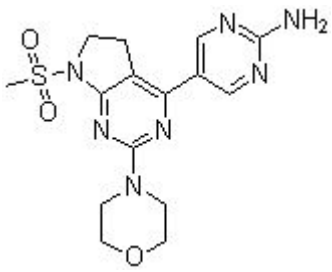
Product Introduction

CH5132799

CH5132799 inhibits class I PI3Ks, particularly **PI3Kα** with **IC50** of 14 nM; less potent to PI3Kβδγ, while sensitive in PIK3CA mutations cell lines. Phase 1.

Technical Data:

Molecular Weight (MW):	377.42	
Formula:	$C_{15}H_{19}N_7O_3S$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 12 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	1007207-67-1	

Biological Activity

CH5132799 selectively inhibits class I PI3Ks, PI3Kα (IC50 = 0.014 μM), PI3Kβ (IC50 = 0.12 μM), PI3Kδ (IC50 = 0.50 μM), PI3Kγ (IC50 = 0.036 μM), but shows less inhibition of class II PI3Ks, class III PI3k and mTOR and also no inhibitory activity (IC50 > 10 μM) against 26 protein kinases. CH5132799 exhibits more inhibitory activities against PI3Kα with oncogenic mutations E542K (IC50 = 6.7 nM), E545K (IC50 = 6.7 nM) and H1047R (IC50 = 5.6 nM) than wild-type PI3Kα. CH5132799 treated breast cnacer KPL-4 cells, which harbor the PIK3CA mutation, phosphorylation of Akt and its direct substrates, PRAS40 and

FoxO1/3a and phosphorylation of downstream factors, including S6K, S6 and 4E-BP1, are effectively suppressed. Cancer cell lines harboring PIK3CA mutations are significantly sensitive to CH5132799 [1] In human tumor cell lines with PI3K pathway activation by mutation, CH5132799 shows potent antiproliferative activity [HCT116(CRC): IC50 = 0.20 lM, KPL-4(BC):13 IC50 = 0.032 lM, T-47D(BC): IC50 = 0.056 lM, SK-OV-3(Ovarian): IC50 = 0.12 lM]. CH5132799 effectively suppresses phosphorylation of AKT in KPL-4 cells. [2]

CH5132799 shows potent in vivo antitumor activity in several different xenograft models with PIK3CA mutations. CH5132799 overcomes mTORC1 inhibition-mediated Akt activation and regrowth of xenograft tumor by long-term everolimus administration. [1] CH5132799 as a clinical candidate that shows excellent oral bioavailability (BA) (101% in mouse), human liver microsomal stability and in vivo antitumor activity in the PC-3 xenograft model (TGI: 101% at 25 mg/kg, po, q.d. × 11 days). CH5132799 exhibits good oral BA in mouse, rat, monkey and dog (F: 54.2-101%). In a human breast cancer (KPL-4: PI3Ka H1047R) xenograft model in mice, oral treatment with CH5132799 (12.5 mg/kg, q.d.) shows strong tumor regression. The strong regression is maintained during the 6 week administration, even in the intermittent dosing schedule (q.d., 2 weeks on/1 week off; q.d., 5 days on/2 days off), suggesting that a flexible administration schedule can be applicable in the clinic. [2]

References

[1] Tanaka H, et al, Clin Cancer Res, 2011, 17(10), 3272-3281.

[2] Ohwada J, et al, Bioorg Med Chem Leff, 2011, 21(6), 1767-1772.