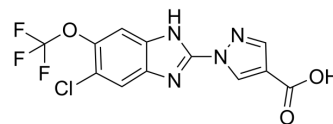


JNJ-42041935

Cat. No.:	HY-12832		
CAS No.:	1193383-09-3		
Molecular Formula:	C ₁₂ H ₆ ClF ₃ N ₄ O 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	2 years
		-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 36 mg/mL (103.85 mM)
 * "≥" means soluble, but saturation unknown.

	Solvent Concentration	Mass		
		1 mg	5 mg	10 mg
Preparing Stock Solutions	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

- 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
- 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
- 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.

IC₅₀ & 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 PHD2₁₈₁₋₄₁₇ with a pIC₅₀ value of 7.0±0.03. JNJ-42041935 also inhibits full-

length PHD1, PHD2, and PHD3 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 ($50 \mu\text{g}/\text{kg}$ i.p.) of an exogenous erythropoietin receptor agonist in an inflammation induced anemia model in rats. JNJ-42041935 ($100 \mu\text{mol}/\text{kg}$, once a day for 14 days) is effective in reversing inflammation induced anemia, whereas erythropoietin has no effect. Administration of JNJ-42041935 ($100 \mu\text{mol}/\text{kg}$ p.o.) for 5 consecutive days resulted in a 2-fold increase in reticulocytes, an increase in hemoglobin by $2.3 \text{ g}/\text{dl}$, and an increase in the hematocrit of 9%. Two hours after oral administration of $300 \mu\text{mol}/\text{kg}$ 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].

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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-1 α 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 $1 \mu\text{M}$ [$2\text{-}^{14}\text{C}$]2-oxoglutarate, in the presence of $10 \mu\text{M}$ 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 $10 \mu\text{M}$ [1].

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Animal Administration [1]

Mice: JNJ-42041935 is administered at doses of 30, 100, and $300 \mu\text{mol}/\text{kg}$ 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 $100 \mu\text{mol}/\text{kg}$ 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-benzimidazol-2-yl)-1H-pyrazole-4-carboxylic acid (JNJ-42041935), a potent and selective hypoxia-inducible factor prolyl hydroxylase inhibitor. *Mol Pharmacol*. 2011

Caution: Product has not been fully validated for medical applications. For research use only.

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