Zamicastat

Cat. No.: HY-106004

CAS No.: 1080028-80-3

Molecular Formula: $C_{21}H_{21}F_2N_3OS$

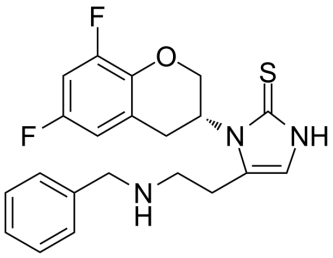
Molecular Weight: 401.47

Target: Dopamine β-hydroxylase; P-glycoprotein; BCRP

Pathway: Metabolic Enzyme/Protease; Membrane Transporter/Ion Channel

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 : 150 mg/mL (373.63 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4908 mL	12.4542 mL	24.9085 mL
	5 mM	0.4982 mL	2.4908 mL	4.9817 mL
	10 mM	0.2491 mL	1.2454 mL	2.4908 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 (6.23 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.23 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.23 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Zamicastat (BIA 5-1058) is a dopamine β-hydroxylase (DBH) inhibitor and can cross the blood-brain barrier (BBB) to cause central as well as peripheral effects. Zamicastat is also a concentration-dependent dual P-gp and BCRP inhibitor with IC_{50} values of 73.8 μM and 17.0 μM, respectively[1]. Zamicastat reduces high blood pressure[2].

IC_{50} & Target

Dopamine β-hydroxylase (DBH)[1]
IC50: 73.8 μM (P-gp), 17.0 μM (BCRP)[1]

In Vitro

Following 4 hours of incubation (5, 10, 20, 50, 80, 100 μM), a significant loss of cell viability is verified with 100 μM Zamicastat (p=0.010) in MDCK-BCRP cells. No significant losses of cell viability are observed after 4 h of incubation for other concentrations in all cell lines. By decreasing the incubation period to 30 min, there is no significant loss of cell viability (p>0.05) at 100 μM in all cell lines[1].

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

Cell Viability Assay[1]

Cell Line:	MDCK II, MDCK-MDR1 and MDCK-BCRP cells
Concentration:	5, 10, 20, 50, 80, 100 μM
Incubation Time:	4 hours (5, 10, 20, 50, 80, 100 μM) or 30 min (only 100 μM)
Result:	A significant loss of cell viability was verified with 100 μM in MDCK-BCRP cells.

In Vivo

Zamicastat (10, 30 and 100 mg/kg/day; oral bolus, 7 days) is tested acutely against salt-induced hypertension in the Dahl SS rat. Zamicastat produces a dose-dependent decrease in blood pressure. 24 h after Zamicastat administration mean systolic blood pressure (SBP) decrease is -12.6±4.1 mm Hg (P=0.0284), -15.2±2.7 mm Hg (P=0.0026) and -19.0±3.7 mm Hg (P=0.0036) for the 10, 30, and 100 mg/kg body weight dose, respectively. Zamicastat administration also produces a significant 24-h average decrease in diastolic blood pressure (DBP) of - 14.6±3.4 mm Hg (P=0.0073) with 10 mg/kg body weight dose, -13.0±4.5 mm Hg (P=0.0347) with 30 mg/kg body weight dose and -15.0±3.1 mm Hg (P=0.0046) with 100 mg/kg body weight dose. Zamicastat administration leads to a decrease in the 24h post-dose mean arterial pressure (MAP) of -13.4±3.8 mm Hg (P=0.0162), -14.0±3.5 mm Hg (P=0.0101) and -20.6±3.7 mm Hg (P=0.0026) for the 10, 30, and 100 mg/kg body weight dose, respectively. There is a small, but significant, effect of Zamicastat on the 24-h mean heart rate (HR) post-dose for all tested doses (10 mg/kg: -19.1±3.2 beats/min, P=0.0019; 30 mg/kg: -13.0±4.5 beats/min, P=0.0347; 100 mg/kg: -21.6±6.6 beats/min, P=0.0235)[2].

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

Animal Model:	Six-week-old male inbred male Dahl SS rats[2]
Dosage:	10, 30, or 100 mg/kg; 4 mL/kg
Administration:	Oral bolus, daily, seven days
Result:	Treatment produced a dose-dependent decrease in blood pressure. Twenty four hours after administration mean SBP decrease was -12.6±4.1 mm Hg (P=0.0284), -15.2±2.7 mm Hg (P=0.0026) and -19.0±3.7 mm Hg (P=0.0036) for the 10, 30, and 100 mg/kg body weight dose, respectively.

Animal Model:	ten-week-old male Wistar Han rats[2]
Dosage:	30 mg/kg/day
Administration:	in animal feedings (mixed in meal rodent food) everyday
Result:	lead to a significant 51% decrease in noradrenaline levels excreted in urine

REFERENCES

[1]. Bicker J, et al. In vitro assessment of the interactions of dopamine β-hydroxylase inhibitors with human P-glycoprotein and Breast Cancer Resistance Protein. Eur J Pharm Sci. 2018 May 30;117:35-40.

[2]. Igreja B, et al. Effects of Zamicastat treatment in a genetic model of salt-sensitive hypertension and heart failure. Eur J Pharmacol. 2019 Jan 5;842:125-132.

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