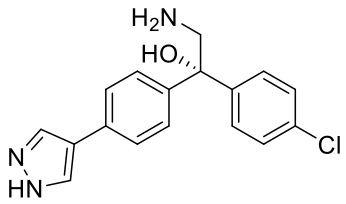
Product data sheet

MedKoo Cat#: 205884 Name: AT13148 CAS#: 1056901-62-2 Chemical Formula: $C_{17}H_{16}ClN_3O$ Exact Mass: 313.09819 Molecular Weight: 313.78	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

AT13148 is a novel oral multi-AGC kinase inhibitor with potent pharmacodynamic and antitumor activity, which shows a distinct mechanism of action from other AKT inhibitors. AT13148 is currently being developed by Astex Pharmaceuticals. AT131148 was identified utilizing high-throughput X-ray crystallography and fragment-based lead discovery techniques. AT13148 caused substantial blockade of AKT, p70S6K, PKA, ROCK and SGK substrate phosphorylation and induction of apoptosis in both a concentration and time-dependent manner in cancer cells with clinically relevant genetic defects both in vitro and in vivo.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	47.33	150.84
DMSO:PBS (pH 7.2) (1:2)	0.33	1.05
DMF	30.0	95.61

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	3.19 mL	15.93 mL	31.87 mL
5 mM	0.64 mL	3.19 mL	6.37 mL
10 mM	0.32 mL	1.59 mL	3.19 mL
50 mM	0.06 mL	0.32 mL	0.64 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Sadok A, McCarthy A, Caldwell J, Collins I, Garrett MD, Yeo M, Hooper S, Sahai E, Kuemper S, Mardakheh FK, Marshall CJ. Rho kinase inhibitors block melanoma cell migration and inhibit metastasis. Cancer Res. 2015 Jun 1;75(11):2272-84. doi: 10.1158/0008-5472.CAN-14-2156. Epub 2015 Apr 3. PMID: 25840982.
2. Yap TA, Walton MI, Grimshaw KM, Te Poele RH, Eve PD, Valenti MR, de Haven Brandon AK, Martins V, Zetterlund A, Heaton SP, Heinzmann K, Jones PS, Feltell RE, Reule M, Woodhead SJ, Davies TG, Lyons JF, Raynaud FI, Eccles SA, Workman P, Thompson NT, Garrett MD. 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. doi: 10.1158/1078-0432.CCR-11-3313. Epub 2012 Jul 10. PMID: 22781553.

In vivo study

1. Rath N, Munro J, Cutiongco MF, Jagiełło A, Gadegaard N, McGarry L, Unbekandt M, Michalopoulou E, Kamphorst JJ, Sumpton D, Mackay G, Vennin C, Pajic M, Timpson P, Olson MF. Rho Kinase Inhibition by AT13148 Blocks Pancreatic Ductal

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Adenocarcinoma Invasion and Tumor Growth. Cancer Res. 2018 Jun 15;78(12):3321-3336. doi: 10.1158/0008-5472.CAN-17-1339. Epub 2018 Apr 18. PMID: 29669760; PMCID: PMC6005347.
2. Yap TA, Walton MI, Grimshaw KM, Te Poele RH, Eve PD, Valenti MR, de Haven Brandon AK, Martins V, Zetterlund A, Heaton SP, Heinzmann K, Jones PS, Feltell RE, Reule M, Woodhead SJ, Davies TG, Lyons JF, Raynaud FI, Eccles SA, Workman P, Thompson NT, Garrett MD. 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. doi: 10.1158/1078-0432.CCR-11-3313. Epub 2012 Jul 10. PMID: 22781553.

7. Bioactivity

Biological target:

AT13148 is an ATP-competitive, multi-AGC kinase inhibitor with IC50s 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.

In vitro activity

AT13148 potently inhibited proliferation with GI50 values of 1.5 to 3.8 μmol/L across a selected panel of cancer cell lines (Supplementary Table S3) representing common human malignancies with deregulation of PI3K-AKT-mTOR or RAS-RAF pathways. The effect of 1-hour exposure to AT13148 on AKT and p70S6K signaling was initially explored in PTEN-deficient U87MG glioblastoma cells (Fig. 2A). Marked induction of pSer473 AKT occurred at all concentrations. Nevertheless, phosphorylation of the 2 AKT substrates GSK3β and PRAS40 was inhibited at AT13148 concentrations >1 and 5 μmol/L AT13148, respectively.

Reference: Clin Cancer Res. 2012 Jul 15;18(14):3912-23. https://clincancerres.aacrjournals.org/content/18/14/3912.long

In vivo activity

In contrast, in AT13148 treated mice, tumor cells homed and grew on the pancreas, but a clearly demarcated border was consistently observed between tumor and normal tissue (Fig. 6A lower panels). When the area of the invasive region, in which tumor cells were intermixed with normal pancreas cells, was expressed as a percentage of the total pancreas for each condition, there was a significant decrease in the invasive region for AT13148 treated mice (Fig. 6A), which approached significance for the less potent ROCK inhibitor fasudil treated mice (Fig. 6B). To determine whether the anti-invasive effect of AT13148 treatment was due to decreased proliferation, mice were injected with bromodeoxyuridine (BrdU) 2 h before sacrifice, and then tissues were stained with anti-BrdU antibody (Fig. 6C). Counting the percentage of BrdU positive tumor cells indicated that there was no effect of AT13148 on proliferation (Fig. 6D), indicating that reduced invasion of pancreatic tissue was a direct effect on invasive behaviors.

Reference: Cancer Res. 2018 Jun 15; 78(12): 3321–3336. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6005347/