R547

Cat. No.: HY-10014

CAS No.: 741713-40-6

Molecular Formula: $C_{18}H_{21}F_2N_5O_4S$

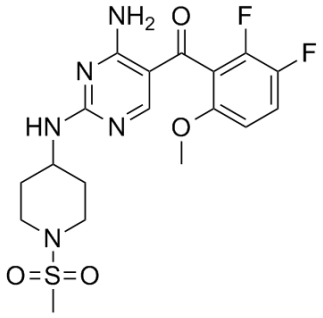
Molecular Weight: 441.45

Target: CDK; GSK-3; Apoptosis

Pathway: Cell Cycle/DNA Damage; PI3K/Akt/mTOR; Stem Cell/Wnt; Apoptosis

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 : ≥ 50 mg/mL (113.26 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2653 mL	11.3263 mL	22.6526 mL
5 mM	0.4531 mL	2.2653 mL	4.5305 mL
10 mM	0.2265 mL	1.1326 mL	2.2653 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 (5.66 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.66 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

R547 is a potent, selective and oral orally bioavailable ATP-competitive CDK inhibitor, with K_is of 2 nM, 3 nM and 1 nM for CDK1/cyclin B, CDK2/cyclin E and CDK4/cyclin D1, respectively[1][2][3][4][5].

IC_{50} & Target

Cdk1/cyclin B 2 nM (Ki)	CDK2/cyclinE 3 nM (Ki)	CDK4/cyclin D 1 nM (Ki)	cdk2/cyclin A 0.1 nM (IC_{50})
CDK2/cyclinE 0.4 nM (IC_{50})	Cdk1/cyclin B 0.2 nM (IC_{50})	CDK3/Cyclin E 0.8 nM (IC_{50})	CDK5/p35 0.1 nM (IC_{50})

	cdk6/cyclin D3 4 nM (IC_{50})	CDK7/cyclin H 171 nM (IC_{50})	GSK-3α 46 nM (IC_{50})	GSK-3β 260 nM (IC_{50})

In Vitro

R547 effectively inhibits CDK1/cyclin B, CDK2/cyclin E, and CDK4/cyclin D1 (Ki = 1–3 nmol/L) and is inactive (Ki > 5,000 nmol/L) against a panel of >120 unrelated kinases in cell-free assays[4].
R547 effectively inhibits the proliferation of tumor cell lines independent of multidrug resistant status, histologic type, retinoblastoma protein, or p53 status, with IC_{50}s <0.60 μM[4].
R547 reduces phosphorylation of the cellular retinoblastoma protein at specific CDK phosphorylation sites at the same concentrations that induced cell cycle arrest[4].
R547 has anti-proliferative activity in tumor cells independent of p53, retinoblastoma, or MDR status[4].
R547 blocks tumor cells in G1 plus G2 and induces apoptosis[4].
R547 induces apoptosis as measured by DNA fragmentation[4].
R547 inhibits phosphorylation of retinoblastoma protein in humantumor cells[4].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Cytotoxicity Assay[4]

Cell Line:	Human tumor cell lines (MDA-MB-468, MDA-MB-435, MCF-7, HCT116, SW480, RKO, HT-29, HCT15, H460a, C33A, DU145, OSA-CL, LOX, JEKO-1, REC-1)
Concentration:	MTT assay
Incubation Time:	5 days
Result:	Has potent in vitro antiproliferative activity.

Cell Cycle Analysis[4]

Cell Line:	R547, HCT116
Concentration:	0.1 μM, 0.2 μM, 0.6 μM
Incubation Time:	20 hours
Result:	Decrease in BrdUrd incorporation and in percentage S phase in a dose-dependent, indicative of a cell cycle block in G1-S plus G2-M.

Western Blot Analysis[4]

Cell Line:	HCT116 cells
Concentration:	0.1 μM, 0.2 μM, 0.6 μM
Incubation Time:	24 hours, 48 hours, 72 hours
Result:	Showed a band corresponding to a p48/retinoblastoma fragment that becomes more intense at 48 and 72 hours.

In Vivo

R547 has significant in vivo efficacy with daily oral and once weekly i.v. dosing[4].
R547 inhibits phosphorylation of retinoblastoma protein in tumors[4].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	13-14 weeks old female immunodeficient nude mice (23-25 g), with HCT116/H460a/MDA-MB-435/DU145/LOX/A549 cells xenograft[4]
Dosage:	40 mg/kg

Administration:	Oral administration; daily; for 3-weeks
Result:	Showed antitumor activity in all of the models in this study.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Cell Chem Biol. 2018 Feb 15;25(2):135-142.e5.

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REFERENCES

[1]. Chu XJ, DePinto W, Bartkovitz D, So SS, Vu BT, Packman K, Lukacs C, Ding Q, Jiang N, Wang K, Goelzer P, Yin X, Smith MA, Higgins BX, Chen Y, Xiang Q, Moliterni J, Kaplan G, Graves B, Lovey A, Fotouhi N.Discovery of [4-Amino-2-(1-methanesulfonylpiperidin-4-ylamino)pyrimidin-5-yl](2,3-difluoro-6- methoxyphenyl)methanone (R547), a potent and selective cyclin-dependent kinase inhibitor with significant in vivo antitumor activity.J Med Chem. 2006 Nov 2;49(22):6549-60.

[2]. Bayés M, Rabasseda X, Prous JR.Gateways to clinical trials. Methods Find Exp Clin Pharmacol. 2007 Jul-Aug;29(6):427-37.

[3]. Martin F, Thomson TM, Sewer A, Drubin DA, Mathis C, Weisensee D, Pratt D, Hoeng J, Peitsch MC.Assessment of network perturbation amplitudes by applying high-throughput data to causal biological networks.BMC Syst Biol. 2012 May 31;6:54.

[4]. DePinto, Wanda et al In vitro and in vivo activity of R547: a potent and selective cyclin-dependent kinase inhibitor currently in phase I clinical trials Molecular Cancer Therapeutics (2006), 5(11), 2644-2658

[5]. Jones, Clifford D.; Andrews, David M. Imidazole pyrimidine amides as potent, orally bioavailable cyclin-dependent kinase inhibitors Bioorganic & Medicinal Chemistry Letters (2008), 18(24), 6486-6489

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