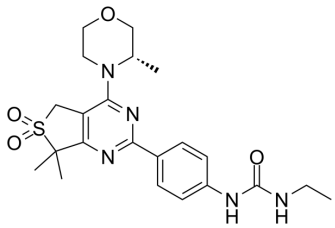
CZ415

Cat. No.:	HY-100222
CAS No.:	1429639-50-8
Molecular Formula:	$C_{22}H_{29}N_5O_4S$
Molecular Weight:	459.56
Target:	mTOR
Pathway:	PI3K/Akt/mTOR
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (217.60 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1760 mL	10.8800 mL	21.7599 mL
	5 mM	0.4352 mL	2.1760 mL	4.3520 mL
	10 mM	0.2176 mL	1.0880 mL	2.1760 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 (5.44 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.44 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.44 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CZ415 is a potent and highly selective mTOR inhibitor with a pIC_{50} of 8.07. CZ415 inhibits mTORC1 and mTORC2 protein complex.

IC_{50} & Target	mTOR	mTORC1	mTORC2
	8.07 (pIC_{50})		

In Vitro

Inhibition of phosphorylation for both downstream targets results in 14.5 nM IC_{50} for pS6RP and 14.8 nM for pAKT. The

	immunosuppressive effect of CZ415 is measured by detecting secreted IFNγ after 18 hours in stimulated human whole blood and the resulting IC_{50} is 226 nM. As a predictor for cardiotoxicity, the activity of CZ415 against the human cardiac ion channel hERG is assessed in a whole-cell patch-clamp assay in HEK293 cells resulting in an IC_{50} of 48 μM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CZ415 is a highly selective mTOR inhibitor showing in vivo efficacy in a collagen induced arthritis (CIA) model. For full characterization of CZ415 and to enable improved dose predictions, the pharmacokinetic (PK) profile is assessed in rat. PK and oral bioavailability are determined after of 1 mg/kg intravenous (iv) bolus and 3 mg/kg oral (po) administration. The observed plasma clearance, corresponding to 45% liver blood flow, suggests that sufficient levels of free compound are circulating in the animal over time. The oral uptake is rapid with a T_{max}max of 0.5 h and bioavailability F = 44% indicates very good absorption from the gut[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice[1] To determine the effects of CZ415 on its pharmacological target, dose-dependent changes in phosphorylation levels of S6 Ribosomal Protein and Akt - both downstream targets of mTOR are assessed. CZ415 is administered orally at 1, 3 and 10 mg/kg to mice 1 h before anti-CD3 stimulus. 15 min after stimulation, spleens are dissected and analyzed for pS6RP and pAKT levels. A dose related significant inhibition of phosphorylation of both S6RP and Akt are observed after compound administration. In particular, 1 and 3 mg/kg CZ415 could fully inhibit S6RP phosphorylation induced by anti-CD3 stimulation and 10 mg/kg additionally decreased the constitutive phosphorylation levels as measured in the control group. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Front Pharmacol. 2020 Nov 11;11:580407.
- Acta Trop. 2020 Dec;212:105708.
- Oncotarget. 2017 May 30;8(47):82027-82036.

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REFERENCES

[1]. Cansfield AD, et al. CZ415, a Highly Selective mTOR Inhibitor Showing in Vivo Efficacy in a Collagen Induced Arthritis Model. ACS Med Chem Lett. 2016 Jun 10;7(8):768-73.

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