Zimlovisertib

Cat. No.: HY-19836

CAS No.: 1817626-54-2

Molecular Formula: $C_{18}H_{20}FN_3O_4$

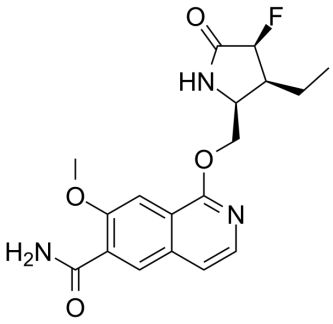
Molecular Weight: 361.37

Target: IRAK

Pathway: Immunology/Inflammation

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 : 62.5 mg/mL (172.95 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7672 mL	13.8362 mL	27.6725 mL
	5 mM	0.5534 mL	2.7672 mL	5.5345 mL
	10 mM	0.2767 mL	1.3836 mL	2.7672 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/saline water
   Solubility: 12.5 mg/mL (34.59 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (5.76 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (5.76 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.76 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Zimlovisertib (PF-06650833) is a potent, selective and orally active inhibitor of interleukin-1 receptor associated kinase 4 (IRAK4) with IC_{50}s of 0.2 and 2.4 nM in the cell and PBMC assay, respectively. Zimlovisertib is used to treat diseases such as rheumatoid arthritis, lupus, and lymphomas[1][2].

IC_{50} & Target

IRAK4

	0.2 nM (IC_{50})
In Vitro	The kinome selectivity profile of Zimlovisertib (Compound 40) is assessed in a panel of 278 kinases (Invitrogen) at 200 nM inhibitor concentration using the ATP K_m for each kinase. Approximately 100% inhibition is observed for IRAK4[1]. Lactam Zimlovisertib is assessed in a whole cell functional VEGF2R assay (PAE-KDR cell line). No activity is observed at concentrations up to and including 30 μM. In a voltage clamp assay, Zimlovisertib inhibits hERG current by 25% at 100 μM[1]. The ability of Zimlovisertib to inhibit five major CYP450 enzymes is assessed using pooled human liver microsomes and probe substrates for the CYP450 enzymes. At a concentration of 3 μM of Zimlovisertib, less than 5% inhibition of CYPs 1A2, 2C8, 2C9, 2D6, and 3A4 is observed. Lactam Zimlovisertib is examined for time dependent inhibition effects on six major CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6) using pooled human liver microsomes and probe substrates. At 100 μM of Zimlovisertib, no time dependent CYP inhibition is observed. The potential induction of CYP3A by Zimlovisertib is assessed using cryopreserved human hepatocytes and afforded a 4.4-fold increase in mRNA at 10 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Zimlovisertib (0.3-30 mg/kg; oral administration; for 2.5 hours; male Sprague-Dawley rats) treatment significantly inhibits LPS-induced TNF-α in a dose dependent manner. Mean exposures of Zimlovisertib in plasma are 2.1 nM, 7.7 nM, 19 nM and 150 nM free, respectively, at 2.5 hours after oral administration of Zimlovisertib at 0.3, 1, 3, and 30 mg/kg. The fraction unbound in rat plasma of Zimlovisertib is 0.3[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male Sprague-Dawley rats[1]
Dosage:	0.1 mg/kg, 1 mg/kg, 3 mg/kg, 30 mg/kg
Administration:	Oral administration; for 2.5 hours
Result:	Significantly inhibited LPS-induced TNF-α in a dose dependent manner.

CUSTOMER VALIDATION

- Research Square Preprint. 2024 Feb 1.

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REFERENCES

[1]. Seganish WM. Inhibitors of interleukin-1 receptor-associated kinase 4 (IRAK4): a patent review (2012-2015). Expert Opin Ther Pat. 2016 Aug;26(8):917-32.

[2]. Lee KL, et al. Discovery of Clinical Candidate 1-{[(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (PF-06650833), a Potent, Selective Inhibitor of Interleukin-1 Receptor Associated Kinase 4 (IRAK4), by Fragmen

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