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Lieferung & Zahlungsart

siehe unsere Liefer- und Versandbedingungen

Zuschläge

- Mindermengenzuschlag
- Trockeneiszuschlag
- Gefahrgutzuschlag
- Expressversand

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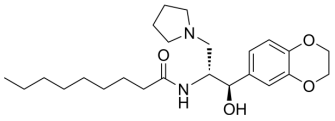
Genz-123346 free base

Cat. No.:	HY-12744
CAS No.:	491833-30-8
Molecular Formula:	$C_{24}H_{38}N_2O_4$
Molecular Weight:	418.57
Target:	Others
Pathway:	Others

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 : ≥ 100 mg/mL (238.91 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.3891 mL	11.9454 mL	23.8909 mL
5 mM	0.4778 mL	2.3891 mL	4.7782 mL
10 mM	0.2389 mL	1.1945 mL	2.3891 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: ≥ 3 mg/mL (7.17 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 3 mg/mL (7.17 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 3 mg/mL (7.17 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Genz-123346 (free base) is an inhibitor of GL1 synthase that blocks the conversion of ceramide to GL1; inhibits GM1 with IC_{50} value of 14 nM.

IC_{50} & Target

IC50: 14 nM (GM1)[1]

In Vitro

Exposure of cells to Genz-123346 and to other GCS inhibitors at nontoxic concentrations can enhance the killing of tumor

	cells by cytotoxic anti-cancer agents. Genz-123346 and a few other GCS inhibitors are substrates for multi-drug resistance efflux pumps such as P-gp (ABCB1, gP-170). In cell lines selected to over-express P-gp or which endogenously express P-gp, chemosensitization by Genz-123346 is primarily due to the effects on P-gp function[2]. Genz-123346(Genz) is an enhancer of autophagy flux[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In the Zucker diabetic fatty rat, Genz-123346 loared glucose and A1C levels and improved glucose tolerance. Drug treatment also prevented the loss of pancreatic beta-cell function and preserved the ability of the animals to secrete insulin. In the diet-induced obese mouse, treatment with Genz-123346 normalized A1C levels and improved glucose tolerance. The oral bioavailability of the drug is shown to be about 10% and 30% in mice and rats, respectively, with a half-life in plasma of 30–60 min[1]. Genz-123346 treatment results in a dose-dependent reduction of renal GlcCer and GM3 levels that translates into effective inhibition of cystic disease. A direct effect of Genz-123346 on the Akt-mTOR signaling pathway is observed, with reduced phosphorylation of Akt and ribosomal protein S6[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Rats: Genz-123346 is dissolved in water. Zucker diabetic fatty rats treated with Genz-123346 (75 mg/kg) for 6 weeks are fasted overnight. The following morning, the fasted rats are anesthetized and injected with 5 units human insulin into the hepatic portal vein. Quadriceps muscle and liver are harvested 2 min after injection and immediately frozen in liquid nitrogen. Insulin receptor is immunoprecipitated. The immunoprecipitates are analyzed by immunoblotting[1]. Mice: C57BL/6 mice are fed on a high-fat (45% of kcal) diet for 8 weeks, obese mice with comparable body weight gain, glucose, and insulin levels are assigned to either the treated or control groups. The mice are then gavaged daily with Genz-123346 or water for 10 weeks[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Am J Respir Crit Care Med. 2019 Nov 1;200(9):1113-1125.
- PeerJ. September 14, 2021.
- Faculty of Life Sciences, University College London. 2019 Oct.

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REFERENCES

[1]. Zhao H, et al. Inhibiting glycosphingolipid synthesis improves glycemic control and insulin sensitivity in animal models of type 2 diabetes. Diabetes. 2007 May;56(5):1210-8.

[2]. Chai L, et al. The chemosensitizing activity of inhibitors of glucosylceramide synthase is mediated primarily through modulation of P-gp function. Int J Oncol. 2011 Mar;38(3):701-11.

[3]. Shen W, et al. Inhibition of glucosylceramide synthase stimulates autophagy flux in neurons. J Neurochem. 2014 Jun;129(5):884-94

[4]. Natoli TA, et al. Inhibition of glucosylceramide accumulation results in effective blockade of polycystic kidney disease in mouse models. Nat Med. 2010 Jul;16(7):788-92.

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

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