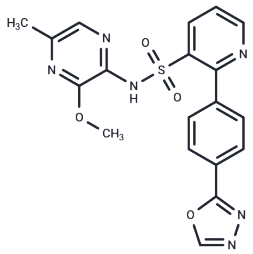
Data Sheet (Cat.No.T6258)

TargetMol

Zibotentan

Chemical Properties



CAS No. : 186497-07-4

Formula: C19H16N6O4S

Molecular Weight: 424.43

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	Zibotentan (ZD4054) (ZD4054) is a specific Endothelin (ET)A antagonist with IC50 of 21 nM, exhibiting no activity at ETB. Phase 3.
Targets(IC50)	Apoptosis,Endothelin Receptor
In vitro	As Zibotentan specifically inhibits ETA-mediated antiapoptotic effects, but not ETB-mediated proapoptotic effects in human and rat smooth muscle cells, Zibotentan binds to endothelin A receptor (ETA) with high affinity with Ki of 13 nM, and has no affinity for endothelin B receptor (ETB) with IC50 of >10 μM. [1] Zibotentan treatment at 1 μM inhibits ET-1 induced mitogenic activity in ovarian carcinoma cell lines HEY and OVCA 433 secreting ET-1 and expressing ETA and ETB mRNA. [2] ZD4054 (1 μM) inhibits ET-1 induced EGFR transactivation in HEY and OVCA 433 cells. Zibotentan (1 μM) reverts ET-1 mediated epithelial-mesenchymal transition (EMT), by enhancing E-cadherin expression and promoter activity, and inhibiting vascular endothelial growth factor (VEGF) secretion and invasiveness in HEY and OVCA 433 cells. [3] Zibotentan also potently inhibits the basal and ET-1 induced cell proliferation in SKOV-3 and A-2780 cells, associated with the inhibition of AKT and p42/44MAPK phosphorylation, and with increased apoptosis through the inhibition of bcl-2 and activation of caspase-3 and poly(ADP-ribose) polymerase proteins. [4]
In vivo	Administration of Zibotentan at 10 mg/kg/day for 21 days potently inhibits the growth of HEY ovarian carcinoma xenografts in mice by 69% with no associated toxicity, which is in association with the blocking of cell proliferation evaluated by 37% inhibition of the Ki-67 expression, and the 62% inhibition of tumor-induced vascularization. Consistently, Zibotentan treatment significantly inhibits the expression of matrix metalloproteinase-2 (MMP-2) and VEGF, as well as the activation of p42/44 MAPK and EGFR, and potently enhances the expression of E-cadherin. [3]
Kinase Assay	Receptor-binding assays: The inhibition by Zibotentan (varying concentrations) of 125iodine-ET-1 binding to cloned human ETA is assessed using standard radioligand-binding techniques. Human recombinant ETA is expressed in mouse erythroleukaemic cells, and cell membranes prepared for competitive binding studies using 125iodine-ET-1 as the radioligand. Incubations are carried out in triplicate in the presence of Zibotentan, 100 pM to 100 μM in half-log increments, and inhibition of ET-1 binding is expressed as the geometric mean pIC50 value (concentration to inhibit 50% of binding) with a 95% confidence interval (CI). The affinity of Zibotentan for cloned human ETA is

Kinase Assay	also assessed using the equation of Cheng and Prusoff to determine the equilibrium dissociation constant (Ki) in a further receptor-binding screen utilizing a greater number of concentration-response curves determined in three separate studies.
Cell Research	Cells are serum starved by incubation for 24 hours in serum-free DMEM before exposed to Zibotentan for 48 hours. After the treatment, cells are lysed and the supernatant is recovered and assayed for histone-associated DNA fragments, at 405 nm by the use of a microplate reader. For detection of early apoptotic events, floating and adherent cells are collected. Cells are double stained with FITC-conjugated Annexin V and propidium iodide using the Vybrant Apoptosis Kit and are immediately analyzed by cytofluorometric analysis.(Only for Reference)

Solubility Information

Solubility	DMSO: 23 mg/mL (54.19 mM),Sonication is recommended. Ethanol: < 1 mg/mL (insoluble or slightly soluble), H2O: < 1 mg/mL (insoluble or slightly soluble), (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+90% Corn Oil: 2 mg/mL (4.71 mM),Sonication is recommended. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.3561 mL	11.7805 mL	23.561 mL
5 mM	0.4712 mL	2.3561 mL	4.7122 mL
10 mM	0.2356 mL	1.1781 mL	2.3561 mL
50 mM	0.0471 mL	0.2356 mL	0.4712 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Morris CD, et al. Br J Cancer, 2005, 92(12), 2148-2152.
Rosanò L, et al. Exp Biol Med (Maywood), 2006, 231(6), 1132-113
Rosanò L, et al. Cancer Res, 2007, 67(13), 6351-635
Rosanò L, et al. Mol Cancer Ther, 2007, 6(7), 22003-201

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