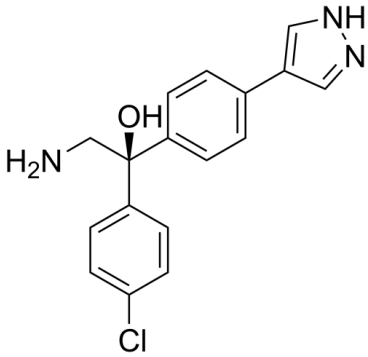
Data Sheet

Product Name:	AT13148
Cat. No.:	CS-3136
CAS No.:	1056901-62-2
Molecular Formula:	$C_{17}H_{16}ClN_3O$
Molecular Weight:	313.78
Target:	Akt; PKA; Ribosomal S6 Kinase (RSK); ROCK
Pathway:	Cell Cycle/DNA Damage; Cytoskeleton; MAPK/ERK Pathway; PI3K/Akt/mTOR; Stem Cell/Wnt; TGF-beta/Smad
Solubility:	DMSO : 50 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

AT13148 is an orally active and ATP-competitive, multi-**AGC kinase** inhibitor with **IC_{50}**s of 38 nM/402 nM/50 nM, 8 nM, 3 nM, and 6 nM/4 nM for Akt1/2/3, p70S6K, PKA, and ROCKI/II, respectively. IC50 & Target:IC50: 38 nM (Akt1), 402 nM (Akt2), 50 nM (Akt3), 8 nM (p70S6K), 3 nM (PKA), 6 nM (ROCKI), 4 nM (ROCKII) ***In Vitro:*** AT13148 inhibits a panel of kinases at 10 μM, and the IC_{50} values for p70S6K, PKA, ROCKI, and ROCKII are all less than 10 nM and those for AKT1, 2, and 3 are 38, 402, and 50 nM, respectively. For the related AGC kinases RSK1 and SGK3, the IC_{50} values are 85 and 63 nM, respectively. In contrast, IC_{50} values for the non-AGC kinases CHK2 and Aurora B are both greater than 800 nM. AT13148 potently inhibits proliferation with GI_{50} values of 1.5 to 3.8 μM across a selected panel of cancer cell lines[1]. AT13148 treatment in gastric cancer cells dramatically suppresses activation of multiple AGC kinases, including Akt (at p-Thr-308), p70S6 kinase (p70S6K), glycogen synthase kinase 3β (GSK-3β) and p90 ribosomal S6 kinase (RSK)[2]. ***In Vivo:*** Oral drug administration of 5 mg/kg of AT13148 results in complete bioavailability. Clear inhibition of phosphorylation of the AKT substrates GSK3β, tuberin, and the p70S6K target S6RP are also observed in PTEN-deficient MES-SA human uterine tumor xenografts after treatment with 40 and 50 mg/kg p.o. of AT13148[1]. Oral gavage of AT13148 at well-tolerated doses significantly inhibits HGC27 xenograft tumor growth in nude mice. AGC activity is also dramatically decreased in AT13148-administrated HGC27 tumors[2].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]AT13148 is assayed against 40 kinases and the percentage inhibition at 10 μM of AT13148 is determined. Individual IC_{50} values are measured for selected kinases using ATP concentrations equivalent to the K_m for each enzyme. **Cell Assay:** [2]Cells are seeded onto 96-well micro-plates at a density of 1×10^4 cells per well. After treatment, MTT solution (0.5 mg/mL) is added for 2-3 h. The MTT-purple formazan productions are dissolved in 0.1 N hydrochloric acid, and optical density (OD) is obtained through the micro-plate reader at 570 nm wavelength. **Animal Administration:** [1]For pharmacokinetic analysis, male athymic BALB/c mice are obtained from Harlan. AT13148 is formulated in 10% DMSO, 1% Tween-20, and 89% saline and administered at 5 mg/kg i.v. or p.o. Duplicate samples of heparinized whole blood are collected by cardiac puncture at 1, 2, 4, 6, 8, 16, 24, and 72 hours after dosing. Plasma and tissues (liver, kidney, spleen, and muscle are also taken) are prepared and frozen at −20°C until analysis. AT13148 is extracted from plasma and tissues using acetonitrile containing an internal standard and quantified using a liquid chromatography tandem mass spectrometry (LC-MS/MS) method and appropriate standard curves. Pharmacokinetic parameters are determined using WinNonLin software version 5.2.

References:

[1]. Yap TA, et al. AT13148 is a novel, oral multi-AGC kinase inhibitor with potent pharmacodynamic and antitumor activity. Clin Cancer Res. 2012 Jul 15;18(14):3912-23.

[2]. Xi Y, et al. AT13148, a first-in-class multi-AGC kinase inhibitor, potently inhibits gastric cancer cells both in vitro and in vivo. Biochem Biophys Res Commun. 2016 Sep 9;478(1):330-6

CAIndexNames:

Benzenemethanol, α-(aminomethyl)-α-(4-chlorophenyl)-4-(1H-pyrazol-4-yl)-, (αS)-

SMILES:

ClC1=CC=C([C@](C2=CC=C(C3=CNN=C3)C=C2)(O)CN)C=C1

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