产品名称：4-(2,6-Dichlorobenzoylamino)-1H-pyrazole-3-carboxylic Acid Piperidin-4-ylamide Monohydrochloride
产品别名：AT7519 Hydrochloride

生物活性：

Description

AT7519 Hydrochloride is 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	CDK5/p35	cdk2/cyclin A	Cdk4/cyclin D1	cdk6/cyclin D3	Cdk1/cyclin B
10 nM (IC_{50})	13 nM (IC_{50})	47 nM (IC_{50})	100 nM (IC_{50})	170 nM (IC_{50})	210 nM (IC_{50})
CDK7/Cyclin H/MAT1	GSK3β				
2400 nM (IC_{50})	89 nM (IC_{50})				

In Vitro

AT7519 (0-4 μM) 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 overcomes proliferative advantage conferred by cytokines and the protective effect of BMSC. AT7519 (0.5 μM) induces apoptosis of MM cells in a time-dependent manner. Moreover, AT7519 (0.5 μM) inhibits phosphorylation of RNA polymerase II CTD and partially inhibits RNA synthesis in MM.1S cells[1]. AT7519 (250 nM) inhibits cell cycle progression in human tumor cell lines. AT7519 also induces apoptosis of human tumor cell lines[2]. AT7519 (100-700 nM) induces apoptosis in leukemia cell lines. AT7519 also inhibits transcription in human tumor cell lines. Furthermore, AT7519 inhibits RNA polymerase II and reduces antiapoptotic protein levels[3].

In Vivo

AT7519 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.) also inhibits the target CDKs in HCT116 tumor-bearing BALB/c nude mice[2].

Solvent&Solubility

In Vitro:

DMSO : ≥ 300 mg/mL (716.49 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3883 mL	11.9414 mL	23.8829 mL
	5 mM	0.4777 mL	2.3883 mL	4.7766 mL
	10 mM	0.2388 mL	1.1941 mL	2.3883 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

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.

实验参考：

Cell Assay	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. [1]
Animal Administration	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. [1]
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.