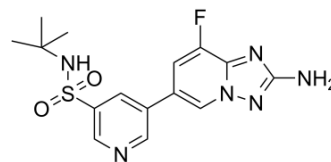


CZC24832

Cat. No.:	HY-15294		
CAS No.:	1159824-67-5		
Molecular Formula:	C ₁₅ H ₁₇ FN ₆ O ₂ S		
Molecular Weight:	364.4		
Target:	PI3K		
Pathway:	PI3K/Akt/mTOR		
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 : ≥ 53 mg/mL (145.44 mM)
 H₂O : < 0.1 mg/mL (insoluble)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent		Mass		
	Concentration		1 mg	5 mg	10 mg
	1 mM		2.7442 mL	13.7212 mL	27.4424 mL
	5 mM		0.5488 mL	2.7442 mL	5.4885 mL
	10 mM		0.2744 mL	1.3721 mL	2.7442 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
 Solubility: 2.5 mg/mL (6.86 mM); Suspended solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
 Solubility: 2.5 mg/mL (6.86 mM); Suspended solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 90% corn oil
 Solubility: ≥ 2.5 mg/mL (6.86 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CZC24832 is a highly selective and potent PI3Kγ inhibitor (IC₅₀=27 nM) with apparent dissociation constants (K_d^{APP}) of 19 nM.

IC₅₀ & Target

PI3Kγ 27 nM (IC ₅₀)	PI3Kβ 1.1 μM (IC ₅₀)	PI3Kδ 8.194 μM (IC ₅₀)
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In Vitro	CZC24832 is active in PI3K γ -dependent cellular C5a-induced AKT Ser473 phosphorylation (IC_{50} =1.2 μ M) and N-formyl-methionine-leucinephenylalanine (fMLP)-induced neutrophil migration assays (IC_{50} =1.0 μ M) ^[1] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	CZC24832 shows suitable pharmacokinetic properties including low clearance (0.84 L per h per kg body weight) and high oral bioavailability (37%), thus allowing further characterization of the inhibitor in rodent models of inflammation. In an IL-8-dependent air pouch model, CZC24832 shows a dose-dependent reduction of granulocyte recruitment (80% inhibition at 10 mg per kg body weight) consistent with the degree of inhibition observed in PI3K γ -null mice. Mice treated orally with 10 mg CZC24832 per kg body weight twice per day show a substantial decrease of bone and cartilage destruction (53% reduction by histopathological analysis) as well as of overall clinical parameters (38% reduction) ^[1] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay ^[1]	RAW264.7 or THP-1 cells are starved for 2.5 h in serum-free medium before CZC24832 (0.1, 1, 10 and 100 μ M) incubation for 30 min at 37°C. RAW264.7 cells are then stimulated for 3 min with C5a at a concentration of 0.6 μ M, and THP-1 cells are stimulated with either insulin (1 μ M, 10 min) or CSF (50 μ g/mL, 5 min) at 37°C and lysed on ice. The detection of AKT phosphorylation (Ser473) is performed using the iBlot system ^[1] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration ^[1]	Rats ^[1] Pharmacokinetics and oral bioavailability of CZC24832 are investigated in male Wistar rats following administration of a single intravenous (0.2 mg per kg body weight) or oral dose (10 mg per kg body weight). The dosing vehicle used is 0.5% (w/v) carboxymethyl cellulose in water for oral gavage. The intravenous dosing vehicle is 10% (v/v) DMSO in 30% (v/v) polyethylene glycol (PEG-400). Heparin blood for pharmacokinetic analysis is withdrawn retro-orbitally from mice or sublingually from rats to prepare plasma samples. These are homogenized with 10% (v/v) water and 3 volumes of acetonitrile and analyzed for CZC24832 by HPLC-MS/MS. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Bergamini G, et al. A selective inhibitor reveals PI3K γ dependence of T(H)17 cell differentiation. Nat Chem Biol. 2012 Apr 29;8(6):576-82.

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

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