Begacestat

Cat. No.: HY-14175

CAS No.: 769169-27-9

Molecular Formula: $C_9H_8ClF_6NO_3S_2$

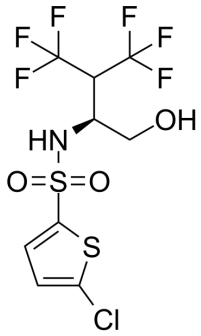
Molecular Weight: 391.74

Target: γ-secretase

Pathway: Neuronal Signaling; Stem Cell/Wnt

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 : 50 mg/mL (127.64 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5527 mL	12.7636 mL	25.5271 mL
	5 mM	0.5105 mL	2.5527 mL	5.1054 mL
	10 mM	0.2553 mL	1.2764 mL	2.5527 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 (6.38 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.38 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.38 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Begacestat (GSI-953) is a selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase ($IC_{50}A\beta_{40}$ =15 nM) for the treatment of Alzheimer's disease[1].

IC_{50} & Target

IC50: 15 nM ($A\beta_{40}$)[1].

In Vivo

Begacestat (5 mg/kg, p.o. in mice) treatment for 4 h significantly reduces the $A\beta_{40}$ and $A\beta_{42}$ in brain (37% lowering of brain A β_{40} and 25% lowering of $A\beta_{40}$ observed)[1].

Begacestat (GSI-953: 0, 2.5, 5, or 10 mg/kg, oral gavage, 3 h) results in a dose-dependent reversal of contextual fear conditioning deficits when compound is orally administered 3 h before training. Significant deficits are observed after treatment with 2.5 mg/kg Begacestat, and there is some reversal of this at 5 mg/kg and full reversal at 10 mg/kg compared with vehicle-dosed Tg2576 mice[2].

A dosage-related trend of slightly lower percentages of SP CD4+ cells in males at all dosages (SP CD4+ cells=~11% in controls compared with ~7% to ~9% in Begacestat-dosed animals) and females at 2000 mg/kg/day (SP CD4+ cells=~10% in controls compared with ~8% in Begacestat-dosed animals) is observed[2].

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

Animal Model:	Tg2576 mice[2]
Dosage:	0, 2.5, 5, or 10 mg/kg
Administration:	Oral gavage for two consecutive days
Result:	Resulted in a dose-dependent reversal of contextual fear conditioning deficits when compound is orally administered 3 h before training.

Animal Model:	Sprague-Dawley rats[2]
Dosage:	0, 200, 600, or 2000 mg/kg/day for 10 (5 males/group and 5 females at 600 mg/kg/day) or 28 (10/sex/group) consecutive days
Administration:	P.O. for 10 (5 males/group and 5 females at 600 mg/kg/day) or 28 (10/sex/group) consecutive days.
Result:	A dosage-related trend of slightly lower percentages of SP CD4+ cells in males at all dosages and females at 2000 mg/kg/day was observed.

REFERENCES

[1]. Mayer SC, et al. Discovery of begacestat, a Notch-1-sparing gamma-secretase inhibitor for the treatment of Alzheimer's disease. J Med Chem. 2008 Dec 11;51(23):7348-51.

[2]. Martone RL, et al. Begacestat (GSI-953): a novel, selective thiophene sulfonamide inhibitor of amyloid precursor protein gamma-secretase for the treatment of Alzheimer's disease. J Pharmacol Exp Ther. 2009 Nov;331(2):598-608.

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