Canertinib

Cat. No.: HY-10367

CAS No.: 267243-28-7

Molecular Formula: $C_{24}H_{25}ClFN_5O_3$

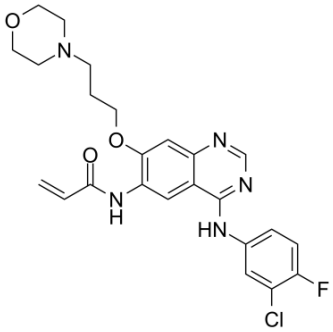
Molecular Weight: 485.94

Target: EGFR

Pathway: JAK/STAT Signaling; Protein Tyrosine Kinase/RTK

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

Ethanol : 12.5 mg/mL (25.72 mM; Need ultrasonic)
DMSO : 4.9 mg/mL (10.08 mM; Need warming)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0579 mL	10.2893 mL	20.5787 mL
5 mM	0.4116 mL	2.0579 mL	4.1157 mL
10 mM	0.2058 mL	1.0289 mL	2.0579 mL

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

In Vivo

1. Add each solvent one by one: 10% EtOH >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1.25 mg/mL (2.57 mM); Clear solution
2. Add each solvent one by one: 10% EtOH >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.25 mg/mL (2.57 mM); Clear solution
3. Add each solvent one by one: 10% EtOH >> 90% corn oil
   Solubility: ≥ 1.25 mg/mL (2.57 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Canertinib (CI-1033;PD-183805) is a potent and irreversible EGFR inhibitor; inhibits cellular EGFR and ErbB2 autophosphorylation with IC_{50}s of 7.4 and 9 nM.

IC_{50} & Target

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

In Vitro	Canertinib 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 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 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). pii: 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]. 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. 2000 Apr 6;43(7):1380-97.

[2]. 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.

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

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