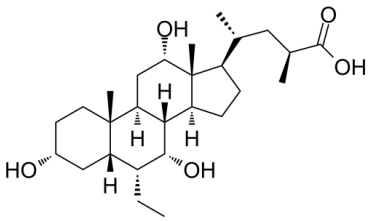
Data Sheet

Product Name:	INT-777
Cat. No.:	CS-3199
CAS No.:	1199796-29-6
Molecular Formula:	C27H46O5
Molecular Weight:	450.65
Target:	GPCR19
Pathway:	GPCR/G Protein
Solubility:	DMSO : ≥ 31 mg/mL (68.79 mM); Ethanol : ≥ 50 mg/mL (110.95 mM)



BIOLOGICAL ACTIVITY:

INT-777 is a potent **TGR5** agonist with an **EC_{50}** of 0.82 μM. IC50 & 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]. **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 cholehepatic 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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: INT-777 is dissolved in DMSO.[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. **Animal Administration:** INT-777 is mixed with diet.[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.

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.

CAIndexNames:

Cholane-23-carboxylic acid, 6-ethyl-3,7,12-trihydroxy-, (3α,5β,6α,7α,12α,23S)-

SMILES:

O[C@@H]1CC[C@@]2(C)[C@@]([C@@H](CC)[C@@H](O)[C@]3([H])[C@]2([H])C[C@H](O)[C@@]4(C)[C@@]3([H])CC[C@@H]4[C@H](C)C[C@H](C)C(O)=O)([H])C1

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