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产品名称: **NVP-BGJ398 (phosphate)**
产品别名: **Infigratinib phosphate; BGJ-398 phosphate**

生物活性:				
Description	Infigratinib phosphate (BGJ-398 phosphate; NVP-BGJ398 phosphate) is a potent inhibitor of the FGFR family with IC50 of 0.9 nM, 1.4 nM, 1 nM, and 60 nM for FGFR1, FGFR2, FGFR3, and FGFR4, respectively.			
IC50 & Target	FGFR1	FGFR2	FGFR3	FGFR4
	0.9 nM (IC50)	1.4 nM (IC50)	1 nM (IC50)	60 nM (IC50)
In Vitro	Infigratinib phosphate inhibits FGFR1, FGFR2, and FGFR3 with IC50=~1 nM, FGFR3K650E with IC50=4.9 nM, and FGFR4 with IC50=60 nM. IC50 values for all other kinases are in the μM range (FYN, LCK, YES, and ABL, IC50=1.9, 2.5, 1.1, and 2.3 μM, respectively) except for VEGFR2, KIT, and LYN, which are inhibited at submicromolar concentrations (IC50=0.18, 0.75, and 0.3 μM, respectively). Infigratinib inhibits the proliferation of the FGFR1-, FGFR2-, and FGFR3-dependent BaF3 cells with IC50 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 IC50 values are greater than 1.5 μM except for VEGFR2 (IC50 1449 and 938 nM), for which there is at least a 400-fold selectivity versus FGFR1, FGFR2, and FGFR3[1]. Infigratinib (ranging between 1 nM and 10 μM) is potent at inhibiting cell growth of FGFR2-mutant endometrial cancer cells[2].			
In Vivo	Infigratinib 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 in this study is 32%. After intravenous dosing, Infigratinib 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 (30 mg/kg) significantly inhibits the growth of FGFR2-mutated endometrial cancer xenograft models[2].			
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.			
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 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			



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	incubated at 37°C (5% CO₂) 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 IC₅₀ 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 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 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 Infigratinib solution or control with 10 µL of the corresponding substrate mixture (peptidic substrate, ATP and [γ-³³P]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 MnCl₂, 3 mM MgCl₂, 1 mM DTT, 250 µg/mL PEG 20000, 2 µg/mL poly(EY) 4:1, 1% DMSO and 0.5 µM ATP (γ-[³³P]-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 ³³P 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% H₃PO₄, and mounted on vacuum manifold with disconnected vacuum source. After spotting, vacuum is connected, and each well rinsed with 0.5% H₃PO₄ (200 µL). Free membranes are removed and washed four times on a shaker with 1% H₃PO₄ 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. IC₅₀ values are calculated by linear regression analysis of the percentage inhibition of NVP-BGJ398^[1].
	[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]-



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