产品名称：Infigratinib
产品别名：NVP-BGJ398； BGJ-398

生物活性：

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].			
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].			
Solvent&Solubility	***In Vitro:*** **DMSO : 27 mg/mL** (**48.17 mM**; Need ultrasonic and warming) **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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

	——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 1.67 mg/mL (2.98 mM); Clear solution 此方案可获得 ≥ 1.67 mg/mL (2.98 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 16.699999 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: 1.67 mg/mL (2.98 mM); Suspended solution; Need ultrasonic 此方案可获得 1.67 mg/mL (2.98 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 16.699999 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 1.67 mg/mL (2.98 mM); Clear solution 此方案可获得 ≥ 1.67 mg/mL (2.98 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 16.699999 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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-methyl-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.

实验参考：

Cell Assay	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].

Animal Administration	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.
Kinase Assay	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]
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.