SCH900776

Cat. No.: HY-15532

CAS No.: 891494-63-6

Molecular Formula: $C_{15}H_{18}BrN_7$

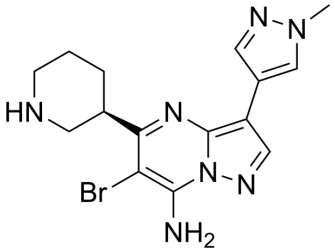
Molecular Weight: 376.25

Target: Checkpoint Kinase (Chk)

Pathway: Cell Cycle/DNA Damage

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (265.78 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.6578 mL	13.2890 mL	26.5781 mL
5 mM	0.5316 mL	2.6578 mL	5.3156 mL
10 mM	0.2658 mL	1.3289 mL	2.6578 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 (6.64 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.64 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.64 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

SCH900776 (MK-8776) is a potent, selective and orally bioavailable inhibitor of checkpoint kinase1 (Chk1) with an IC_{50} of 3 nM. SCH900776 shows 50- and 500-fold selectivity over CDK2 and Chk2, respectively[1][2].

IC_{50} & Target

Chk1	Chk2	CDK2
3 nM (IC_{50})	1500 nM (IC_{50})	160 nM (IC_{50})

In Vitro	SCH900776 (300 nM) shows potent inhibitory activities against phosphorylation at ser296-Chk1. SCH900776 (1 μM) causes a 30-fold decrease in the IC_{50} for NSC-32065 in MDA-MB-231 cells[1]. The K_d value of SCH 900776 for the CHK1 kinase domain is 2 nM. SCH 900776 exhibits an approximate EC_{50} of 60 nM in cells exposure to NSC-32065. SCH 900776 induces dose-dependent suppression of CHK1 pS296 and concomitant accumulation of phospho-RPA signal in U2OS cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	SCH 900776 induces the γ-H2AX biomarker at 4 mg/kg (i.p.), and enhances tumor pharmacodynamic and regression responses in A2780 xenograft model. SCH 900776 (16 and 32 mg/kg, i.p.) induces incremental improvements in tumor response. Escalation of SCH 900776 dose to 20 and 50 mg/kg in combination with LY 188011 results in improvements in TTP 10× in the A2780 xenograft systems[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	The Kinase Profiler service is used to generate general selectivity data for SCH 900776 against a broad range of serine/threonine and tyrosine kinases. Assays are typically run at two concentrations of SCH 900776 (0.5 and 5 μM), at a fixed (10 μM) concentration of ATP. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	For cell growth assays, cells are seeded at low density (500-1000 cells) in 96-well plates and then incubated with drug for 24 h (8 wells per concentration). Following treatment, cells are washed and grown in fresh media for 5-7 days at 37°C. Prior to attaining confluence, cells are washed, lysed, and stained with Hoechst 33258. Fluorescence is read on a microplate spectrofluorometer. Results are expressed as mean and standard error for the concentration of drug that inhibited growth by 50%. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	For tumor implantation, specific cell lines are grown in vitro, washed once with PBS and resuspended in 50% Matrigel in PBS to a final concentration of 4×10^7 to 5×10^7 cells per mL. Nude mice are injected with 0.1 mL of this suspension subcutaneously in the flank region. Tumor length (L), width (W), and height (H) are measured by a caliper twice a week on each mouse and then used to calculate tumor volume using the formula: (L×W×H)/2. Animals (N=10) are randomized to treatment groups and treated intraperitoneally with either SCH 900776 (formulated in 20% hydroxypropyl β-cyclodextrin) or individual chemotherapeutic agents, formulated as recommended. Tumor volumes and body weights are measured during and after the treatment periods. Data are recorded as means±SEM before being normalized to starting volume. Time to progression to 10x starting volume (TTP 10x) is monitored in some experiments. For pharmacodynamic marker analyses in mice, tumors and adjacent skin are collected at necropsy, fixed overnight in 10% formalin, and washed/stored in 70% ethanol. For skin punch biopsies, an area of approximately 4 square inches is shaved. Rats are anesthetized using inhaled isofluorane and dogs are locally anesthetized using subcutaneous administration of lidocaine. Samples are collected using a 4 mm biopsy punch. Skin punches are fixed in 10% formalin overnight before washing/storage in 70% ethanol. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2021 Jan 20;13(577):eaba7401.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Sci Adv. 2022 Jan 21;8(3):eabj8357.
- Blood Cancer J. 2021 Jul 31;11(7):137.
- Cell Syst. 2018 Apr 25;6(4):424-443.e7.

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REFERENCES

[1]. Montano R, et al. Preclinical development of the novel Chk1 inhibitor SCH900776 in combination with DNA-damaging agents and antimetabolites. Mol Cancer Ther. 2012 Feb;11(2):427-38.

[2]. Guzi TJ, et al. Targeting the replication checkpoint using SCH 900776, a potent and functionally selective CHK1 inhibitor identified via high content screening. Mol Cancer Ther. 2011 Apr;10(4):591-602.

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