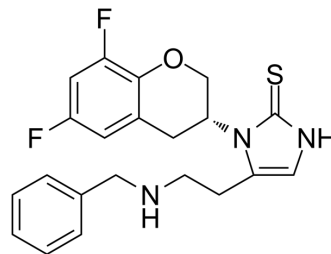


Zamicastat

| | | | | | | | | | | | | | |
|---------------------------|--|---------|-------|---------|--|-----|---------|------------|-------|---------|--|-------|--------|
| Cat. No.: | HY-106004 | | | | | | | | | | | | |
| CAS No.: | 1080028-80-3 | | | | | | | | | | | | |
| Molecular Formula: | C ₂₁ H ₂₁ F ₂ N ₃ OS | | | | | | | | | | | | |
| Molecular Weight: | 401.47 | | | | | | | | | | | | |
| Target: | Dopamine β-hydroxylase; P-glycoprotein; BCRP | | | | | | | | | | | | |
| Pathway: | Metabolic Enzyme/Protease; Membrane Transporter/Ion Channel | | | | | | | | | | | | |
| Storage: | <table border="0"> <tr> <td>Powder</td> <td>-20°C</td> <td>3 years</td> </tr> <tr> <td></td> <td>4°C</td> <td>2 years</td> </tr> <tr> <td>In solvent</td> <td>-80°C</td> <td>2 years</td> </tr> <tr> <td></td> <td>-20°C</td> <td>1 year</td> </tr> </table> | Powder | -20°C | 3 years | | 4°C | 2 years | In solvent | -80°C | 2 years | | -20°C | 1 year |
| 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) | | | | |
| | | Solvent Concentration | Mass 1 mg | 5 mg | 10 mg |
| | Preparing Stock Solutions | 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 | <ol style="list-style-type: none"> 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 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 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] . |
| IC₅₀ & Target | Dopamine β-hydroxylase (DBH) ^[1] IC ₅₀ : 73.8 μM (P-gp), 17.0 μM (BCRP) ^[1] |

In Vitro

Following 4 hours of incubation (5, 10, 20, 50, 80, 100 μ M), a significant loss of cell viability is verified with 100 μ M 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 μ M 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 μ M |
| Incubation Time: | 4 hours (5, 10, 20, 50, 80, 100 μ M) or 30 min (only 100 μ M) |
| Result: | A significant loss of cell viability was verified with 100 μ M 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 \pm 4.1 mm Hg ($P=0.0284$), -15.2 \pm 2.7 mm Hg ($P=0.0026$) and -19.0 \pm 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 \pm 3.4 mm Hg ($P=0.0073$) with 10 mg/kg body weight dose, -13.0 \pm 4.5 mm Hg ($P=0.0347$) with 30 mg/kg body weight dose and -15.0 \pm 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 \pm 3.8 mm Hg ($P=0.0162$), -14.0 \pm 3.5 mm Hg ($P=0.0101$) and -20.6 \pm 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 \pm 3.2 beats/min, $P=0.0019$; 30 mg/kg: -13.0 \pm 4.5 beats/min, $P=0.0347$; 100 mg/kg: -21.6 \pm 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 \pm 4.1 mm Hg ($P=0.0284$), -15.2 \pm 2.7 mm Hg ($P=0.0026$) and -19.0 \pm 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.

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

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