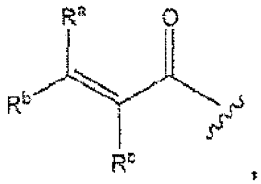
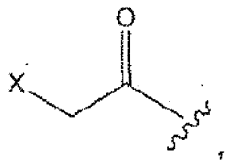
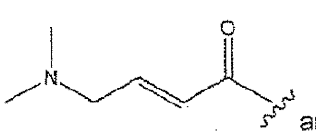
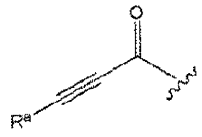
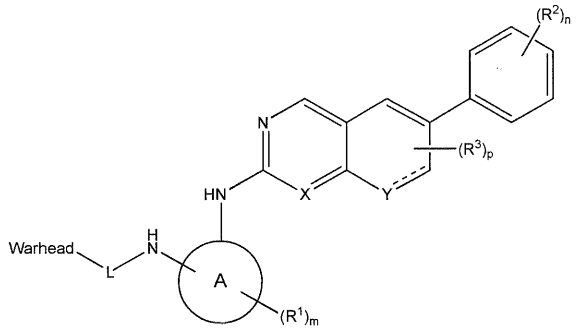
Warhead is selected from:  

 and , wherein the X group of the Warhead is a leaving group selected from

halo and triflate; and each of R^a, R^b, and R^c is, independently, H; substituted or unsubstituted C_{1-4} alkyl; or substituted or unsubstituted C_{1-4} cycloalkyl.

In one embodiment, the disclosure features a compound of Formula 1, or pharmaceutically acceptable salt thereof:



Formula I

wherein Warhead is a moiety that is capable of forming a covalent bond with a nucleophile; ring A is a 3-8 membered aryl, heteroaryl, heterocyclic or alicyclic group; X is CH or N; Y is CH or N-R^4 where R^4 is H or C_{1-6} alkyl; L is $-[C(R^5)(R^6)]_q-$, where each of R^5 and R^6 is, independently, H or C_{1-6} alkyl; and q is 0-4; each of R^1-R^3 is, independently, halo, cyano, optionally substituted C_{1-6} alkoxy, hydroxy, oxo, amino, amido, alkyl urea, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heterocyclyl; m is 0-3; n is 0-4; and p is 0-2. In some embodiments, ring A is phenyl, e.g., a 1,2-disubstituted phenyl; R^2 is halo or methoxy; n is 2 or 4; X is N; R^1 is methyl; and/or m is 1.

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

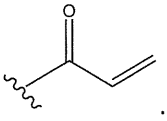
Typically, inhibition is expressed as IC_{50} (the concentration of inhibitor at which 50% of the activity of the enzyme is inhibited) and thus fold-selectivity is measured by the equation: (IC_{50} FGFR-1)/ (IC_{50} FGFR-4). The same measurements and calculations can be used to measure selectivity over 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, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound disclosed herein.

In another embodiment, the disclosure features a covalent inhibitor of FGFR-4. In some embodiments, the covalent inhibitor of FGFR-4 inhibits FGFR-4 activity more potently, when measured in a biochemical assay, than it inhibits FGFR-1 activity. The inhibitor can contain a warhead.

In another embodiment, the disclosure features a compound that inhibits FGFR-4 activity more potently, when measured in a biochemical assay, than it inhibits FGFR-1 activity, wherein the compound has a molecular weight of less than 1500 daltons. For example, the compound can inhibits FGFR-4 activity at least 10, 50, 100, 200, or 500 times more potently, when measured in a biochemical assay, than it inhibits FGFR-1 activity. In some instances, this compound can form a covalent bond to FGFR-4, e.g. with Cys 522 of FGFR-4.

In another embodiment, the disclosure features an inhibited FGFR-4 protein comprising an inhibitor having a covalent bond to a cysteine residue of FGFR-4. The covalent bond can be formed between a portion of a warhead moiety on the inhibitor and a portion of a cysteine residue of FGFR-4, e.g., cysteine residue 552 of the protein. The warhead can be .

In another embodiment the 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 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 one aspect, there is provided a compound or pharmaceutical composition as defined herein for use as a medicament.

In one aspect, there is provided use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for treatment of a condition mediated by FGFR-4.

In one aspect, there is provided use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a condition characterized by overexpression of FGFR-4.

In one aspect, there is provided a compound or pharmaceutical composition as defined herein for use in the treatment of a disorder selected from hepatocellular carcinoma, breast cancer, ovarian cancer, lung cancer, liver cancer, a sarcoma, and hyperlipidemia.

In one aspect, there is provided the use of a compound or pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of a disorder selected from hepatocellular carcinoma, breast cancer, ovarian cancer, lung cancer, liver cancer, a sarcoma, and hyperlipidemia.

The disclosure includes all possible combinations of the embodiments described above.

Brief Description of Drawings

Fig. 1 is a spectrum showing masses for FGFR4 protein without, and with bound inhibitor.

Fig. 2 is a spectrum showing masses for FGFR4 protein without, and with bound inhibitors.

Fig. 3 is a graph showing caspase activity of a Compound 25.

Fig. 4 is a drawing of the crystal structure of Compound 52 bound to FGFR4 protein.

Fig. 5 is a drawing of the crystal structure of Compound 25 bound to FGFR4 protein.

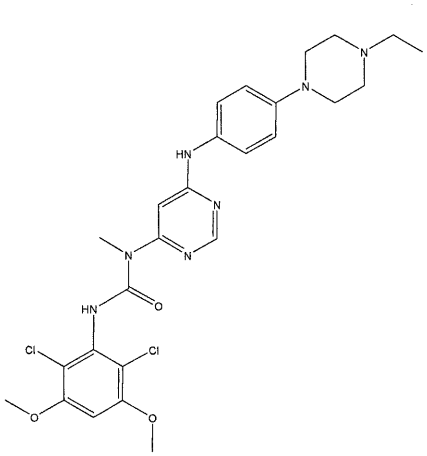
Fig. 6 is a line graph depicting the antitumor effect of Compound 25.

Fig. 7 is a bar graph depicting the tumor weights of Hep3B-bearing nude mice.

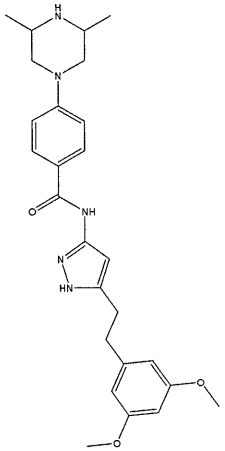
Fig. 8 is a line graph depicting body weight change (%) of Hep3B-bearing nude mice.

Detailed Description

Pan-FGFR inhibitors, such as BGJ398 and AZD4547, are known.



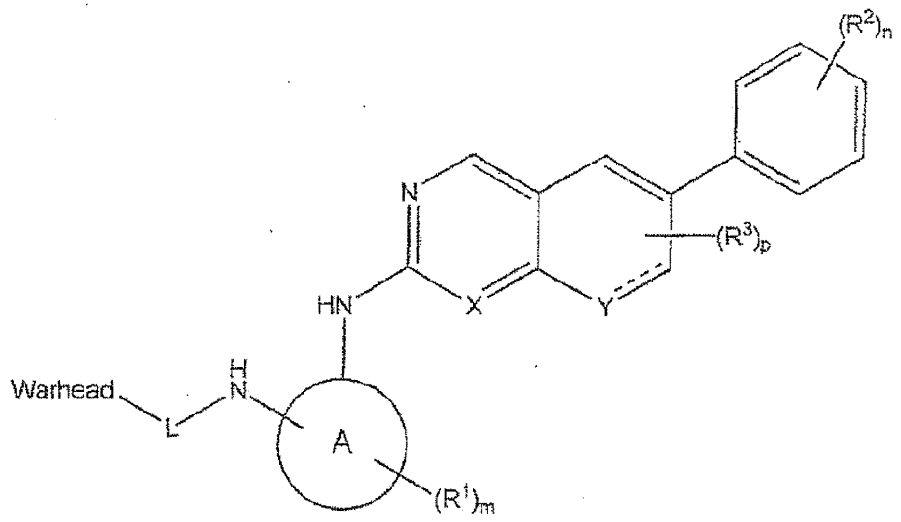
BGJ398



AZD4547

Claims

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



Formula I

wherein:

ring A is a 3-8 membered aryl, heteroaryl, heterocyclic or alicyclic group;

X is CH or N;

Y is CH or N-R^4 where R^4 is H or C_{1-6} alkyl;

L is -$[C(R^5)(R^6)]_q$-, where each of R^5 and R^6 is, independently, H or C_{1-6} alkyl; wherein q is 0-4;

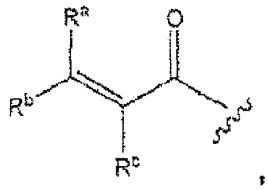
each R^1, R^2 and R^3 is independently, halo, cyano, optionally substituted C_{1-6} alkoxy, hydroxy, oxo, amino, amido, alkyl urea, optionally substituted C_{1-6} alkyl, or optionally substituted C_{1-6} heterocyclyl;

m is 0-3;

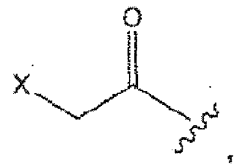
n is 4;

p is 0-2; and

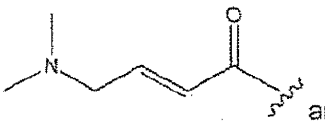
Warhead is selected from:



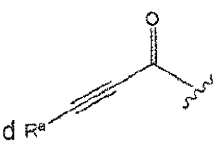
,



,



and



, wherein the X group of the Warhead is a leaving group selected from

13. A compound or pharmaceutical composition of any of claims 1 to 12 for use as a medicament.

14. Use of a compound or pharmaceutical composition of any of claims 1 to 12 in the manufacture of a medicament for treatment of a condition mediated by FGFR-4.

15. Use of a compound or pharmaceutical composition of any of claims 1 to 12 in the manufacture of a medicament for treatment of a condition characterized by overexpression of FGFR-4.

16. A compound or pharmaceutical composition of any of claims 1 to 12 for use in the treatment of a disorder selected from hepatocellular carcinoma, breast cancer, ovarian cancer, lung cancer, liver cancer, a sarcoma, and hyperlipidemia.

17. Use of a compound or pharmaceutical composition of any of claims 1 to 12 in the manufacture of a medicament for the treatment of a disorder selected from hepatocellular carcinoma, breast cancer, ovarian cancer, lung cancer, liver cancer, a sarcoma, and hyperlipidemia.