Siponimod

Cat. No.: HY-12355

CAS No.: 1230487-00-9

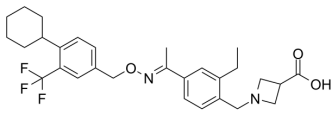
Molecular Formula: $C_{29}H_{35}F_3N_2O_3$

Molecular Weight: 516.6

Target: LPL Receptor

Pathway: GPCR/G Protein

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 1 years; -20°C, 6 months (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 30 mg/mL (58.07 mM)
* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9357 mL	9.6787 mL	19.3573 mL
	5 mM	0.3871 mL	1.9357 mL	3.8715 mL
	10 mM	0.1936 mL	0.9679 mL	1.9357 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.84 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.84 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.84 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: 1.67 mg/mL (3.23 mM); Suspended solution; Need ultrasonic
5. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: 1.67 mg/mL (3.23 mM); Suspended solution; Need ultrasonic
6. Add each solvent one by one: 1% DMSO >> 99% saline
   Solubility: 0.33 mg/mL (0.64 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Siponimod (BAF-312) is an orally active and selective sphingosine-1-phosphate (S1P) receptor modulator. Siponimod is

	selective for $S1P_1$ and $S1P_5$ over $S1P_2$, $S1P_3$, and $S1P_4$, with EC_{50}s of 0.4, 0.98, >10000, >1000, and 750 nM, respectively. Siponimod can be used for multiple sclerosis (MS) research[1]-[4].

IC_{50} & Target				
	S1PR1 0.39 nM (EC50)	S1PR5 0.98 nM (EC50)	S1PR4 750 nM (EC50)	S1PR3 >1000 nM (EC50)
	S1PR2 >10000 nM (EC50)			

In Vitro

Siponimod (compound 32) exhibits selectivity to $S1P_1$ and $S1P_5$, and spares activity on the S1P2, S1P3 and S1P4 receptors[1].

Siponimod (1 mM; 0-1 h) promotes internalization of S1P1 receptors, results 94% S1P1 receptors localized intracellularly at 1 h[2].

Siponimod (0.001 nM-1 μM; 1 h) activates the GIRK channel in atrial myocytes, with an EC_{50} value of 15.8 nM in CHO cell line CCL-61[2].

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

In Vivo

Siponimod (1 g/kg; i.v.; single dose) shows low to moderate in monkey, but high in rat in metabolism studies with liver microsomes. The absolute bioavailability is 50 and 71% in the rat and monkey, respectively, indicating no major presystemic first pass metabolism[1].

Siponimod (0.3, 3 mg/kg; p.o.; once daily; 23 d) suppresses experimental autoimmune encephalomyelitis (EAE) in rats by internalizing S1P1 receptors[2].

Parmacokinetics of Siponimod in rats and monkey[1]

/td>	CL (L/h/kg)	V_{ss} (L/kg)	$T_{1/2}$ (h)	F (%)
Rat	0.36	2.15	6	50
Monkey	0.098/td>	2.12	19	71

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

Animal Model:	Experimental autoimmune encephalomyelitis (EAE) model in Lewis rats (200-250 g)[2]
Dosage:	0.03, 0.3, 3 mg/kg
Administration:	Oral gavage; once daily; 23 days
Result:	Decreased peripheral lymphocyte counts by 88% at the T_{max} of 8 h postadministration.

CUSTOMER VALIDATION

- Theranostics. 2023 Feb; 13(4):1217-1234.
- Proc Natl Acad Sci U S A. 2019 May 21;116(21):10557-10562.
- Aging Dis. 2022.
- Vet Microbiol. 2021, 109177.
- Neurosci Res. 5 August 2022.

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REFERENCES

[1]. Behrangi N, et al. Mechanism of Siponimod: Anti-Inflammatory and Neuroprotective Mode of Action. Cells. 2019 Jan 7;8(1):24.

[2]. Gergely P, et al. The selective sphingosine 1-phosphate receptor modulator BAF312 redirects lymphocyte distribution and has species-specific effects on heart rate. Br J Pharmacol. 2012 Nov;167(5):1035-47.

[3]. Pan S, et al. Discovery of BAF312 (Siponimod), a Potent and Selective S1P Receptor Modulator. ACS Med Chem Lett. 2013 Jan 4;4(3):333-7.

[4]. McGinley M, et al. Prospects of siponimod in secondary progressive multiple sclerosis. Ther Adv Neurol Disord. 2018 Jul 17;11:1756286418788013.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA