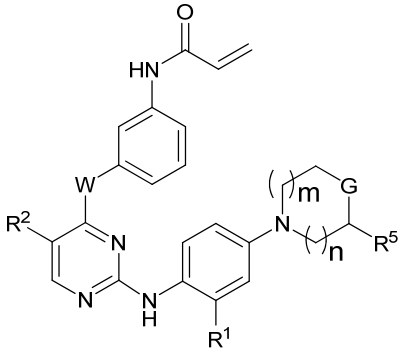
resistant patients. Moreover, T790M may also be pre-existing, there may be an independent, oncogenic role for the T790M mutation. For example, there are patients with the L858R/T790M mutation who never received gefitinib treatment. In addition, germline EGFR T790M mutations are linked with certain familial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

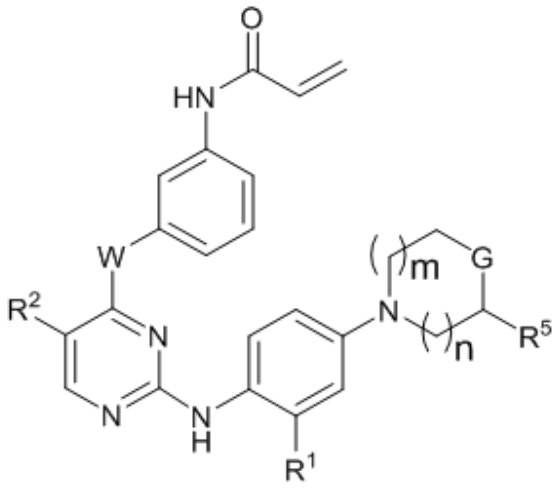
[0008] It has now been found that compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as mutant-selective EGFR kinase inhibitors. Such compounds have general formula **I**:



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 one aspect, the present disclosure refers to a use of a compound in the manufacture of a medicament for treatment of a mutant EGFR-mediated proliferative disorder, wherein the compound is represented by a structural 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;

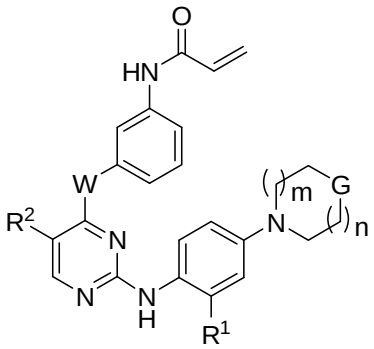
R^2 is $–CF_3$, Cl, or Br;

G is $–NR^3$- or $-S(O)_2$-;

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 another aspect, the present disclosure refers to a use of a compound in the manufacture of a medicament for treatment of a mutant EGFR-mediated proliferative disorder, wherein the compound is represented by structural 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 $–NR^3$-; and

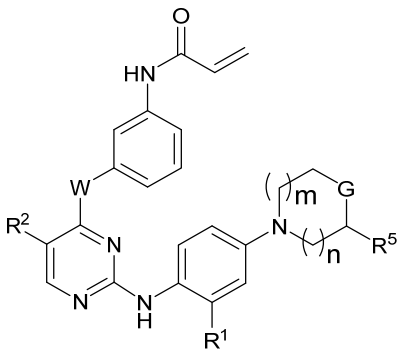
[0009] R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $–SO_2$-R, $-SO_2NH_2$, -C(O)-C_{1-4} alkylene-OH or $–SO_2$-C_{1-4} alkylene-OH.Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating cancers associated with one or more EGFR mutations. Such diseases, disorders, or conditions include those described herein.

[0010] Compounds provided by this disclosureare 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. Use of a compound in the manufacture of a medicament for treatment of a mutant EGFR-mediated proliferative disorder, wherein the compound is represented by a structural 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;

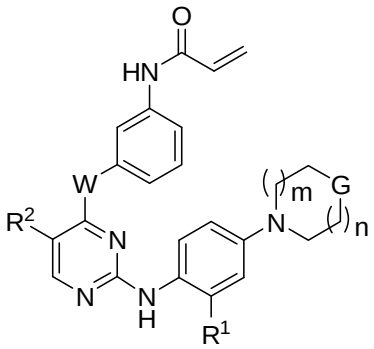
R^2 is $–CF_3$, Cl, or Br;

G is $–NR^3$- or $-S(O)_2$-;

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. Use of a compound in the manufacture of a medicament for treatment of a mutant EGFR-mediated proliferative disorder, wherein the compound is represented by structural 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;

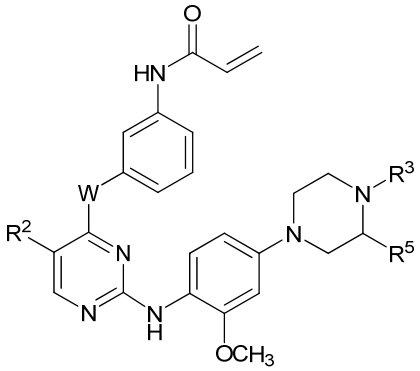
G is $–NR^3$-; and

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.

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

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

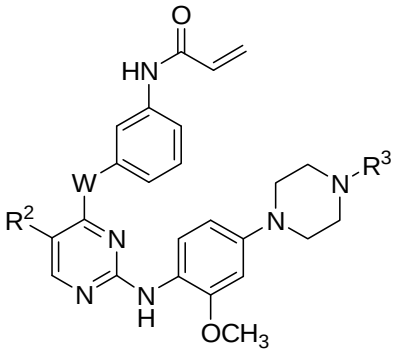
5. Use according to claim 1, wherein the compound is represented by structural formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein W, R^2, R^3 and R^5 are as defined in claim 1.

6. Use according to claim 1, wherein the compound is represented by structural formula **III-a**:



III-a

or a pharmaceutically acceptable salt thereof, wherein W, R^2 and R^3 are as defined in claim 1.

7. Use according to claim 5 or 6, wherein W is –NH-.

8. Use according to claim 5 or 6, wherein R^2 is $–CF_3$.

9. Use according to claim 5 or 6, wherein at least one of definitions (a) and (b) apply:
(a) R^2 is $–CF_3$ or Cl; and
(b) R^3 is $–C(O)CH_3$ or $–SO_2CH_3$.

10. Use according to claim 9, wherein both definitions (a) and (b) apply.

11. Use according to claim 5 or 6, 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 $–C(O)CH_3$.

12. Use according to claim 11, wherein at least two of definitions (a), (b), and (c) apply.

13. Use according to claim 12, wherein all three of definitions (a), (b), and (c) apply.

14. Use according to claim 5 or 6, 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 $–SO_2CH_3$.

15. Use according to claim 14, wherein at least two of definitions (a), (b), and (c) apply.

16. Use according to claim 15, wherein all three of definitions (a), (b), and (c) apply.

17. Use according to claim 5 or 6, 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. Use according to claim 17, wherein at least two of definitions (a), (b), and (c) apply.

19. Use according to claim 18, wherein all three of definitions (a), (b), and (c) apply.

20. Use according to claim 5 or 6, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –O–;

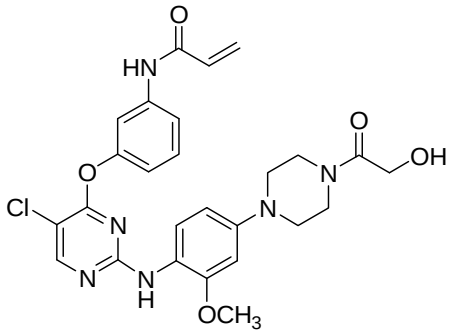
(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–SO_2CH_3$.

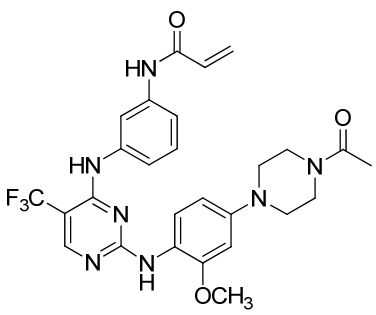
21. Use according to claim 20, wherein at least two of definitions (a), (b), and (c) apply.

22. Use according to claim 21, wherein all three of definitions (a), (b), and (c) apply.

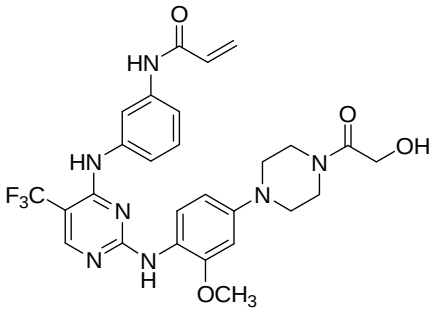
23. Use according to claim 1, wherein the compound is selected from:



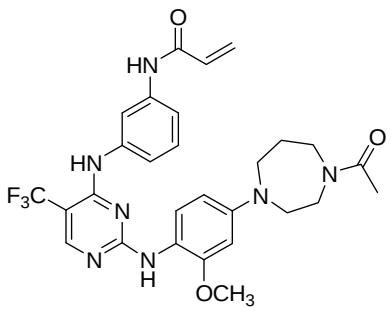
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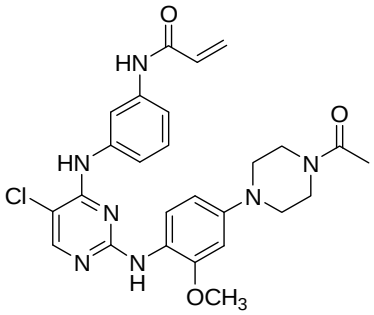
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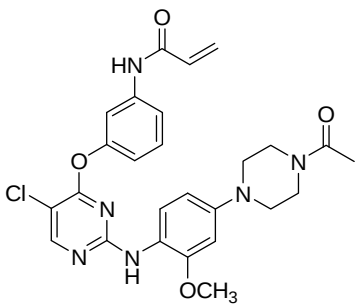
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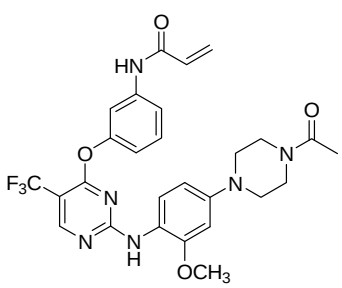
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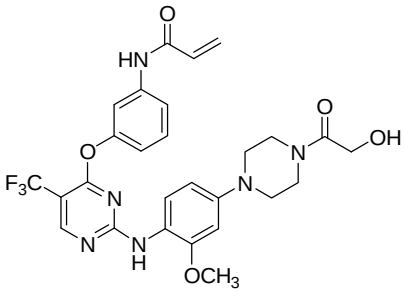
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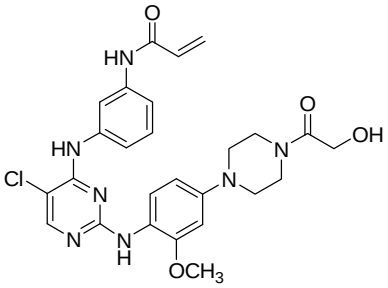
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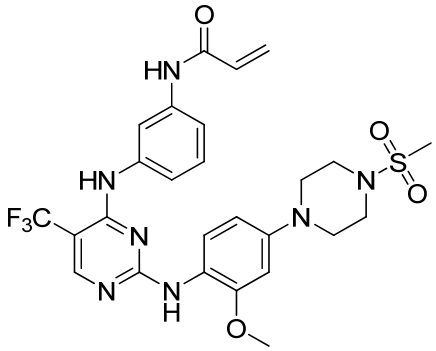
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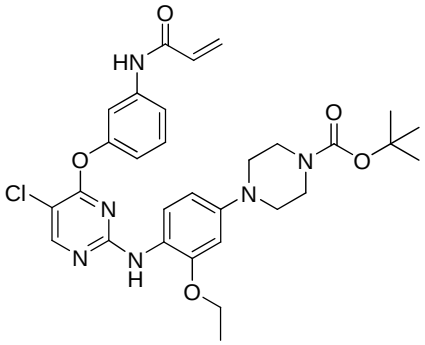
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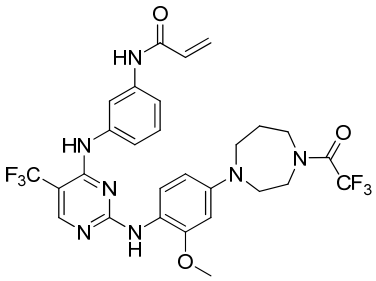
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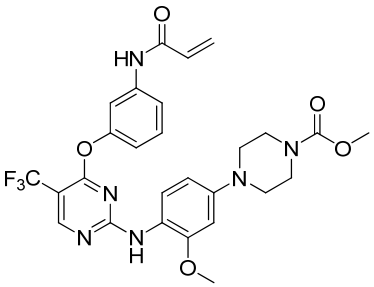
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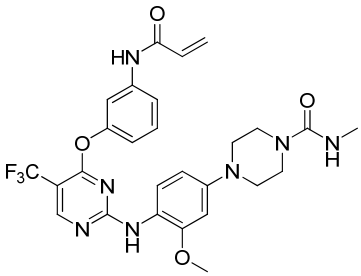
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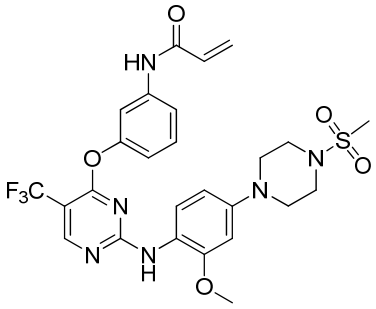
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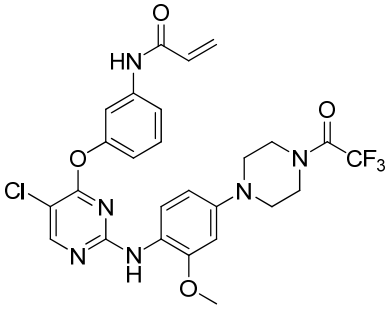
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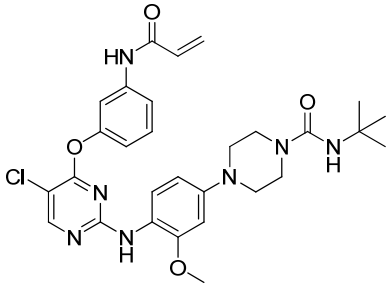
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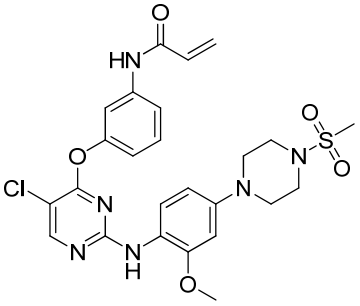
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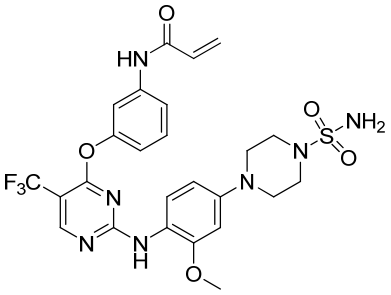
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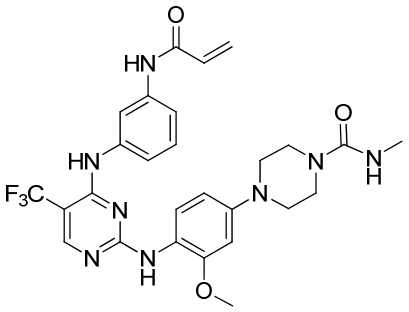
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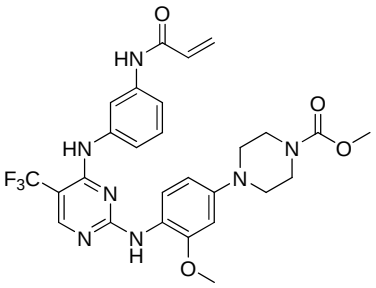
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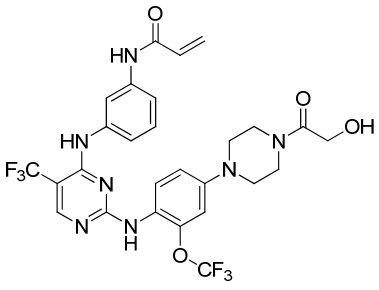
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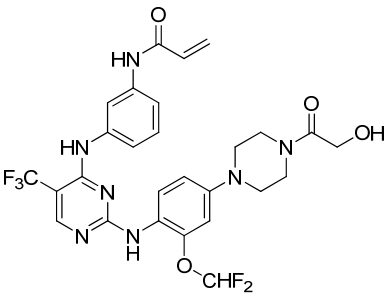
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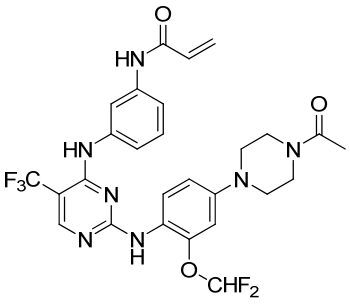
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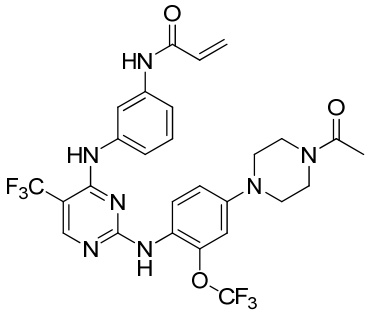
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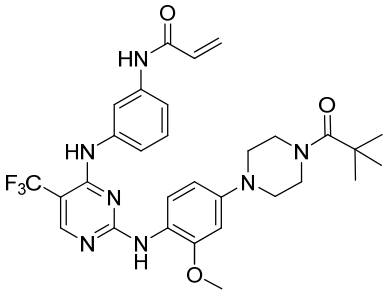
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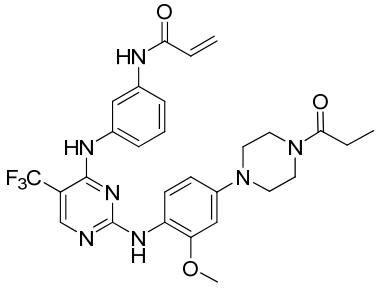
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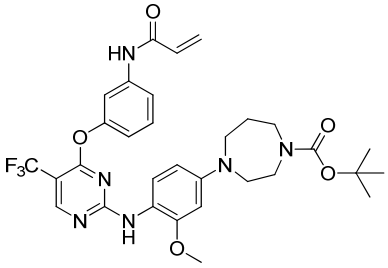
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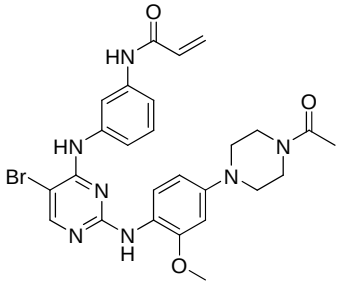
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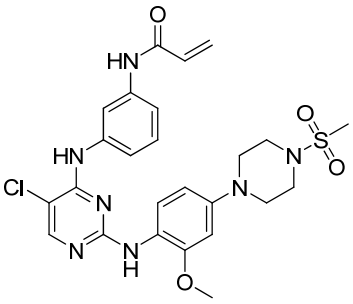
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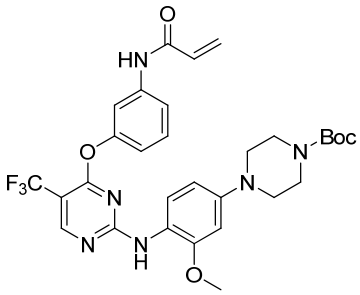
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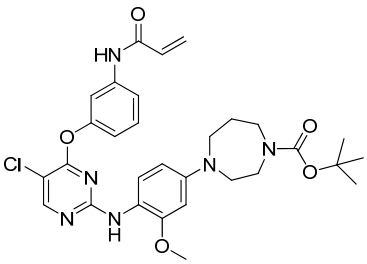
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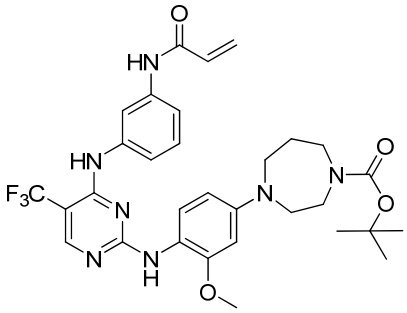
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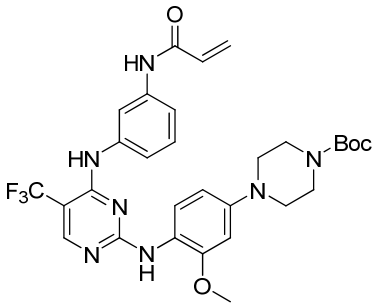
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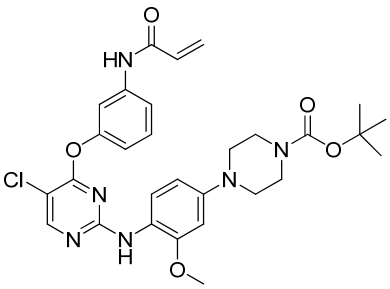
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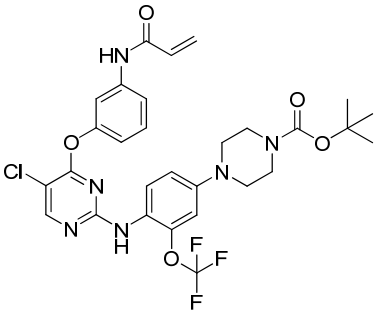
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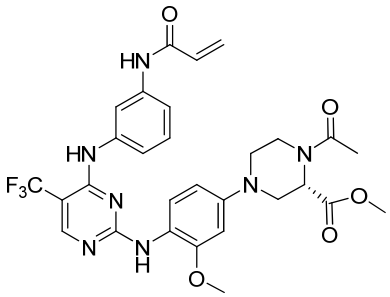
I-45



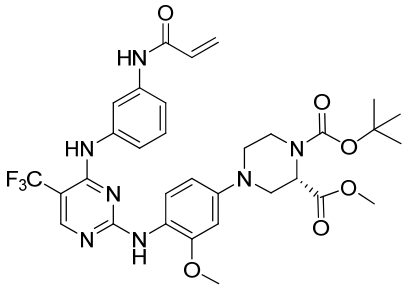
I-46



I-47



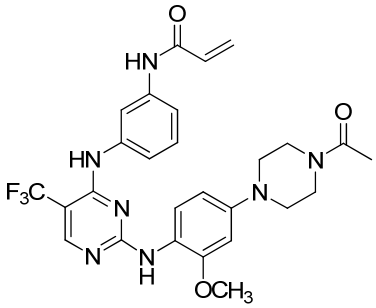
I-48



I-50

or a pharmaceutically acceptable salt thereof.

24. Use according to claim 1, wherein the compound is of formula:



I-4

or a pharmaceutically acceptable salt thereof.

25. Use according to claim 1, wherein the mutant EGFR-mediated proliferative disorder is a cancer selected from breast cancer, glioblastoma, lung cancer, cancer of the head and neck, colorectal cancer, and bladder cancer.

26. Use according to claim 25, wherein the cancer is a lung cancer.

27. Use according to claim 26, wherein the lung cancer is non-small cell lung cancer.