

In some embodiments, R^{12} is selected from the group consisting of: hydrogen, fluoro, chloro, methyl, methoxy, N,N-dimethylaminoethyl, piperazin-1-yl, 4-ethylpiperazin-1-yl, 4-ethylpiperazin-1-yl-methyl, 1-methylpiperidine-4-yl, 1-ethylpiperidine-4-yl, N,N-dimethylaminomethyl, N,N-dimethylaminopropyl, piperidine-4-yl, morpholino, 3,5-dimethylpiperazin-1-yl, 4-(methylsulfonyl)piperazin-1-yl, N,N-dimethylaminoethoxy, 4-(2-hydroxyethyl)piperazin-1-yl, hydroxyethoxy, methoxyethoxy, hydroxymethyl, methoxymethyl, 2-methoxypropyl, 2-hydroxypropyl, 2-aminopropyl, 4-methylpiperazin-1-yl-carbonyl, 4-ethylpiperazin-1-yl-carbonyl, 4-[2-propyl]piperazin-1-yl, 4-acetyl piperazin-1-yl, N-methyl-N-hydroxyethyl-amino, N,N-dimethylamido, and 4-(2-aminoethyl)piperazin-1-yl.

In some embodiments, R^{12} is selected from the group consisting of: hydrogen, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, R^5R^6 heterocyclyl, R^5R^6 heterocyclyl C_{1-6} alkyl, $-C(O)NR^5R^6$, $NR^5R^6C_{1-6}$ alkyl, $NR^5R^6C_{1-6}$ alkoxy, C_{1-6} alkoxy, and C_{1-6} alkoxy C_{1-6} alkyl, wherein R^5 and R^6 are each independently selected from the group consisting of: hydrogen, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl and C_{1-6} alkylsulfonyl.

In some embodiments, R^{12} is R^5R^6 heterocyclyl, wherein R^5 and R^6 are as defined above.

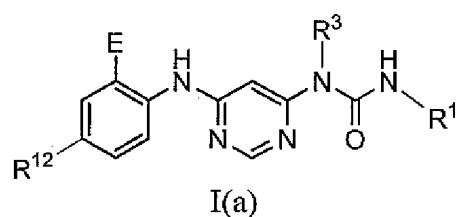
In some embodiments, R^5R^6 heterocyclyl is R^5R^6 piperazinyl, wherein R^5 and R^6 are as defined above.

In some embodiments, R^{12} is 4-ethylpiperazin-1-yl.

In some embodiments, R^{12} is not hydrogen.

In some embodiments, R^1 is 2,6-dichloro-3,5-dimethoxyphenyl.

In some embodiments, the compound is a compound of Formula I(a):



wherein R^3 , E, R^{12} and R^1 are as defined above,

or a pharmaceutically acceptable salt thereof.

A further purpose is a pharmaceutical composition comprising a compound or salt as described herein and a pharmaceutically acceptable carrier. In some embodiments, the composition is formulated for oral or parenteral administration.

Also described herein is a method of treating hepatocellular carcinoma in a subject in need thereof comprising administering to said subject a treatment effective amount of a compound or

salt or composition as described herein. In some examples, hepatocellular carcinoma has altered FGFR4 and/or FGF19 status (e.g., increased expression of FGFR4 and/or FGF19).

Also described herein is a method of treating hepatocellular carcinoma in a subject in need thereof, comprising: detecting an altered FGFR4 and/or FGF19 status (e.g., increased expression of FGFR4 and/or FGF19) in a biological sample containing cells of said hepatocellular carcinoma, and if said hepatocellular carcinoma has said altered FGFR4 and/or FGF19 status, administering a compound or composition described herein to said subject in a treatment-effective amount.

Another aspect of the present invention is the use of a compound or salt or a composition as described herein in the manufacture of a medicament for treating hepatocellular carcinoma.

Another aspect of the present invention refers to the compound or salt described herein for use as a medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 presents the results of *in vivo* efficacy testing in hepatocellular carcinoma model using HUH7 cells. Compound 108 (25 mg/kg or 37.5 mg/kg) or Vehicle control was administered via intraperitoneal injection, and tumor volume was measured twice weekly over the course of 15 days.

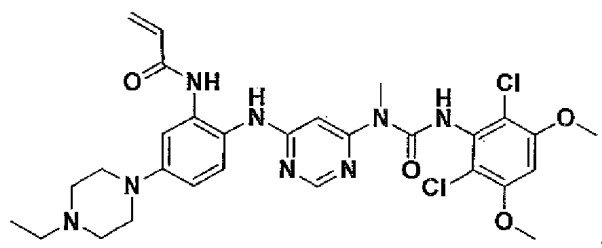
FIG. 2 presents the results of *in vivo* efficacy testing in hepatocellular carcinoma model using HEP3B cells. Compound 108 (12.5 mg/kg, 25 mg/kg or 37.5 mg/kg) or Vehicle control was administered via intraperitoneal injection, and tumor volume was measured twice weekly over the course of 15 days.

FIG. 3 presents the results of *in vivo* efficacy testing in hepatocellular carcinoma model using JHH7 cells. Compound 108 (12.5 mg/kg, 25 mg/kg or 37.5 mg/kg) or Vehicle control was administered via intraperitoneal injection, and tumor volume was measured twice weekly over the course of 15 days.

FIG. 4 presents the results of comparative *in vivo* efficacy testing in hepatocellular carcinoma model using HEP3B cells. Compound 108 (25 mg/kg, 37.5 mg/kg or 50 mg/kg) was administered twice daily via intraperitoneal injection, or BGJ398 (30 mg/kg or 60 mg/kg) was administered orally twice daily.

DETAILED DESCRIPTION OF EMBODIMENTS

Provided herein are compounds useful as FGFR4 inhibitors. In some embodiments, the compounds are selective FGFR4 inhibitors in that they have a greater binding affinity and/or



or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound or salt of any one of claims 1-17 and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition of claim 18, wherein said composition is formulated for oral, intravenous or subcutaneous administration.

20. Use of a compound or salt of any one of claims 1-17 or the pharmaceutical composition

of any one of claims 18 or 19 in the manufacture of a medicament for treating hepatocellular carcinoma.

21. The use of claim 20, wherein said hepatocellular carcinoma has altered FGFR4 and/or FGF19 status.

22. The use of claim 21, wherein said altered FGFR4 and/or FGF19 status comprises increased expression of FGFR4 and/or FGF19.

23. A compound or salt of any one of claims 1-17 for use as a medicament.