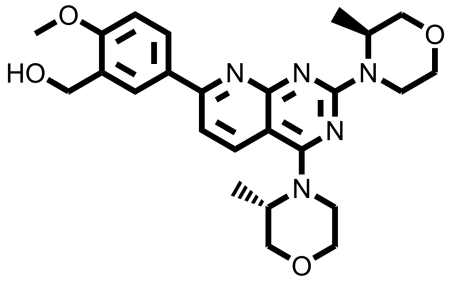
Xcess Biosciences Inc.
7144 N Harlem Ave #169
Chicago, IL 60631 USA

http://www.xcessbio.com
Toll free: 1-866-706-2330
Fax: 1-619- 810-0718
Email: info@xcessbio.com

mTOR Inhibitor – AZD8055

Chemical Name: (5-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-2-methoxyphenyl)methanol



Molecular Weight:	465.54
Formula:	$C_{25}H_{31}N_5O_4$
Purity:	≥ 98%
CAS#:	1009298-09-2
Solubility:	DMSO up to 100 mM
Storage	Powder: 4°C 1 year DMSO: 4°C 3 month -20°C 1 year

Biological Activity:

AZD8055 is a highly potent, selective and ATP-competitive mTOR inhibitor (IC_{50} = 0.8 nM). It has >1,000-fold selectivity against all PI3K isoforms (α, β, γ, δ) and other members of the PI3K-like kinase family (ATM and DNA-PK). It has no significant activity against a panel of 260 kinases at concentrations up to 10 μM. AZD8055 inhibits the phosphorylation of mTORC1 downstream targets (p70S6K and 4E-BP1) as well as phosphorylation of the mTORC2 downstream proteins (e.g., Akt). The rapamycin-resistant T37/46 phosphorylation sites on 4E-BP1 can be fully inhibited by AZD8055, resulting in significant inhibition of cap-dependent translation. AZD8055 potently inhibits proliferation of U87MG, A549 and H838 cells with IC_{50} of 53, 50, and 20 nM, respectively. It also induces autophagy and increases LC3-II levels in H838 and A549 cells. AZD8055 decreases AML blast cell proliferation and cell cycle progression, reduces the clonogenic growth of leukemic progenitors, and induces caspase-dependent apoptosis in leukemic cells but not in normal immature CD34+ cells. It also shows significant antitumor activity in many xenografts, including U87MG, BT474c, A549, Calu-3, LoVo, SW620, PC3 and MES-SA at a dose of 10-20 mg/kg. AZD8055 was previously evaluated in a phase I clinical study in patients with advanced tumors.

How to Use:

In vitro: AZD8055 was used at 2.5 μM concentration in vitro and cellular assays.

In vivo: AZD8055 was orally dosed to mice at 2.5-20 mg/kg once or twice per day to inhibit tumor growth.

Reference:

1. Chresta CM, et al. AZD8055 is a potent, selective, and orally bioavailable ATP-competitive mammalian target of rapamycin kinase inhibitor with in vitro and in vivo antitumor activity. (2010) Cancer Res. 70(1):288-98.
2. García-Martínez JM, et al. Effect of PI3K- and mTOR-specific inhibitors on spontaneous B-cell follicular lymphomas in PTEN/LKB1-deficient mice. (2011) Br J Cancer. 104(7):1116-25.
3. Jiang Q, et al. mTOR kinase inhibitor AZD8055 enhances the immunotherapeutic activity of an agonist CD40 antibody in cancer treatment.(2011) Cancer Res. 71(12):4074-84.
4. Huang S, et al. Inhibition of mTOR kinase by AZD8055 can antagonize chemotherapy-induced cell death through autophagy induction and down-regulation of p62/sequestosome 1. (2011) J Biol Chem. 286(46):40002-12.
5. Willems L, et al. The dual mTORC1 and mTORC2 inhibitor AZD8055 has anti-tumor activity in acute myeloid leukemia. (2012) Leukemia. 26(6):1195-202.
6. Holt SV, et al. Enhanced apoptosis and tumor growth suppression elicited by combination of MEK (selumetinib) and mTOR kinase inhibitors (AZD8055). (2012) Cancer Res. 72(7):1804-13.

Xcess Biosciences Inc.
7144 N Harlem Ave #169
Chicago, IL 60631 USA

http://www.xcessbio.com
Toll free: 1-866-706-2330
Fax: 1-619- 810-0718
Email: info@xcessbio.com

7. Naing A, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of AZD8055 in advanced solid tumours and lymphoma. (2012) Br J Cancer. 107(7):1093-9.
8. Pike KG, et al. Optimization of potent and selective dual mTORC1 and mTORC2 inhibitors: The discovery of AZD8055 and AZD2014. (2013) Bioorg Med Chem Lett. In press.