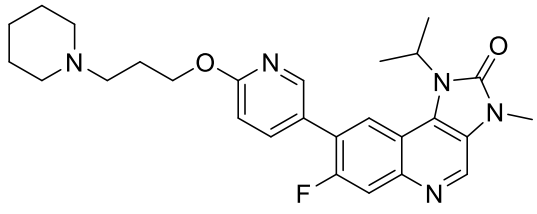
Product data sheet

MedKoo Cat#: 206857 Name: AZD1390 CAS#: 2089288-03-7 Chemical Formula: $C_{27}H_{32}FN_5O_2$ Exact Mass: 477.254 Molecular Weight: 477.58	
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:
AZD1390 is a potent and selective ATM inhibitor with the ability to cross the blood-brain barrier suitable for the treatment of intracranial malignancies.AZD1390 is an exceptionally potent inhibitor of ATM in cells (IC50 = 0.78 nM) with >10,000-fold selectivity over closely related members of the PIKK family of enzymes and excellent selectivity across a broad panel of kinases. AZD1390 displays excellent oral bioavailability in preclinical species (66% in rat and 74% in dog), is not a substrate for human efflux transporters, and has been shown to efficiently cross the BBB in non-human primate PET studies.

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	10	20.93
Ethanol	80	168.51

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	2.09 mL	10.47 mL	20.94 mL
5 mM	0.42 mL	2.09 mL	4.19 mL
10 mM	0.21 mL	1.05 mL	2.09 mL
50 mM	0.04 mL	0.21 mL	0.42 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. Durant ST, Zheng L, Wang Y, Chen K, Zhang L, Zhang T, Yang Z, Riches L, Trinidad AG, Fok JHL, Hunt T, Pike KG, Wilson J, Smith A, Colclough N, Reddy VP, Sykes A, Janefeldt A, Johnström P, Varnäs K, Takano A, Ling S, Orme J, Stott J, Roberts C, Barrett I, Jones G, Roudier M, Pierce A, Allen J, Kahn J, Sule A, Karlin J, Cronin A, Chapman M, Valerie K, Illingworth R, Pass M. The brain-penetrant clinical ATM inhibitor AZD1390 radiosensitizes and improves survival of preclinical brain tumor models. Sci Adv. 2018 Jun 20;4(6):eaat1719. doi: 10.1126/sciadv.aat1719. PMID: 29938225; PMCID: PMC6010333.

In vivo study

1. Durant ST, Zheng L, Wang Y, Chen K, Zhang L, Zhang T, Yang Z, Riches L, Trinidad AG, Fok JHL, Hunt T, Pike KG, Wilson J, Smith A, Colclough N, Reddy VP, Sykes A, Janefeldt A, Johnström P, Varnäs K, Takano A, Ling S, Orme J, Stott J, Roberts C, Barrett I, Jones G, Roudier M, Pierce A, Allen J, Kahn J, Sule A, Karlin J, Cronin A, Chapman M, Valerie K, Illingworth R, Pass M. The brain-penetrant clinical ATM inhibitor AZD1390 radiosensitizes and improves survival of preclinical brain tumor models. Sci Adv. 2018 Jun 20;4(6):eaat1719. doi: 10.1126/sciadv.aat1719. PMID: 29938225; PMCID: PMC6010333.

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7. Bioactivity

Biological target:

AZD1390 is a potent, highly selective, orally bioavailable, brain-penetrant ATM inhibitor with an IC50 of 0.78 nM in cell.

In vitro activity

In cell activity screens, AZD1390 caused inhibition of ATM, as indicated by the inhibition of phosphorylation of ATMSer1981 in HT29 cells (used historically and routinely as a consistent cell assay for other projects and selectivity studies) following treatment with irradiation. The reported IC50 values were calculated as the geometric mean of IC50 individual values and the arithmetic mean of pIC50 values. The cellular effects of AZD1390 on the ATM-dependent DDR was investigated. Figure 2 (A and B) illustrates that ATM autophosphorylation inhibition by AZD1390 occurred at 4 hours after treatment, and 3 nM produced a strong inhibition of ATM in LN18 GBM cells (other time points were investigated in fig. S1, A to C). Other DDR inhibitors tested under the same conditions at relevant IC50 concentrations did not affect pATM levels. After removing AZD1390 and allowing cells to recover, evidence for ATM pathway reactivation was observed at 6 hours as pChk2 levels started to rise (Fig. 2B). To confirm selectivity observed in our cell screens, effects on DNA-PK and ATR pathway activation were checked and appreciable effects in Western blots were not seen (fig. S1, B and C). Figure 2C shows the effects of AZD1390 added 1 hour before irradiation to NCI-H2228 lung cancer cells (used in subsequent orthotopic brain metastatic in vivo model) in high-content immunofluorescence cell imaging (using the confocal CV7000 imaging microscope) analyzing pATM and γH2AX DDR biomarkers. The median 50% excitatory concentration (XC50) values for AZD1390 using total nuclear staining of pATM and γH2AX are in general agreement with the pATM assay potencies (0.78 nM) reported in the HT29 cell screen (Table 1 and fig. S2A). However, XC50 concentrations required to inhibit discreet nuclear pATM foci were higher (2.7 nM) and in agreement with the Western blot data and antiproliferation effects (seen in subsequent results). The data also show that radiation combined with AZD1390 dose-dependently increased the formation of micronuclei—DNA-containing structures indicative of incompletely replicated or broken chromosome fragments. This suggest that AZD1390 results in increased genome instability.

Reference: Sci Adv. 2018 Jun 20;4(6):eaat1719. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/29938225/

In vivo activity

A series of efficacy studies were performed using a lung NCI-H2228 xenograft model either implanted into nude mice brains directly (intracranial brain) or injected into the carotid artery [intracarotid artery (ICA)] and allowed to establish in the brain. Figure 4A shows data that demonstrate a dose-dependent tumor growth inhibition (TGI), with marginal inhibition observed using AZD1390 (5 mg/kg) dosed an hour before each daily fraction of IR. Superior efficacy was observed dosing at 20 mg/kg once daily (QD) or twice daily (BID) in combination with the four daily fractions of IR. The data show the survival of the same mice. Figure S5 (A and B) shows a repeat experiment using BID dosing.

Reference: Sci Adv. 2018 Jun 20;4(6):eaat1719. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/29938225/