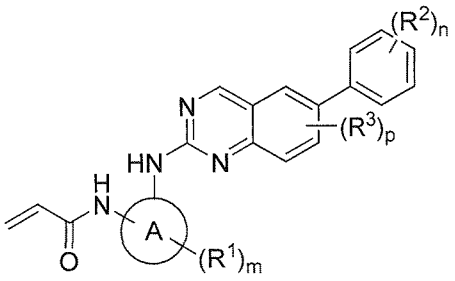
In some embodiments, ring A is bicyclic cycloalkyl.

In some embodiments, ring A is heterocyclyl. In some embodiments, ring A is pyrrolidinyl, piperidinyl, tetrahydrofuranyl, or tetrahydropyranyl. In some embodiments, R^3 is, independently, halo.

In an embodiment, the present disclosure features a compound of Formula II, or a pharmaceutically acceptable salt thereof:



Formula II

wherein

ring A is a 3-6 membered cycloalkyl or heterocyclyl;

R^1, is, independently, halo, cyano, C_{1-6} alkoxy, hydroxy, oxo, amino, amido, sulfonyl, sulfonamido, ester, alkyl urea, C_{1-6} alkyl, -C(O)O-, -C(O)-C_{1-6} alkyl, -C(O)-C_{1-6} alkylamino, or C_{1-6} heteroalkyl;

R^2 is halo, or C_{1-6} alkoxy;

R^3 is halo; and

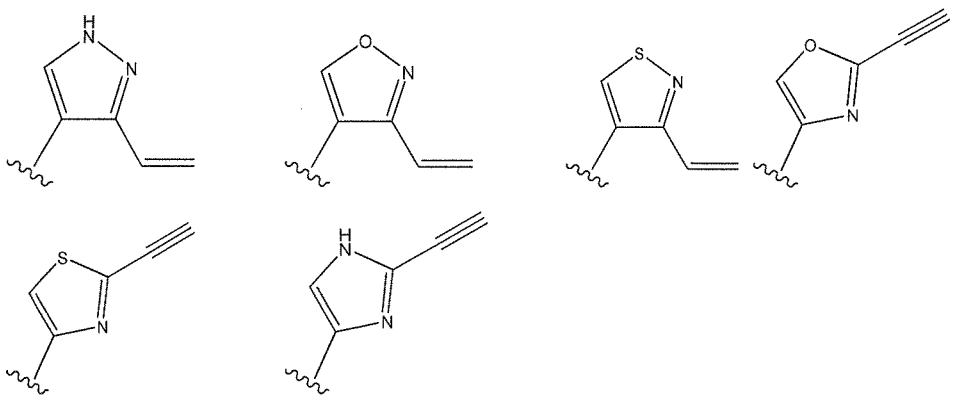
m is 0-1; n is 0-4; and p is 0-1.

In some embodiments, ring A is cycloalkyl.

In some embodiments, ring A is heterocyclyl. In some embodiments, R^3 is, independently, halo.

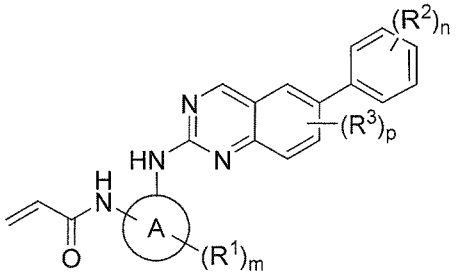
In some embodiments, ring A is cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl, or tetrahydropyranyl.

In the compounds disclosed herein, a warhead is a moiety that is reactive with a nucleophile, for example, capable of forming a covalent bond with a nucleophile. Examples of warheads include, without limitation, alkyl halides, alkyl sulfonates, heteroaryl halides, epoxides, haloacetamides, maleimides, sulfonate esters, alpha-beta unsaturated ketones, alpha-beta unsaturated esters, vinyl sulfones, propargyl amides, acrylamides. In some of these instances,



Other examples of warheads can be found, *e.g.*, in WO 2010/028236 and WO 2011/034907.

In one aspect, there is provided a compound of Formula II, or a pharmaceutically acceptable salt thereof:



Formula II

wherein:

ring A is atetrahydrofuranyl or tetrahydropyranyl;

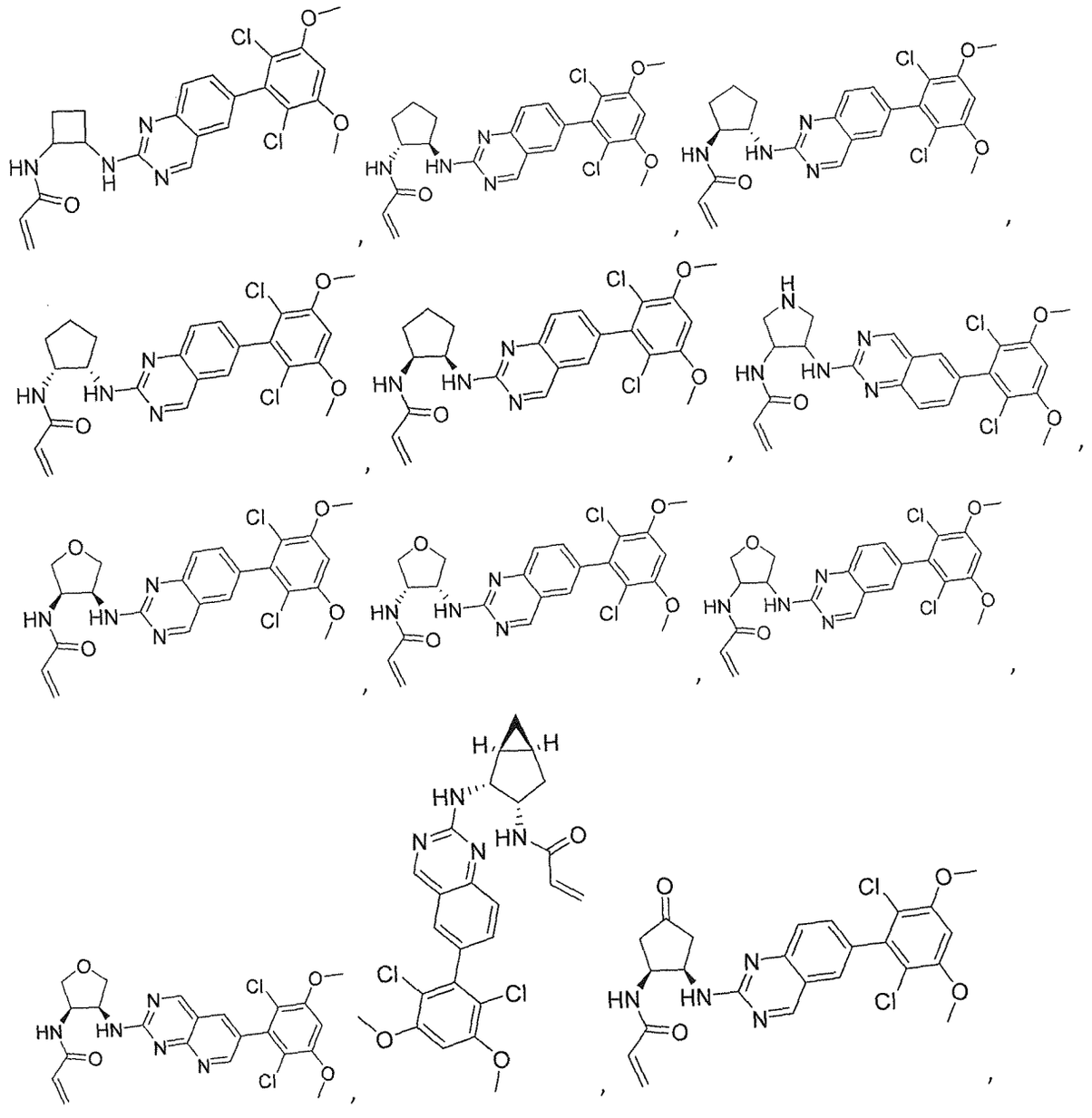
R^1 is halo, cyano, C_{1-6} alkoxy, hydroxy, oxo, amino, amido, or C_{1-6} alkyl;

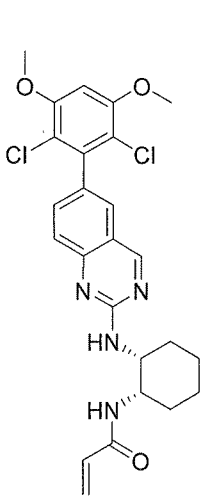
each R^2 is, independently, halo or C_{1-6} alkoxy;

R^3 is halo; and

m is 0-1; n is 1-4; and p is 0-1.

In another aspect, there is provided a compound selected from the compounds below, or a pharmaceutically acceptable salt thereof:

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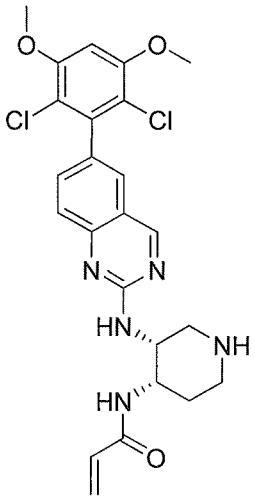
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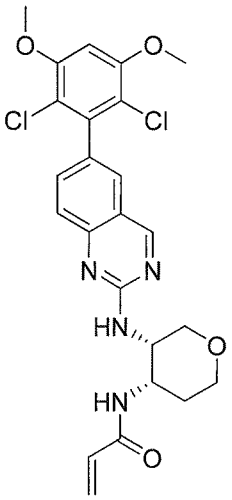
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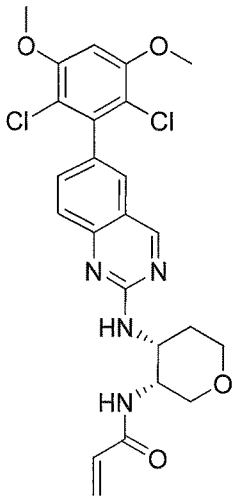
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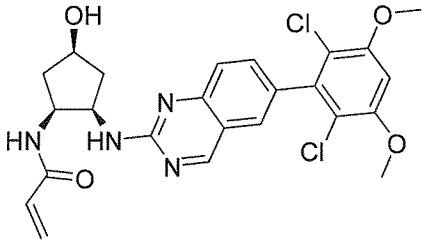
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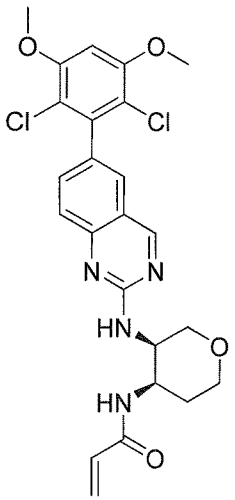
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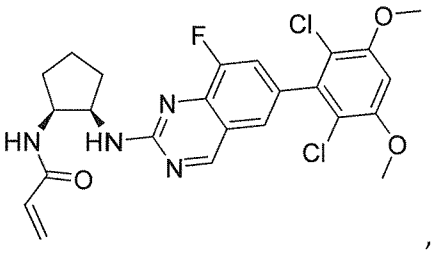
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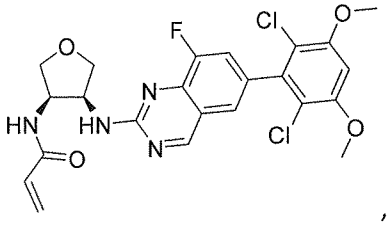
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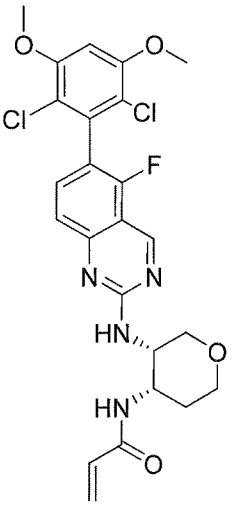
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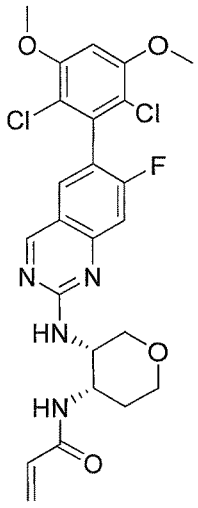
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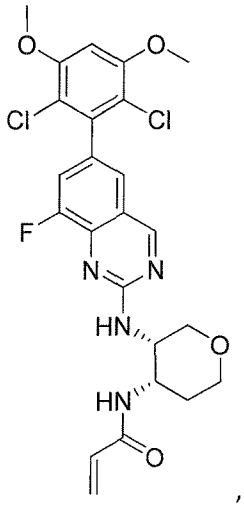
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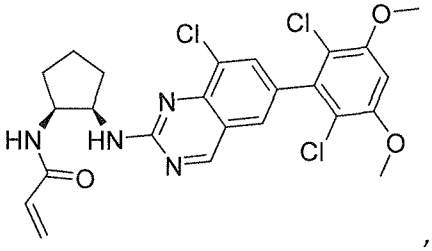
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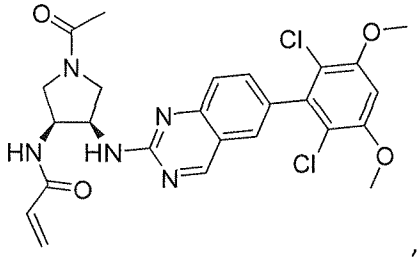
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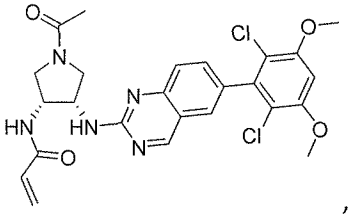
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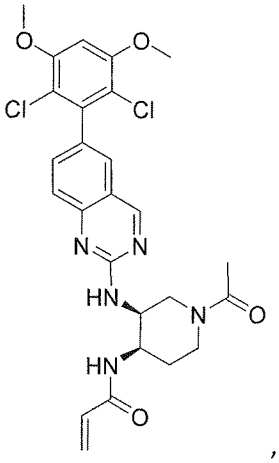
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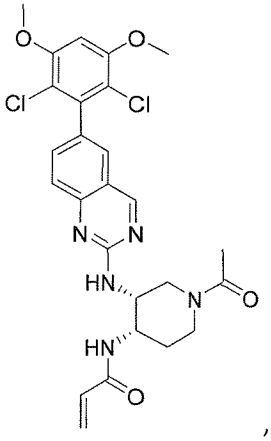
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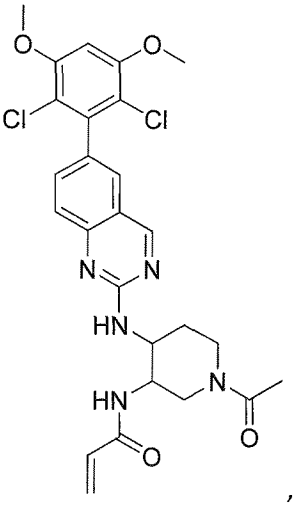
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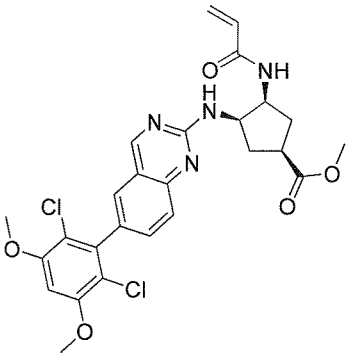
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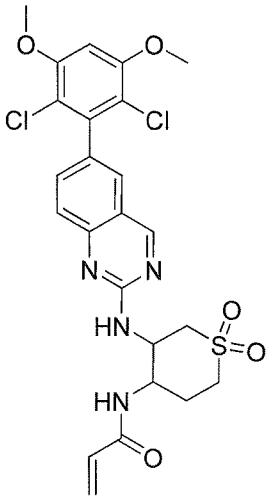
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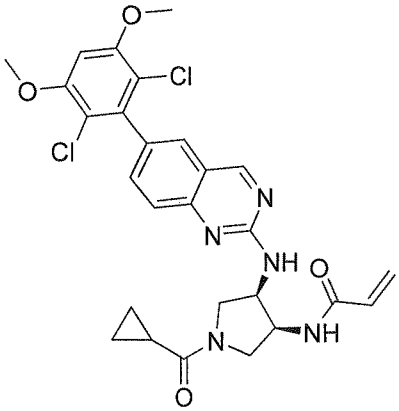
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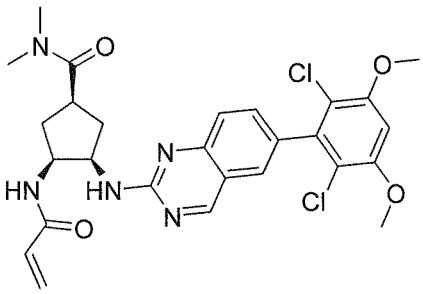
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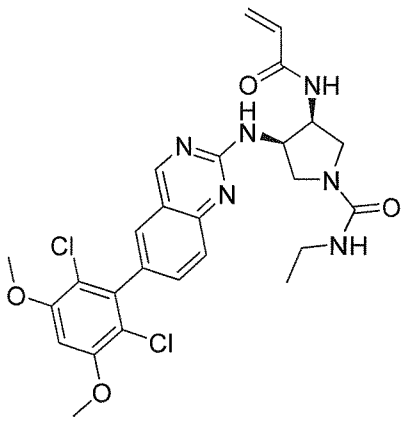
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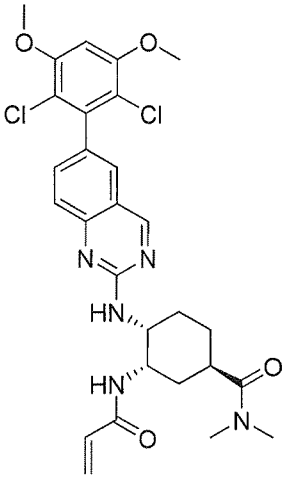
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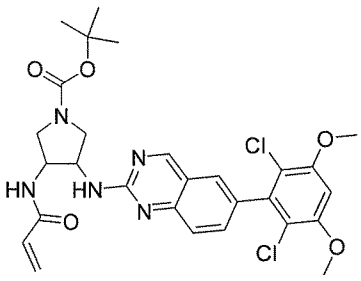
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In certain embodiments, the FGFR-4 inhibitors of the present disclosure inhibit FGFR-4 activity more potently than they inhibit FGFR-1 activity. For example, the FGFR-4 inhibitors of the present disclosure can inhibit FGFR-4 activity at least 10 times, at least 50 times, at least 100 times, at least 200 times, or at least 500 times more potently than they inhibit FGFR-1 activity.

In one embodiment, selectivity is measured by comparing the inhibition of FGFR-1 and FGFR-4 caused by the compound of this disclosure in the same type of assay. In one embodiment, the assays used to measure inhibition of FGFR-1 and FGFR-4 are any of the assays described herein. Typically, inhibition is expressed as IC_{50} (the concentration of inhibitor at which 50% of the activity of the enzyme is inhibited) and thus fold-selectivity is measured by the equation:

(IC_{50} FGFR-1)/ (IC_{50} FGFR-4). The same measurements and calculations can be used to measure selectivity over FGFR-2 and FGFR-3 as well.

Any other assays of FGFR activity may be utilized to determine the relative inhibition of FGFR-1and FGFR-4 by the compounds of this disclosure as long as such assays utilize what one of skill in the art would deem to be the same parameters in measuring FGFR activity.

In another aspect, the present disclosure features a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound disclosed herein.

In another embodiment the present disclosure features a method for treating a condition mediated by FGFR-4, a condition characterized by overexpression of FGFR-4, a condition characterized by amplification of FGFR4, a condition mediated by FGF19, a condition characterized by amplified FGF-19, or a condition characterized by overexpression of FGF19, any of these methods comprising administering a therapeutically effective amount of a compound disclosed herein to a subject.

In another embodiment, the present disclosure features a method of treating any of the following conditions by administering a therapeutically effective amount of a compound disclosed herein to a subject: hepatocellular carcinoma, breast cancer, ovarian cancer, lung cancer, liver cancer, a sarcoma, or hyperlipidemia.

In an aspect, there is provided the use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition mediated by FGFR-4.

In another aspect, there is provided the use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition characterized by overexpression of FGFR-4.

In another aspect, there is provided the use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition characterized by amplified FGF-19.

In another aspect, there is provided the use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition characterized by overexpression of FGF-19.

In another aspect, there is provided the use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating cancer, wherein the cancer is selected from liver cancer, breast cancer, lung cancer, ovarian cancer, and a sarcoma.

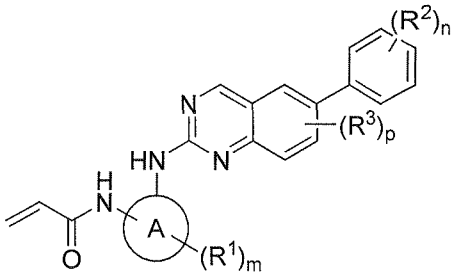
In another aspect, there is provided the use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating hepatocellular carcinoma.

In another aspect, there is provided the use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating hyperlipidemia.

The invention includes all possible combinations of the embodiments described above and below.

We claim:

1. A compound of Formula II, or a pharmaceutically acceptable salt thereof:



Formula II

wherein:

ring A is atetrahydrofuranyl or tetrahydropyranyl;

R^1 is halo, cyano, C_{1-6} alkoxy, hydroxy, oxo, amino, amido, or C_{1-6} alkyl;

each R^2 is, independently, halo or C_{1-6} alkoxy;

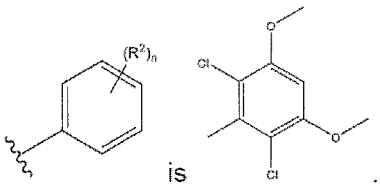
R^3 is halo; and

m is 0-1; n is 1-4; and p is 0-1.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring A is tetrahydrofuranyl.

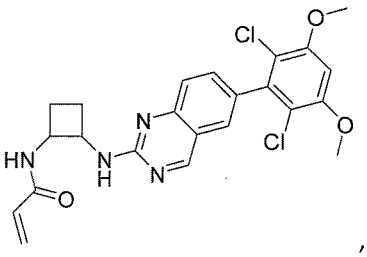
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein ring A is tetrahydropyranyl.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein the portion of the compound represented by



is .

5. A compound selected from the compounds below, or a pharmaceutically acceptable salt thereof:



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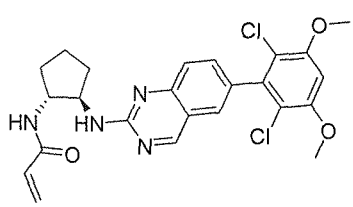
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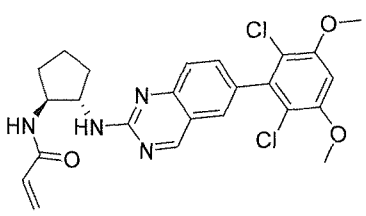
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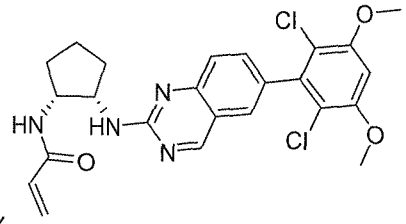
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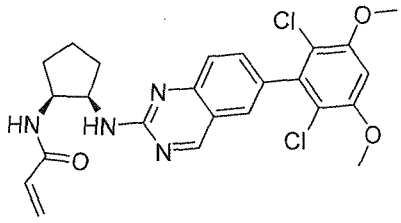
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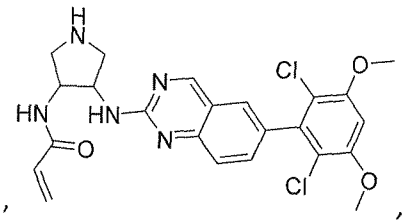
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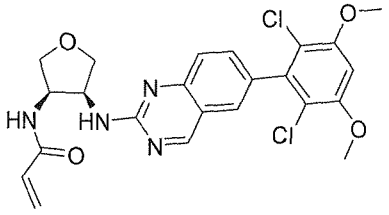
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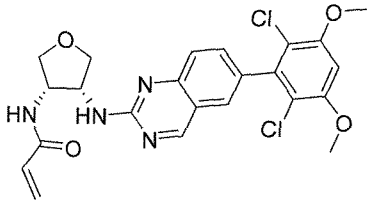
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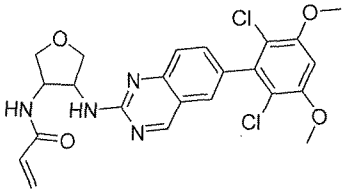
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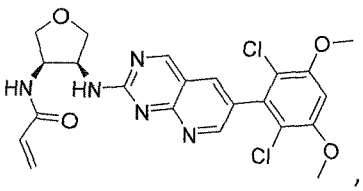
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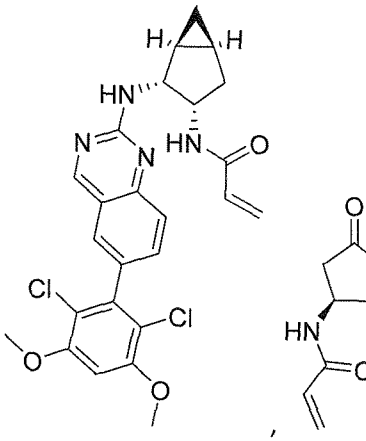
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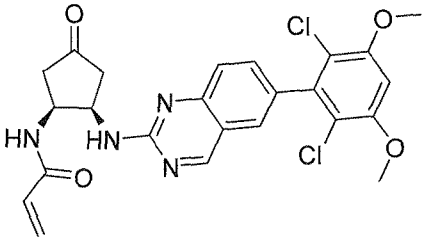
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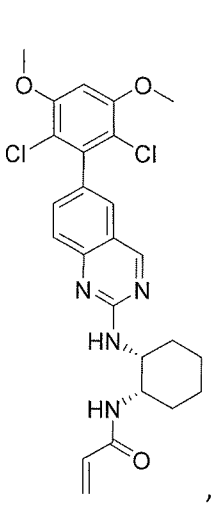
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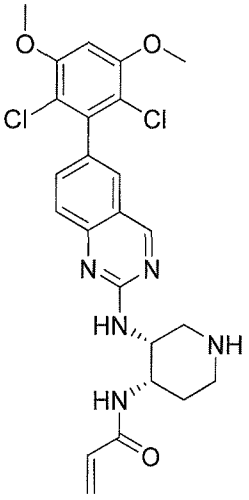
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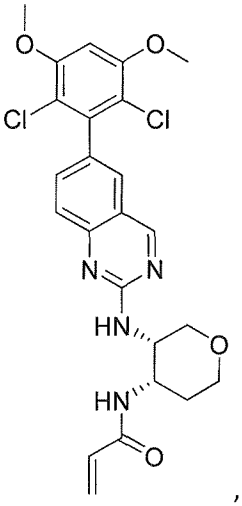
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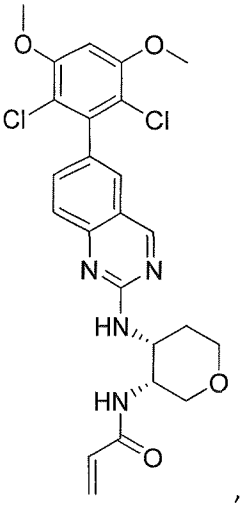
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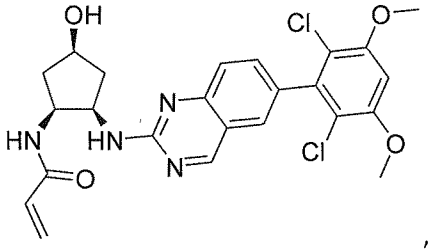
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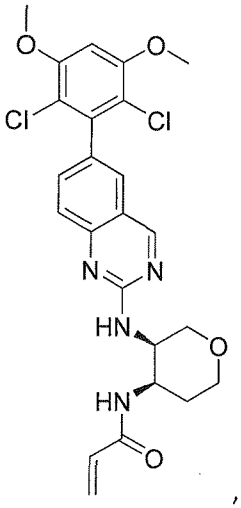
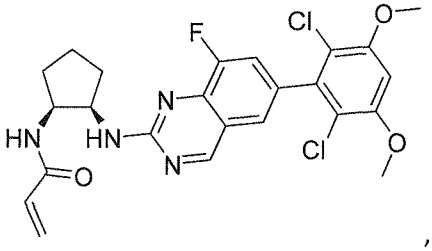
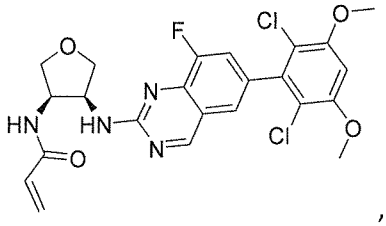
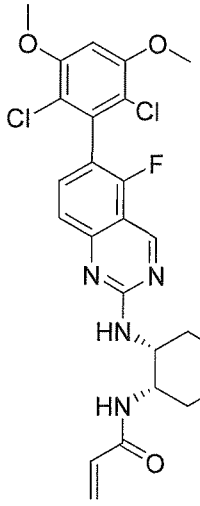
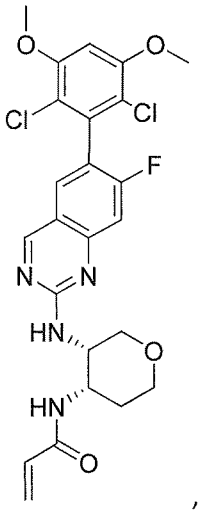

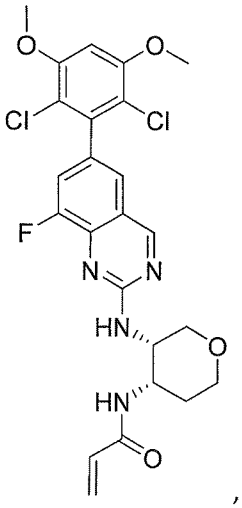
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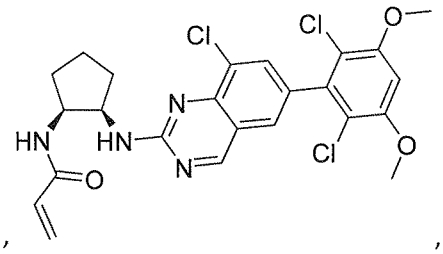
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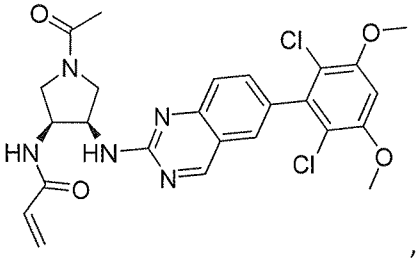
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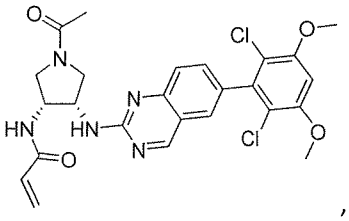
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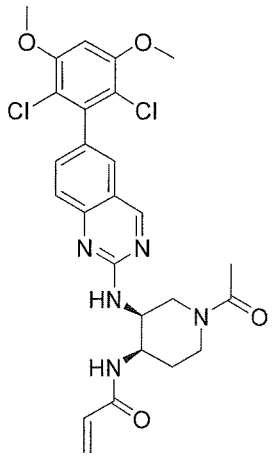
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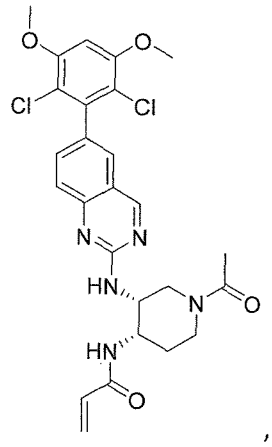

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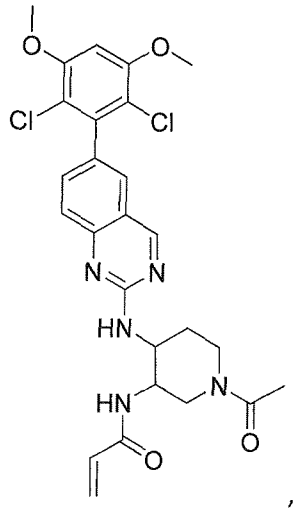

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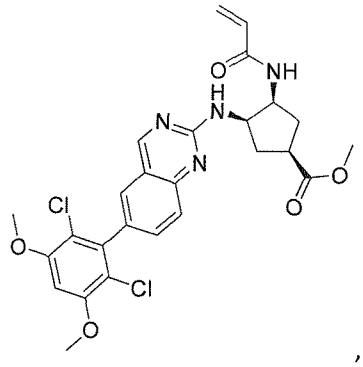

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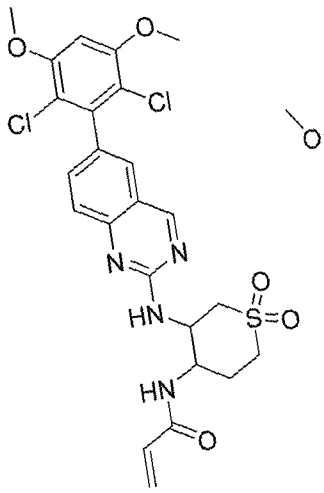
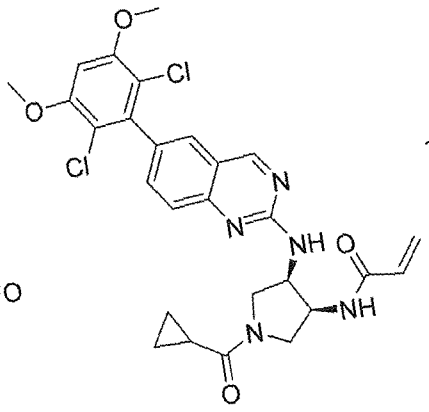
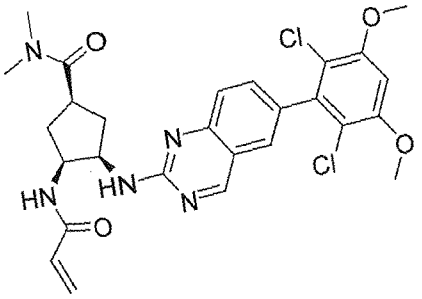
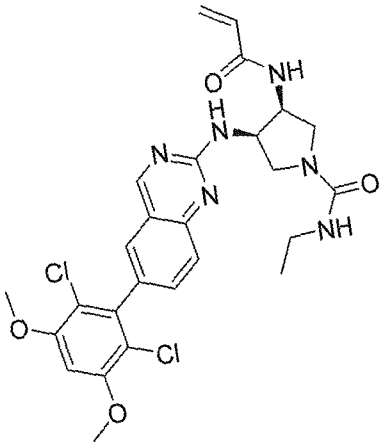
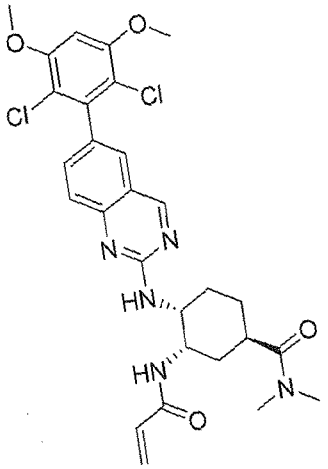
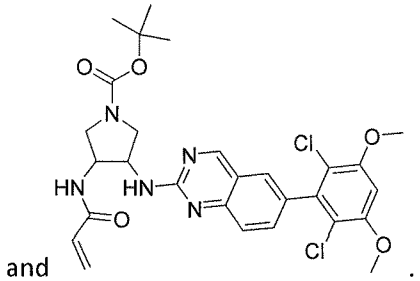




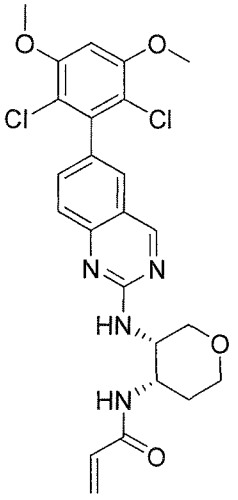






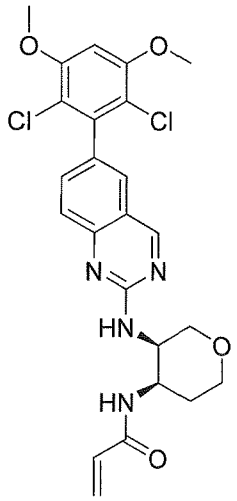
and  .

6. A compound which is



or a pharmaceutically acceptable salt thereof.

7. A compound which is



or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof.

9. Use of a compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating a condition mediated by FGFR-4.

10. Use of a compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating a condition characterized by overexpression of FGFR-4.

11. Use of a compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating a condition characterized by amplified FGF-19.

12. Use of a compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating a condition characterized by overexpression of FGF-19.

13. Use of compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8, in the manufacture of a medicament for treating cancer, wherein the cancer is selected from liver cancer, breast cancer, lung cancer, ovarian cancer, and a sarcoma.

14. Use of a compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating hepatocellular carcinoma.

15. Use of a compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating hyperlipidemia.