalent inhibitors, such as BIBW2992, HKI-272 and PF-0299804, are effective against the T790M resistance mutation but exhibit dose-limiting toxicities due to concurrent inhibition of WT EGFR. Accordingly, there remains a need to find mutant-selective EGFR kinase inhibitors useful as therapeutic agents.

SUMMARY ~~OF THE INVENTION~~

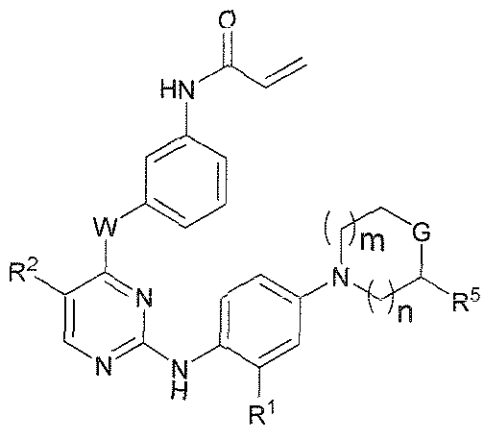
[0008] It has now been found that compounds of ~~this invention~~the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as mutant-selective EGFR kinase inhibitors. Such compounds have general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each of n, m, W, G, R^1 R^2, and R^5 is as defined and described herein.

[0008a] In a first aspect of the present disclosure, there is provided a compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is —O— or —NH—;

R^1 is —OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is —CF_3, Cl, or Br;

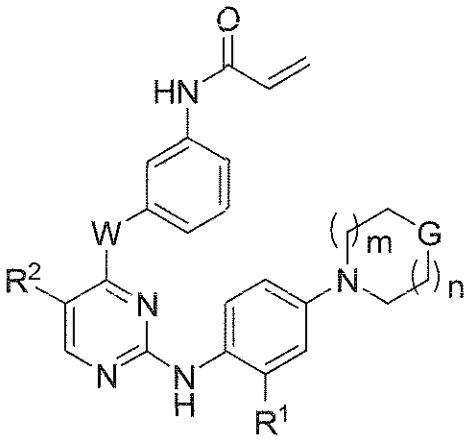
G is —NR^3—;

R^3 is —C(O)—R, —C(O)OR, —C(O)NHR, —SO_2—R, —SO_2NH_2, —C(O)—C_{1-4} alkylene-OH or —SO_2—C_{1-4} alkylene-OH;

and

R^5 is hydrogen or —C(O)OR.

[0008b] In a second aspect of the present disclosure, there is provided a compound of formula I-a:



or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is —O— or —NH—;

R^1 is —OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is —CF_3, Cl, or Br;

G is —NR^3—; and

R^3 is —C(O)—R, —C(O)OR, —C(O)NHR, —SO_2—R, —SO_2NH_2, —C(O)—C_{1-4} alkylene-OH or —SO_2—C_{1-4} alkylene-OH.

[0008c] In a third aspect of the present disclosure, there is provided a composition comprising a compound as defined above and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

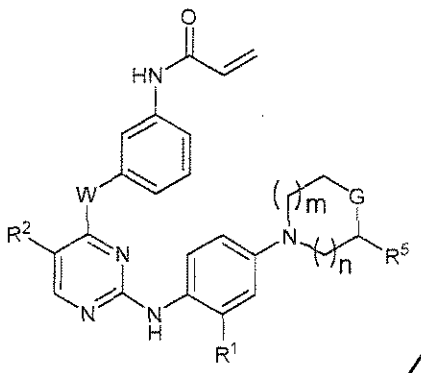
[0009] Compounds of the present ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating cancers associated with one or more EGFR mutations. Such diseases, disorders, or conditions include those described herein.

[0010] Compounds provided by ~~this invention~~the present disclosure are also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

CLAIMS

We claim:

1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is –O– or –NH-;

R^1 is –OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is $–CF_3$, Cl, or Br;

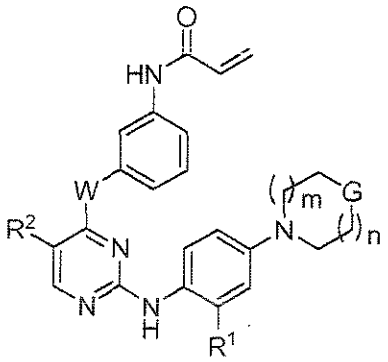
G is –O-, $–NR^3$-, $-S(O)_2$-, or $–CH(OR^4)$-;

R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $–SO_2$-R, $-SO_2NH_2$, -C(O)-C_{1-4} alkylene-OH or $–SO_2$-C_{1-4} alkylene-OH;

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} fluoroalkyl; and

R^5 is hydrogen or -C(O)OR.

2. A compound of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is –O– or –NH-;

R^1 is –OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is $–CF_3$, Cl, or Br;

G is –O-, $–NR^3$-, or $–CH(OR^4)$-;

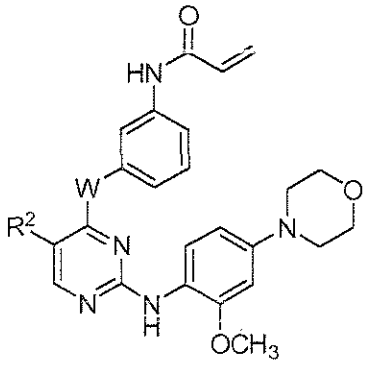
R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $–SO_2$-R, $-SO_2NH_2$, $-C(O)-C_{1-4}$ alkylene-OH or $–SO_2-C_{1-4}$ alkylene-OH; and

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} fluoroalkyl.

3. The compound according to claim 1 or 2, wherein W is –NH-.

4. The compound according to claim 3, wherein R^2 is $–CF_3$.

5. The compound according to claim 1 or 2, wherein said compound is of formula **II**:



II

or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 5, wherein W is –NH-.

7. The compound according to claim 6, wherein R^2 is $–CF_3$.

8. The compound according to claim 5, wherein at least one of definitions (a) and (b) apply:

(a) W is –O– or –NH-; and

(b) R^2 is $–CF_3$ or Cl.

9. The compound according to claim 8, wherein:

(a) W is –O– or –NH-; and

(b) R^2 is $–CF_3$ or Cl.

10. The compound according to claim 5, wherein at least one of definitions (a) and (b) apply:

(a) W is –O–; and

(b) R^2 is $–CF_3$ or Cl.

11. The compound according to claim 10, wherein:

(a) W is –O–; and

(b) R^2 is $–CF_3$ or Cl.

12. The compound according to claim 5, wherein at least one of definitions (a) and (b) apply:

(a) W is –NH-; and

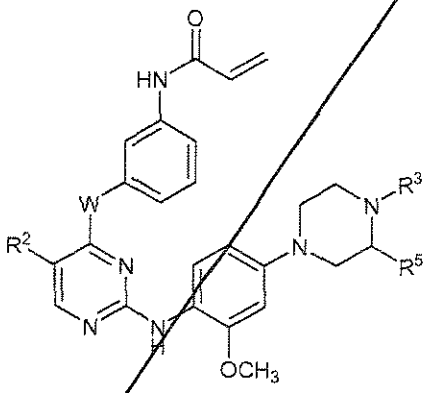
(b) R^2 is $-CF_3$ or Cl.

13. The compound according to claim 5, wherein:

(a) W is –O–; and

(b) R^2 is $-CF_3$ or Cl.

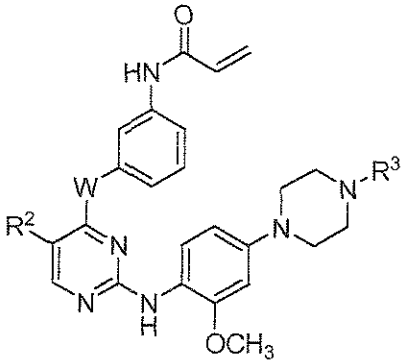
14. The compound according to claim 1, wherein said compound is of formula **III**:



III

or a pharmaceutically acceptable salt thereof.

15. The compound according to claim 1, wherein said compound is of formula **III-a**:



III-a

or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 14 or 15, wherein W is –NH-.

17. The compound according to claim 14 or 15, wherein R^2 is $–CF_3$.

18. The compound according to claim 14 or 15, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –O– or –NH-;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–C(O)CH_3$ or $–SO_2CH_3$.

19. The compound according to claim 18, wherein at least two of definitions (a), (b), and (c) apply.

20. The compound according to claim 18, wherein all three of definitions (a), (b), and (c) apply.

21. The compound according to claim 14 or 15, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –NH-;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–C(O)CH_3$.

22. The compound according to claim 21, wherein at least two of definitions (a), (b), and (c) apply.

23. The compound according to claim 22, wherein all three of definitions (a), (b), and (c) apply.

24. The compound according to claim 14 or 15, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –NH–;

(b) R^5 is $–CF_3$ or Cl; and

(c) R^6 is $–SO_2CH_3$.

25. The compound according to claim 24, wherein at least two of definitions (a), (b), and (c) apply.

26. The compound according to claim 25, wherein all three of definitions (a), (b), and (c) apply.

27. The compound according to claim 14 or 15, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –O-;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–C(O)CH_3$.

28. The compound according to claim 27, wherein at least two of definitions (a), (b), and (c) apply.

29. The compound according to claim 28, wherein all three of definitions (a), (b), and (c) apply.

30. The compound according to claim 14 or 15, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –O–;

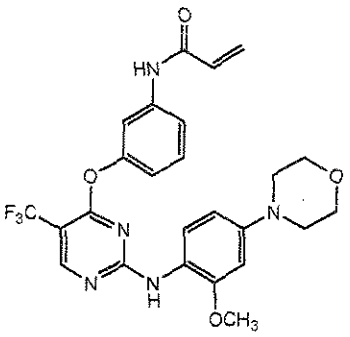
(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–SO_2CH_3$.

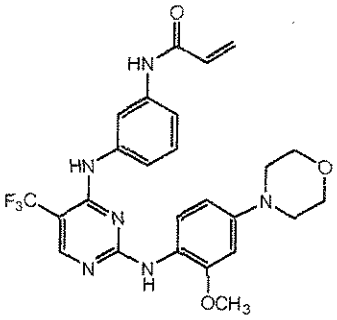
31. The compound according to claim 30, wherein at least two of definitions (a), (b), and (c) apply.

32. The compound according to claim 31, wherein all three of definitions (a), (b), and (c) apply.

33. The compound according to claim 1, selected from:



I-1



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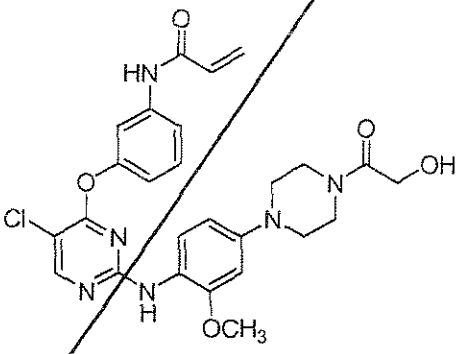

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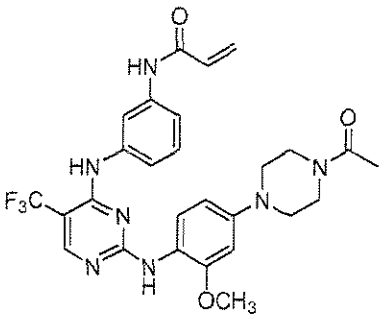

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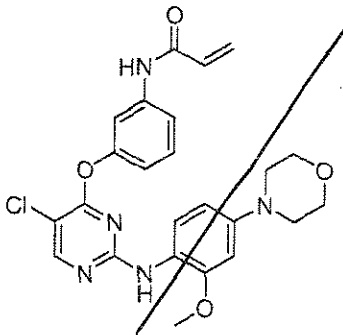

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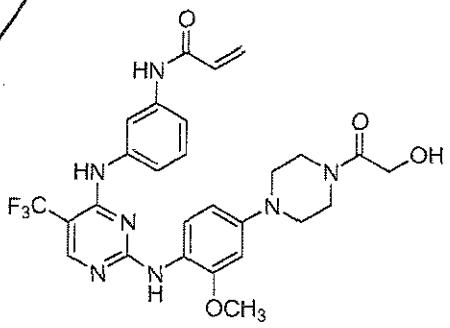

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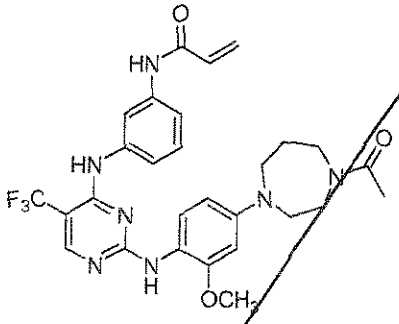

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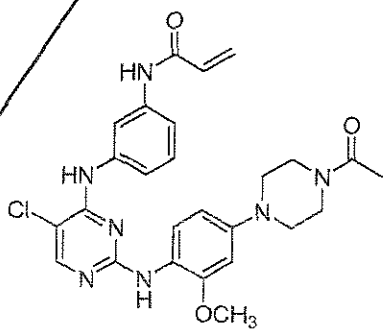

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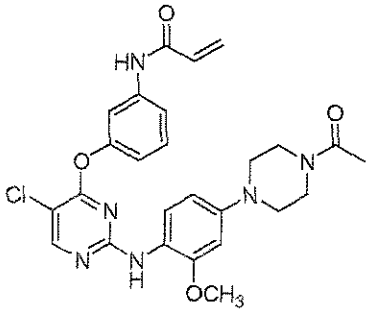

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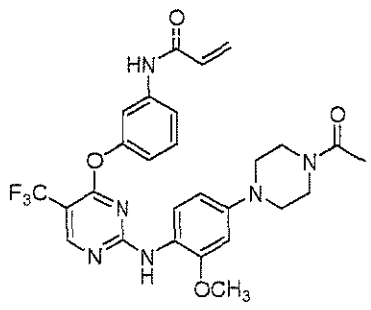

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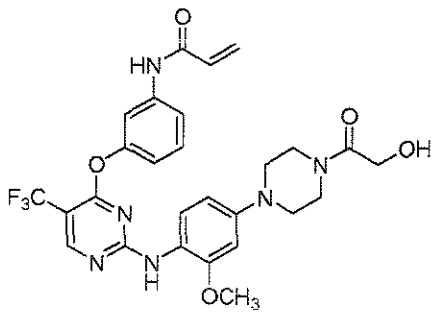

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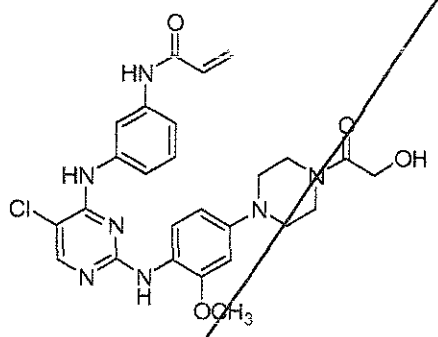

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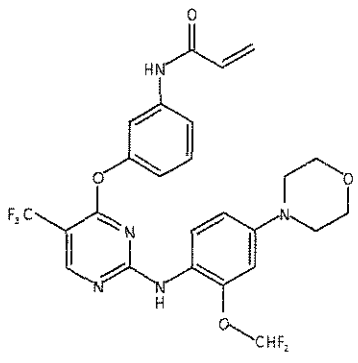

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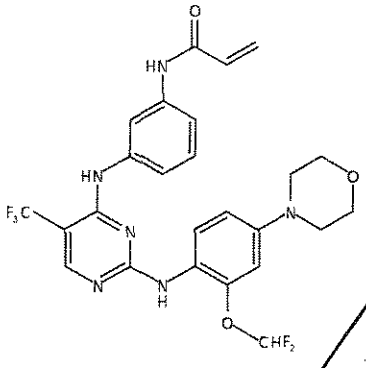

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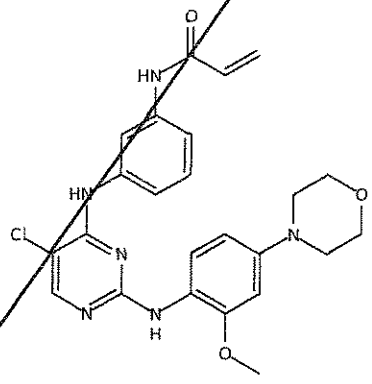

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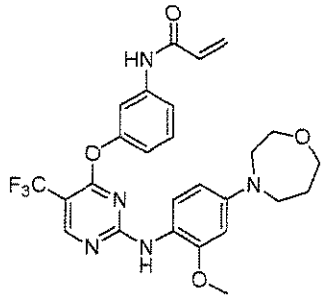

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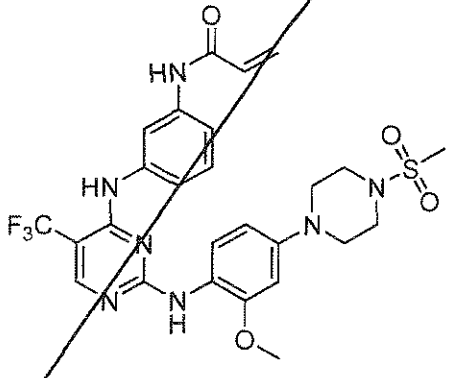

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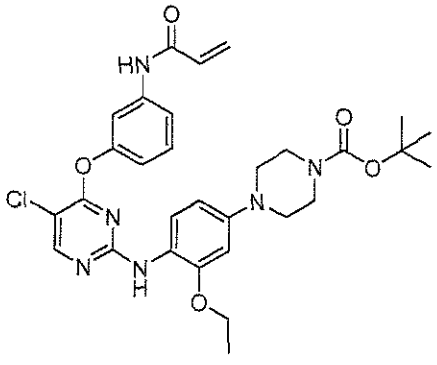

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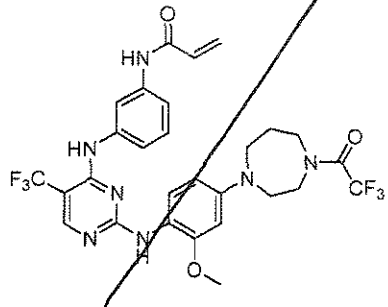

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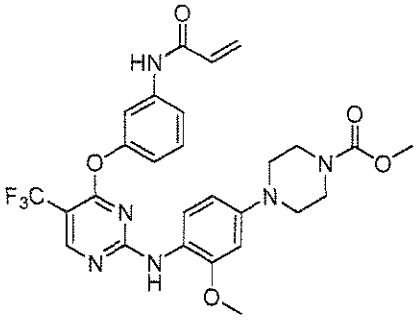

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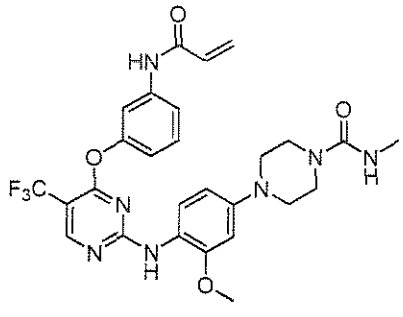

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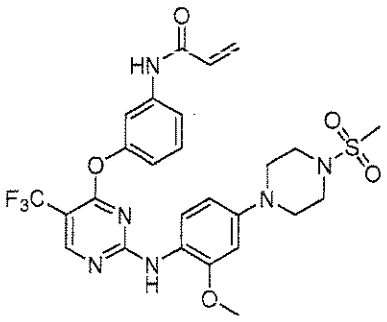

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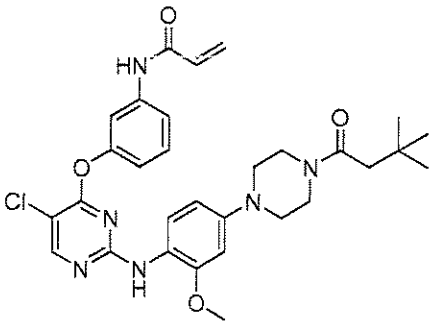

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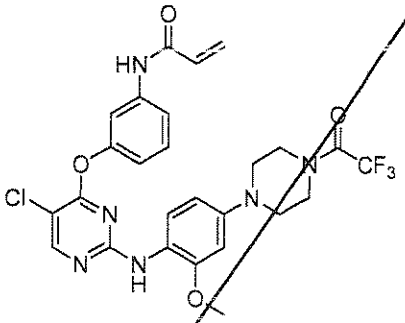

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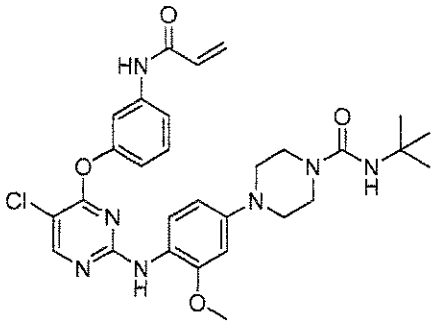
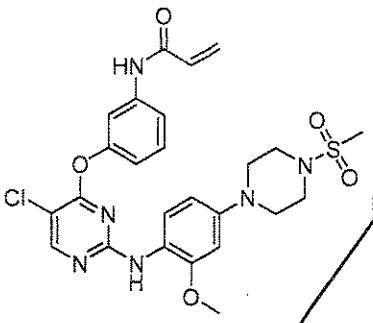
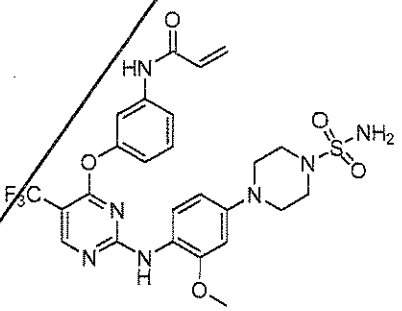


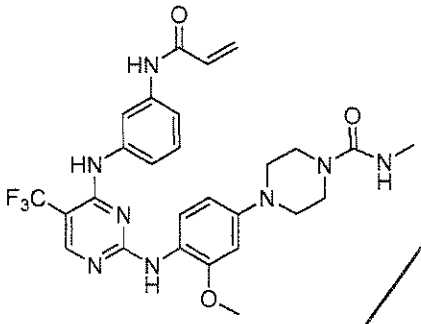
I-25



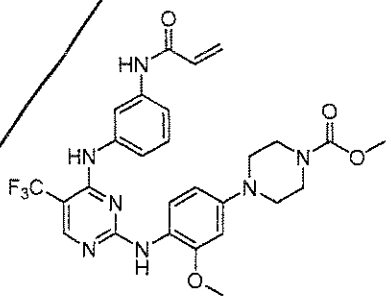
I-26



I-27



I-28



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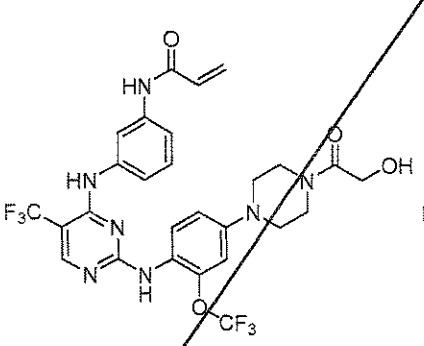
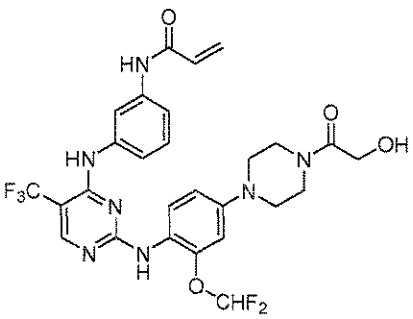


I-30



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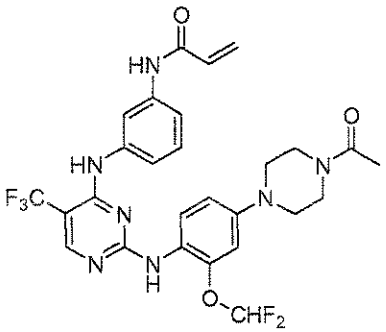
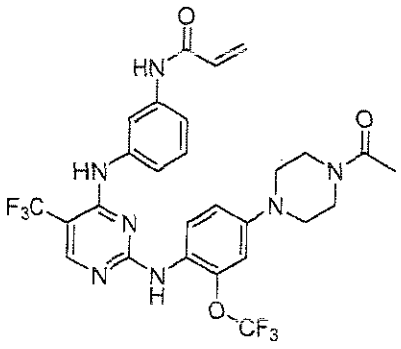
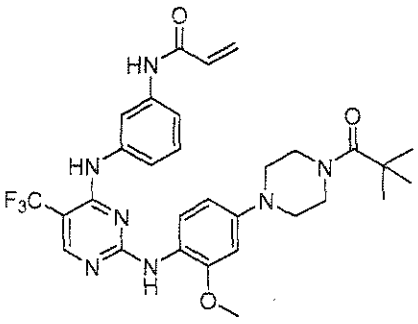


I-32



I-33



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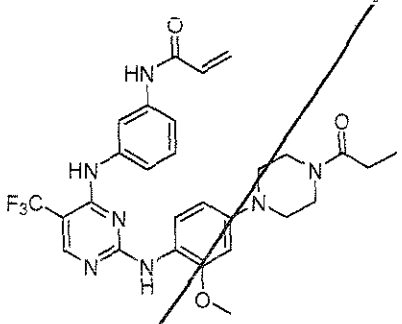

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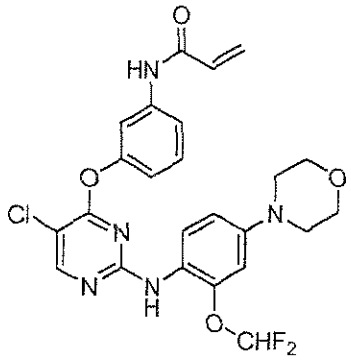

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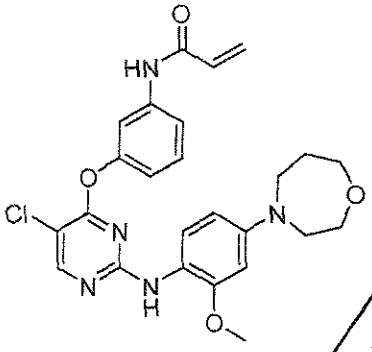

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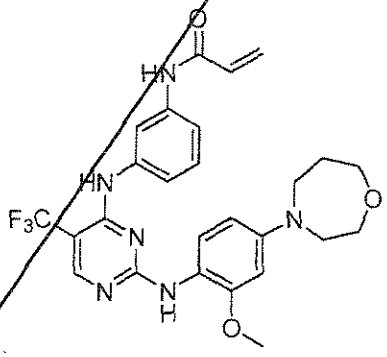

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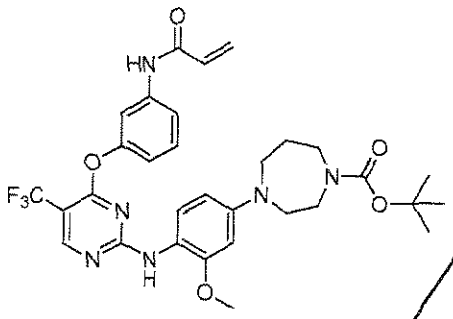

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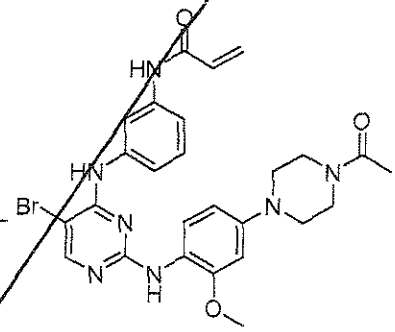

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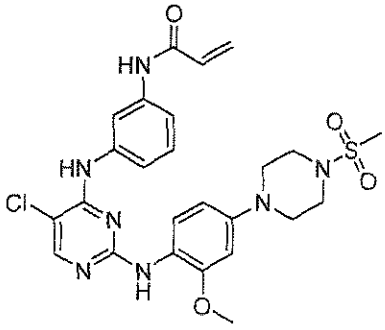

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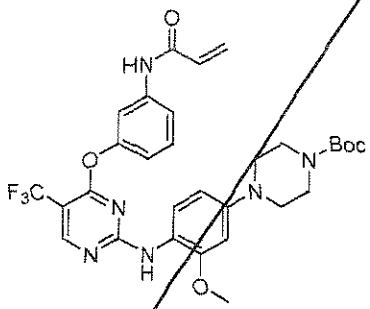

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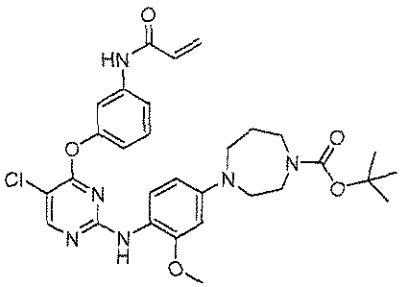

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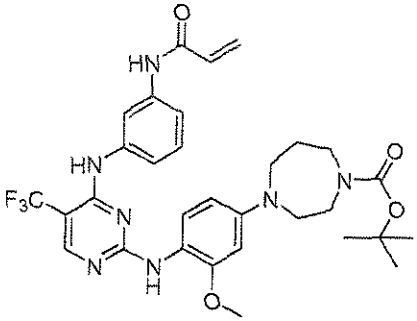

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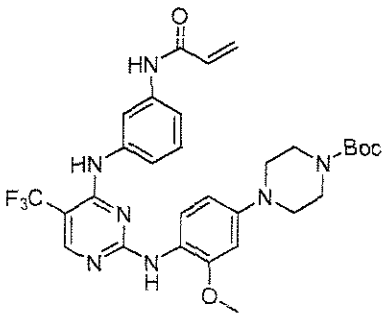

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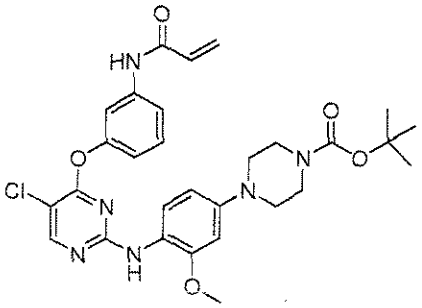

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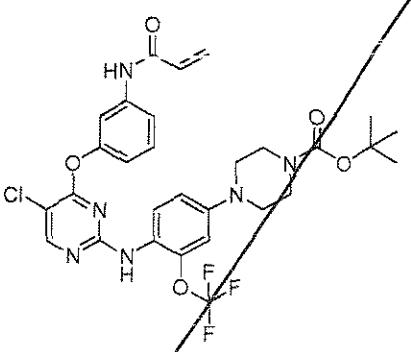

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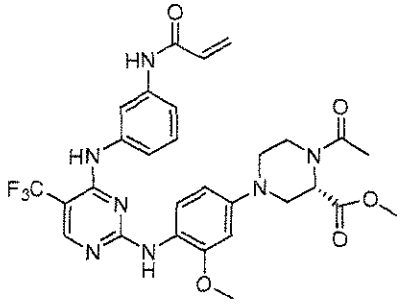

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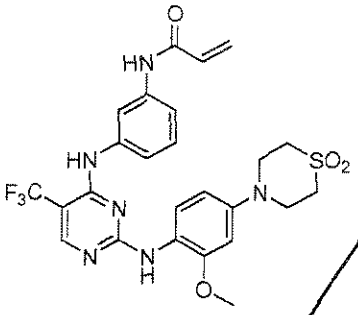

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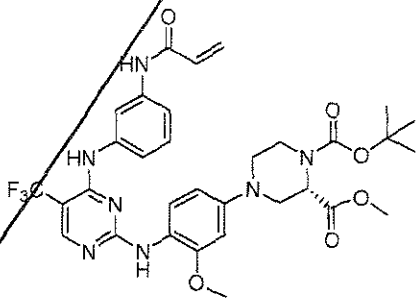


I-50

or a pharmaceutically acceptable salt thereof.

34. A composition comprising a compound according to any one of claims 1 through 29 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

35. The composition according to claim 34, in combination with an additional therapeutic agent.

36. The composition according to claim 35, wherein the additional therapeutic agent is a chemotherapeutic agent.

37. A method for inhibiting at least one mutant of EGFR selectively as compared to WT EGFR, in a biological sample or in a patient, comprising contacting the biological sample with, or administering to the patient, a compound according to any of claims 1 through 33, or a composition thereof.

38. The method according to claim 37, wherein said method is sparing for WT EGFR.

39. The method according to claim 37, wherein the at least one mutant is T790M.

40. The method according to claim 38, wherein the at least one mutant is T790M.

41. The method according to claim 37, wherein the at least one mutant of EGFR is an activating mutant.

42. The method according to claim 39, wherein the at least one activating mutant of EGFR is a deletion mutant.

43. The method according to claim 41, wherein the at least one activating mutant of EGFR is a point mutation.

44. The method according to claim 42, wherein the at least one activating mutant is delE746-A750.

45. The method according to claim 43, wherein the at least one activating mutant is L858R.

46. The method according to claim 43, wherein the at least one activating mutant is G719S.

47. The method according to claim 37, wherein the compound selectively inhibits at least one activating mutant and T790M.

48. The method according to claim 47, wherein the at least one activating mutant of EGFR is a deletion mutant.

49. The method according to claim 47, wherein the at least one mutant of EGFR is a point mutation.

50. The method according to claim 48, wherein the at least one activating mutant is delE746-A750.

51. The method according to claim 49, wherein the at least one activating mutant is L858R.

52. The method according to claim 49, wherein the at least one activating mutant is G719S.

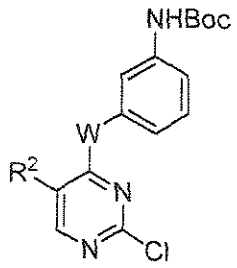
53. The method according to any one of claims 41 through 52, wherein the compound is sparing for WT EGFR.

54. A method for treating a mutant EGFR-mediated disorder or condition in a patient, comprising administering to the patient a composition according to claim 34.

55. The method according to claim 54, wherein the disorder or condition is a cancer.

56. The method according to claim 55, wherein the cancer is non-small cell lung cancer.

57. A compound of formula:

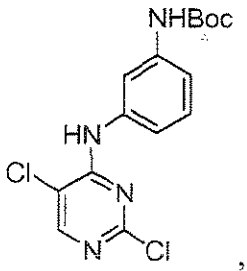


wherein:

W is –O– or –NH-; and

R^2 is $-CF_3$, Cl, or Br.

58. The compound according to claim 57, wherein the compound is selected from:



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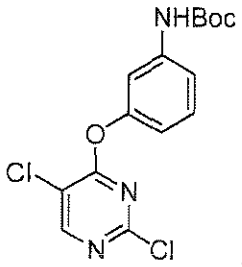

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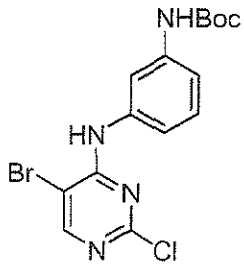

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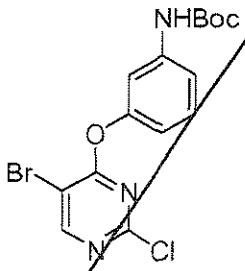

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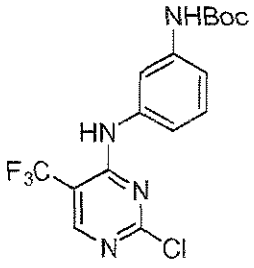

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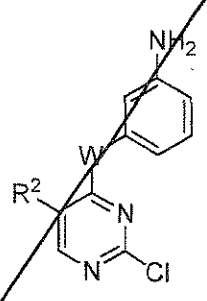
59. A compound of formula:

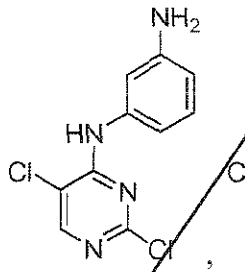


wherein:

W is –O– or –NH-; and

R^2 is $-CF_3$, Cl, or Br.

60. The compound according to claim 59, wherein the compound is selected from:



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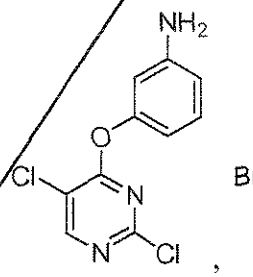

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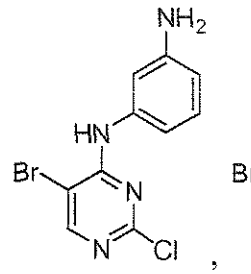

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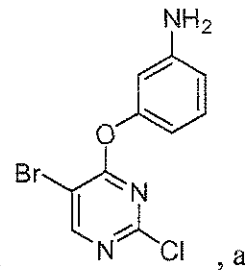

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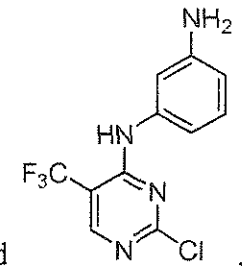

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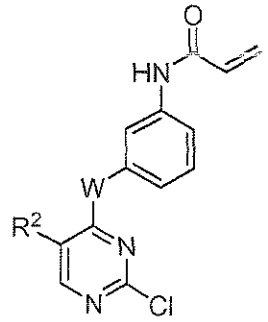
61. A compound of formula:

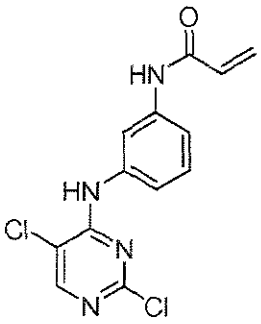


wherein:

W is –O– or –NH-; and

R^2 is $–CF_3$, Cl, or Br.

62. The compound according to claim 61, wherein the compound is selected from: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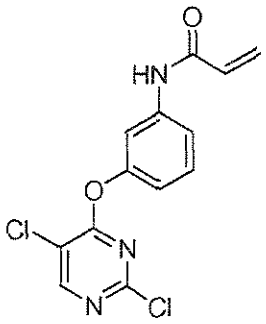
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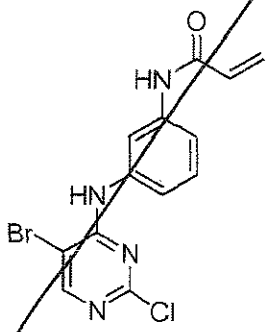
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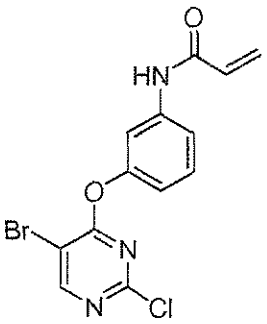
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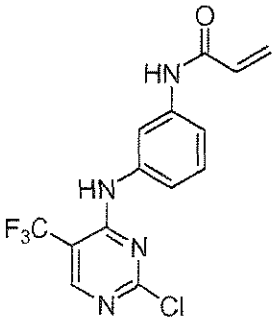
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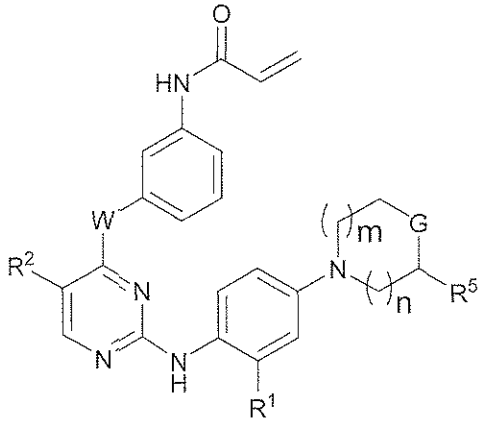
CLAIMS

1. A compound of formula I:



or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is —O— or —NH—;

R^1 is —OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is —CF_3, Cl, or Br;

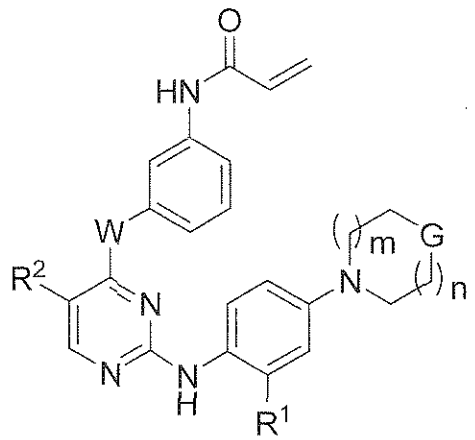
G is —NR^3—;

R^3 is —C(O)—R, —C(O)OR, —C(O)NHR, —SO_2—R, —SO_2NH_2, —C(O)—C_{1-4} alkylene-OH or —SO_2—C_{1-4} alkylene-OH;

and

R^5 is hydrogen or —C(O)OR.

2. A compound of formula I-a:



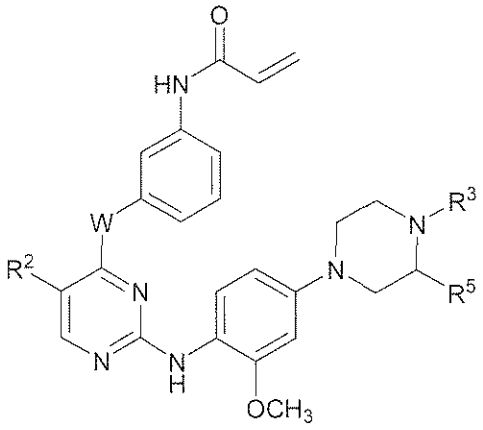
or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;
m is 0, 1, or 2, wherein m and n are not simultaneously 0;
W is —O— or —NH—;
R^1 is —OR;
each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;
R^2 is —CF_3, Cl, or Br;
G is —NR^3—; and
R^3 is —C(O)—*R*, —C(O)O*R*, —C(O)N*HR*, —SO_2—*R*, —SO_2NH_2, —C(O)—C_{1-4} alkylene-OH or —SO_2—C_{1-4} alkylene-OH.

3. The compound according to claim 1, wherein W is —NH—.

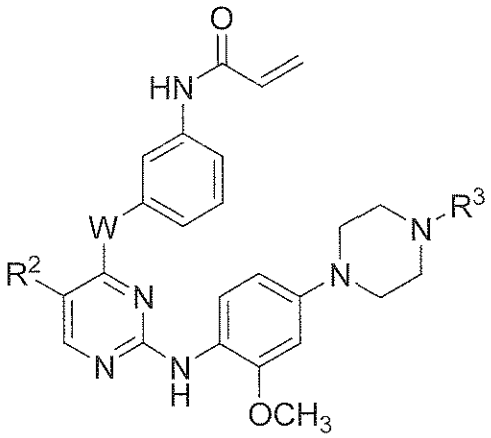
4. The compound according to claim 3, wherein R^2 is —CF_3.

5. The compound according to claim 1, wherein said compound is of formula III:



or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein said compound is of formula III-a:



or a pharmaceutically acceptable salt thereof.

7. The compound according to claim 5, wherein W is —NH—.

8. The compound according to claim 5, wherein R^2 is —CF_3.

9. The compound according to claim 5, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is —O— or —NH—;

(b) R^2 is —CF_3 or Cl; and

(c) R^3 is —$C(O)CH_3$ or —SO_2CH_3.

10. The compound according to claim 9, wherein at least two of definitions (a), (b), and (c) apply.

11. The compound according to claim 9, wherein all three of definitions (a), (b), and (c) apply.

12. The compound according to claim 5, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is —NH—;

(b) R^2 is —CF_3 or Cl; and

(c) R^3 is —$C(O)CH_3$.

13. The compound according to claim 12, wherein at least two of definitions (a), (b), and (c) apply.

14. The compound according to claim 13, wherein all three of definitions (a), (b), and (c) apply.

15. The compound according to claim 5, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is —NH—;

(b) R^2 is —CF_3 or Cl; and

(c) R^3 is —SO_2CH_3.

16. The compound according to claim 15, wherein at least two of definitions (a), (b), and (c) apply.

17. The compound according to claim 5, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is —O—;

(b) R^2 is —CF_3 or Cl; and

(c) R^3 is —$C(O)CH_3$.

18. The compound according to claim 17, wherein at least two of definitions (a), (b), and (c) apply.

19. The compound according to claim 5, wherein at least one of definitions (a), (b), and (c) apply:

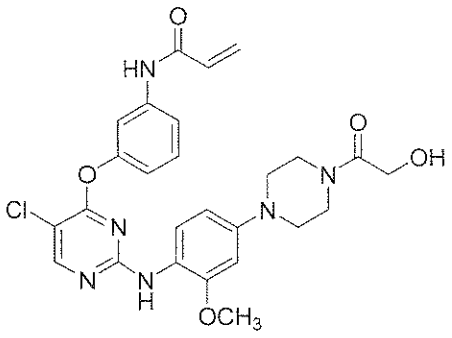
(a) W is —O—;

(b) R^2 is —CF_3 or Cl; and

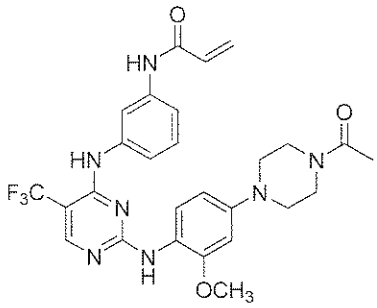
(c) R^3 is —SO_2CH_3.

20. The compound according to claim 1, selected from:

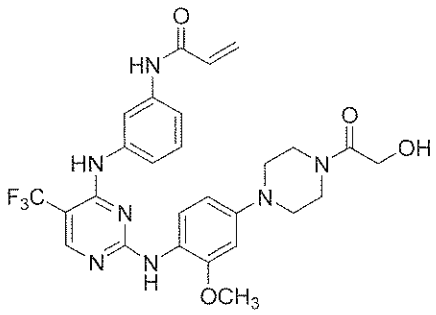
I-3



I-4



I-6



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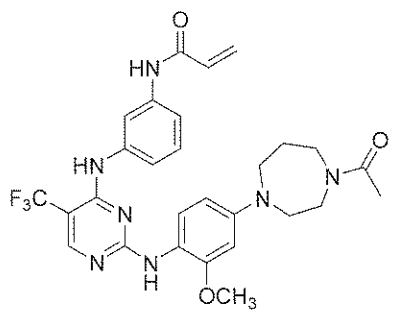

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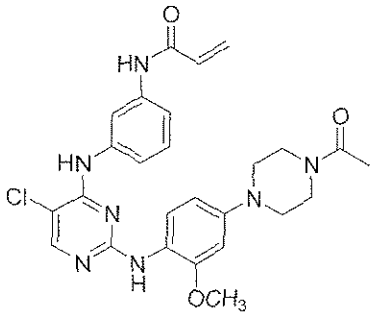

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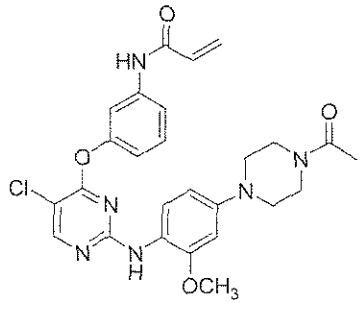

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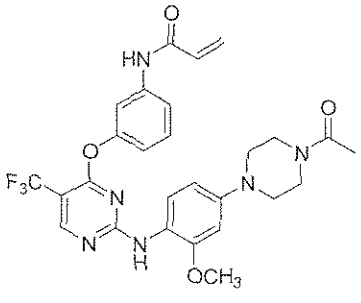
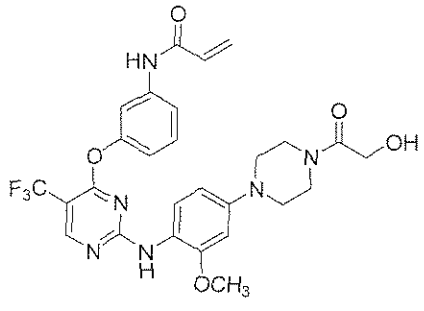


I-11



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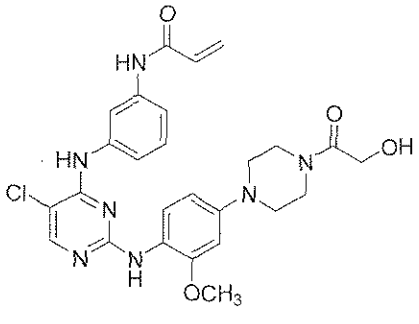

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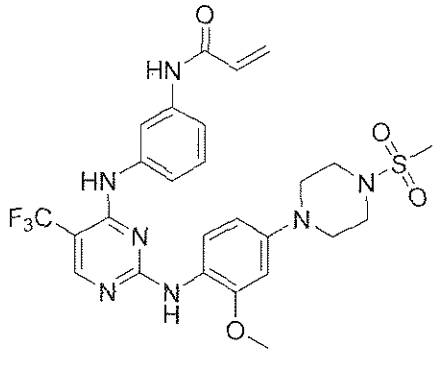

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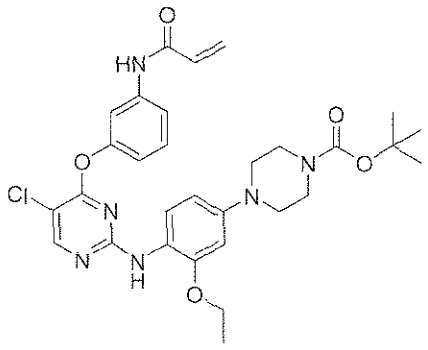

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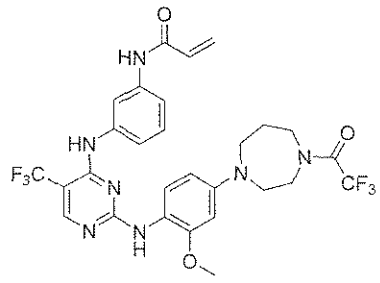

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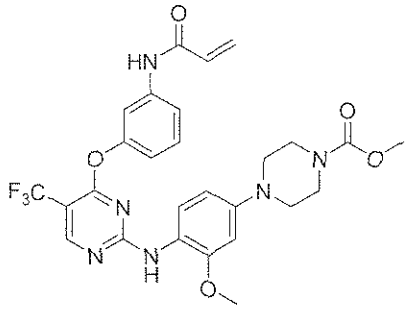

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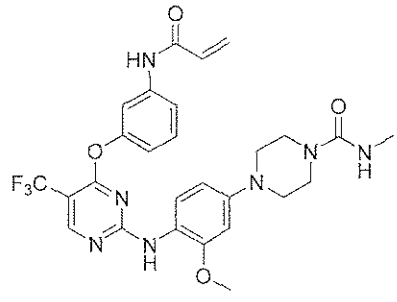

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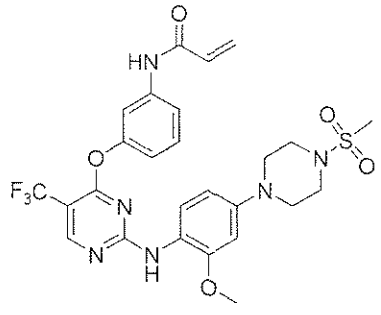

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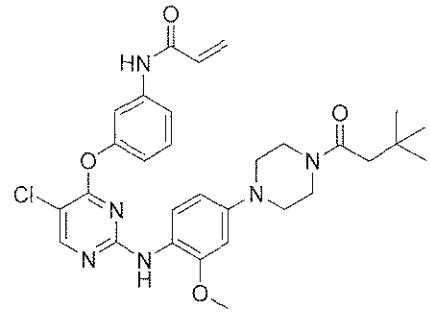

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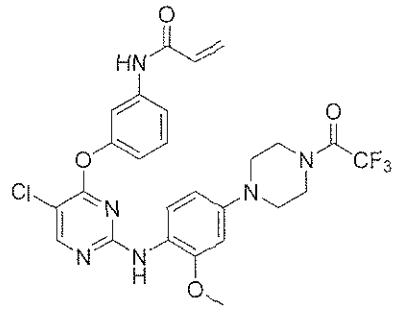

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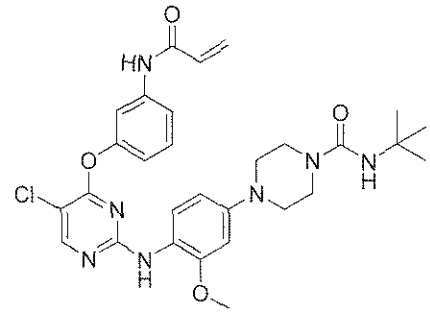

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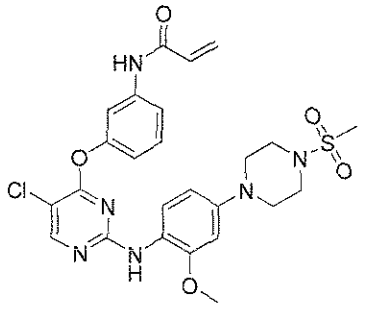

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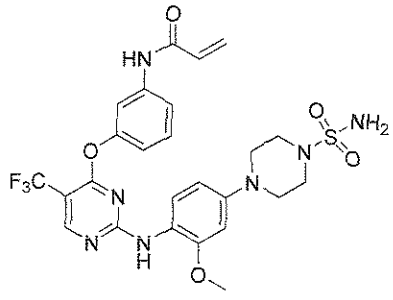

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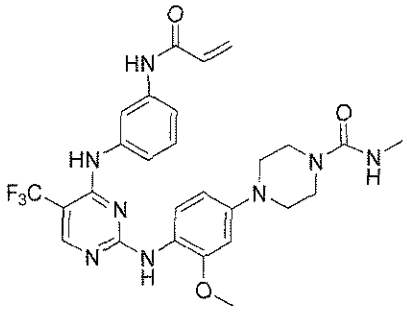

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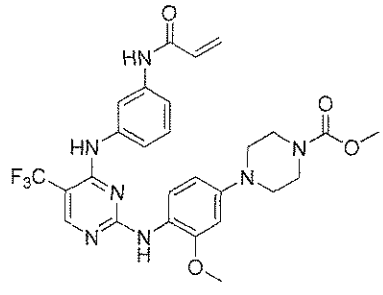

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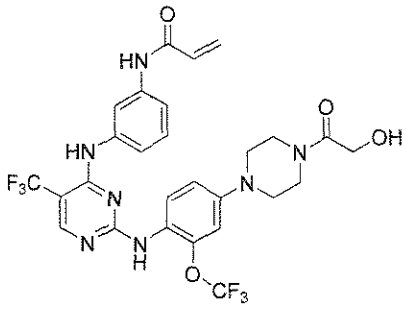

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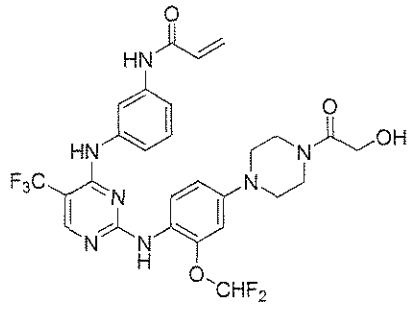

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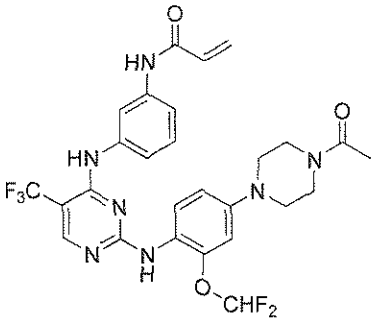

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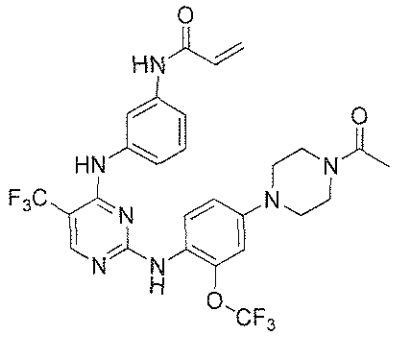

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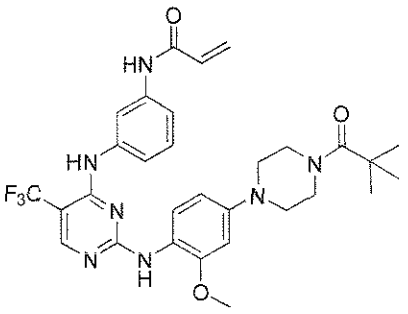

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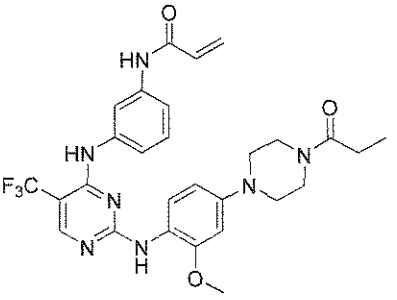

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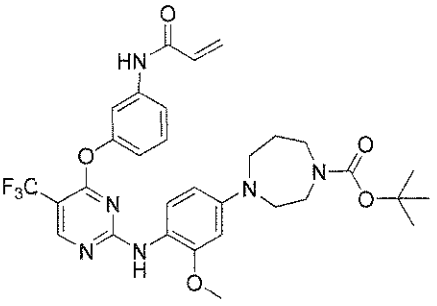

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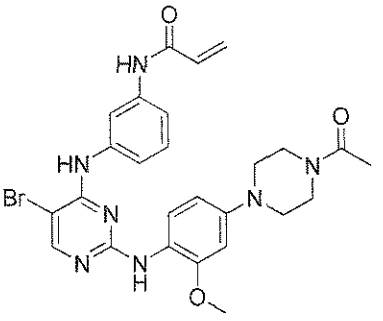

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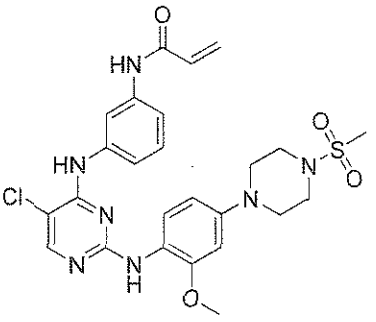

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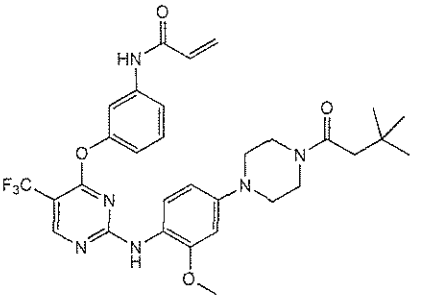

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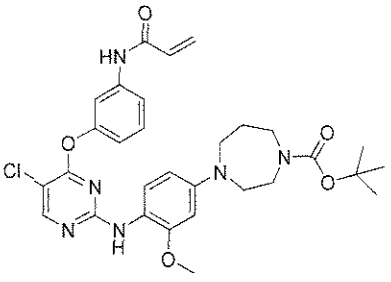

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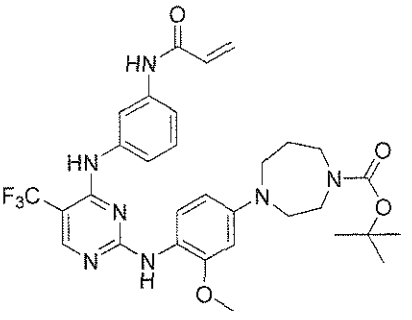

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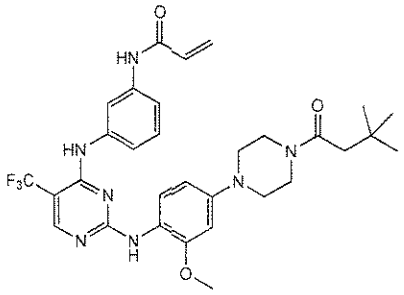

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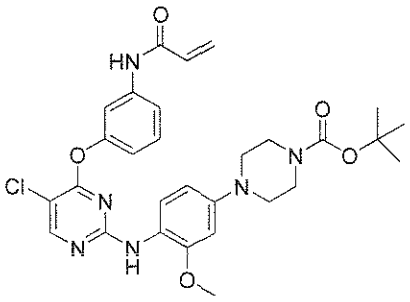

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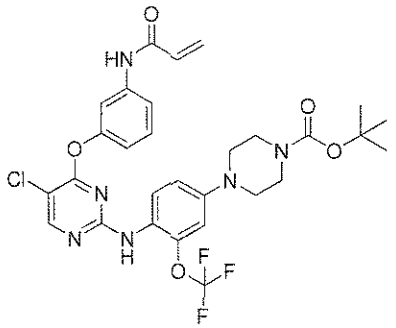

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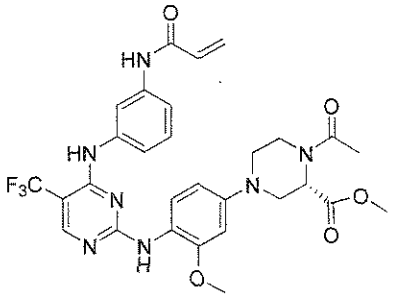

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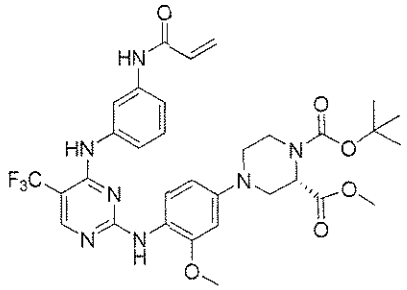


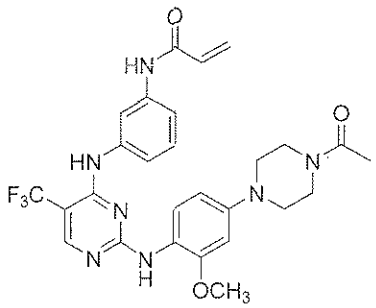
or a pharmaceutically acceptable salt thereof.

21. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

22. The composition according to claim 21, in combination with an additional therapeutic agent.

23. The composition according to claim 22, wherein the additional therapeutic agent is a chemotherapeutic agent.

24. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

25. A composition comprising a compound according to claim 24 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.