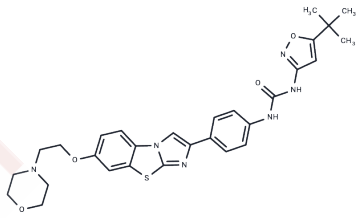
Data Sheet (Cat.No.T2066)

TargetMol

Quizartinib

Chemical Properties



CAS No. : 950769-58-1

Formula: C29H32N6O4S

Molecular Weight: 560.67

Appearance: no data available

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year

Biological Description

Description	Quizartinib (AC220) is an inhibitor of FLT3 (Kd: 1.6 nM) and demonstrates high selectivity for FLT3 when tested against a panel of 227 additional kinases.
Targets(IC50)	Apoptosis,FLT,Autophagy,Ligands for Target Protein for PROTAC
In vitro	The highest affinity target identified for Quizartinib (AC220) was FLT3. The only other kinases with binding constants within 10-fold that for FLT3 were the closely related receptor tyrosine kinases (RTKs) KIT, PDGFRA, PDGFRB, RET, and CSF1R, and only 4 additional kinases, also related RTKs (FLT1, FLT4, DDR1, VEGFR2), bound with Kds within 100-fold of that for FLT3. In primary cells, treatment with AC220 for 1 hour inhibited FLT3 autophosphorylation (IC50: 2 nM), comparable with the activity observed in the MV4-11 cell line. The primary cells were sensitive to AC220 (IC50: 0.3 nM), again comparable with the activity observed in the MV4-11 cell line [1]. It inhibits the proliferation of the human leukemia cell line MV4-11, which harbors a homozygous FLT3-ITD mutation, with an IC50 value of 0.56 nM [2].
In vivo	Treatment with AC220 at 10 mg/kg resulted in rapid and complete regression of tumors in all animals, and no tumor regrowth was observed during the 60-day posttreatment observation period. AC220 prolonged survival in a dose-dependent manner. At 10 mg/kg, 80% of animals treated survived until the study was terminated on day 172, 119 days after discontinuation of treatment, corresponding to at least a 250% increase in life span (ILS). At the time the study was terminated the animals did not exhibit any signs of disease. At 1 mg/kg a significant increase in the mean survival time was observed, to 77 days. At the lowest dose tested of 0.1 mg/kg, a marginal 10% ILS relative to vehicle was observed [1]. At 1 mg/kg of AC220, tumor growth was completely inhibited during the dosing period, after which growth resumed. At 3 and 10 mg/kg of AC220, tumors regressed almost completely and the tumor volume stayed suppressed after dosing was halted. At 3 mg/kg, tumors appeared to regrow after day 49 (21 days post last dose), while there was no sign of tumor regrowth until day 60 (32 days post last dose) in the animals treated with 10 mg/kg of AC220 [2].
Kinase Assay	KinomeScan kinase binding assays were performed as previously described. For the FLT3 assay, we used a kinase construct that spanned the catalytic domain only (amino acids 592 to 969 in NP_004110.2). This construct does not include the juxtamembrane domain and is designed to measure the intrinsic binding affinity of the open FLT3 active site for inhibitors [1].

Cell Research	MV4-11 and RS4;11 cells were cultured in Iscove media with 10% fetal bovine serum (FBS) and RPMI complete with 10% FBS, respectively. For proliferation assays, cells were cultured overnight in low serum media (0.5% FBS), then seeded in a 96-well plate at 40 000 cells per well. Inhibitors were added to the cells and incubated at 37°C for 72 hours. Cell viability was measured using the Cell Titer-Blue Cell Viability Assay. To measure inhibition of FLT3 autophosphorylation, cells were cultured in low serum media (0.5% FBS) overnight and seeded at a density of 400 000 cells per well in a 96-well plate the following day. The cells were incubated with inhibitors for 2 hours at 37°C. To induce FLT3 autophosphorylation in RS4;11 cells, 100 ng/mL FLT3 ligand was added for 15 minutes after the 2-hour compound incubation. Cell lysates were prepared and incubated in 96-well plates pre-coated with a total FLT3 capture antibody. The coated plates were incubated with either a biotinylated antibody against FLT3 to detect total FLT3 or an antibody against phosphotyrosines to detect FLT3 autophosphorylation. In both cases, a SULFO-tagged streptavidin secondary antibody was used for electrochemiluminescence detection on the Meso Scale Discovery platform [1].
Animal Research	The model was performed according to published procedures.20 For intravenous bone marrow engraftment, nonobese diabetic/severe combined immunodeficient mice were acclimated for 2 weeks before pretreatment with 150 mg/kg cyclophosphamide delivered intraperitoneally once a day for 2 days. After a 48-hour rest period, animals were given an intravenous injection of 5 × 10^6 MV4-11 cells into the tail vein. AC220 was formulated and delivered as described for pharmacokinetic studies [1].

Solubility Information

Solubility	DMSO: 16.67 mg/mL (29.73 mM),Sonication is recommended. Ethanol: < 1 mg/mL (insoluble or slightly soluble), 10% DMSO+40% PEG300+5% Tween 80+45% Saline: 3.32 mg/mL (5.92 mM),Suspension. (< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	1.7836 mL	8.9179 mL	17.8358 mL
5 mM	0.3567 mL	1.7836 mL	3.5672 mL
10 mM	0.1784 mL	0.8918 mL	1.7836 mL
50 mM	0.0357 mL	0.1784 mL	0.3567 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.

Reference

Zarrinkar PP, et al. AC220 is a uniquely potent and selective inhibitor of FLT3 for the treatment of acute myeloid leukemia (AML). Blood. 2009 Oct 1;114(14):2984-92.
Zhang Y, Wang P, Wang Y, et al.Sitravatinib as a potent FLT3 inhibitor can overcome gilteritinib resistance in acute myeloid leukemia.Biomarker Research.2023, 11(1): 1-16.
Aikawa T, et al. Quizartinib, a selective FLT3 inhibitor, maintains antileukemic activity in preclinical models of RAS-mediated midostaurin-resistant acute myeloid leukemia cells. Oncotarget. 2020 Mar 17;11(11):943-955.
Huang F, Liang J, Lin Y, et al.Repurposing of Ibrutinib and Quizartinib as potent inhibitors of necroptosis. Communications Biology.2023, 6(1): 972.
Wang P, Zhang Y, Xiang R, et al.Foretinib is effective in acute myeloid leukemia by inhibiting FLT3 and overcoming secondary mutations that drive resistance to quizartinib and gilteritinib.Cancer Research.2024
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Hu C, Zhang Y, Yang J, et al.Ningetinib, a novel FLT3 inhibitor, overcomes secondary drug resistance in acute myeloid leukemia.Cell Communication and Signaling.2024, 22(1): 1-14.