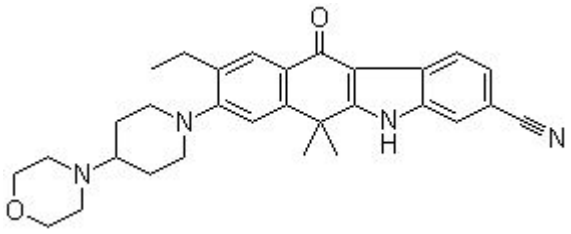
Product Introduction

Alectinib (CH5424802)

CH5424802 is a potent **ALK** inhibitor with **IC50** of 1.9 nM, sensitive to L1196M mutation and higher selectivity for ALK than PF-02341066, NVP-TAE684 and PHA-E429. Phase 1/2.

Technical Data:

Molecular Weight (MW):	482.62	
Formula:	$C_{30}H_{34}N_4O_2$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 2 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	1256580-46-7	

Biological Activity

The dissociation constant (KD) value of CH5424802 for ALK in an ATP-competitive manner is 2.4 nM. CH5424802 has substantial inhibitory potency against both native ALK and L1196M with K_i of 0.83 nM and 1.56 nM, respectively. CH5424802 prevents autophosphorylation of ALK in NCI-H2228 NSCLC cells expressing EML4-ALK. CH5424802 also suppresses the phosphorylation of STAT3 and AKT, but not of ERK1/2. CH5424802 completely inhibits the phosphorylation of STAT3 at Tyr705. CH5424802 is preferentially efficacious against NCI-H2228 cells expressing EML4-ALK, but not ALK fusion-negative

NSCLC cell lines, including HCC827 cells (EGFR exon 19 deletion), A549 cells (KRAS mutant), or NCI-H522 cells (EGFR wild-type, KRAS wild-type, and ALK wild-type) in monolayer culture. CH5424802 elicits an apoptotic marker—caspase-3/7-like activation—in NCI-H2228 spheroid cells. CH5424802 blocks the growth of two lymphoma lines, KARPAS-299 and SR, with NPM-ALK fusion protein but does not influence the growth of an HDLM-2 lymphoma line without ALK fusion. [1] CH5424802 displays high target selectivity and the stronger anti-proliferative activity against KARPAS-299. CH5424802 inhibits KAPRAS-299 with an IC50 of 3 nM, and KDR with IC50 of 1.4 μM. The metabolic stability of CH5424802 is very high.[2]

Oral administration of CH5424802 dose-dependently inhibits tumor growth with an ED50 of 0.46 mg/kg and tumor regression. Treatment of 20 mg/kg CH5424802 reveals rapid tumor regression by 168%, the tumor volume in any mouse is <30 mm^3 after 11 days of treatment (at day 28), a potent antitumor effect is maintained, and tumor regrowth does not occur throughout the 4-week drug-free period. The half-life and the oral bioavailability of CH5424802 in mice are 8.6 hours and 70.8%, respectively. At a repeated dose of 6 mg/kg, the mean plasma levels reached 1.7, 1.5, and 0.3 nM at 2, 7, and 24 hours post-dose, respectively. Administration of CH5424802 leads to tumor growth prevention and tumor regression. Tumor growth inhibition at 20 mg/kg is 119% for KARPAS-299 and 104% for NB-1 on day 20. CH5424802 inhibits the phosphorylation of STAT3 in a dose-dependent manner (2–20 mg/kg). A partial decrease in AKT phosphorylation is also observed in CH5424802-treated xenograft tumors. [1]

References

[1] Sakamoto H, et al. Cancer Cell. 2011, 19(5), 679-690.

[2] Kinoshita K, et al. Bioorg Med Chem. 2012, 20(3), 1271-1280.