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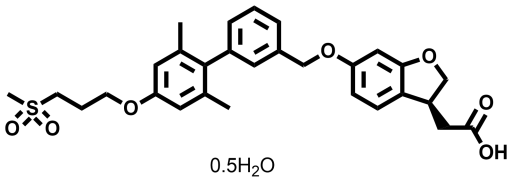
GPR40 Agonist TAK-875 (Fasiglifam)

Chemical Name: (S)-2-(6-((2',6'-dimethyl-4'-(3-(methylsulfonyl)propoxy)-[1,1'-biphenyl]-3-yl)methoxy)-2,3-dihydrobenzofuran-3-yl)acetic acid



$0.5H_2O$

Molecular Weight:	533.63
Formula:	$C_{29}H_{32}O_7S.1/2H_2O$
Purity:	≥98%
CAS#:	1374598-80-7
Solubility:	DMSO up to 100 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

TAK-875 (Fasiglifam) is the potent, selective and orally bioavailable partial GPR40 agonist with an EC_{50} ~14 nM. It has binding affinity to the human GPR40 receptor with Ki of 38 nM and the rat GPR40 receptor with Ki of 140 nM. TAK-875 has no agonist potency to other members of the FFA receptor family with EC_{50} >10 μM. The 2.3 Å resolution co-complex structure of hGPR40-TAK-875 reveals a unique binding mode of TAK-875 and suggests that entry to the non-canonical binding pocket most probably occurs via the lipid bilayer. Consistent with the activation of the Gqα-mediated signaling pathway, TAK-875 augments glucose-dependent insulin secretion in pancreatic β cells. Prolonged stimulation of GPR40/FFA1 by TAK-875 does not cause pancreatic β Cell dysfunction or induction of apoptosis. Termination phase III development of TAK-875 (Fasiglifam) for the potential treatment of type-2 diabetes mellitus was announced in 2013 due to concerns about liver safety.

How to Use:

In vitro: TAK-875 was used at 1 μM final concentration in various in vitro assays.

In vivo: TAK-875 was dosed to female Wistar fatty rats subjected to oral glucose tolerance test via oral gavage at 3 mg/kg one hour before an oral glucose challenge. Formulation is 0.5% CMC/0.25% Tween 80 in water. In type 2 diabetic N-STZ-1.5 rats, administration of TAK-875 (1-10 mg/kg PO) shows a clear improvement in glucose tolerance and augments insulin secretion. TAK-875 (10 mg/kg, PO) significantly augments plasma insulin levels and reduces fasting hyperglycemia in male Zucker diabetic fatty rats.

Reference:

1. Negoro N, et al. Discovery of TAK-875: A Potent, Selective, and Orally Bioavailable GPR40 Agonist. (2010) ACS Med Chem Lett. 1(6):290-4.
2. 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. (2011) J Pharmacol Exp Ther. 339(1):228-37.
3. Srivastava A, et al. High-resolution structure of the human GPR40 receptor bound to allosteric agonist TAK-875. (2014) Nature. 513(7516):124-7.