Canertinib dihydrochloride

Cat. No.: HY-10367A

CAS No.: 289499-45-2

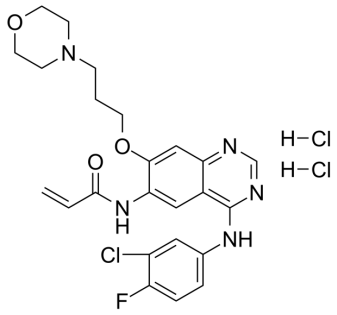
Molecular Formula: $C_{24}H_{27}Cl_3FN_5O_3$

Molecular Weight: 558.86

Target: EGFR; Orthopoxvirus

Pathway: JAK/STAT Signaling; Protein Tyrosine Kinase/RTK; Anti-infection

Storage: 4°C, sealed storage, away from moisture
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 62.5 mg/mL (111.83 mM; Need ultrasonic)
H_2O : 25 mg/mL (44.73 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7894 mL	8.9468 mL	17.8936 mL
	5 mM	0.3579 mL	1.7894 mL	3.5787 mL
	10 mM	0.1789 mL	0.8947 mL	1.7894 mL

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

In Vivo

1. Add each solvent one by one: PBS
   Solubility: 10 mg/mL (17.89 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.08 mg/mL (3.72 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (3.72 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: 2.08 mg/mL (3.72 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Canertinib dihydrochloride (CI-1033 dihydrochloride) is a potent and irreversible EGFR inhibitor; inhibits cellular EGFR and ErbB2 autophosphorylation with IC_{50}s of 7.4 and 9 nM. Canertinib dihydrochloride is active against vaccinia virus respiratory infection in mice[1][2][3][4].

IC_{50} & Target	EGFR	ErbB2
	7.4 nM (IC_{50})	9 nM (IC_{50})

In Vitro	Canertinib dihydrochloride (CI-1033 dihydrochloride) significantly inhibits growth of cultured melanoma cells, RaH3 and RaH5, in a dose-dependent manner. IC_{50} is approximately 0.8 μM and by 5μM both cell lines are completely growth-arrested within 72 h of treatment. Incubation of exponentially growing RaH3 and RaH5 with 1 μM canertinib accumulated the cells in the G1-phase of the cell cycle within 24 h of treatment without induction of apoptosis. 1 μM canertinib inhibits ErbB1-3 receptor phosphorylation with a concomitant decrease of Akt-, Erk1/2- and Stat3 activity in both cell lines[2]. Canertinib dihydrochloride also is a potent activator of exosome secretion[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Canertinib dihydrochloride (CI-1033 dihydrochloride) shows superior in vivo antitumor activity, giving growth delays in A431 xenografts exceeding 50 days following oral administration[1]. The growth of human malignant melanoma xenografts, RaH3 and RaH5, in nude mice is significantly inhibited by i.p. injections of 40 mg/kg/day canertinib (Fig. 4). The anti-proliferative effect on melanoma xenografts is visible already within 4 days of treatment and further increased throughout the treatment period as observed through the differences in tumor volumes, reaching statistical significance within 18 days of treatment[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Enzyme assays for IC_{50} determinations are performed in 96-well filter plates. The total volume is 0.1 mL containing 20 mM Hepes, pH 7.4, 50 mM sodium vanadate, 40 mM magnesium chloride, 10 μM adenosine triphosphate (ATP) containing 0.5 mCi of [^{32}P]ATP, 20 mg of polyglutamic acid/tyrosine, 10 ng of EGFR tyrosine kinase, and appropriate dilutions of inhibitor (Canertinib). All components except the ATP are added to the well and the plate is incubated with shaking for 10 min at 25°C. The reaction is started by adding [^{32}P]ATP, and the plate is incubated at 25°C for 10 min. The reaction is terminated by addition of 0.1 mL of 20% trichloroacetic acid (TCA). The plate is kept at 4°C for at least 15 min to allow the substrate to precipitate. The wells is then washed five times with 0.2 mL of 10% TCA and ^{32}P incorporation determined with a plate counter[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	RaH3 and RaH5 cells are treated with increasing concentrations (0-10 μM) of Canertinib for 72 h. The cells are suspended in buffer and counted[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice: Canertinib treatment starts when the tumors show reliable growth. The mice are randomized into control and treatment groups. In the canertinib treated RaH3 group (n=4) and RaH5 group (n=7) each mouse receives i.p. injections of 1.2 mg canertinib (40 mg/kg/day) in 0.1 ml 0.15 M NaCl 5 days a week. The control RaH3 (n=3) and RaH5 (n=7) mice receive i.p. injections of vehicle only according to the same regimen. At the end of the treatment period, the mice are sacrificed by cervical dislocation where after the tumors are removed and weighed[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- J Med Chem. 2019 May 9;62(9):4772-4778.
- J Cell Sci. 2015 Sep 1;128(17):3317-29.
- J Biol Chem. 2012 Mar 23;287(13):9742-52.
- Biochemistry. 2018 Feb 27;57(8):1369-1379.

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REFERENCES

[1]. Smee DF, et, al. Progress in the discovery of compounds inhibiting orthopoxviruses in animal models. Antivir Chem Chemother. 2008;19(3):115-24.

[2]. Smaill JB, et al. Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions. J Med Chem.

[3]. Djerf Severinsson EA, et al. The pan-ErbB receptor tyrosine kinase inhibitor canertinib promotes apoptosis of malignant melanoma in vitro and displays anti-tumor activity in vivo. Biochem Biophys Res Commun. 2011 Oct 28;414(3):563-8.

[4]. McAndrews KM, et, al. Mechanisms associated with biogenesis of exosomes in cancer. Mol Cancer. 2019 Mar 30;18(1):52.

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