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产品名称：PRN1371
产品别名：PRN1371

生物活性：

Description	PRN1371 is a highly selective and potent FGFR1-4 and CSF1R inhibitor with IC_{50}s of 0.6, 1.3, 4.1, 19.3 and 8.1 nM for FGFR1, FGFR2, FGFR3, FGFR4 and CSF1R, respectively[1].

IC_{50} & Target	FGFR1	FGFR2	FGFR3	FGFR4	CSF1R
	0.6 nM (IC_{50})	1.3 nM (IC_{50})	4.1 nM (IC_{50})	19.3 nM (IC_{50})	8.1 nM (IC_{50})

In Vitro	PRN1371 presents a unique profile of high biochemical and cellular potency (FGFR1 IC_{50}=0.6 nM, SNU16 IC_{50}=2.6 nM), prolonged target engagement (FGFR1 occupancy 24 h=96%), < 30% hERG inhibition at 1 μM, and good predicted ADME stability with BME reactivity K_d>100 μM. Broader kinome-wide biochemical profiling of PRN1371 against 251 kinases identifies only FGFR1−4 and CSF1R as being potently inhibited[1].
In Vivo	PK studies of PRN1371 in rat, dog, and cynomolgus monkey show rapid iv clearance in all species. PRN1371 shows rapid clearance (Cl=160 mL per min per kg), yet dosing po (20 mg/kg) demonstrates high oral exposure (AUC=4348 h·ng/mL) and a reasonable half-life ($t_{1/2}$=3.8 h). Low levels of pFGFR2 confirms the ability of PRN1371 to block FGFR2 activity in tumor tissue. PRN1371 induces a dose-dependent reduction in tumor volume and up to 68% tumor growth inhibition at the highest dose of 10 mg/kg b.i.d. following 27 days of treatment. All doses are well tolerated with no significant body weight loss. PRN1371 free base has been administered orally once daily as powder in a capsule on a 28-day continuous schedule. Human plasma concentrations for doses ranging from 15 to 35 mg confirm good oral exposure, rapid systemic clearance, no accumulation from day 1 to day 15, and a dose-dependent increase in AUC. Serum phosphate, a pharmacodynamic marker of FGFR inhibition, is increased for all doses studied and shows a dose-dependent increase between 20 and 35 mg, despite the administration of prophylactic phosphate binders[1].

Solvent&Solubility

In Vitro:

DMSO : 25 mg/mL (44.53 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7811 mL	8.9054 mL	17.8107 mL
	5 mM	0.3562 mL	1.7811 mL	3.5621 mL
	10 mM	0.1781 mL	0.8905 mL	1.7811 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: ≥ 2.5 mg/mL (4.45 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.45 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 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: 2.5 mg/mL (4.45 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (4.45 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 25.0 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: ≥ 2.5 mg/mL (4.45 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.45 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 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Brameld KA, et al. Discovery of the Irreversible Covalent FGFR Inhibitor 8-(3-(4-Acryloylpiperazin-1-yl)propyl)-6-(2,6-dichloro-3,5-dimethoxyphenyl)-2-(methylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (PRN1371) for the Treatment of Solid Tumors. J Med Chem. 2017 Aug 10;60(15):6516-6527.

实验参考：

Cell Assay	SNU16 cells are first seeded into 384- well plates and PRN1371 added such that the highest final compound concentration is 5 μM. Cells are incubated with PRN1371 for 72 h at 37°C. To detect viability, the Presto-Blue cell viability reagent is added. Plates are read using an Analyst HT with a fluorescent mode employing 530 nm excitation and 590 nm emission[1].
Animal Administration	Mice: PRN1371 is evaluated in pharmacodynamics and efficacy studies using a SNU16 gastric cancer xenograft mouse model with high overexpression of FGFR2. In nude mice implanted with subcutaneous SNU16 tumors, pFGFR2 levels in the tumor are measured via Western blotting at 8 h following a 10 mg/kg oral dose. Low levels of pFGFR2 confirmed the ability of compound 34 to block FGFR2 activity in tumor tissue. Efficacy is determined by measuring tumor growth inhibition in the same SNU16 xenograft model[1].
Kinase Assay	Enzyme inhibition is determined using a Caliper capillary electrophoresis system that separates phosphorylated and nonphosphorylated peptides on the basis of charge. Different concentrations of PRN1371 are first preincubated with enzyme for 15 min. The reaction is initiated with addition of peptide substrate, ATP, and Mg^{2+} and incubated at 25°C for 3 h. To stop the reaction, the mixture is quenched with EDTA. The buffer is 100 mM HEPES, pH 7.5, 0.1% BSA, 0.01% Triton X-100, 1 mM DTT, 10 mM $MgCl_2$, 10 mM sodium orthovanadate, 10 μM β-glycerophosphate, and 1% DMSO. The

	ATP concentration of the reaction is at the predetermined value of the K_m for ATP[1].
References	[1]. Brameld KA, et al. Discovery of the Irreversible Covalent FGFR Inhibitor 8-(3-(4-Acryloylpiperazin-1-yl)propyl)-6-(2,6-dichloro-3,5-dimethoxyphenyl)-2-(methylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (PRN1371) for the Treatment of Solid Tumors. J Med Chem. 2017 Aug 10;60(15):6516-6527.