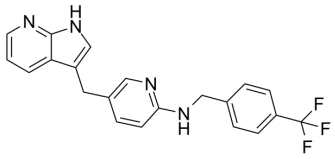
PLX647

Cat. No.:	HY-13838
CAS No.:	873786-09-5
Molecular Formula:	$C_{21}H_{17}F_3N_4$
Molecular Weight:	382.38
Target:	c-Fms; c-Kit
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 25 mg/mL (65.38 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.6152 mL	13.0760 mL	26.1520 mL
5 mM	0.5230 mL	2.6152 mL	5.2304 mL
10 mM	0.2615 mL	1.3076 mL	2.6152 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.54 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.54 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PLX647 is an orally active, highly specific dual FMS and KIT kinase inhibitor, with IC_{50}s of 28 and 16 nM, respectively. PLX647 shows selectivity for FMS and KIT over a panel of 400 kinases at a concentration of 1 μM except FLT3 and KDR (IC_{50}s=91 and 130 nM, respectively)[1].

In Vitro

In vitro, PLX647 potently inhibits proliferation of BCR-FMS cells, with an IC_{50} of 92 nM. A corresponding Ba/F3 cell line expressing BCR-KIT is also quite sensitive to PLX647, with an IC_{50} of 180 nM. PLX647 also inhibits endogenous FMS and KIT, as demonstrated by inhibition of the ligand-dependent cell lines M-NFS-60 (IC_{50}=380 nM) and M-07e (IC_{50}=230 nM), which express FMS and KIT, respectively[1].

PLX647 potently inhibits the growth of FLT3–ITD-expressing MV4-11 cells (IC_{50}=110 nM). PLX647 displayed minimal inhibition of the proliferation of Ba/F3 cells expressing BCR–KDR (IC_{50}=5 μM). PLX647 inhibits osteoclast differentiation with an IC_{50} of

0.17 μM[1].

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

In Vivo

PLX647 (40 mg/kg; p.o.; twice daily for 7 days) reduces macrophage accumulation in UUO kidney and blood monocytes[1].

PLX647 (40 mg/kg; p.o.; male Swiss Webster mice) reduces LPS-induced TNF-α and IL-6 release[1].

PLX647 (20-80 mg/kg; p.o.; daily or twice daily from 27-41 days) shows effects on collagen-induced arthritis[1].

PLX647 (30 mg/kg) results in significant inhibition of TRAP5b immunostaining and bone osteolysis. PLX647 (30 mg/kg BID) is able to prevent bone damage by the tumor cells[1].

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

Animal Model:	Male C57BL/6 mice (mouse unilateral ureter obstruction model)[1]
Dosage:	40 mg/kg
Administration:	P.o.; twice daily for 7 days
Result:	Resulted in reduction in the levels of F4/80+ macrophages by 77%.

Animal Model:	7-9 wk old Male DBA/1J mice (Mouse collagen-induced arthritis model)[1]
Dosage:	20 mg/kg, 80 mg/kg
Administration:	P.o.; daily (20 mg/kg) from 27-41 days, twice daily (80 mg/kg) from 27-41 days
Result:	20 mg/kg PLX647 had no initial effect on the development of severe arthritis. However, starting on day 33, no further development of disease severity was recorded, and a 30% inhibition of the macroscopic signs of arthritis was evident in clinical score on day 41. Mice treated with 80 mg/kg BID PLX647 initially shows delayed development of severe arthritic signs. Starting on day 33, the signs of arthritis began to decrease in this treatment group, reaching a maximum reversal of 76% on day 41.

REFERENCES

[1]. Zhang C, et al. Design and pharmacology of a highly specific dual FMS and KIT kinase inhibitor. Proc Natl Acad Sci U S A. 2013 Apr 2;110(14):5689-94.

[2]. Louvet C, et al. Tyrosine kinase inhibitors reverse type 1 diabetes in nonobese diabetic mice. Proc Natl Acad Sci U S A. 2008 Dec 2;105(48):18895-900.

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