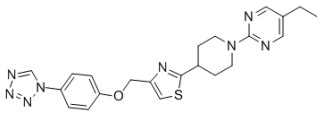
MBX-2982

Cat. No.:	HY-15291
CAS No.:	1037792-44-1
Molecular Formula:	$C_{22}H_{24}N_8OS$
Molecular Weight:	448.54
Target:	GPR119
Pathway:	GPCR/G Protein; Neuronal Signaling
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (111.47 mM; Need ultrasonic)
H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2295 mL	11.1473 mL	22.2946 mL
	5 mM	0.4459 mL	2.2295 mL	4.4589 mL
	10 mM	0.2229 mL	1.1147 mL	2.2295 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.75 mg/mL (6.13 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MBX-2982 is a selective, orally-available G protein-coupled receptor 119 (GPR119) agonist.

IC_{50} & Target

GPR119[1]

In Vitro

In cells pre-treated with MBX-2982 (1 μM) in “chronic incubation/washout” experiments, cAMP accumulation captured by IBMX inclusion is significantly increased compared to control cells (P<0.01; ANOVA; n=3-6) despite extensive washing to remove excess agonist. AR-231,453 produces sustained responses in a similar concentration range to those observed with acute stimulation (a small 1.82 fold shift), with pEC_{50}s of 8.67±0.11 and 8.93±0.17, respectively. Likewise, a large but less severe shift in concentration responses (57.54 fold) is observed for MBX-2982 with respective sustained and acute pEC_{50}s of 7.03±0.13 and 8.79±0.12[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	To examine whether the observations in GLUTag and the primary intestinal cells has physiological relevance, C57BL/6 mice are treated with the GPR119 agonist MBX-2982 at a dose of 10 mg/kg. Note that in order to examine a direct GPR119 effect, no DPP-IV inhibitor is co-administered in this experiment, but a DPP-IV inhibitor is used to preserve active GLP-1 in the blood samples. The plasma GLP-1 levels from the mice dosed with MBX-2982 are increased without a glucose load, indicating that GPR119-mediated GLP-1 secretion is not dependent on glucose[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	HEK-GPR119 cells are transfected with GloSensor 22F plasmid and used for dynamic cAMP measurements 24-30 h later. Cell suspensions are made by dislodging the cells using PBS wash and Accutase treatment followed by resuspension in culture media. Cells are then washed twice by pelleting through centrifugation (300g, 5 min) and resuspension in assay buffer (Hank's Balanced Salt Solution supplemented with 20 mM HEPES and 0.01% fatty acid free BSA, pH 7.4). Cells are then counted and diluted to 600,000 cells/mL in buffer, before GloSensor cAMP reagent is added (2% v/v) and equilibrated with the cells for 2 h at 20°C with periodic mixing. 50 µl/well of cells are added to white-bottomed 384 well plates (30,000 cells/well) in triplicate and baseline luminescence is measuring using an Envision plate-reader. 5 µL of MBX-2982 (serially diluted in DMSO and then diluted 1:100 in assay buffer to obtain ×10 concentrated solution) is manually added to the assay wells to achieve the stated final concentration. Plates are incubated at 20°C with luminescence read at regular intervals to detect dynamic cAMP changes over time within the same wells. cAMP responses at each time-point are expressed as fold over control (vehicle-treated cells)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	HEK-GPR119 cells are grown to confluency in flasks, and cell suspensions are made by dislodging cells using PBS wash and accutase treatment followed by resuspension in culture media. Cells are then washed twice by pelleting through centrifugation (227g, 7 min, 20°C) and resuspension in warm assay buffer (Hank's Balanced Salt Solution supplemented with 20 mM HEPES and 0.01% fatty acid free BSA, pH 7.4), with a 5 min incubation at 37°C after the second wash. Cells are then counted and diluted to 200,000 cells/mL in warm assay buffer[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] C57BL/6 male mice are used. Overnight fasted, 10 week-old male mice (n=20 per group) are given either vehicle (15% polyethylene glycol 400+85% of 23.5% hydroxypropyl-β-cyclodextrin) or MBX-2982 at 10 mg/kg via oral gavage. Half of the animals (n=10 per group) are killed by CO2 asphyxiation 30 min after compound dosing, and blood is collected by cardiac puncture. To preserve active GLP-1, a DPP-IV inhibitor (10 µL per 1 mL of blood) is pre-added to the blood collection tubes and, before the cardiac puncture, the walls of the syringes are rinsed with the DPP-IV inhibitor. The other half of the animals (n=10 per group) received a bolus of oral glucose (3 g/kg) 30 min after compound dosing, and are killed for blood collection 10 min after the glucose load. GLP-1 levels in the plasma samples are measured using the active GLP-1 (ver 2) kit. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Exp Clin Cancer Res. 2018 Nov 29;37(1):295.
- FASEB J. 2016 Jan;30(1):324-35.
- Cell Commun Signal. 2019 May 23;17(1):49
- Invest Ophthalmol Vis Sci. 2017 Jun 1;58(7):2930-2938.
- Patent. US9895370B2.

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REFERENCES

[1]. Hothersall JD, et al. Sustained wash-resistant receptor activation responses of GPR119 agonists. Eur J Pharmacol. 2015 Sep 5;762:430-42.

[2]. Lan H, et al. Agonists at GPR119 mediate secretion of GLP-1 from mouse enteroendocrine cells through glucose-independent pathways. Br J Pharmacol. 2012 Apr;165(8):2799-807.

[3]. Yang JW, et al. GPR119: a promising target for nonalcoholic fatty liver disease. FASEB J. 2016 Jan;30(1):324-35.

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