CZC24832

Cat. No.: HY-15294

CAS No.: 1159824-67-5

Molecular Formula: $C_{15}H_{17}FN_6O_2S$

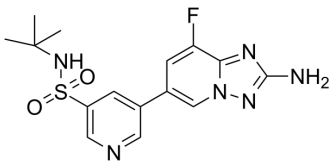
Molecular Weight: 364.4

Target: PI3K

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 : ≥ 53 mg/mL (145.44 mM)

* "≥" 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

1. 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
2. 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
3. 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 (IC_{50}=27 nM) with apparent dissociation constants (K_d^{app}) of 19 nM.

IC_{50} & Target

PI3Kγ	PI3Kβ	PI3Kδ
27 nM (IC_{50})	1.1 μM (IC_{50})	8.194 μM (IC_{50})

In Vitro	CZC24832 is active in PI3Kγ-dependent cellular C5a-induced AKT Ser473 phosphorylation (IC_{50}=1.2 μM) and N-formyl-methionine-leucinephenylalanine (fMLP)-induced neutrophil migration assays (IC_{50}=1.0 μM)[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 PI3Kγ-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 μM) incubation for 30 min at 37°C. RAW264.7 cells are then stimulated for 3 min with C5a at a concentration of 0.6 μM, and THP-1 cells are stimulated with either insulin (1 uM, 10 min) or CSF (50 μg/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 PI3Kγ dependence of T(H)17 cell differentiation. Nat Chem Biol. 2012 Apr 29;8(6):576-82.

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