Apremilast

Cat. No.: HY-12085

CAS No.: 608141-41-9

Molecular Formula: $C_{22}H_{24}N_2O_7S$

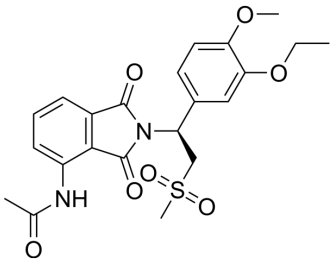
Molecular Weight: 460.5

Target: Phosphodiesterase (PDE); Apoptosis; TNF Receptor

Pathway: Metabolic Enzyme/Protease; Apoptosis

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : 44 mg/mL (95.55 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1716 mL	10.8578 mL	21.7155 mL
	5 mM	0.4343 mL	2.1716 mL	4.3431 mL
	10 mM	0.2172 mL	1.0858 mL	2.1716 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 >> 0.5% Tween-80
   Solubility: 5 mg/mL (10.86 mM); Suspened solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.43 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.43 mM); Suspended solution; Need ultrasonic
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.43 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Apremilast (CC-10004) is an orally available inhibitor of type-4 cyclic nucleotide phosphodiesterase (PDE-4) with an IC_{50} of 74 nM. Apremilast inhibits TNF-α release by lipopolysaccharide (LPS) with an IC_{50} of 104 nM[1].

IC_{50} & Target

PDE4

74 nM (IC_{50})

In Vitro	Apremilast (CC-10004) inhibits TNF-α release by lipopolysaccharide (LPS) with an IC_{50} of 104 nM (pIC_{50}=6.98±0.2), which almost exactly replicates previous reported TNF-α inhibition by Apremilast on peripheral blood mononuclear cells (PBMCs) (IC_{50}=110 nM) and which is similar to the potency of Apremilast for PDE4 enzymatic inhibition (IC_{50}=74 nM). These results are clearly consistent with the hypothesis that Apremilast inhibits TNF-α by increasing intracellular cAMP levels. PKA, Epac1 and Epac2 knockdowns prevented TNF-α inhibition and IL-10 stimulation by Apremilast[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Apremilast (CC-10004), orally administered (5 mg/kg), significantly inhibits TNF-α production in the air pouch by 39 % (61±6 % of vehicle, P <0.001) and diminishes (by 28 %) the number of leukocytes present (72±12 % of vehicle, P<0.05). In agreement, immunohistologic analysis shows that neutrophil accumulation in the air pouch membrane is dramatically reduced by Apremilast. In the murine air pouch model, both Apremilast and methotrexate (MTX) significantly inhibit leukocyte infiltration, while Apremilast, but not MTX, significantly inhibits TNF-α release. The addition of MTX (1 mg/kg) to Apremilast (5 mg/kg) yields no more inhibition of leukocyte infiltration or TNF-α release than with Apremilast alone[1]. Apremilast is a novel, oral PDE4 inhibitor that has been shown to regulate inflammatory mediators. After oral administration of Apremilast, a mean maximum plasma concentration (C_{max}) is found to be 67.00±14.87 ng/mL. The plasma concentration of Apremilast decreases rapidly and is eliminated from plasma with a terminal half-life of 0.92±0.46 h[2] MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Raw 264.7 cells (100,000) are grown in 96-well plates. After 24 h, cells are stimulated with vehicle (final concentration of 0.025% DMSO) or with Apremilast at the indicated concentrations. After 30 minutes cells are stimulated with LPS 1 μg/mL for 4 h. When studying CGS21680 , SCH58261, ZM241385, BAY60-6583, or GS6201, the adenosine receptor ligands are added 15 minutes before Apremilast. Methotrexate is added 24 h and 1 h before Apremilast. Supernates are then collected and TNF-α levels are quantified with the Mouse TNF-α Quantikine ELISA Kit. IC_{50} (EC_{50}) calculations are made using non-linear regression, sigmoidal dose-response, constraining the top to 100 % and bottom to 0 %, allowing variable slope, using GraphPad Prism v6.00[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][2]	Mice[1] Male mice are given weekly intraperitoneal injections of either MTX (1 mg/kg) or vehicle (PBS) for 4 weeks. Air pouches are generated by subcutaneous injection of 3 mL of sterile air and reinflated with 1.5 mL of sterile air 2 days later. Vehicle (0.5 % carboxymethylcellulose and 0.25 % Tween 80) or Apremilast (5 mg/kg) are orally dosed, with a syringe through a blunt-ended curved feeding tube, 24 h and 1 h before inflammation is induced on day 6 by injection of 1 mL of 2 % carrageenan suspension. Four hours later, mice are killed by CO_2 narcosis, and exudates harvested with 2 mL PBS. Leukocytes are counted in a hemocytometer chamber and concentrations of cytokines are measured by ELISA or by the Luminex platform. Rats[2] Male Sprague Dawley rats (180-220 g) are used to study the pharmacokinetics of Apremilast. Diet is prohibited for 12 h before the experiment, but water is freely available. Blood samples (0.3 mL) are collected from the tail vein into heparinized 1.5 mL polythene tubes at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 12 h after oral administration of Apremilast (6.0 mg/kg). The samples are immediately centrifuged at 4,000 g for 8 min. The plasma obtained (100 μL) is stored at −20°C until analysis. Plasma Apremilast concentration versus time data for each rat is analyzed by DAS (Drug and statistics) software. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Int J Mol Med. 2021 Mar;47(3):12.
- Eur J Pharmacol. 2020 Oct 15;885:173508.

- J Dermatol Sci. 2023 Apr 28.
- J Dermatol Sci. 2019 Apr;94(1):244-251.
- Heinrich-Heine-Universität Düsseldorf. Medizinische Fakultät. 2022 May.

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REFERENCES

[1]. Perez-Aso M, et al. Apremilast, a novel phosphodiesterase 4 (PDE4) inhibitor, regulates inflammation through multiple cAMP downstream effectors. Arthritis Res Ther. 2015 Sep 15;17:249.

[2]. Chen LG, et al. Determination of Apremilast in Rat Plasma by UPLC-MS-MS and Its Application to a Pharmacokinetic Study. J Chromatogr Sci. 2016 Sep;54(8):1336-40.

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