INT-777

Cat. No.: HY-15677

CAS No.: 1199796-29-6

Molecular Formula: $C_{27}H_{46}O_5$

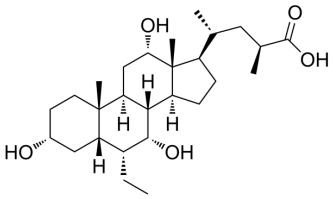
Molecular Weight: 450.65

Target: G protein-coupled Bile Acid Receptor 1

Pathway: GPCR/G Protein

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

Ethanol : ≥ 50 mg/mL (110.95 mM)

DMSO : ≥ 31 mg/mL (68.79 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2190 mL	11.0951 mL	22.1902 mL
5 mM	0.4438 mL	2.2190 mL	4.4380 mL
10 mM	0.2219 mL	1.1095 mL	2.2190 mL

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

In Vivo

1. Add each solvent one by one: 0.5% CMC-Na/saline water
   Solubility: 5 mg/mL (11.10 mM); Suspension solution; Need ultrasonic
2. Add each solvent one by one: 10% EtOH >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.55 mM); Clear solution
3. Add each solvent one by one: 10% EtOH >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.55 mM); Clear solution
4. Add each solvent one by one: 10% EtOH >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.55 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

INT-777 is a potent TGR5 agonist with an EC_{50} of 0.82 μM[1].

IC_{50} & Target

EC50: 0.82 μM (TGR5)[1]

In Vitro	INT-777 is a novel potent and selective TGR5 agonist with remarkable in vivo activity[1]. INT-777 (3 μM) increases ATP production in the human enteroendocrine cell line NCI-H716 in a cAMP-dependent manner[2]. INT-777 (10 μM) lowers Isc and increases TEER when added on the serosal side of seromuscular stripped distal colon segments. INT-777 effect on basal secretion is reduced in neuron-free and TTX-treated mucosal-submucosal preparations[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	INT-777 (1 μM/min/kg, p.o.) has a potent choleretic effect, prevents carboxyl CoA activation and subsequent conjugation, thereby favoring its chole-hepatic shunt pathway with a ductular absorption and a potent choleretic effect in HF-fed TGR5-Tg male mice[1]. INT-777 (30 mg/kg/day, p.o.) increases energy expenditure and reduces hepatic steatosis and obesity upon high-fat feeding in TGR5-Tg mice[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	The experiments are carried out in STC-1 or NCI-H716 cells treated with vehicle (DMSO) or INT-777. INT-777 is assessed for its agonistic activity on TGR5. cAMP production is performed. Cytochrome C oxidase activity is evaluated by following the oxidation of fully reduced cytochrome C at 550 nm. ATP/ADP ratio and GLP-1 release is measured according to the manufacturer's instruction. Primary brown adipocytes are prepared and ileal explants are prepared. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Age-matched male mice are used for all experiments. Genetically engineered mouse models (GEMMs), i.e. TGR5-Tg and TGR5-/- mice are generated. Diet-induced obesity (DIO) in the GEMMs or C57BL/6J mice is induced by feeding 8-week-old mice with a HF-diet (60%Cal/fat, D12492) for at least 8 weeks, as mentioned in the text and figure legends. In the dietary intervention experiments, INT-777 is mixed with diet at the dose sufficient to reach an in vivo dose of 30mg/kg/d. Mouse phenotyping experiments are performed according to EMPRESS protocols and aimed to assess food and water intake, body composition, energy expenditure, glucose and lipid homeostasis, and plasma biochemistry. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Res. 2019 Mar;29(3):193-205.
- Immunity. 2016 Oct 18;45(4):944.
- Cell Host Microbe. 2018 Sep 12;24(3):353-363.e5.
- Nat Commun. 2022 Jun 14;13(1):3419.
- Brain Behav Immun. 2021 Jan;91:587-600.

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REFERENCES

[1]. Pellicciari R, et al. Discovery of 6alpha-ethyl-23(S)-methylcholic acid (S-EMCA, INT-777) as a potent and selective agonist for the TGR5 receptor, a novel target for diabesity. J Med Chem. 2009 Dec 24;52(24):7958-61.

[2]. Thomas C, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab. 2009 Sep;10(3):167-77.

[3]. Duboc H, et al.Reduction of epithelial secretion in male rat distal colonic mucosa by bile acid receptor TGR5 agonist, INT-777: role of submucosal neurons. Neurogastroenterol Motil. 2016 Jun 3. doi: 10.1111/nmo.

[4]. Baiqiang Li, et al. INT-777, a bile acid receptor agonist, extenuates pancreatic acinar cells necrosis in a mouse model of acute pancreatitis. Biochem Biophys Res Commun. 2018 Sep 3;503(1):38-44.

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