THZ1

Cat. No.: HY-80013

CAS No.: 1604810-83-4

Molecular Formula: $C_{31}H_{28}ClN_7O_2$

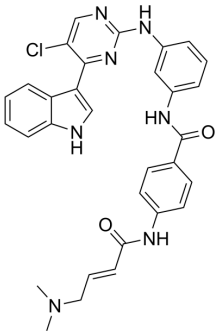
Molecular Weight: 566.05

Target: CDK

Pathway: Cell Cycle/DNA Damage

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 : 100 mg/mL (176.66 mM; Need ultrasonic)
Ethanol : < 1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7666 mL	8.8331 mL	17.6663 mL
5 mM	0.3533 mL	1.7666 mL	3.5333 mL
10 mM	0.1767 mL	0.8833 mL	1.7666 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% saline
   Solubility: 5 mg/mL (8.83 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.42 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.42 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.08 mg/mL (3.67 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

THZ1 is a selective and potent covalent CDK7 inhibitor with an IC_{50} of 3.2 nM. THZ1 also inhibits the closely related kinases CDK12 and CDK13 and downregulates MYC expression[1][2].

IC_{50} & Target	CDK7	CDK12	CDK13

	3.2 nM (IC_{50})		
In Vitro	THZ1 inhibits Jurkat cell and Loucy cell with IC_{50} of 50 nM, and 0.55 nM, respectively. THZ1 (9, 27, 83, 250, 750, and 2500 nM) inhibits CDK12 but at higher concentrations compared to CDK7. THZ1 (1 μM) irreversibly inhibits RNAPII CTD and CAK phosphorylation. THZ1 (2.5 μM) irreversibly inhibits RNAPII CTD phosphorylation by covalently targeting a unique cysteine located outside the kinase domain of CDK7 in Hela S3 cells. THZ1 (250 nM) causes decreased cellular proliferation and an increase in apoptotic index with concomitant reduction in anti-apoptotic proteins, most notably MCL-1 and XIAP in T-ALL cell lines[1]. ?All genotypically-distinct human (hSCLC) cell lines exhibit high sensitivity to THZ1, with an IC_{50} in the range of 5-20 nM[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.		
In Vivo	THZ1 (10 mg/kg) demonstrates potent killing of primary chronic lymphocytic leukemia (CLL) cells and anti-proliferative activity against primary TALL cells and in vivo against a human T-ALL xenograft[1]. ?THZ1 (10 mg/kg, i.v.) inhibits tumor growth in a mouse model of human MYCN-amplified NB and shows no toxicity[4]. ?THZ1 (10?mg/kg, i.p.) completely suppresses oesophageal squamous cell carcinoma tumour growth in vivo without loss of body weight or other common toxic effects[5]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.		

PROTOCOL

Cell Assay [1]	Jurkat, Loucy, KOPTK1, and DND-41 cell lines are seeded in 384-well microplates at 15% confluency in medium. Cells are treated with THZ1 (2, 10, 50, 250, 1250, and 6250 nM) or DMSO for 72 hrs and cell viability is determined using resazurin[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Thirty-two NOD-SCIDIL2Rcγnull (NSG) 9-week old female mice are divided into treatment groups based on mean BLI as follows: THZ1 10 mg/kg qD, THZ1 10 mg/kg BID, and vehicle (10% DMSO in D5W) BID (n=10 for all groups). Two mice are excluded, one with the highest and one with the lowest BLI. All treatments are administered via IV injection in the lateral tail vein in a volume of 3.3 μL/g (non-blinded). Mice are imaged and weighed every 3-5 days. Mice are treated for four weeks and on the final day mice are imaged, dosed and sacrificed approximately 5-6 hrs post dose. Upon sacrifice, blood is collected via cardiac puncture in EDTA tubes; a portion (300 uL) is processed for plasma. Liver and spleen tissues are collected from each mouse with half of each sample flash frozen and half of each sample fixed. Blood plasma and liver samples are processed for pharmacokinetics analysis of THZ1. Spleen tissues are homogenized and lysed and processed for pharmacodynamics analysis of THZ1 target engagement. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Med. 2019 Feb;25(2):292-300.
- Cell. 2018 Sep 20;175(1):171-185.e25.
- Cell. 2017 Sep 7;170(6):1209-1223.e20.
- Science. 2021 Apr 30;372(6541):eaba8490.
- Cancer Discov. 2019 Nov;9(11):1538-1555.

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REFERENCES

[1]. Jiang YY, et al. Targeting super-enhancer-associated oncogenes in oesophageal squamous cell carcinoma. Gut. 2016 May 10. pii: gutjnl-2016-311818.

[2]. Kwiatkowski N, et al. Targeting transcription regulation in cancer with a covalent CDK7 inhibitor. Nature. 2014 Jul 31;511(7511):616-20.

[3]. Zeng M, et al. Targeting MYC dependency in ovarian cancer through inhibition of CDK7 and CDK12/13. Elife. 2018 Nov 13;7. pii: e39030.

[4]. Christensen CL, et al. Targeting transcriptional addictions in small cell lung cancer with a covalent CDK7 inhibitor. Cancer Cell. 2014 Dec 8;26(6):909-22.

[5]. Chipumuro, et al. CDK7 inhibition suppresses super-enhancer-linked oncogenic transcription in MYCN-driven cancer. Cell. 2014 Nov 20;159(5):1126-39. ?

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