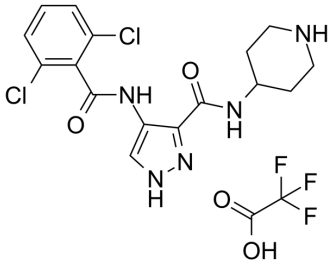
AT7519 TFA

Cat. No.:	HY-50940A
CAS No.:	1431697-85-6
Molecular Formula:	$C_{18}H_{18}Cl_2F_3N_5O_4$
Molecular Weight:	496.27
Target:	CDK
Pathway:	Cell Cycle/DNA Damage
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (201.50 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0150 mL	10.0752 mL	20.1503 mL
	5 mM	0.4030 mL	2.0150 mL	4.0301 mL
	10 mM	0.2015 mL	1.0075 mL	2.0150 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 (5.04 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.04 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.04 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

AT7519 (AT7519M) TFA as a potent inhibitor of CDKs, with IC_{50}s of 210, 47, 100, 13, 170, and <10 nM for CDK1, CDK2, CDK4 to CDK6, and CDK9, respectively.

IC_{50} & Target

CDK9/Cyclin T 10 nM (IC_{50})	CDK5/p35 13 nM (IC_{50})	cdk2/cyclin A 47 nM (IC_{50})	Cdk4/cyclin D1 100 nM (IC_{50})
cdk6/cyclin D3 170 nM (IC_{50})	Cdk1/cyclin B 210 nM (IC_{50})	CDK7/Cyclin H/MAT1 2400 nM (IC_{50})	GSK3β 89 nM (IC_{50})

In Vitro	AT7519 (0-4 μM) TFA results in dose-dependent cytotoxicity with IC_{50}s ranging from 0.5 to 2 μM in MM cells, and this induced cytotoxicity is associated with GSK-3β activation independent of transcriptional inhibition. AT7519 TFA overcomes proliferative advantage conferred by cytokines and the protective effect of BMSC. AT7519 (0.5 μM) TFA induces apoptosis of MM cells in a time-dependent manner. Moreover, AT7519 (0.5 μM) TFA inhibits phosphorylation of RNA polymerase II CTD and partially inhibits RNA synthesis in MM.1S cells[1]. AT7519 (250 nM) TFA inhibits cell cycle progression in human tumor cell lines. AT7519 TFA also induces apoptosis of human tumor cell lines[2]. AT7519 (100-700 nM) TFA induces apoptosis in leukemia cell lines. AT7519TFA also inhibits transcription in human tumor cell lines. Furthermore, AT7519 TFA inhibits RNA polymerase II and reduces antiapoptotic protein levels[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AT7519 TFA inhibits tumor growth in a human MM xenograft mouse model[1]. AT7519 (4.6 and 9.1 mg/kg/dose) inhibits the growth of early-stage HCT116 tumor xenografts. AT7519 (10 mg/kg, i.p.) TFA also inhibits the target CDKs in HCT116 tumor-bearing BALB/c nude mice[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	AT7519's effects on viability of MM cell lines, primary MM cells, and PBMNCs is assessed by measuring 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrasodium bromide (MTT) dye absorbance. DNA synthesis is measured by tritiated thymidine uptake (3H-TdR). MM cells (2-3 × 10^4 cells/well) are incubated in 96-well culture plates with media and different concentrations of AT7519 and/or recombinant IL-6 (10 ng/mL) or IGF-1 (50 ng/mL) for 24 or 48 h at 37°C and 3H-TdR incorporation is measured. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	To evaluate the in vivo anti-MM activity of AT7519, male SCID mice are inoculated subcutaneously with 5×10^6 MM.1S cells in 100 μL serum-free RPMI 1640 medium. When tumors are measurable, mice are treated intraperitoneally (IP) with vehicle or AT7519 dissolved in saline 0.9%. The first group of 10 mice is treated with 15 mg/kg once a day for five days for 2 weeks, and the second group is treated with 15 mg/kg once a day three times a week for four consecutive weeks. The control group receives the carrier alone at the same schedule. Tumor size is measured every alternate day in 2 dimensions using calipers, and tumor volume is calculated with the formula: V= 0.5 a × b^2 (a= long diameter of the tumor, b= short diameter of the tumor). Animals are sacrificed when the tumor reaches 2 cm^3 or when the tumor is ulcerated. Survival and tumor growth are evaluated from the first day of treatment until death. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Cell Chem Biol. 2018 Feb 15;25(2):135-142.e5.
- RNA Biol. 2021 Sep 30;1-8.
- Glycobiology. 2022 Jun 16;cwac038.
- Sci Rep. 2021 Mar 8;11(1):5374.

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REFERENCES

[1]. Santo L, et al. AT7519, A novel small molecule multi-cyclin-dependent kinase inhibitor, induces apoptosis in multiple myeloma via GSK-3beta activation and RNA

polymerase II inhibition. Oncogene. 2010 Apr 22;29(16):2325-36.

[2]. Squires MS, et al. Biological characterization of AT7519, a small-molecule inhibitor of cyclin-dependent kinases, in human tumor cell lines. Biological characterization of AT7519, a small-molecule inhibitor of cyclin-dependent kinases, in human tumor cell lines.

[3]. Squires MS, et al. AT7519, a cyclin-dependent kinase inhibitor, exerts its effects by transcriptional inhibition in leukemia cell lines and patient samples. Mol Cancer Ther. 2010 Apr;9(4):920-8.

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