Product Data Sheet

Product Name: Genz-123346
Cat. No.: GC19163

Chemical Properties

Cas. No.	943344-58-9		
SMILES	CCCCCCCCC(N[C@H](CN1CCCC1)[C@@H](C2=CC=C(OCCO3)C3=C2)O)=O.CCCCCCCCC(N[C@H](CN4CCCC4)[C@@H](C5=CC=C(OCCO6)C6=C5)O)=O.O=C(O)[C@H](O)[C@@H](O)C(O)=O		
Formula	$C_{52}H_{82}N_4O_{14}$	M.Wt	987.23
Solubility	DMSO : ≥ 100 mg/mL (238.91 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	Genz-123346		

Protocol

Animal experiment: 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].

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com
Address: 10292 Central Ave. #205, Montclair, CA, USA

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.

Background

Genz-123346 is an inhibitor of GL1 synthase that blocks the conversion of ceramide to GL1; inhibits GM1 with IC50 value of 14 nM.

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].

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].

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.
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