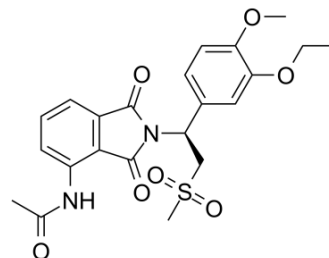


Apremilast

Cat. No.:	HY-12085												
CAS No.:	608141-41-9												
Molecular Formula:	C ₂₂ H ₂₄ N ₂ O ₇ S												
Molecular Weight:	460.5												
Target:	Phosphodiesterase (PDE); Apoptosis; TNF Receptor												
Pathway:	Metabolic Enzyme/Protease; Apoptosis												
Storage:	<table border="0"> <tr> <td>Powder</td> <td>-20°C</td> <td>3 years</td> </tr> <tr> <td></td> <td>4°C</td> <td>2 years</td> </tr> <tr> <td>In solvent</td> <td>-80°C</td> <td>6 months</td> </tr> <tr> <td></td> <td>-20°C</td> <td>1 month</td> </tr> </table>	Powder	-20°C	3 years		4°C	2 years	In solvent	-80°C	6 months		-20°C	1 month
Powder	-20°C	3 years											
	4°C	2 years											
In solvent	-80°C	6 months											
	-20°C	1 month											



SOLVENT & SOLUBILITY

In Vitro	DMSO : 44 mg/mL (95.55 mM; Need ultrasonic)			
		Solvent Concentration	Mass	
			1 mg	5 mg
			10 mg	
Preparing Stock Solutions	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	<ol style="list-style-type: none"> 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 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 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] .	
IC₅₀ & Target	PDE4 74 nM (IC ₅₀)	TNF-α 104 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 μ g/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 CO₂ 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 μ L) 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

- J Dermatol Sci. 2019 Apr;94(1):244-251.
- Eur J Pharmacol. 2020 Oct 15;885:173508.
- Int J Mol Med. 2021 Jan 5.

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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.

Caution: Product has not been fully validated for medical applications. For research use only.