Dacomitinib

Cat. No.: HY-13272

CAS No.: 1110813-31-4

Molecular Formula: $C_{24}H_{25}ClFN_5O_2$

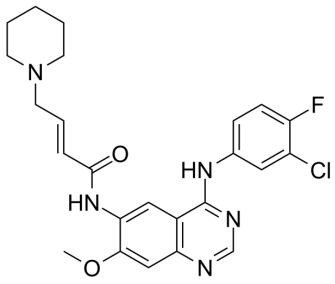
Molecular Weight: 469.94

Target: EGFR; Apoptosis

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

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : 40 mg/mL (85.12 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1279 mL	10.6397 mL	21.2793 mL
	5 mM	0.4256 mL	2.1279 mL	4.2559 mL
	10 mM	0.2128 mL	1.0640 mL	2.1279 mL

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

In Vivo

1. Add each solvent one by one: 0.5% CMC/saline water
   Solubility: 5 mg/mL (10.64 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.32 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.32 mM); Suspended solution; Need ultrasonic
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.32 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Dacomitinib (PF-00299804) is a specific and irreversible inhibitor of the ERBB family of kinases with IC_{50}s of 6 nM, 45.7 nM and 73.7 nM for EGFR, ERBB2, and ERBB4, respectively[1].

IC_{50} & Target			
	EGFR	ErbB2	ErbB4
	6 nM (IC_{50})	45.7 nM (IC_{50})	73.7 nM (IC_{50})

In Vitro	Dacomitinib (PF00299804) effectively inhibits the in vitro kinase activity of wild-type EGFR (IC50=6 nM)with similar efficacy. Dacomitinib also effectively inhibits wild-type ERBB2 with IC_{50} of 45.7 nM. In H441, an IC_{50} is reached with Dacomitinib but only at a very high concentration (4 μM) and likely reflects off-target effects. In cell lines wild-type for both EGFR and K-ras (H322, H1819, and Calu-3), ZD1839 and Dacomitinib both effectively inhibit growth of H1819 and Calu-3 cells but not of H322 cells. Dacomitinib is a pan-ERBB inhibitor and most EGFR mutant cell lines express multiple ERBB family members, the effects on EGFR phosphorylation could potentially be indirect. Dacomitinib inhibits EGFR phosphorylation in all of the different EGFR T790M proteins whereas ZD1839 is ineffective even at 10 μM. In the NIH3T3 cells, phosphorylation of EGFR L858R/T790M is completely inhibited by 1 nM Dacomitinib, whereas 100 nM or greater is required to inhibit EGFR WT/T790M or Del/T790M[1]. The HER2-amplified cell lines are most sensitive to growth inhibition by Dacomitinib (IC_{50}<1 μM in 14 of 16 lines; 87.5%) as compared with 5 of 28 (17.9%) of HER2-nonamplified lines (excluding immortalized lines)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	To evaluate the efficacy of Dacomitinib, xenografts in nu/nu mice are generated using HCC827 GFP and HCC827 Del/T790M cells and treated the mice with Dacomitinib. Dacomitinib (10 mg/kg/d by daily oral gavage) effectively inhibits the growth of HCC827 GFP xenografts. In contrast, HCC827 Del/T790M xenografts are resistant to ZD1839, whereas Dacomitinib treatment is substantially more effective at inhibiting growth of this xenograft model[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Cells are seeded in duplicate at 5×10^3 to 5×10^4 cells per well in 24-well plates, and growth inhibition data is calculated. Briefly, day after plating, Dacomitinib is added at 10 μM and 2-fold dilutions over 12 concentrations are carried out to generate a dose-response curve. Control wells without the drug are also seeded. The cells are counted on day 1 when the drug is added, as well as after 6 days when the experiment ended. After the trypsinization cells are placed in an Isotone solution and immediately counted using a Coulter Z1 particle counter. The suspension cultures are counted using a Coulter Vi-Cell counter[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Nude mice (nu/nu; 6-8 weeks old) are used for in vivo studies. A suspension of 5×10^6 HCC827-GFP or HCC827-Del/T790M lung cancer cells (in 0.2 mL of PBS) are inoculated s.c. into the lower-right quadrant of the flank of each mouse. Five mice are inoculated with either HCC827-GFP or HCC827-Del/T790M cells in the ZD1839 treatment group. Tumors are measured twice weekly using calipers, and volume is calculated using the following formula: length×$width^2$×0.52. Mice are monitored daily for body weight and general condition. Mice are randomized to treatment when the mean tumor volume is 400 to 500 mm^3. ZD1839 is administered at 150 mg/kg/d by daily oral gavage. Dacomitinib is administered at 10 mg/kg/d by daily oral gavage. The experiment is terminated when the mean size of the control tumors reached 2000 mm^3. 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.
- Cell Rep Med. 2023 Jan 10;100911.
- Mol Cancer Ther. 2018 Mar;17(3):603-613.
- Front Chem. 2020 Jul 28;8:596.
- Molecules. 2024 Jan 4, 29(1), 274.

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REFERENCES

[1]. Engelman JA, et al. PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to ZD1839. Cancer Res. 2007 Dec 15;67(24):11924-32.

[2]. Kalous O, et al. Dacomitinib (PF-00299804), an irreversible Pan-HER inhibitor, inhibits proliferation of HER2-amplified breast cancer cell lines resistant to Anti-Human HER2 and GW572016. Mol Cancer Ther. 2012 Sep;11(9):1978-87.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA