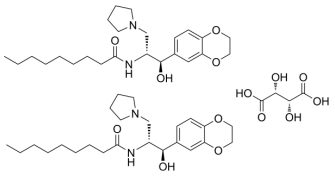
Genz-123346

Cat. No.:	HY-12744A
CAS No.:	943344-58-9
Molecular Formula:	$C_{52}H_{82}N_4O_{14}$
Molecular Weight:	987.23
Target:	Glucosylceramide Synthase (GCS)
Pathway:	Neuronal Signaling
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Genz-123346 is a potent, orally available glucosylceramide synthase inhibitor. Genz-123346 blocks the conversion of ceramide to glucosylceramide (GL1) and inhibits GM1 with an IC_{50} value of 14 nM[1].
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]. A group of WT mice received Genz-123346 (0.11% final concentration in regular chow); after 2 weeks of feeding,renal Gb3 was reduced by approximately 50%, in comparison with WT mice fed with chow diet only[5]. 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.

[5]. Morace I, et al. Renal globotriaosylceramide facilitates tubular albumin absorption and its inhibitionprotects against acute kidney injury. Kidney Int. 2019 Aug;96(2):327-341.

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