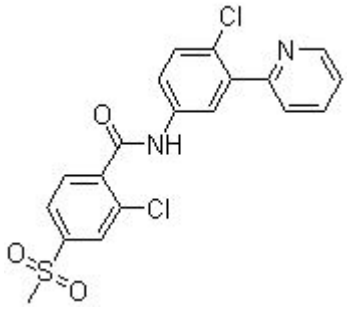
Product Introduction

Vismodegib (GDC-0449)

Vismodegib (GDC-0449) is a potent, novel and specific **hedgehog** inhibitor with **IC50** of 3 nM and also inhibits P-gp with **IC50** of 3.0 μM.

Technical Data:

Molecular Weight (MW):	421.3	
Formula:	$C_{19}H_{14}Cl_2N_2O_3S$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 84mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	879085-55-9	

Biological Activity

GDC-0449 targets the Hedgehog signaling pathway, blocking the activities of the Hedgehog-ligand cell surface receptors PTCH and/or SMO and suppressing Hedgehog signaling. GDC-0449 prevents multiple ATP-binding cassette (ABC) transporters. GDC-0449 also blocks ABCG2, Pgp, and MRP1-important ABC transporters associated with MDR. GDC-0449 is a potent inhibitor of ABC transporters, ABCG2/BCRP and

ABCB1/Pgp, and is a mild inhibitor of ABCC1/MRP1. In ABCG2-overexpressing HEK293 cells, GDC-0449 increases retention of the fluorescent ABCG2 substrate BODIPY-prazosin and resensitizes these cells to mitoxantrone. In Madin-Darby canine kidney II cells engineered to overexpress Pgp or MRP1, GDC-0449 increases the retention of calcein-AM and resensitizes them to colchicine. GDC-0449 also resensitizes human non-small cell lung carcinoma cells NCI-H460/par and NCI-H460/MX20, which overexpress ABCG2 in response to mitoxantrone, to mitoxantrone, and to topotecan or SN-38. The IC50 values of GDC-0449 for prevention of ABCG2 and Pgp are about 1.4 μM and 3.0 μM, respectively. [2] GDC-0449 alters intracellular Ca^{2+} homeostasis and inhibits cell growth in cisplatin-resistant lung cancer cells. [3]

GDC-0449 has been used to treat medulloblastoma in animal models. [2] GDC-0449 prevents the growth of primary pancreatic xenografts without non-specifically inhibiting pancreatic cell proliferation. Oral dosing of GDC-0449 causes tumor regressions in the Ptch(+/-) allograft model of medulloblastoma at doses ≥25 mg/kg and tumor growth inhibition at doses up to 92 mg/kg dosed twice daily in two ligand-dependent colorectal cancer models, D5123, and 1040830. Analysis of Hh pathway activity and PK/PD modeling reveals that GDC-0449 inhibits Gli1 with a similar IC50 in both the medulloblastoma and D5123 models (0.165 μM and 0.267 μM, respectively). Pathway modulation is linked to efficacy using an integrated PK/PD model revealing a steep relationship where > 50% of the activity of GDC-0449 is associated with >80% repression of the Hh pathway. [4]

References

[1] Scales SJ, et al. Trends Pharmacol Sci. 2009, 30(6), 303-312.

[2] Zhang Y, et al. Neoplasia. 2009, 11(1), 96-101.

[3] Tian F, et al. Anticancer Res. 2012, 32(1), 89-94.

[4] Wong H, et al. Clin Cancer Res. 2011, 17(14), 4682-4692.