Quizartinib

Cat. No.: HY-13001

CAS No.: 950769-58-1

Molecular Formula: $C_{29}H_{32}N_6O_4S$

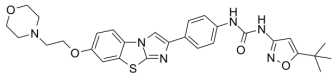
Molecular Weight: 561

Target: FLT3; Autophagy; Ligands for Target Protein for PROTAC; Apoptosis

Pathway: Protein Tyrosine Kinase/RTK; Autophagy; PROTAC; Apoptosis

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 33 mg/mL (58.82 mM)

DMF : 10 mg/mL (17.83 mM; Need ultrasonic)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.7825 mL	8.9127 mL	17.8253 mL
5 mM	0.3565 mL	1.7825 mL	3.5651 mL
10 mM	0.1783 mL	0.8913 mL	1.7825 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMF >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1 mg/mL (1.78 mM); Clear solution
2. Add each solvent one by one: 10% DMF >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1 mg/mL (1.78 mM); Clear solution
3. Add each solvent one by one: 10% DMF >> 90% corn oil
   Solubility: 1 mg/mL (1.78 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Quizartinib (AC220) is an orally active, highly selective and potent second-generation type II FLT3 tyrosine kinase inhibitor, with a K_d of 1.6 nM. Quizartinib inhibits wild-type FLT3 and FLT3-ITD autophosphorylation in MV4-11 cells with IC_{50}s of 4.2 and 1.1 nM, respectively. Quizartinib can be linked to the VHL ligand via an optimized linker to form a PROTAC FLT3 degrader. Quizartinib induces apoptosis[1].

IC_{50} & Target	Kd: 1.6±0.7 nM (Flt3)[1]
In Vitro	Quizartinib (AC220) is a novel compound expressly optimized as a FLT3 inhibitor for the treatment of acute myeloid leukemia (AML). Quizartinib inhibits FLT3-WT and FLT3-ITD autophosphorylation with IC_{50} of 4.2±0.3 nM and 1.1±0.1 nM, respectively. Quizartinib inhibits MV4-11 and A375 cells with IC_{50} of 0.56±0.3 nM and >10 000 nM, respectively. Quizartinib inhibits FLT3 with low nanomolar potency in cellular assays and is highly selective when screened against the majority of the human protein kinome[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Quizartinib (AC220) inhibits FLT3 activity in vivo, significantly extends survival in a mouse model of FLT3-ITD AML at doses as low as 1 mg/kg when dosed orally once a day, eradicates tumors in a FLT3-dependent mouse xenograft model at 10 mg/kg, and potently inhibits FLT3 activity in primary patient cells. The oral bioavailability of Quizartinib, determined in rats by comparing oral and intravenous pharmacokinetics at 3 mg/kg, is approximately 40%. A single 10 mg/kg dose of Quizartinib is administered by oral gavage, and mice are killed at 2 time points after dosing, using groups of 4 animals each. Quantitation of total FLT3 and phospho-FLT3 in tumor samples revealed time-dependent inhibition of FLT3 autophosphorylation. FLT3 activity is inhibited by 90% at 2 hours, and 40% at 24 hours after administration. The extent of inhibition therefore correlated well with the expected free Quizartinib plasma levels, based on pharmacokinetic experiments[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	KinomeScan kinase binding assays are performed. For the FLT3 assay, a kinase construct that spanned the catalytic domain only (amino acids 592 to 969) is used. 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [1]	MV4-11 and RS4;11 cells are cultured in Iscove media with 10% fetal bovine serum (FBS) and RPMI complete with 10% FBS, respectively. For proliferation assays, cells are cultured overnight in low serum media (0.5% FBS), then seeded in a 96-well plate at 40 000 cells per well. Inhibitors (e.g., Quizartinib) are added to the cells and incubated at 37°C for 72 hours. Cell viability is measured using the Cell Titer-Blue Cell Viability Assay. To measure inhibition of FLT3 autophosphorylation, cells are 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 are incubated with inhibitors (e.g., Quizartinib) for 2 hours at 37°C. To induce FLT3 autophosphorylation in RS4;11 cells, 100 ng/mL FLT3 ligand is added for 15 minutes after the 2-hour compound incubation. Cell lysates are prepared and incubated in 96-well plates precoated with a total FLT3 capture antibody. The coated plates are 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 is used for electrochemiluminescence detection on the Meso Scale Discovery platform[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female NU/NU or severe combined immunodeficient mice are used. Quizartinib (hydrochloride salt) is formulated in 22% hydroxypropyl-β-cyclodextrin, CEP-701 is formulated in 20% gelucire 44/14 in water (vol/vol), MLN-518 and SU 11248 are formulated in 10 mM sodium citrate (pH 3.5), PKC-412 is formulated in 3:1 gelucire 44/14-propylene glycol (vol/vol), and Bay 43-9006 is formulated in 80% PEG-400. Compound concentrations are chosen to deliver the desired dose in a volume of 10 mL/kg. Compounds are administered by oral gavage and plasma samples collected 0.25, 0.5, 1, 2, 4, 6, and 24 hours after dosing. To collect plasma samples, eye bleeds (150 µL) are taken semilongitudinally using 3 groups of 3 animals each, taking 2 to 3 time points per animal to obtain a total of 3 independent plasma concentration time courses. Plasma samples and controls (25 µL) are extracted with 4 volumes of acetonitrile containing an internal standard and analyzed by liquid chromatography tandem mass spectrometry. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Cell. 2018 Oct 8;34(4):674-689.e8.
- Cancer Cell. 2014 Feb 10;25(2):226-42.
- Cancer Discov. 2023 Apr 3;CD-22-0411.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nat Commun. 2018 Jan 24;9(1):358.

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REFERENCES

[1]. Zarrinkar PP, et al. AC220 is a uniquely potent and selective inhibitor of FLT3 for the treatment of acute myeloid leukemia (AML). Blood, 2009, 114(14), 2984-2992.

[2]. Puissant A, et al. SYK is a critical regulator of FLT3 in acute myeloid leukemia. Cancer Cell. 2014 Feb 10;25(2):226-42.

[3]. Sun X, et al. PROTACs: great opportunities for academia and industry. Signal Transduct Target Ther. 2019 Dec 24;4:64.

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