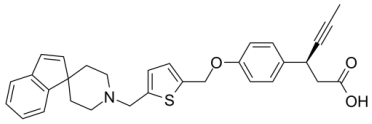
Data Sheet

Product Name:	GPR40 Activator 1
Cat. No.:	CS-2101
CAS No.:	1309435-60-6
Molecular Formula:	C31H31NO3S
Molecular Weight:	497.65
Target:	GPR40
Pathway:	GPCR/G Protein
Solubility:	10 mM in DMSO



BIOLOGICAL ACTIVITY:

GPR40 Activator 1 is a potent GPR40 activator for treatment of type 2 diabetes. IC50 value: Target: GPR40 Preparation of spiropiperidine derivatives for use as antidiabetic agents By Hamdouchi, Chafiq; Lineswala, Jayana Pankaj; Maiti, Pranab From PCT Int. Appl. (2011), WO 2011066183 A1 20110603.

PROTOCOL (Extracted from published papers and Only for reference)

Cell assay [1] GDIS assays are performed using the mouse insulinoma cell line Min6. Min6 cells are maintained in Dulbecco's Modified Eagle's Medium (DMEM) containing nonessential amino acids, 10% FBS, 50 mM 2-mercaptoethanol and 1% penicillin and streptomycin at 37 °C plus 5% CO2. On the day of the experiment, the cells are washed twice with 200 µ? of pre- warmed Krebs-ringer buffer without glucose. Addition of 200 µ? of pre-warmed Krebs-ringer buffer containing 2.5 mM glucose is used to starve the cells followed by the addition of compounds in the presence of a high concentration of glucose (25 mM). The plate is incubated at 37 °C for 2 hours. At the end of the 2 h incubation, the supernatant is gently transferred into a Millipore filter plate and spun at 200 g (gravitational force) for 3 minutes. Insulin is assayed using a Mercodia Insulin estimation kit. Addition of Example 1 at 1 µM plus 25 mM glucose to the Min6 cells resulted in a statistically significant, two-fold increase in insulin secretion compared to that achieved with 25 mM glucose alone. Animal administration [1] Male Balb/c (Albino mice) mice (8-9 weeks of age) are single housed and fed with normal rodent chow diet and water ad libitum. Animals are weighed and randomized by body weight and daily body weights are recorded. Upon study initiation, animals are dosed once per day orally for three days using a formulation carrying methylcellulose and tween-80. On the night before the 4-day IPGTT study, animals are fasted overnight in clean cages. On the morning of the IPGTT (Day 4), animals are dosed orally with compound or vehicle alone 60 minutes prior to the IPGTT (glucose 2g/kg, i.p.). Blood glucose levels are determined from tail bleeds taken at 0, 3, 7, 15, 30, and 60 min after glucose challenge. Plasma is isolated and used to estimate respective insulin levels. The blood glucose excursion profile from t=0 to t=60 min is used to integrate an area under the curve (AUC) for each treatment. Percent lowering in glucose is calculated from the AUC data of the compounds with respect to the AUC of vehicle group. The test compound is orally administered at 0.1, 0.3, 1.0, 3.0, or 10 mg/kg, and a positive control is administered at 10 mg/kg. No concentration of the compound of Example 1 or the positive control significantly lowered glucose levels at the 3 minute time point during the GTT. In contrast, glucose levels are significantly lowered with the 0.3, 1.0, 3.0, and 10 mg/kg doses of the compound of Example 1 and the positive control at the 7 minute time point and with 0.1, 0.3, 1.0, and 3.0 mg/kg doses ofthe compound of Example 1 at the 15, 30, and 60 minute time points. The positive control significantly lowered glucose levels at the 30 and 60 min. time points. The ED5o for the compound of Example 1 based on AUCs for glucose lowering is 0.21 mg/kg. In this study, insulin levels were significantly elevated at the 3.0 and 10.0 mg/kg dose of the compound of Example 1 which is consistent with activation of GPR40. The results of this study demonstrate that activation of GPR40 by Example 1 leads to in-vivo anti-diabetic efficacy.

References:

[1]. Novel spiropiperidine compounds , Patent WO 2011066183 A1

CAIndexNames:

Benzenepropanoic acid, β-1-propyn-1-yl-4-[[5-(spiro[1H-indene-1,4'-piperidin]-1'-ylmethyl)-2-thienyl]methoxy]-, (βS)-

SMILES:

OC(C[C@H](C#CC)C(C=C1)=CC=C1OCC2=CC=C(CN3CCC4(C=CC5=C4C=CC=C5)CC3)S2)=O

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