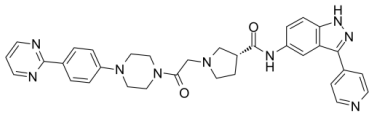
Data Sheet

Product Name:	SCH772984
Cat. No.:	CS-1421
CAS No.:	942183-80-4
Molecular Formula:	C33H33N9O2
Molecular Weight:	587.67
Target:	ERK
Pathway:	MAPK/ERK Pathway; Stem Cell/Wnt
Solubility:	DMSO : 14.29 mg/mL (24.32 mM; Need ultrasonic); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

SCH772984 is a highly selective and ATP-competitive **ERK** inhibitor, with **IC_{50}**s of 4 and 1 nM for ERK1 and ERK2, respectively. SCH772984 has antitumor activity in MAPK inhibitor-naïve and MAPK inhibitor-resistant cells containing **BRAF** or **RAS** mutations[1].
IC50 & Target: IC50: 4/1 nM (ERK1/2)[1] **In Vitro:** SCH772984 (300 nM; 24-48hours) results in a G1 arrest in SCH772984-sensitive melanoma cells[1].
SCH772984 (3-300 nM; 24 hours) inhibits ERK and RSK phosphorylation[1].
SCH772984 shows EC_{50} values less than 500 nM in approximately 88% and 49% of BRAF-mutant (n=25) or RAS-mutant (n=35) tumor lines, respectively[1]. **In Vivo:** SCH772984 (12.5-50 mg/kg; i.p.; twice daily for 14 days) leads to 98% tumor regression[1].
Dose-dependent antitumor activity is also observed in the KRAS-mutant pancreatic MiaPaCa model, with 36% regression at 50 mg/kg twice daily. Importantly, tumor regression is accompanied by robust inhibition of ERK phosphorylation in tumor tissue. SCH772984 is well tolerated on this schedule as measured by morbidity, lethality, or body weight loss[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]SCH772984 is tested in 8-point dilution curves in duplicate against purified ERK1 or ERK2. The enzyme is added to the reaction plate and incubated with the compound before adding a solution of substrate peptide and ATP. Fourteen microliters of diluted enzyme (0.3 ng active ERK2 per reaction) is added to each well of a 384-well plate. The plates are gently shaken to mix the reagents and incubated for 45 minutes at room temperature. The reaction is stopped with 60 µL of IMAP Binding Solution (1:2,200 dilutions of IMAP beads in 1× binding buffer). The plates are incubated at room temperature for an additional 0.5 hours to allow complete binding of phosphopeptides to the IMAP beads. Plates are read on the LJL Analyst[1]. **Cell Assay:** SCH772984 is dissolved in DMSO and stored, and then diluted with appropriate media before use[1].[1]Cell proliferation experiments are carried out in a 96-well format (six replicates), and the $BRAF^{V600E}$-mutant human melanoma cell line LOXIMV1 (LOX) are plated at a density of 4,000 cells per well. At 24 hours after cell seeding, cells are treated with DMSO or a 9-point IC_{50} dilution (0.001-10 µM) at a final concentration of 1% DMSO for all concentrations. Viability is assayed 5 days after dosing using the ViaLight luminescence kit. For the cell line panel viability assay, cells are treated with SCH772984 for 4 days and assayed by the CellTiterGlo luminescent cell viability assay[1]. **Animal Administration:** SCH772984 is dissolved in DMSO and then diluted with PBS or saline[1].[1]Mice[1]
Nude mice are injected subcutaneously with specific cell lines, grown to approximately 100 mm^3, randomized to treatment groups (10 mice/group), and treated intraperitoneally with either SCH772984 (12.5, 25, or 50 mg/kg) or vehicle. Tumor length (L), width (W), and height (H) are measured during and after the treatment periods by a caliper twice weekly on each mouse and then used to calculate tumor volume using the formula (L×W×H)/2. Animal body weights are measured on the same days twice weekly. Upon completion of the experiment, vehicle- and SCH772984-treated tumor biopsies are processed for Western blot analysis.

References:

[1]. Morris EJ, et al. Discovery of a novel ERK inhibitor with activity in models of acquired resistance to BRAF and MEK inhibitors. Cancer Discov. 2013 Jul;3(7):742-50.

CAIndexNames:

3-Pyrrolidinecarboxamide, 1-[2-oxo-2-[4-[4-(2-pyrimidinyl)phenyl]-1-piperazinyl]ethyl]-N-[3-(4-pyridinyl)-1H-indazol-5-yl]-, (3R)-

SMILES:

O=C([C@H](CC1)CN1CC(N(CC2)CCN2C(C=C3)=CC=C3C4=NC=CC=N4)=O)NC5=CC6=C(C=C5)NN=C6C7=CC=NC=C7

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