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 IC₅₀ value of 14 nM[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 multidrug 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 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[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].

**PROTOCOL**

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.

**REFERENCES**


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

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