上海源叶生物科技有限公司
Shanghai yuanye Bio-Technology Co., Ltd
电话：021-61312973　　传真：021-55068248
网址：www.shyuanye.com
邮箱：shyysw@sina.com

产品名称：TAK-875
产品别名：Fasiglifam

生物活性：

Description	Fasiglifam (TAK-875) is a potent, selective and orally bioavailable GPR40 agonist with EC50 of 72 nM.
IC_{50} & Target	EC50: 72 nM (GPR40)
In Vitro	Fasiglifam (TAK-875) (0.01-10 μM) produces a concentration-dependent increase in intracellular IP production in CHO-hGPR40, with EC_{50} of 0.072 μM. Fasiglifam (TAK-875) (0.1-10 μM) dose-dependently augments intracellular IP production in CHO cells[1]. Fasiglifam (TAK-875) (3-30 μM) concentration-dependently augments $[Ca^{2+}]_i$. In the presence of 10 mM glucose, TAK-875 (0.001-10 μM) dose-dependently stimulats insulin secretion from INS-1 833/15 cells[2].
In Vivo	Fasiglifam (TAK-875) (10 mg/kg, p.o.) increases plasma insulin levels in ZDF rats. Fasiglifam (TAK-875) (30 mg/kg, p.o.) improves fasting hyperglycemia without affecting fasting normoglycemia. Fasiglifam (TAK-875) at 30 mg/kg, which is a 3- to 10-fold higher dose compared with the dose that improved glucose tolerance in diabetic rats, does not alter fasting glucose levels in SD rats with normal glucose homeostasis. Likewise, Fasiglifam (TAK-875) does not significantly alter insulin secretion in SD rats with normal fasting glucose levels [1].

Solvent&Solubility

In Vitro:

DMSO : ≥ 128 mg/mL (243.98 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9061 mL	9.5305 mL	19.0611 mL
5 mM	0.3812 mL	1.9061 mL	3.8122 mL
10 mM	0.1906 mL	0.9531 mL	1.9061 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (4.77 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (4.77 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

	2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (4.77 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.77 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (4.77 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.77 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Tsujihata Y,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 [2]. Yoshiyuki Tsujihata, et al. TAK-875, an Orally Available GPR40/FFA1 Agonist Enhances Glucose-Dependent Insulin Secretion and Improves Both Postprandial and Fasting Hyperglycemia in Type 2 Diabetic Rats. JPET July 13, 2011 [3]. Nagatake T, et al. 17,18-EpETE-GPR40 axis ameliorates contact hypersensitivity by inhibiting neutrophil mobility in mice and cynomolgus macaques. J Allergy Clin Immunol. 2017 Dec 26. pii: S0091-6749(17)32949-4. [4]. Urano Y, et al. Comparative hepatic transcriptome analyses revealed possible pathogenic mechanisms of fasiglifam (TAK-875)-induced acute liver injury in mice. Chem Biol Interact. 2018 Sep 20;296:185-197.

实验参考：

Cell Assay	INS-1 832/13 cells are suspended in RPMI medium and seeded in a 96-well plate at a density of 2×10^4 cells/well; 1% BSA and 0.1% DMSO alone (control), palmitic acid (10, 100, and 1000 μM), oleic acid (10, 100, and 1000 μM), or Fasiglifam (TAK-875: 1, 10, and 100 μM) is added to the plate. After 72-h culture, medium is discarded, and cells are preincubated for 2 h with KRBH containing 1 mM glucose and 0.2% BSA at 37°C. After discarding of the preincubation buffer, KRBH containing 1 or 20 mM glucose and 0.2% BSA is added, and the plate is further incubated for 2 h. The insulin concentration in the supernatant is measured as described above. To measure intracellular insulin content, INS-1 832/13 cells are exposed to 1% BSA and 0.1% DMSO alone (control), palmitic acid (1000 μM), oleic acid (1000 μM), or Fasiglifam (TAK-875) (100 μM) with 1% BSA and 0.1% DMSO. After incubation, cells are washed once with phosphate-buffered saline, and acid-ethanol solution is added to each well, followed by sonication on ice. Intracellular insulin is extracted by overnight incubation at −30°C, followed by separation of supernatant by centrifugation at 12,000 rpm×5 min at 4°C. [1]
	At 18 weeks of age, the N-STZ-1.5 rats are fasted overnight and orally given vehicle (0.5% methylcellulose) or Fasiglifam (TAK-8751, 3, and 10 mg/kg). Sixty minutes later, all animals receive an oral glucose load (1 g/kg). Blood samples are collected from the tail vein before drug administration, before glucose load (time 0), and 10, 30, 60, and 120 min after the glucose load.

Animal Administration	Plasma glucose and insulin levels are measured with an AutoAnalyzer 7080 and radioimmunoassay, respectively. To see the effects of Fasiglifam (TAK-875) on fasting normoglycemia and hyperglycemia, SD rats (8 weeks old) or ZDF and ZL rats (12 weeks old) are fasted overnight and orally given vehicle (0.5% methylcellulose), Fasiglifam (TAK-875) (10 or 30 mg/kg), nateglinide (50 mg/kg), or glibenclamide (10 mg/kg). Blood samples are collected from the tail vein before drug administration (time 0) and 0.5, 1, 2, and 3 h (SD rats) and 0.5, 1, 2, 4, and 6 h (ZDF and ZL rats) after drug administration, and plasma glucose and insulin levels are measured as described above. [1]
References	[1]. Tsujihata Y,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 [2]. Yoshiyuki Tsujihata, et al. TAK-875, an Orally Available GPR40/FFA1 Agonist Enhances Glucose-Dependent Insulin Secretion and Improves Both Postprandial and Fasting Hyperglycemia in Type 2 Diabetic Rats. JPET July 13, 2011 [3]. Nagatake T, et al. 17,18-EpETE-GPR40 axis ameliorates contact hypersensitivity by inhibiting neutrophil mobility in mice and cynomolgus macaques. J Allergy Clin Immunol. 2017 Dec 26. pii: S0091-6749(17)32949-4. [4]. Urano Y, et al. Comparative hepatic transcriptome analyses revealed possible pathogenic mechanisms of fasiglifam (TAK-875)-induced acute liver injury in mice. Chem Biol Interact. 2018 Sep 20;296:185-197.