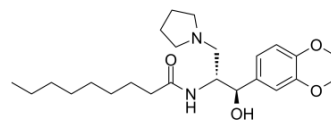


## Genz-123346 free base

<b>Cat. No.:</b>	HY-12744		
<b>CAS No.:</b>	491833-30-8		
<b>Molecular Formula:</b>	C <sub>24</sub> H <sub>38</sub> N <sub>2</sub> O <sub>4</sub>		
<b>Molecular Weight:</b>	418.57		
<b>Target:</b>	Others		
<b>Pathway:</b>	Others		
<b>Storage:</b>	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



### SOLVENT & SOLUBILITY

#### In Vitro

DMSO : ≥ 100 mg/mL (238.91 mM)  
 \* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent	1 mg	5 mg	10 mg
	Concentration	Mass	Mass	Mass
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

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline  
 Solubility: ≥ 3 mg/mL (7.17 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)  
 Solubility: ≥ 3 mg/mL (7.17 mM); Clear solution
- 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<sub>50</sub> value of 14 nM.

#### IC<sub>50</sub> & Target

IC<sub>50</sub>: 14 nM (GM1)<sup>[1]</sup>

#### 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<sup>[2]</sup>. Genz-123346(Genz) is an enhancer of autophagy flux<sup>[3]</sup>.

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 lowered 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<sup>[1]</sup>. 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<sup>[4]</sup>.

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## PROTOCOL

### Animal Administration <sup>[1]</sup>

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<sup>[1]</sup>.

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<sup>[1]</sup>.

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.
- 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.

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

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