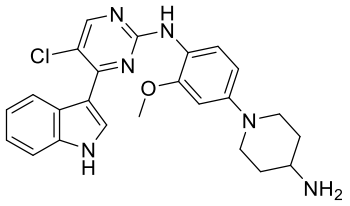
Product data sheet

MedKoo Cat#: 206039 Name: AZD-3463 CAS#: 1356962-20-3 Chemical Formula: $C_{24}H_{25}ClN_6O$ Exact Mass: 448.17784 Molecular Weight: 448.95	
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:
AZD-3463 is a potent ALK/IGF1R inhibitor with potential anticancer activity. AZD3463 inhibits neuroblastoma growth by overcoming crizotinib resistance and inducing apoptosis. AZD3463 effectively suppressed the proliferation of NB cell lines with wild type ALK (WT) as well as ALK activating mutations (F1174L and D1091N) by blocking the ALK-mediated PI3K/AKT/mTOR pathway and ultimately induced apoptosis and autophagy. In addition, AZD3463 enhanced the cytotoxic effects of doxorubicin on NB cells. AZD3463 also exhibited significant therapeutic efficacy on the growth of the NB tumors with WT and F1174L activating mutation ALK in orthotopic xenograft mouse models.

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	9.77	21.76
DMF	2.5	5.57

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	2.23 mL	11.14 mL	22.27 mL
5 mM	0.45 mL	2.23 mL	4.45 mL
10 mM	0.22 mL	1.11 mL	2.23 mL
50 mM	0.04 mL	0.22 mL	0.45 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. Moharram SA, Shah K, Khanum F, Rönnstrand L, Kazi JU. The ALK inhibitor AZD3463 effectively inhibits growth of sorafenib-resistant acute myeloid leukemia. Blood Cancer J. 2019 Jan 15;9(2):5. doi: 10.1038/s41408-018-0169-1. Erratum in: Blood Cancer J. 2019 Jul 25;9(8):54. PMID: 30647405; PMCID: PMC6333797.
2. Wang Y, Wang L, Guan S, Cao W, Wang H, Chen Z, Zhao Y, Yu Y, Zhang H, Pang JC, Huang SL, Akiyama Y, Yang Y, Sun W, Xu X, Shi Y, Zhang H, Kim ES, Muscal JA, Lu F, Yang J. Novel ALK inhibitor AZD3463 inhibits neuroblastoma growth by overcoming crizotinib resistance and inducing apoptosis. Sci Rep. 2016 Jan 20;6:19423. doi: 10.1038/srep19423. PMID: 26786851; PMCID: PMC4726162.

In vivo study

1. Hu GF, Wang C, Hu GX, Wu G, Zhang C, Zhu W, Chen C, Gu Y, Zhang H, Yang Z. AZD3463, an IGF-1R inhibitor, suppresses breast cancer metastasis to bone via modulation of the PI3K-Akt pathway. Ann Transl Med. 2020 Mar;8(6):336. doi: 10.21037/atm.2020.02.110. PMID: 32355780; PMCID: PMC7186597.

2. Wang Y, Wang L, Guan S, Cao W, Wang H, Chen Z, Zhao Y, Yu Y, Zhang H, Pang JC, Huang SL, Akiyama Y, Yang Y, Sun W, Xu X, Shi Y, Zhang H, Kim ES, Muscal JA, Lu F, Yang J. Novel ALK inhibitor AZD3463 inhibits neuroblastoma growth by overcoming crizotinib resistance and inducing apoptosis. Sci Rep. 2016 Jan 20;6:19423. doi: 10.1038/srep19423. PMID: 26786851; PMCID: PMC4726162.

7. Bioactivity

Biological target:

AZD-3463 (ALK/IGF1R inhibitor) is an ALK/IGF1R inhibitor, with a Ki of 0.75 nM for ALK.

In vitro activity

Wild-type FLT3 is required for normal hematopoiesis. Therefore, inhibition of wild-type FLT3 is likely to cause unwanted side effects. For this reason, this study checked whether AZD3463 also inhibits wild-type FLT3 signaling. Ligand-induced activation of FLT3 results in activation of AKT and ERK1/2 signaling. In contrast, FLT3-ITD is constitutively active and activates downstream signaling cascades. This study observed that treatment with AZD3463 inhibited FLT3-ITD-mediated activation of AKT, ERK1/2, and p38 in a dose-dependent manner in MOLM-13 cells (Fig. 2a) as well as in MV4-11 cells (Fig. 5SA). Tyrosine phosphorylation of FLT3 was also reduced in a similar fashion (Fig. 2A and Fig. S5A). Both MOLM-13 and MV4-11 carry an FLT3-ITD mutation, but MOLM-13 cells also express one copy of wild-type FLT3. However, AZD3463 did not affect FL-stimulated tyrosine phosphorylation of FLT3 or its downstream signaling in MOLM-13 cells (Fig. 2a and Fig. S5B), in Ba/F3 cells transfected with FLT3-WT (Fig. 2b) or in THP-1 cells (expressing wild-type FLT3; Fig. S5C) suggesting that AZD3463 selectively inhibits oncogenic FLT3-ITD but not wild-type FLT3.

Reference: Blood Cancer J. 2019 Feb; 9(2): 5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6333797/

In vivo activity

Significant tumor growth inhibition was observed in both AZD3463 treatment groups (SH-SY5Y and NGP) compared with the control groups. Treatment in SH-SY5Y xenograft mice with AZD3463 resulted in almost complete tumor regression and significant regression was observed in NGP xenograft mice (Fig. 5A,C). After the mice had been bearing the SH-SY5Y and NGP tumors for 4 weeks, the mice were treated with either AZD3463 or DMSO via intraperitoneal injection for 48 hours. Then this study examined the effect of AZD3463 on the PI3K/AKT/mTOR signaling in the tumor tissues and found that AZD3463 efficiently blocked Akt and RPS6 phosphorylation and induced the cleavage of PARP, caspase 3, and LC3 A/BII (Fig. 5E) in vivo. These results suggest that AZD3463 can effectively induce apoptosis and autophagy as a single agent in orthotopic xenograft mouse models of NB.

Reference: Sci Rep. 2016; 6: 19423. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4726162/