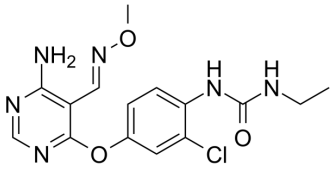
JNJ-38158471

Cat. No.:	HY-18317
CAS No.:	951151-97-6
Molecular Formula:	$C_{15}H_{17}ClN_6O_3$
Molecular Weight:	364.79
Target:	VEGFR; c-Kit; RET
Pathway:	Protein Tyrosine Kinase/RTK
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 : 100 mg/mL (274.13 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7413 mL	13.7065 mL	27.4130 mL
	5 mM	0.5483 mL	2.7413 mL	5.4826 mL
	10 mM	0.2741 mL	1.3707 mL	2.7413 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: 2.5 mg/mL (6.85 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

JNJ-38158471 is a well tolerated, orally available, highly selective VEGFR-2 inhibitor, with an IC_{50} of 40 nM. JNJ-38158471 also inhibits Ret and Kit with IC_{50}s of 180 and 500 nM, respectively[1].

IC_{50} & Target			
	VEGFR-2	RET	c-Kit
	40 nM (IC_{50})	180 nM (IC_{50})	500 nM (IC_{50})

In Vitro

JNJ-38158471 (1-500 nM; 1 hour) inhibits VEGF-stimulated VEGFR-2 autophosphorylation in HUVECs[1].
JNJ-38158471 (50-1000 nM; 12-16 hours) significantly inhibits VEGF-dependent HUVEC migration. Cellular toxicity is not observed following JNJ-38158471 treatment of HUVECs[1].

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

Western Blot Analysis[1]

Cell Line:	Human umbilical vein endothelial cells (HUVECs)
Concentration:	1, 10, 100, 500 nM
Incubation Time:	1 hour
Result:	Reduced phospoho-VEGFR2 levels at 95, 88, 77 and 73% with the concentration of 500, 100, 10 and 1 nM, respectively.

In Vivo

JNJ-38158471 (10 or 100 mg/kg; p.o.; once-daily) inhibits VEGF-induced corneal neovascularization[1].
JNJ-38158471 (10-200 mg/kg; p.o.) inhibits the growth of human tumor xenografts in a dose-dependent manner in both A431 and HCT116 models. JNJ-38158471 treatment is well tolerated, following continuous administration for 24 days, body weights were comparable with control animals[1].
JNJ-38158471 (100 mg/kg; p.o.; once-daily) treatment shows statistically significant activity compare with vehicle treat animals. The body weights of both JNJ-38158471-treated and vehicle-treated groups were comparable at study end[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Female C57BL/6J mice are implanted with rhVEGF$_{165}$[1]
Dosage:	10 or 100 mg/kg
Administration:	Daily oral administration for 6 days
Result:	Caused a marked and apparently dose-dependent inhibition of VEGF-dependent blood vessel formation (100 mg/kg, resulted in 83% inhibition; 10 mg/kg, resulted in 15% inhibition).

Animal Model:	Female athymic nude mice; 5-6 weeks; implanted subcutaneously human colorectal carcinoma cells (HCT116) or human epidermoid carcinoma cells (A431)[1]
Dosage:	10, 50, 100, 200 mg/kg
Administration:	Oral administration for 35 days
Result:	Achieved optimum efficacy with the dose from 100 to 200 mg/kg daily.

Animal Model:	Female athymic nude mice; 5-6 weeks; implanted subcutaneously human skin melanoma cells (A375)[1]
Dosage:	100 mg/kg
Administration:	Once-daily oral administration for 28 days
Result:	Inhibited 90% growth of tumor with daily doses of 100 mg/kg.

Animal Model:	Female C57BL/6J-Apc Min mice; 5 weeks of age[1]
Dosage:	100 mg/kg
Administration:	Once-daily oral administration for two weeks
Result:	Inhibited polyp formation in the transgenic APC min-mouse model.

REFERENCES

[1]. Kenneth RL, et, al. A Highly Selective, Orally Bioavailable, Vascular Endothelial Growth Factor receptor-2 Tyrosine Kinase Inhibitor Has Potent Activity in Vitro and in Vivo. Angiogenesis. 2009; 12(3): 287-96.

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