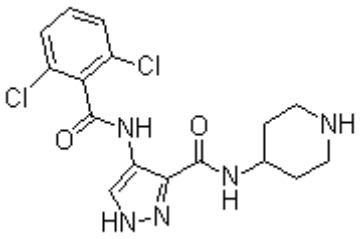
Product Introduction

AT7519

AT7519 is a multi-**CDK** inhibitor for CDK1, 2, 4, 6 and 9 with **IC50** of 10-210 nM. It is less potent to CDK3 and little active to CDK7. Phase 1.

Technical Data:

Molecular Weight (MW):	382.24	
Formula:	$C_{16}H_{17}Cl_2N_5O_2$	
Solubility (25 ℃) * <1 mg/ml means slightly soluble or insoluble:	DMSO 10 mg/mL	
	Water <1mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃ Powder	
	6 months-80℃ in DMSO	
CAS No.:	844442-38-2	

Biological Activity

AT7519 is an ATP competitive CDK inhibitor with a Ki value of 38 nM for CDK1. AT7519 is inactive against all non-CDK kinases with the exception of GSK3β (IC50 = 89 nM). AT7519 shows potent antiproliferative activity in a variety of human tumor cell lines with IC50 values ranging from 40 nM for MCF-7 to 940 nM for SW620 consistent with the inhibition of CDK1 and CDK2. [1] AT7519 induces dose-dependent cytotoxicity in multiple myeloma (MM) cell lines with IC50 values ranging from 0.5 to 2 μM at 48 hours, with the most sensitive cell lines being MM.1S (0.5 μM) and U266 (0.5 μM) and the most resistant MM.1R (>2 μM). It

does not induce cytotoxicity in peripheral blood mononuclear cells (PBMNC). AT7519 partially overcomes the proliferative advantage conferred by IL6 and IGF-1 as well as the protective effect of bone marrow stromal cells (BMSCs). AT7519 induces rapid dephosphorylation of RNA pol II CTD at serine 2 and serine 5 sites, and leads to the inhibition of transcription, partially contributing to AT7519 induced cytotoxicity of MM cells. AT7519 induces activation of GSK-3β by down-regulating GSK-3β phosphorylation, which also contributes to AT7519 induced apoptosis independent of the inhibition of transcription. [2]

A twice daily dosing of AT7519 (9.1 mg/kg) causes tumor regression of both early-stage and advanced-stage s.c. tumors in the HCT116 and HT29 colon cancer xenograft models. [1] AT7519 treatment (15 mg/kg) inhibits tumor growth and prolongs the median overall survival of mice in the human MM xenograft mouse model in association with increased caspase 3 activation. [2]

References

[1] Squires MS, et al. Mol Cancer Ther, 2009, 8(2), 324-332.

[2] Santo L, et al. Oncogene, 2010, 29(16), 2325-2336.