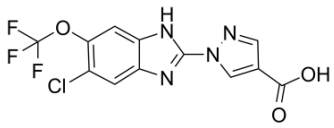
JNJ-42041935

Cat. No.:	HY-12832
CAS No.:	1193383-09-3
Molecular Formula:	$C_{12}H_6ClF_3N_4O_3$
Molecular Weight:	346.65
Target:	HIF/HIF Prolyl-Hydroxylase
Pathway:	Metabolic Enzyme/Protease
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 : ≥ 36 mg/mL (103.85 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.8848 mL	14.4238 mL	28.8475 mL
5 mM	0.5770 mL	2.8848 mL	5.7695 mL
10 mM	0.2885 mL	1.4424 mL	2.8848 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 (7.21 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (7.21 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.21 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	JNJ-42041935 is a potent, competitive and selective inhibitor of prolyl hydroxylase PHD; inhibits PHD1, PHD2, and PHD3 with pK_i values of 7.91±0.04, 7.29 ±0.05, and 7.65±0.09, respectively.
IC_{50} & Target	pK_i: 7.91±0.04 (PHD1), 7.29 ±0.05 (PHD2), 7.65±0.09(PHD3)[1]
In Vitro	JNJ-42041935 is the most potent inhibitor of $PHD2_{181–417}$ with a pIC_{50} value of 7.0±0.03. JNJ-42041935 also inhibits full-

	length PHD1, PHD2, andPHD3 enzymes (pK_i values 7.91±0.04, 7.29 ±0.05, and 7.65±0.09, respectively) [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	JNJ-42041935 is used to compare the effect of selective inhibition of PHD to intermittent, high doses (50 μg/kg i.p.) of an exogenous erythropoietin receptor agonist in an inflammation induced anemia model in rats. JNJ-42041935 (100 μmol/kg, once a day for 14 days) is effective in reversing inflammation induced anemia, whereas erythropoietin has no effect. Administration of JNJ-42041935 (100 μmol/kg p.o.) for 5 consecutive days resulted in a 2-fold increase in reticulocytes, an increase in hemoglobin by 2.3 g/dl, and an increase in the hematocrit of 9%. Two hours after oral administration of 300 μ mol/kg JNJ-42041935, the bioluminescence over the peritoneal area is increased by 2.2 ± 0.3-fold relative to luciferase-treated vehicle controls in the mouse [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The potency of JNJ-42041935 for inhibition of the structurally related enzyme FIH is assessed by methods similar to those described for PHD2. In brief, activity of FIH is determined using purified glutathione transferase-tagged full-length FIH amino acids 1 to 350 and a synthetic HIF-1α peptide corresponding to residues Asp788 to Leu822. Compounds are preincubated with 17.1 nM FIH for 30 min, followed by a 10-min incubation with 1 μM [2-^{14}C]2-oxoglutarate, in the presence of 10 μM $FeNH_4SO_4$ in reaction buffer. The selectivity of JNJ-42041935 for inhibition of a range of other targets available for testing in commercial assays is also assessed at concentrations of 1 and 10 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice: JNJ-42041935 is administered at doses of 30, 100, and 300 μmol/kg to Balb/C mice . Plasma is collected 6 h after the dose. Plasma erythropoietin concentration is measured. The hematological effects of JNJ-42041935 are assessed by administering the 100 μmol/kg dose on 5 consecutive days and collecting blood anticoagulated with EDTA on day 8 (3 days after the last dose)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Barrett TD, et al. Pharmacological characterization of 1-(5-chloro-6-(trifluoromethoxy)-1H-benzoimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (JNJ-42041935), a potent and selective hypoxia-inducible factor prolyl hydroxylase inhibitor. Mol Pharmacol. 2011

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