

Product Data Sheet

Product Name: TAK-875

Cat. No.: GC16555

Chemical Properties

Cas. No. 1000413-72-8

Chemical Name 2-[(3S)-6-[[3-[2,6-dimethyl-4-(3-methylsulfonylpropoxy)phenyl]phenyl]methoxy]-2,3-dihydro-1-benzofuran-3-yl]acetic acid

SMILES CC1=CC(=CC(=C1C2=CC(=CC=C2)COC3=CC4=C(C=C3)C(CO4)CC(=O)O)C)OCCCS(=O)(=O)C

Formula C₂₉H₃₂O₇S

M.Wt 524.64

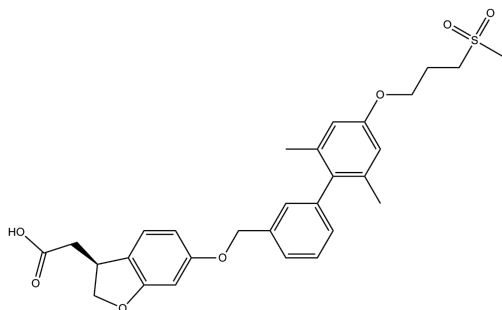
Solubility ≥ 26.25mg/mL in DMSO

Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C 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



Protocol

Cell experiment [1]:

Cell lines INS-1 832/13 cells

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

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Cells were seeded at a density of 2×10^4 cells/well in a 96-well black plate coated with poly-D-lysine, and 1% BSA and 0.1% DMSO alone (control), palmitic acid (62.5, 125, 250, 500 and 1000 μ M), oleic acid (62.5, 125, 250, 500 and 1000 μ M), or TAK-875 (6.25, 12.5, 25, 50 and 100 μ M) was added to the plate with 1% BSA and 0.1% DMSO, followed by culture for 72h. After the culture, caspase 3/7 activity was measured with the Apo-one homogeneous caspase 3/7 assay.

Reaction Conditions 6.25, 12.5, 25, 50 and 100 μ M; 72h

Applications In these cells, 72h exposure to palmitic acid (62.5-1000 μ M) and oleic acid (62.5-1000 μ M) caused dose-dependent enhancement of caspase 3/7 activity, and statistically significant effects were observed at doses above 250 μ M palmitic acid and 500 μ M oleic acid. In contrast, TAK-875 (6.25-100 μ M) did not show any effect on caspase 3/7 activity under the same conditions.

Animal experiment [1]:

Animal models SD rats (8 weeks old)

SD rats (8 weeks old) were fasted overnight and orally given vehicle (0.5% methylcellulose), TAK-875 (10 or 30mg/kg), nateglinide (50mg/kg), or glibenclamide (10mg/kg). Blood samples were collected from the tail vein before drug administration (time 0) and 0.5, 1, 2, and 3h after drug administration, and plasma glucose and insulin levels were measured as described above.

Dosage form 10 or 30mg/kg; p.o.

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Applications

Nateglinide (50mg/kg) lowered plasma glucose levels below normal fasting levels in SD rats by increasing plasma insulin. glibenclamide (10mg/kg) gradually decreased plasma glucose levels below normal fasting levels with a significant increase in plasma insulin levels. In contrast, TAK-875 at 30mg/kg, which is a 3- to 10-fold higher dose compared with the dose that improved glucose tolerance in diabetic rats, did not alter fasting glucose levels in SD rats with normal glucose homeostasis. TAK-875 did not significantly alter insulin secretion in SD rats with normal fasting glucose levels.

References:

[1] Tsujihata Y, Ito R, Suzuki M, et al. TAK-875, an orally available G protein-coupled receptor 40/free fatty acid receptor 1 agonist, enhances glucose-dependent insulin secretion and improves both postprandial and fasting hyperglycemia in type 2 diabetic rats. J Pharmacol Exp Ther. 2011;339(1):228-237.

Background

TAK-875 is a potent, selective and orally bioavailable GPR40 (G protein-coupled receptor 40) agonist with an EC₅₀ value of 0.014μM for human GPR40. GPR40 is highly expressed in pancreatic β cells and β cell lines in humans and rodents, and has also been found in multiple regions of the human brain. TAK-875 demonstrates potent plasma hypoglycemic and insulin-promoting effects in oral glucose tolerance tests of female Wistar fat rats with impaired glucose tolerance, and has been selected as a clinical candidate drug for the treatment of diabetes^[1].

In vitro, TAK-875 dose-dependently increased intracellular inositol monophosphate (IP) production and Ca²⁺ levels at 0.1-10μM and 3-30μM in rat insulinoma INS-1 833/15 cells under 1-10mM glucose, and stimulated insulin secretion at 0.001-10μM in the presence of 10mM glucose^[2]. TAK-875 at 6.25-100μM for 72h did not alter glucose-stimulated insulin secretion, insulin content, or caspase-3/7 activity in INS-1 833/15 cells^[2].

In vivo, intravenous administration of TAK-875 at 1mg/kg in rats resulted in a plasma clearance (CL) of 34.16mL/h·kg, a terminal half-life ($t_{1/2\lambda}$) of 4.7h, and a steady-state volume of distribution ($V_{d(ss)}$) of 208.49mL/kg, whereas oral gavage at 3mg/kg resulted in good absorption, with an AUC_{0-24h} of

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65 μ g·h/mL, a $C_{\max}$ of 5.77 μ g/mL, and an oral bioavailability of 76%^[1]. TAK-875 (1-10mg/kg; p.o.) significantly improved glucose tolerance and enhanced insulin secretion in type 2 diabetic N-STZ-1.5 rat models^[2]. TAK-875 (10mg/kg; p.o.) significantly increased plasma insulin levels and reduced fasting hyperglycemia in male Zucker diabetic fatty rats^[2].

References:

[1] Negoro N, Sasaki S, Mikami S, et al. Discovery of TAK-875: A Potent, Selective, and Orally Bioavailable GPR40 Agonist. ACS Med Chem Lett. 2010;1(6):290-294.

[2] Tsujihata Y, Ito R, Suzuki M, et al. TAK-875, an orally available G protein-coupled receptor 40/free fatty acid receptor 1 agonist, enhances glucose-dependent insulin secretion and improves both postprandial and fasting hyperglycemia in type 2 diabetic rats. J Pharmacol Exp Ther. 2011;339(1):228-237.

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