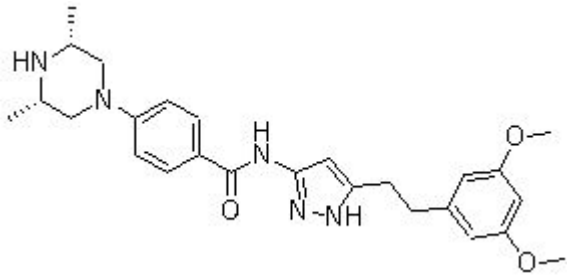
Product Introduction

AZD4547

AZD4547 is a novel selective **FGFR** inhibitor targeting FGFR1/2/3 with **IC50** of 0.2 nM/2.5 nM/1.8 nM, weaker activity against FGFR4, VEGFR2(KDR), and little activity observed against IGFR, CDK2, and p38. Phase 1/2.

Technical Data:

Molecular Weight (MW):	463.57	
Formula:	$C_{26}H_{33}N_5O_3$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 92 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	1035270-39-3	

Biological Activity

Compared to FGFR1-3, AZD4547 displays weaker activity against FGFR4 with IC50 of 165 nM. AZD4547 only inhibits recombinant VEGFR2 (KDR) kinase activity with IC50 of 24 nM, in the in vitro selectivity test against a diverse panel of representative human kinases. AZD4547 at 0.1 μM exhibits no activity against a range of recombinant kinases including ALK, CHK1, EGFR, MAPK1, MEK1, p70S6K, PDGFR, PKB, Src, Tie2,

and PI3-kinase. Consistently, the potent selectivity of AZD4547 for FGFR1-3 over FGFR4, IGFR, and KDR is also observed in cellular phosphorylation assays. AZD4547 has potent in vitro antiproliferative activity only against tumor cell lines expressing deregulated FGFRs such as KG1a, Sum52-PE, and KMS11 with IC50 of 18-281 nM, and is inactive against MCF7 as well as more than 100 additional tumor cell lines. AZD4547 treatment potently inhibits FGFR and MAPK phosphorylation in human tumor cell lines in a dose-dependent manner. AZD4547 also potently inhibits the phosphorylation of FRS2 and PLCγ, downstream markers of FGFR signaling. Notably, AZD4547 affects the AKT phosphorylation in the breast cell lines, MCF7 and Sum52-PE but not in KG1a and KMS11 lines. AZD4547 treatment significantly induces apoptosis in Sum52-PE and KMS11 cells, dramatically increases G1 arrest but not apoptosis in KG1a cells, and has no effect on cell cycle distribution or apoptosis in MCF7 cells. [1]

Oral administration of AZD4547 at 3 mg/kg twice daily in mice bearing KMS11 tumors results in significant tumor growth inhibition of 53% when compared with vehicle-treated controls, and AZD4547 at 12.5 mg/kg once daily or 6.25 mg/kg twice daily leads to complete tumor stasis, which is associated with dose proportional pharmacodynamic modulation of phospho-FGFR3 and reduced KMS11 tumor cell proliferation. Moreover, oral administration of AZD4547 at 12.5 mg/kg once daily results in 65% tumor growth inhibition in the FGFR1-fusion KG1a xenograft model. At efficacious dose levels, AZD4547 does not exhibit antiangiogenic effects. AZD4547 has no significant effect on blood pressure and therefore lacks in vivo anti-KDR activity. Consistently, dosing of 6.25 mg/kg orally twice daily AZD4547 is inactive in the cediranib-sensitive xenograft models including Calu-6, HCT-15 and LoVo. [1]

Greater selectivity for FGFR1-3 over FGFR4. AZD4547 is active against the tyrosine kinase activity of both the wild-type and mutant forms of FGFR.

References

[1] Gavine PR, et al. Cancer Res, 2012, 72(8), 2045-2056.

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