PYRIMIDINE COMPOUNDS, COMPOSITIONS, AND MEDICINAL APPLICATIONS THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/108,185 filed October 30, 2020; U.S. Provisional Patent Application No. 63/236,194 filed August 23, 2021; and U.S. Provisional Patent Application No. 63/271,991 filed October 26, 2021; each of which is incorporated herein by reference in its entirety.

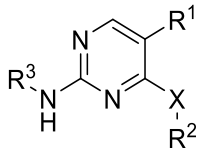
BACKGROUND OF THE DISCLOSURE

[0002] Lung cancer accounts for the greatest number of cancer deaths, and approximately 85% of lung cancer cases are non-small cell lung cancer (NSCLC). The development of targeted therapies for lung cancer has primarily focused on tumors displaying specific oncogenic drivers, namely mutations in epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Three generations of tyrosine kinase inhibitors (TKIs) have been developed for cancers with the most frequently observed EGFR mutations, however, other oncogenic drivers in the EGFR family of receptor tyrosine kinases have received less research and development focus and several oncogenic drivers, including insertions in the exon 20 gene of EGFR, have no currently approved therapeutics to treat their cancers.

[0003] Given that many patients with mutations in EGFR do not derive clinical benefit from currently available therapies against these targets, there remains a significant unmet need for the development of novel therapies for the treatment of cancers associated with EGFR mutations.

BRIEF SUMMARY

[0003a] In an aspect of the present disclosure there is provided a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^1 is $–(C(R^4)_2)_nR^5$;

X is –NH;

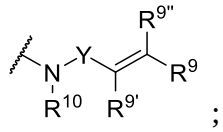
n is 0;

R^5 is phenyl substituted with 0 or 1 $R^{5'}$;

R^2 is phenyl substituted with at least one R^7 and 0, 1, or 2 R^8; and

R^3 is pyrazolyl substituted with 0, 1, 2, or 3 R^{12};

each $R^{5'}$ is independently alkyl, haloalkyl, heterocycloalkyl, halo, hydroxy, or alkoxy;

R^7 is  ;

R^8 is fluoro;

Y is –C(=O)–;

R^9, $R^{9'}$, and $R^{9''}$ are hydrogen;

R^{10} is hydrogen; and

each R^{12} is independently methyl, *iso*-propyl, *tert*-butyl, hydroxyethyl, methoxyethyl, trifluoromethyl, trifluoroethyl, chloro, cyano, morpholinyl, or cyclopropyl.

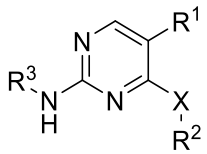
[0003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound as disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[0003c] In a further aspect of the present disclosure, there is provided a use of a compound as disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition as disclosed herein, in the manufacture of a medicament for treating cancer.

[0003d] In another aspect of the present disclosure, there is provided a compound as disclosed herein, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition as disclosed herein, for use in therapy.

SUMMARY OF THE DISCLOSURE

[0004] In one aspect, provided herein is a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

X is –NH– or –O–;

R^1 is $–(C(R^4)_2)_nR^5$, wherein R^5 is unsubstituted or substituted with 1 $R^{5'}$;

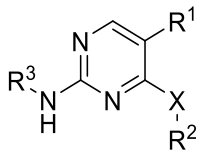
n is 0, 1, 2, or 3;

each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is $C_{4\text{-}10}$cycloalkyl, aryl, or heteroaryl;

CLAIMS

1. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt or stereoisomer thereof, wherein:

R^1 is $–(C(R^4)_2)_nR^5$;

X is –NH;

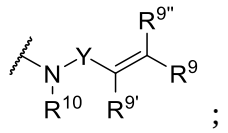
n is 0;

R^5 is phenyl substituted with 0 or 1 $R^{5'}$;

R^2 is phenyl substituted with at least one R^7 and 0, 1, or 2 R^8; and

R^3 is pyrazolyl substituted with 0, 1, 2, or 3 R^{12};

each $R^{5'}$ is independently alkyl, haloalkyl, heterocycloalkyl, halo, hydroxy, or alkoxy;

R^7 is  ;

R^8 is fluoro;

Y is –C(=O)–;

R^9, $R^{9'}$, and $R^{9''}$ are hydrogen;

R^{10} is hydrogen; and

each R^{12} is independently methyl, *iso*-propyl, *tert*-butyl, hydroxyethyl, methoxyethyl, trifluoromethyl, trifluoroethyl, chloro, cyano, morpholinyl, or cyclopropyl.

2. The compound of claim 1, wherein each $R^{5'}$ is independently methyl, ethyl, *tert*-butyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, fluoro, chloro, hydroxy, –methoxy, ethoxy, fluoromethyl, difluoromethyl, or trifluoromethyl.

3. The compound of claim 2, wherein each $R^{5'}$ is independently methyl, morpholinyl, fluoro, chloro, methoxy, fluoromethyl, difluoromethyl, or trifluoromethyl.

4. The compound of any one of claims 1 to 3, wherein R^2 is substituted with 1 or 2 R^8.

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

6. The compound of any one of claims 1 to 5, wherein R^3 is unsubstituted.

7. The compound of any one of claims 1 to 5, wherein R^3 is substituted with at least 1 R^{12}.

8. The compound of claim 7, wherein R^3 is substituted with at least 2 R^{12}.

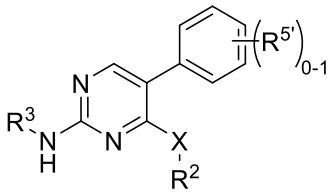
9. The compound of claim 8, wherein each R^{12} is independently methyl, hydroxyethyl, methoxyethyl, trifluoroethyl, or chloro.

10. The compound of claim 9, wherein each R^{12} is independently methyl or chloro.

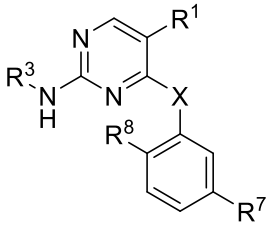
11. The compound of any one of claims 1 to 10, wherein $R^{5'}$ is fluoromethyl, difluoromethyl, or trifluoromethyl.

12. The compound of any one of claims 1 to 11, wherein R^{12} is methyl.

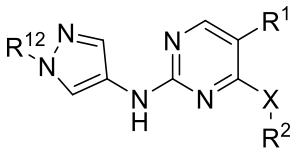
13. The compound of any one of claims 1 to 12, wherein the compound is of Formula I-A, Formula I-B, Formula I-C, Formula I-D, Formula I-E, Formula I-F, or Formula I-G:



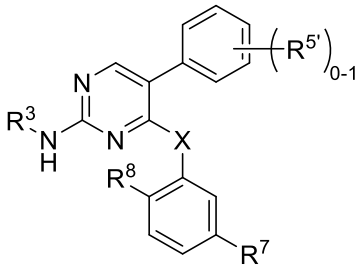
Formula I-A;



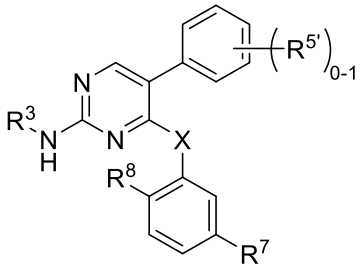
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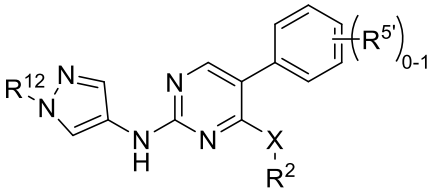
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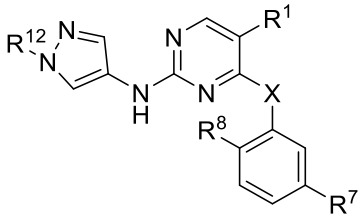
Formula I-D;



Formula I-E;



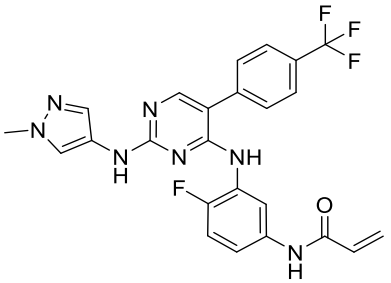
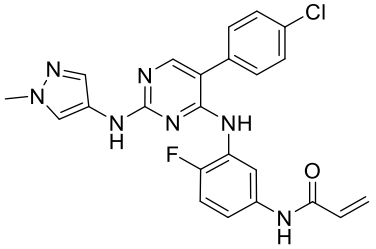
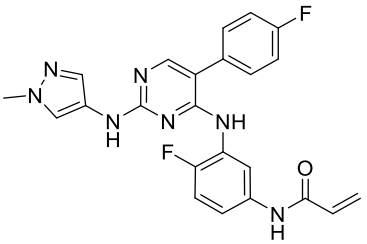
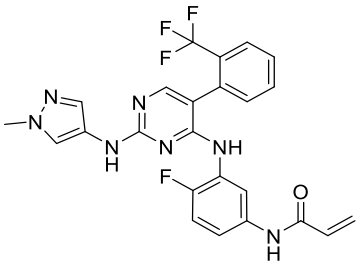
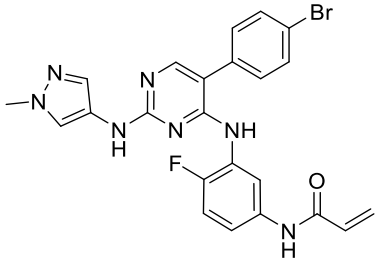
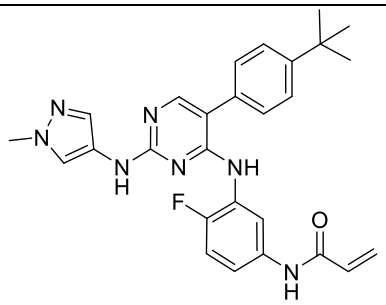
Formula I-F;

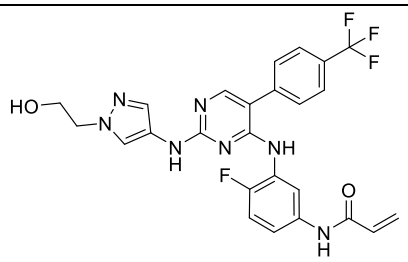
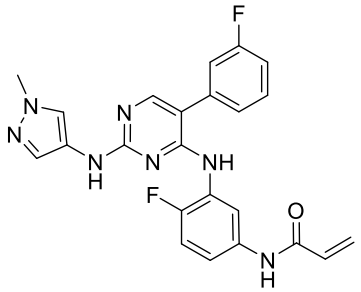
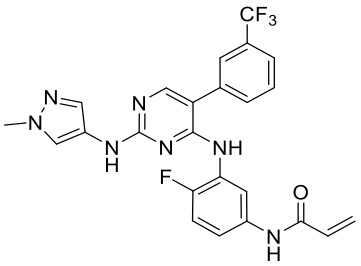
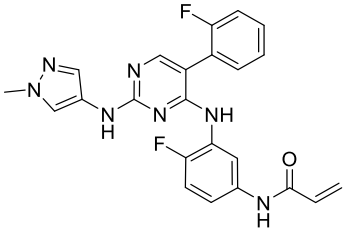
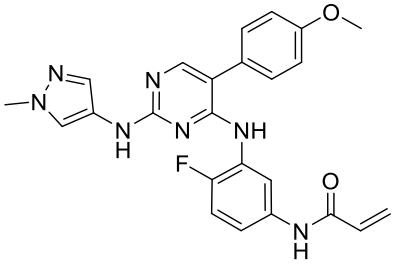
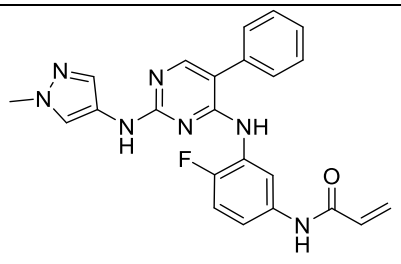


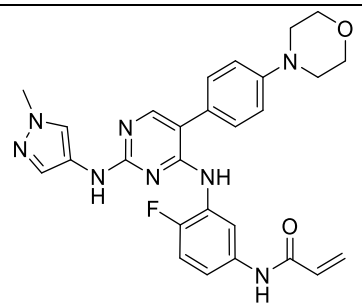
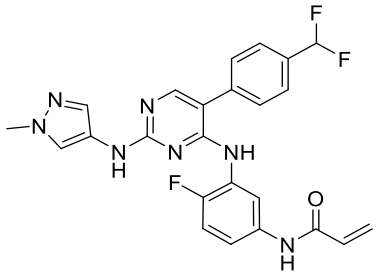
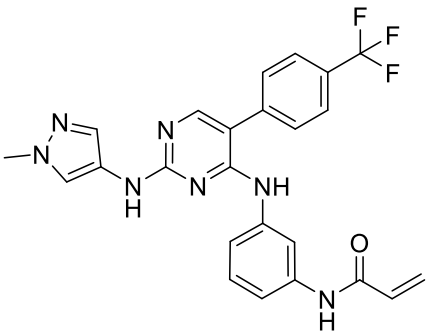
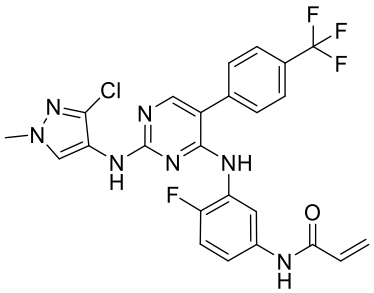
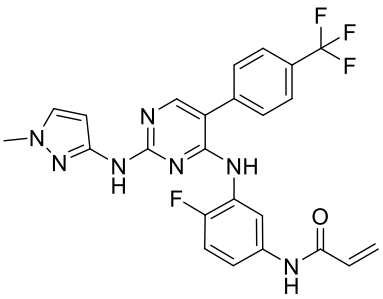
Formula I-G;

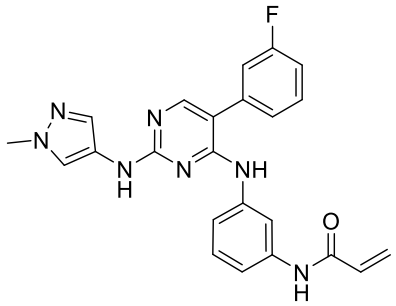
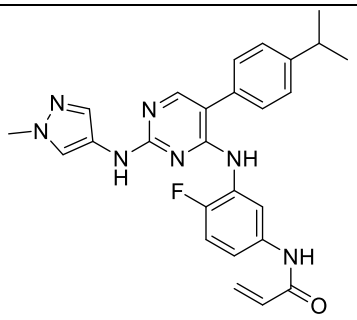
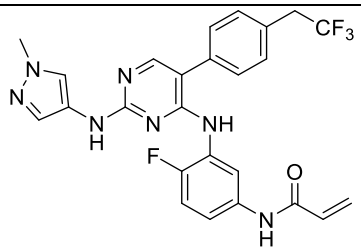
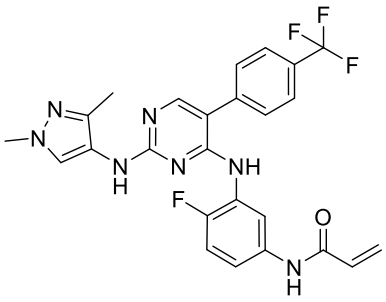
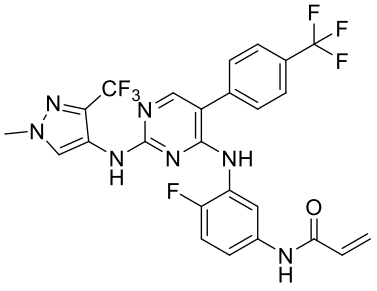
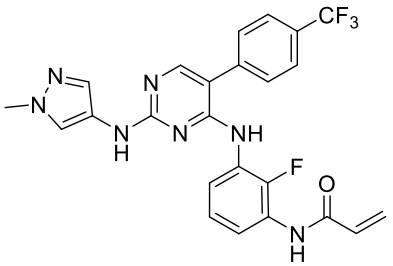
or a pharmaceutically acceptable salt or stereoisomer thereof.

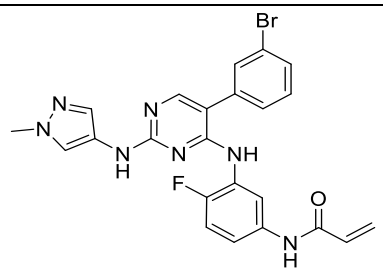
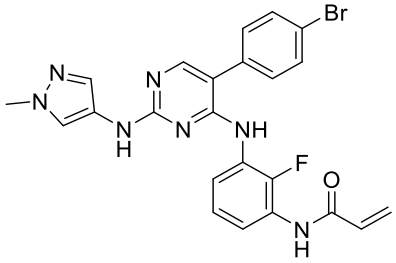
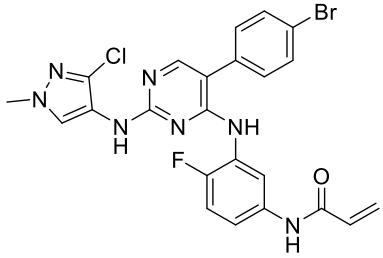
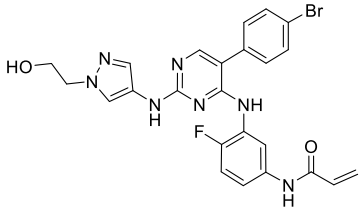
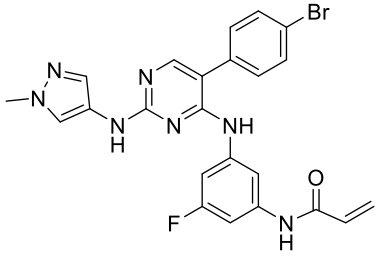
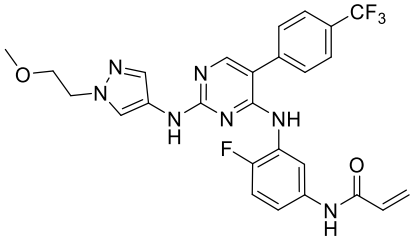
14. The compound of claim 1, wherein the compound is selected from:

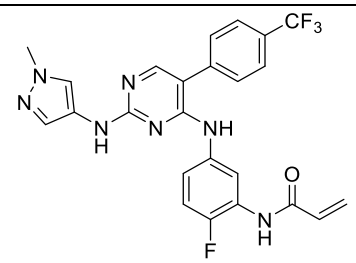
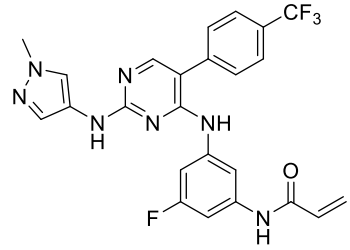
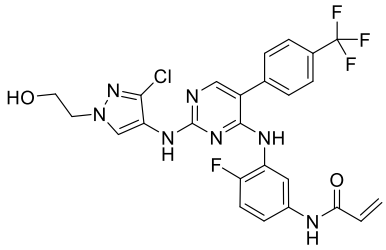
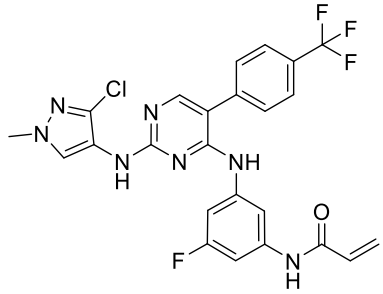
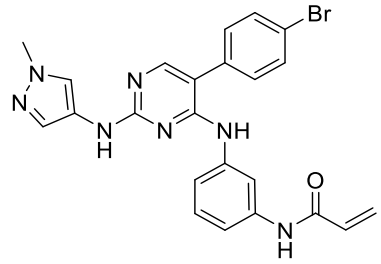
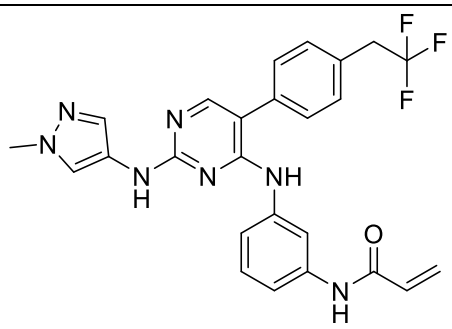
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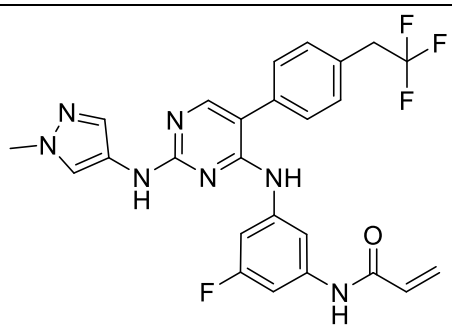
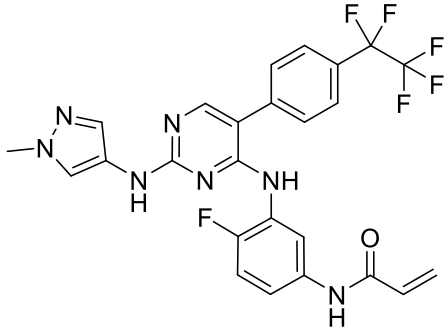
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, or a pharmaceutically acceptable salt of any of the foregoing.

15. A pharmaceutical composition comprising a compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt or stereoisomer thereof, and a pharmaceutically acceptable carrier.

16. Use of a compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of claim 15, in the manufacture of a medicament for treating cancer.

17. The use of claim 16, wherein the cancer is bladder cancer, prostate cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, or non-small cell lung cancer.

18. The use of claim 17, wherein the EGFR mutation comprises a substitution in exon 20 or an insertion in exon 20.

19. The use of claim 18, wherein the EGFR mutation is selected from del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR,763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG

EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, A767_dupASV EGFR, 773insAH EGFR, M766_A767insAI EGFR, and any combination thereof.

20. A compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt or stereoisomer thereof, or a pharmaceutical composition of claim 15, for use in therapy.