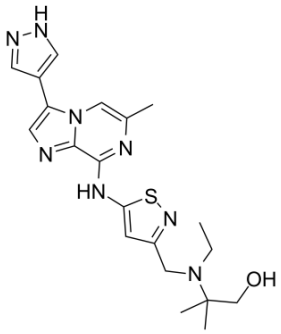
SCH-1473759

Cat. No.:	HY-10482
CAS No.:	1094069-99-4
Molecular Formula:	$C_{20}H_{26}N_8OS$
Molecular Weight:	426.54
Target:	Aurora Kinase
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



BIOLOGICAL ACTIVITY

Description	SCH-1473759 is an aurora inhibitor with IC_{50}s of 4 and 13 nM for aurora A and B, respectively.
IC_{50} & Target	Aurora A 4 nM (IC_{50}) Aurora B 13 nM (IC_{50})
In Vitro	SCH-1473759 directly binds to aurora A and B with K_ds of 20 and 30 nM, respectively. SCH-1473759 also inhibits the Src family of kinases (IC_{50}<10 nM), Chk1 (IC_{50}=13 nM), VEGFR2 (IC_{50}=1 nM), and IRAK4 (IC_{50}=37 nM). It does not have significant activity (IC_{50}>1000 nM) against 34 other kinases representing different families of the kinome. SCH-1473759 inhibits HCT116 cells proliferation with an IC_{50} of 6 nM[1]. SCH 1473759 inhibits tumor cell lines from different tissues (breast, ovarian, prostate, lung, colon, brain, gastric, renal, skin, and leukemia). The most sensitive cell lines includ A2780, LNCap, N87, Molt4, K562, and CCRF-CEM with IC_{50} values <5 nM[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	SCH-1473759 at a low dose of 5 mg/kg (ip, bid) is well-tolerated in a continuous dosing schedule and shows 50% tumor growth inhibition(TGI) on day 16. A higher dose of 10mg/kg(ip, bid) is well-tolerated in an intermittent schedule (5 days on, 5 days off) and gave 69% TGI on day 16. SCH-1473759 shows good exposure in all species with the clearance being high in rodents and moderate in dog and monkey. The half-life is also moderate, but the tissue distribution is high[1]. SCH 1473759 dose- and schedule-dependent anti-tumor activity in four human tumor xenograft models. Further, the efficacy is enhanced in combination with taxanes and found to be most efficacious when SCH 1473759 is dosed 12-h post-taxane treatment[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Aurora A and Aurora B kinase assays are performed in low protein binding 384-well plates. SCH-1473759 is diluted in 100% DMSO to the desired concentrations. For the Aurora A assay, each reaction consists of 8 nM enzyme Aurora A, 100 nM Tamra-PKAtide, 25μM ATP, 1 mM DTT, and kinase buffer. For the Aurora B assay, each reaction consisted of 26 nM enzyme Aurora B, 100 nM Tamra-PKAtide, 50 μM ATP, 1 mM DTT, and kinase buffer. Dose-response curves are plotted from inhibition data generated in duplicate, from 8 point serial dilutions of SCH-1473759[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [1]	Cells are plated at a cell density ranging from 625 to 3,750 cells per well and treated in triplicate wells with SCH-1473759 (0.1% final DMSO concentration). A plate is stained at the start of the study (zero hour) and a second plate is incubated for 72 hour at 37°C and then stained. Cells are fixed with fixation solution plus 1,000 nM Hoechst 33342 dye and incubated for 30 minutes. The fixation solution is removed and cells are ished twice with PBS. Then 15 immunofluorescence images are captured at 10X using automated fluorescent microscope [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice: Anti-tumor efficacy of SCH 1473759 dosed i.p. is evaluated in mice bearing established A2780 ovarian tumor xenografts. Three schedules are tested at their respective maximum tolerated doses: 10 mg/kg bid (twice daily), 20 mg/kg qd (daily), and 100 mg/kg day 0, 4, 7. Additionally, 60 mg/kg day 0, 4, 7 is tested[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Yu T, et al. Discovery of a Potent, Injectable Inhibitor of Aurora Kinases Based on the Imidazo-[1,2-a]-Pyrazine Core. ACS Med Chem Lett. 2010 Jun 7;1(5):214-8.

[2]. Basso AD, et al. SCH 1473759, a novel Aurora inhibitor, demonstrates enhanced anti-tumor activity in combination with taxanes and KSP inhibitors. Cancer Chemother Pharmacol. 2011 Oct;68(4):923-33.

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