Fingolimod hydrochloride

Cat. No.: HY-12005

CAS No.: 162359-56-0

Molecular Formula: $C_{19}H_{34}ClNO_2$

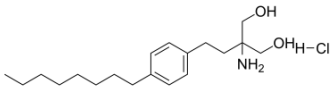
Molecular Weight: 343.93

Target: LPL Receptor; PAK

Pathway: GPCR/G Protein; Cell Cycle/DNA Damage; Cytoskeleton

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 : ≥ 100 mg/mL (290.76 mM)

H_2O : 50 mg/mL (145.38 mM; Need ultrasonic)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.9076 mL	14.5378 mL	29.0757 mL
	5 mM	0.5815 mL	2.9076 mL	5.8151 mL
	10 mM	0.2908 mL	1.4538 mL	2.9076 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: ≥ 2.08 mg/mL (6.05 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (6.05 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (6.05 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Fingolimod hydrochloride (FTY720), an analog of sphingosine, is a potent sphingosine 1-phosphate (S1P) receptors modulator. Fingolimod hydrochloride is phosphorylated by sphingosine kinases, particularly by SK2, and then binds S1PR1, 3, 4, and 5. Fingolimod hydrochloride induces the internalization of S1P1, and consequently, inhibits S1P activity. Fingolimod hydrochloride also is a pak1 activator[1][4].

IC_{50} & Target	S1P 0.033 nM (IC_{50}, in K562 and NK cells)	PAK1

In Vitro

Fingolimod hydrochloride (FTY720) is a S1P antagonist with an IC_{50} of 0.033 nM in K562 and NK cells[1].
The monocyte-derived immature dendritic cells (iDCs) are pretreated with various concentrations of S1P for various periods of time prior to their incubation with NK cells. Four hours incubation of autologous or allogeneic iDCs with 0.2-20 μM of S1P significantly protectes these cells from NK cell lysis. The IC_{50} values of S1P are calculated at 160 nM for autologous iDCs, and 34 nM for allogeneic iDCs. Next, the inhibitory effect of S1P is revered by various concentrations of Fingolimod hydrochloride (FTY720) or SEW2871, with an IC_{50} effect of 173 or 15 nM, respectively[1]. The immunomodulator Fingolimod hydrochloride (FTY720) is a structural analogue of S1P and acts in its phosphorylated isoform as an unselective agonist on $S1P_1$ and $S1P_{3-5}$ and a selective functional antagonist on $S1P_1$.
FTY720 enhances serum S1P levels by inhibiting S1P lyase activity[2].
The number of $Iba1^+$ cells in ipsilateral CA3 is counted, and the corresponding graph shows a significantly lower number of $Iba1^+$ cells in CA3 of the Kainic acid (KA)+FTY720 group than in CA3 of KA group[3].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Administration of the immunomodulator Fingolimod hydrochloride (0.1 mg/kg i.v.) increases serum S1P, improves impaired systolic contractility and activates the PI3K-pathway in the heart. Administration of Fingolimod hydrochloride (FTY720) causes a significant rise in serum S1P levels in both sham-operated animals and animals challenged with LPS/PepG ($P<0.0001$)[2]. FTY720 attenuates microgliosis, modulates the microglia inflammatory phenotype by reducing LPS-mediated activation of p38 MAPK signalling pathway. Thus, FTY720 shares both direct neuroprotective and anti-inflammatory properties that can contribute to overall neuroprotection. In particular, the potential of FTY720 to switch microglia phenotype from a detrimental to a protective one represents a therapeutic mechanism for attenuating acute and chronic CNS damage[3].
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PROTOCOL

Cell Assay [1]

Immature dendritic cells (DCs) are left intact or are incubated with 2 μM S1P, 10 nM Fingolimod hydrochloride, 10 nM SEW2871 or the combinations of S1P with these drugs for 4 h. As a control 1 μg/mL LPS is used. The cells are washed and incubated in a 96-well plate (v-bottom, 2×10^5 cells per well), washed again and resuspended in PBS buffer containing 0.1% sodium azide. They are labeled with 1 μg/mL FITC-conjugated mouse anti-human CD80, 1 μg/mL FITC-conjugated mouse anti-human CD83, 1 μg/mL FITC-conjugated mouse anti-human CD86, 1 μg/mL FITC-conjugated mouse anti-human HLA-class I, 1 μg/mL FITC-conjugated mouse anti-human HLA-DR, 1 μg/mL FITC-conjugated mouse anti-human HLA-E, or 1 μg/mL FITC-conjugated mouse IgG as a control. The cells are washed twice, and examined in the flow cytometer. Markers are set according to the isotype control FITC-conjugated mouse IgG[1].
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Animal Administration [2][3]

Mice[2]
This study is carried out on 2-month-old male C57BL/6J mice or sphingosine kinase-2 deficient ($SPHK\text{-}2^{-/-}$) mice weighing 25-30 g, receiving a standard diet and water ad libitum. C57BL/6J wild-type or $SPHK\text{-}2^{-/-}$ mice receives i.p.-injections of LPS (9 mg/kg)/PepG (1 mg/kg) or its vehicle (0.9% saline). Sham mice are not subjected to LPS/PepG, but are otherwise treated in the same way. At 1 h after LPS/PepG challenge, mice are treated with Fingolimod hydrochloride (0.1 mg/kg i.v.) or its vehicle (10% DMSO). To elucidate the role of different S1P receptors in the observed effects of Fingolimod hydrochloride, mice receive (45 min after LPS/PepG and 15 min prior to Fingolimod hydrochloride) the selective PI3K inhibitor LY294002 (0.3 mg/kg i.v.) or the selective $S1P_2$ receptor antagonist JTE 013 (1 mg/kg i.v.) or (1 h after LPS/PepG) the selective S1P1 receptor agonist SEW2871 (1 mg/kg i.v.) or vehicle (10% DMSO).
Rat[3]
The Sprague-Dawley rats (200 to 250 g) are used. Fingolimod hydrochloride is applied icv (1 μg/2 μL), together with Kainic acid (KA), plus intraperitoneally (ip; 1 mg/kg) 24 h before, and daily, until sacrifice 3 days aftericv. Rats are evaluated for neurological score, neuronal loss in CA3 hippocampal region and activation of microglia at the lesion site.

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CUSTOMER VALIDATION

- Cancer Lett. 2018 Aug 16;436:75-86.
- Haematologica. 2020 Mar;105(3):674-686.
- Breast Cancer Res. 2017 Aug 4;19(1):90.
- Front Pharmacol. 2018 Oct 31;9:1237.
- Commun Biol. 2021 Mar 25;4(1):399.

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REFERENCES

[1]. Rolin J, et al. FTY720 and SEW2871 reverse the inhibitory effect of S1P on natural killer cell mediated lysis of K562 tumor cells and dendritic cells but not on cytokine release. Cancer Immunol Immunother. 2010, 59(4), 575-586.

[2]. Coldewey SM, et al. Elevation of serum sphingosine-1-phosphate attenuates impaired cardiac function in experimental sepsis. Sci Rep. 2016 Jun 9;6:27594.

[3]. Cipriani R, et al. FTY720 attenuates excitotoxicity and neuroinflammation. J Neuroinflammation. 2015 May 8;12:86.

[4]. Arielle M Bryan, et al. Sphingosine-1-phosphate receptors and innate immunity. Cell Microbiol. 2018 May;20(5):e12836.

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