Infigratinib

Cat. No.: HY-13311

CAS No.: 872511-34-7

Molecular Formula: $C_{26}H_{31}Cl_2N_7O_3$

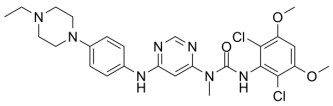
Molecular Weight: 560.48

Target: FGFR; Apoptosis

Pathway: Protein Tyrosine Kinase/RTK; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 12 mg/mL (21.41 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7842 mL	8.9209 mL	17.8419 mL
5 mM	0.3568 mL	1.7842 mL	3.5684 mL
10 mM	0.1784 mL	0.8921 mL	1.7842 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 1.67 mg/mL (2.98 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1.67 mg/mL (2.98 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1.57 mg/mL (2.80 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 0.6 mg/mL (1.07 mM); Clear solution
5. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.6 mg/mL (1.07 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Infigratinib (BGJ-398; NVP-BGJ398) is a potent inhibitor of the FGFR family with IC_{50}s of 0.9 nM, 1.4 nM, 1 nM, and 60 nM for FGFR1, FGFR2, FGFR3, and FGFR4, respectively.

IC_{50} & Target	FGFR1	FGFR2	FGFR3	FGFR4
	0.9 nM (IC_{50})	1.4 nM (IC_{50})	1 nM (IC_{50})	60 nM (IC_{50})

In Vitro

Infigratinib (BGJ-398) inhibits FGFR1, FGFR2, and FGFR3 with IC_{50}=~1 nM, $FGFR3^{K650E}$ with IC_{50}=4.9 nM, and FGFR4 with IC_{50} =60 nM. IC_{50} values for all other kinases are in the μM range (FYN, LCK, YES, and ABL, IC_{50}=1.9, 2.5, 1.1, and 2.3 μM, respectively) except for VEGFR2, KIT, and LYN, which are inhibited at submicromolar concentrations (IC_{50}=0.18, 0.75, and 0.3 μM, respectively).

Infigratinib (BGJ-398) inhibits the proliferation of the FGFR1-, FGFR2-, and FGFR3-dependent BaF3 cells with IC_{50} values which are in the low nanomolar range and comparable to those observed for the inhibition of the receptors kinase activity in the enzymatic assay.

For the remaining cells, all IC_{50} values are greater than 1.5 μM except for VEGFR2 (IC_{50} 1449 and 938 nM), for which there is at least a 400-fold selectivity versus FGFR1, FGFR2, and FGFR3[1].

Infigratinib (BGJ-398) (ranging between 1 nM and 10 μM) is potent at inhibiting cell growth of FGFR2-mutant endometrial cancer cells[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Infigratinib (BGJ-398) is administered to athymic nude mice implanted subcutaneously with RT112/luc1 tumors: either as a 5 mg/kg intravenous bolus in NMP/PEG200 (1:9, v/v) or orally by gavage as a suspension in PEG300/D5W (2:1, v/v) at a 20 mg/kg dose.The relevant pharmacokinetic (PK) parameters indicate that the oral bioavailability of Infigratinib (BGJ-398) in this study is 32%. After intravenous dosing, Infigratinib (BGJ-398) shows a rapid distribution from the vascular compartment into the peripheral tissues, translating into a high volume of distribution (26 L/kg). The plasma clearance is high at 3.3 L/h/kg (61% of liver blood flow). The ratio of tumor to plasma after oral dosing based on AUC is determined to be 10[1].

Infigratinib (BGJ-398) (30 mg/kg) significantly inhibits the growth of FGFR2-mutated endometrial cancer xenograft models[2] .

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

The enzymatic kinase activity is assessed by measuring the phosphorylation of a synthetic substrate by the purified GST-fusion FGFR3-K650E kinase domain, in the presence of radiolabeled ATP. Enzyme activities are measured by mixing 10 μL of a 3-fold concentrated NVP-BGJ398 solution or control with 10 μL of the corresponding substrate mixture (peptidic substrate, ATP and [γ^{33}P]ATP). The reactions are initiated by addition of 10 μL of a 3-fold concentrated solution of the enzyme in assay buffer. The final concentrations of the assay components are as following: 10 ng of GST-FGFR3-K650E, 20 mM Tris-HCl, pH 7.5, 3 mM $MnCl_2$, 3 mM $MgCl_2$, 1 mM DTT, 250 μg/mL PEG 20000, 2 μg/mL poly(EY) 4:1, 1% DMSO and 0.5 μM ATP (γ-[^{33}P]-ATP 0.1 μCi). The assay is carried out according to the filter binding (FB) method in 96-well plates at room temperature for 10 min in a final volume of 30 μL including the components as indicated above. The enzymatic reactions are stopped by the addition of 20 μL of 125 mM EDTA, and the incorporation of ^{33}P into the polypeptidic substrates is quantified as following: 30 μL of the stopped reaction mixture are transferred onto Immobilon-PVDF membranes previously soaked for 5 min with methanol, rinsed with water, soaked for 5 min with 0.5% H_3PO_4, and mounted on vacuum manifold with disconnected vacuum source. After spotting, vacuum is connected, and each well rinsed with 0.5% H_3PO_4 (200 μL). Free membranes are removed and washed four times on a shaker with 1% H_3PO_4 and once with ethanol. Membranes are dried and overlaid with addition of 10 μL/well of a scintillation fluid. The plates are eventually sealed and counted in a microplate scintillation counter. IC_{50} values are calculated by linear regression analysis of the percentage inhibition of NVP-BGJ398[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [1]

Murine BaF3 cell lines are cultured in RPMI-1640 media supplemented with 10% FBS, 4.5 g/L glucose, 1.5 g/L sodium bicarbonate, and Pen/Strep. Cells are passaged twice weekly. Compound-mediated inhibition of BaF3 cell proliferation and viability is assessed using a Luciferase bioluminescent assay. Exponentially growing BaF3 or BaF3 Tel-TK cells are seeded into 384-well plates (4250 cells/well) at 50 μL/well using a μFill liquid dispenser in fresh medium. Infigratinib (BGJ-398) is serially diluted in DMSO and arrayed in a polypropylene 384-well plate. Then 50 nL of compound are transferred into the plates containing the cells by using the pintool transfer device, and the plates incubated at 37°C (5% CO_2) for 48 h. Then 25 μL of Bright-Glo are added, and luminescence is quantified using an Analyst-GT. Custom curve-fitting software is used to

	produce a logistic fit of percent cell viability as a function of the logarithm of inhibitor concentration. The IC_{50} value is determined as the concentration of compound needed to reduce cell viability to 50% of a DMSO control[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female HsdNpa: Athymic Nude-nu mice are used. Infigratinib (BGJ-398) is formulated as a suspension in PEG300/D5W (2:1, v/v) and administered orally for 12 consecutive days at the doses of 10 and 30 mg/kg/qd. Tumor and body weight data are analyzed by ANOVA with post hoc Dunnett's test for comparison of treatment versus control group. The post hoc Tukey test is used for intragroup comparison. Statistical analysis is performed using GraphPad prism 4.02. As a measure of efficacy, the T/C (%) value is calculated. Rats[1] Female nude Rowett rats 6-9 weeks of age are used. Infigratinib (BGJ-398) is formulated as a solution in acetic acid-acetate buffer pH 4.6/PEG300 (1:1, v/v) and applied daily by gavage to the tumor-bearing rats (n=8) for 20 consecutive days at doses of 5, 10, and 15 mg/kg/qd (free base equivalents). The application volume is 5 mL/kg. Tumor volumes are measured with calipers and determined according to the formula: length×width×height×π/6. Antitumor activity is expressed as T/C (%): (mean change of tumor volume of treated animals/mean change of tumor volume of control animals)×100. Regressions (%) are calculated. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2022 Aug;608(7923):609-617.
- Cancer Discov. 2019 Dec;9(12):1686-1695.
- Cancer Discov. 2018 Mar;8(3):354-369.
- Ann Rheum Dis. 2016 May;75(5):883-90.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.

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REFERENCES

[1]. Guagnano V, et al. Discovery of 3-(2,6-Dichloro-3,5-dimethoxy-phenyl)-1-{6-[4-(4-ethyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-yl}-1-me thyl-urea (NVP-BGJ398), A Potent and Selective Inhibitor of the Fibroblast Growth Factor Receptor Family of Receptor T

[2]. Konecny GE, et al. Activity of the fibroblast growth factor receptor inhibitors dovitinib (TKI258) and NVP-BGJ398 in human endometrial cancer cells. Mol Cancer Ther. 2013 May;12(5):632-42.

[3]. Liu H, et al. Identifying and Targeting Sporadic Oncogenic Genetic Aberrations in Mouse Models of Triple Negative Breast Cancer. Cancer Discov. 2018 Mar;8(3):354-369.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA