Molidustat

Cat. No.: HY-12654

CAS No.: 1154028-82-6

Molecular Formula: $C_{13}H_{14}N_8O_2$

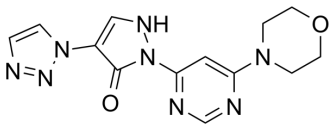
Molecular Weight: 314.3

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 : 5 mg/mL (15.91 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	3.1817 mL	15.9084 mL	31.8167 mL
	5 mM	0.6363 mL	3.1817 mL	6.3633 mL
	10 mM	0.3182 mL	1.5908 mL	3.1817 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: ≥ 0.5 mg/mL (1.59 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 0.5 mg/mL (1.59 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.5 mg/mL (1.59 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Molidustat (BAY 85-3934) is a novel inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PH) with mean IC_{50} values of 480 nM for PHD1, 280 nM for PHD2, and 450 nM for PHD3.

IC_{50} & Target

IC50: 480 nM (PHD1), 280 nM (PHD2), 450 nM (PHD3)[1]

In Vitro

The mean IC_{50} values of BAY 85-3934 for PHD1, PHD2, and PHD3 are 480 nM, 280 nM, and 450 nM, respectively. Exposure of HeLa cells to 5 μM BAY 85-3934 for 20 min is sufficient to induce detectable concentrations of HIF-1α. In a cellular reporter

	assay, BAY 85-3934 induces the expression of the firefly luciferase reporter gene under the control of a hypoxia responsive element promoter at a mean (± SD) EC50 of 8.4±0.7 μM (n=4) [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	HIF stabilization by oral administration of the HIF-PH inhibitor BAY 85-3934 (molidustat) results in dose-dependent production of EPO in healthy Wistar rats and cynomolgus monkeys. Molidustat therapy is aldo effective in the treatment of renal anemia in rats with impaired kidney function and, unlike treatment with rhEPO, resulted in normalization of hypertensive blood pressure in a rat model of CKD[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Rats: BAY 85-3934 is prepared as a solution in ethanol:Solutol HS 15:water (10:20:70). In a repeat-dose, 26-day experiment, male Wistar rats (240–340 g in body weight) are administered vehicle or BAY 85-3934 at doses of 0.5 mg/kg, 1.25 mg/kg, 2.5 mg/kg, and 5 mg/kg. The efficacy of BAY 85-3934 (2.5 mg/kg, once-daily, oral) is also compared with that of rhEPO (25 IU/kg, 50 IU/kg, and 100 IU/kg, twice-weekly, s.c. injection). The time-course of induction of EPO mRNA expression and plasma EPO is determined at baseline and 0.5 h, 1 h, 2 h, 4 h, 6 h, and 8 h after oral administration of a single dose of BAY 85-3934 (5 mg/kg)[1]. Monkey: BAY 85-3934 is prepared as a solution in 0.5% tylose. Male and female cynomolgus monkeys (2.8–5.6 kg in body weight) are administered at doses of 0.5 mg/kg and 1.5 mg/kg at 0 h, 24 h, 48 h, 72 h, and 96 h. Blood samples are taken at 7 h, 31 h, 55 h, 79 h, 103 h, and 168 h. Erythropoietic parameters are also evaluated after a 2-week treatment period with s.c. administration of rhEPO (100 IU/kg twice weekly at days 1, 4, 8, and 11) and BAY 85-3934 (1.5 mg/kg) once daily[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Pharmaceut Biomed. 2020, 113870.
- Biochem Biophys Res Commun. 2018 Sep 3;503(1):297-303.

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REFERENCES

[1]. Flamme I, et al. Mimicking hypoxia to treat anemia: HIF-stabilizer BAY 85-3934 (Molidustat) stimulates erythropoietin production without hypertensive effects. PLoS One. 2014 Nov 13;9(11):e111838.

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