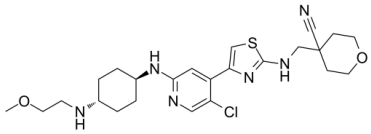
Data Sheet

Product Name:	JSH-150
Cat. No.:	CS-0014379
CAS No.:	2247481-21-4
Molecular Formula:	C24H33ClN6O2S
Molecular Weight:	505.08
Target:	CDK
Pathway:	Cell Cycle/DNA Damage
Solubility:	DMSO : 16.67 mg/mL (33.00 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

JSH-150 is a highly selective and potent **CDK9** inhibitor with an IC_{50} of 1 nM. IC50 & Target: IC50: 1 nM (CDK9/Cyclin T1), 292 nM (CDK16/Cyclin Y), 1.34 μM (CDK1/Cyclin B), 1.68 μM (CDK14/Cyclin Y), 1.72 μM (CDK7/Cyclin H/MNAT1), 2.86 μM (CDK2/Cyclin A), 4.64 μM (CDK5/p25)[1] **In Vitro:** The antiproliferative effect of JSH-150 is examined ton a panel of established cancer cell lines. JSH-150 exhibits potent antiproliferative activities in solid tumor cell lines such as A375 (melanoma), A431 (squamous), BE(2)M17 (neuroblastoma), GIST-T1 (GIST) and COLO205 (colon cancer) with GI_{50} values from 0.002 to 0.044 μM. In the leukemia cell lines including acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and B cell lymphoma cell lines, JSH-150 also displays strong growth inhibition efficacies with GI_{50}s ranging from single to double digit nM. In addition, JSH-150 is much less sensitive in normal CHO cells (GI_{50}: 1.1 μM) compared with the cancer cell lines[1]. **In Vivo:** Treatment of JSH-150 at all dosages, i.e., 10, 20 and 30 mg/kg/day, can almost completely suppress the tumor progression in the first two weeks and does not affect the animal's weight indicating that there is no general cytotoxicity at these doses. After stopping the treatment of JSH-150, the tumors of the animals treated with 10 mpk drug dosage start to grow again. However, this tumor recurrence is not observed in the 20 and 30 mpk dosage groups during the following week after administration of JSH-150 is stopped and p values are quantified on the 21st day, which are 0.042, 0.0035 and 0.0028, respectively. The PK properties of JSH-150 are evaluated in different species including mice, Sprague-Dawley rats and beagle dogs through intravenous injection and oral administration. JSH-150 is absorbed rapidly in dogs and mice (T_{max}=1.33 h and 2.00 h respectively) but slowly in rats (T_{max}=3.33 h). JSH-150 also displays different half-lives in three different species via oral administration ($T_{1/2}$=1.55 h in mice, 3.37 h in rats and 20.37 h in dogs), which indicates that it is metabolized very slowly in dogs compared with mice and rats. In addition, JSH-150 exhibits acceptable bioavailability in mice, rats and dogs (F=45.01%, 45.10% and 39.15%, respectively). The PK properties indicated that JSH-150 is suitable for oral administration[1].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]The A375 (melanoma), A431 (squamous), BE(2)M17 (neuroblastoma), BE(2)M17 (neuroblastoma), CRL-2234 (hepatoma), COLO205 (colon cancer), A549 (lung adenocarcinoma), Ramos (B cell lymphoma), MV4-11 (AML), Ramos (B cell lymphoma), U937 (AML), CHL (hamster lung cell), and CHO (hamster ovary cell) cell lines are used. OCI-AML-3 (AML), SKM-1 (AML), MEC-1 (CLL), MEC-2 (CLL) and HL-60 (human promyelocytic leukemia cells) are used. Human GIST-T1 cells are used. MOLM-13 and MOLM14 cell lines are used. All the cells are grown in a humidified incubator at 37°C under 5% CO2. A375, A431, GIST-T1, A549, Colo205 and CHO cells are maintained in DMEM supplemented with 10% FBS, 1% Penicillin/Streptomycin. BE(2)M17 cells are cultured with 1:1 mixture of ATCC-formulated Eagle's minimum essential medium, and F12 Medium. MV4-11, MEC-1 and MEC-2 are grown in IMDM supplemented with 10% FBS, 1% Penicillin/Streptomycin. CRL-2234, U2932, U937, Ramos, MOLM13, MOLM14, OCI-AML-3, SKM-1, HL-60 and CHL are grown in RPMI 1640 medium supported with 10% FBS and 1% Penicillin/Streptomycin. Adherent cells are grown in tissue culture flasks until they are 85-95% confluent prior to use. For suspension cells, cells are collected by spin down at 800 rpm/min for 5 min before use. Cells are grown in 96-well culture plates (3000 cells/well). The compounds (e.g., JSH-150) at various concentrations are

added into the plates. Cell proliferation is determined after treatment with compounds (e.g., JSH-150) for 72 h. Cell viability is measured using the Cell Titer-Glo assay and luminescence is measured in a multilabel reader[1]. **Animal Administration:** JSH-150 is prepared in a HKI solution (0.5% methocellulose/0.4% Tween80 in ddH_2O)[1].[1]Mice[1]
Five-week-old female nu/nu mice are used. Prior to implantation, cells are harvested during exponential growth. Five million MV4-11 cells in PBS are formulated as a 1:1 mixture with Matrigel and injected into the subcutaneous space on the right flank of nu/nu mice. Daily oral administration is initiated when MV4-11 tumors have reached a size of 200-400 mm^3. Animals are then randomized into treatment groups of 5 mice each for efficacy studies. JSH-150 is delivered daily in a HKI solution (0.5% methocellulose/0.4% Tween80 in ddH_2O) by oral gavage. A range of doses of JSH-150 or its vehicle as control are administered. Female nu/nu mice bearing established MV4-11 tumor xenografts are treated with **JSH-150** at **10, 20, and 30 mg/kg/d** dosage or vehicle. Body weight is measured daily and tumor growth is measured every day after JSH-150 treatment. Tumor volume is calculated[1].

References:

[1]. Beilei Wang, et al. Discovery of 4-(((4-(5-chloro-2-(((1s,4s)-4-((2-methoxyethyl)amino)cyclohexyl)amino)pyridin-4-yl)thiazol-2-yl)amino)methyl)tetrahydro-2H-pyran-4-carbonitrile (JSH-150) as a novel highly selective and potent CDK9 kinase inhibitor. Eur J Med Chem. 13 September 2018.

CAIndexNames:

2H-Pyran-4-carbonitrile, 4-[[[4-[5-chloro-2-[[trans-4-[(2-methoxyethyl)amino]cyclohexyl]amino]-4-pyridinyl]-2-thiazolyl]amino]methyl]tetrahydro-

SMILES:

COCCN[C@@H]1CC[C@@H](NC2=NC=C(Cl)C(C3=CSC(NCC4(C#N)CCOCC4)=N3)=C2)CC1

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