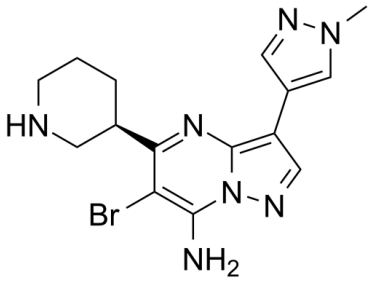
Data Sheet

Product Name:	SCH900776
Cat. No.:	CS-1117
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
Solubility:	DMSO : ≥ 100 mg/mL (265.78 mM)



BIOLOGICAL ACTIVITY:

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]. IC50 & Target: IC50: 3 nM (Chk1), 160 nM (CDK2), 1500 nM (Chk2)[2] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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. **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%. **Animal Administration:** SCH 900776 is formulated in 20% hydroxypropyl β-cyclodextrin.[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.

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.

CAIndexNames:

Pyrazolo[1,5-a]pyrimidin-7-amine, 6-bromo-3-(1-methyl-1H-pyrazol-4-yl)-5-(3R)-3-piperidinyl-

SMILES:

NC1=C(Br)C([C@H]2CNCCC2)=NC3=C(C4=CN(C)N=C4)C=NN13

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