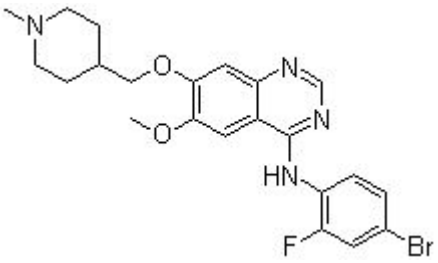
Product Introduction

Vandetanib (ZD6474)

Vandetanib (ZD6474) is a potent inhibitor of **VEGFR2** with **IC50** of 40 nM.

Technical Data:

Molecular Weight (MW):	473.35	
Formula:	$C_{22}H_{24}BrFN_4O_2$	
Solubility (25°C) * <1 mg/ml means slightly soluble or insoluble:	DMSO 4 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	443913-73-3	

Biological Activity

Vandetanib also inhibits VEGFR3 and EGFR with IC50 of 110 nM and 500 nM, respectively. Vandetanib is not sensitive to PDGFRβ, Flt1, Tie-2 and FGFR1 with IC50 of 1.1-3.6 μM, while almost has no activity against MEK, CDK2, c-Kit, erbB2, FAK, PDK1, Akt and IGF-1R with IC50 above 10 μM. Vandetanib inhibits VEGF-, EGF- and bFGF-stimulated HUVEC proliferation with IC50 of 60 nM, 170 nM and 800 nM, with no effect on basal endothelial cell growth. Vandetanib inhibits tumor cell growth with IC50 of 2.7 μM (A549) to 13.5 μM (Calu-6). [1] Vandetanib displays an inhibitory effect on the basal ABCG2-ATPase. Parental and ABCG2-expressing A431 cells showed similar sensitivities toward Vandetanib. Exposure to EGFR inhibitors

decreases pEGFR levels in A431 cells, with Vandetanib displaying only a moderate effect. Vandetanib displays a slight but measurable effect, whereas gefitinib, pelitinib and neratinib completely inhibit ABCG2-mediated efflux of mitoxantrone from A431/ABCG2 cells, similarly to the specific ABCG2 inhibitor Ko143. [2] Vandetanib inhibits both PC3wt and PC3R cell lines with similar IC50 of 13.3 μM and 11.5 μM, respectively. [3] Vandetanib suppresses phosphorylation of VEGFR2 in HUVEC and EGFR in hepatoma cells and inhibits cell proliferation. [4] Vandetanib causes an accumulation of cells in the G0-G1 phases in GEO and OVCAR-3 cells and increases apoptosis in OVCAR-3, ZR-75-1, MCF-10A ras, and GEO cells. Vandetanib causes a dose-dependent inhibition of EGFR phosphorylation in mouse NIH-EGFR fibroblasts and human MCF-10A ras breast cancer cells, two cell lines that overexpress the human EGFR. Vandetanib treatment results in a dose-dependent inhibition of soft agar growth in seven human cell lines (breast, colon, gastric, and ovarian) with functional EGFR but lacking VEGFR2. [5]

Vandetanib (2.5 mg/kg, i.v.), reverses a VEGF-induced hypotension by 63% but does not significantly affect a bFGF-induced hypotension. Vandetanib (100 mg/kg) inhibits the tumor-induced blood vessel formation by 79%. Vandetanib (12.5-100 mg/kg, orally) shows great tumor growth inhibition in human tumor xenografts including Calu-6, PC-3, MDA-MA-231, SKOV-3, SW620, A549, A431, B16-F10(AP3) and Lewis Lung, with little effects on body weight. [1] In PC3wt xenografts, administration of Vandetanib alone exerts paradoxical tumor growth stimulating effects. In PC3R xenografts, the low dose of Vandetanib (25 mg/kg) has no significant effect relative to control, whereas the high dose (50 mg/kg) significantly inhibits tumor growth compared with control. In contrast, the high-dose combination reveals a significant negative interaction between Vandetanib 50 mg/kg and docetaxel 30 mg/kg in PC3R cells. [3] In tumor-bearing mice, Vandetanib suppresses phosphorylation of VEGFR2 and EGFR in tumor tissues, significantly decreases tumor vessel density, enhances tumor cell apoptosis, suppresses tumor growth, improves survival, reduces number of intrahepatic metastases, and up-regulates VEGF, TGF-alpha and EGF in tumor tissues. Treatment with Vandetanib is not associated with serious adverse events, including ALT abnormality, bone marrow suppression or body weight loss. [4] Vandetanib treatment of nude mice bearing palpable GEO colon cancer xenografts (which are sensitive to inhibition of EGFR signaling) induces dose-dependent tumor growth inhibition. [5]

References

[1] Wedge SR, et al. Cancer Res. 2002, 62(16), 4645-4655.

[2] Hegedüs, et al. Biochem Pharmacol. 201

[3] Guérin O, et al. Urol Oncol. 201

[4] Inoue K, et al. Clin Cancer Res. 2012.

[5] Ciardiello F, et al. Clin Cancer Res. 2003, 9(4), 1546-1556.

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