Sapitinib

Cat. No.: HY-13050

CAS No.: 848942-61-0

Molecular Formula: $C_{23}H_{25}ClFN_5O_3$

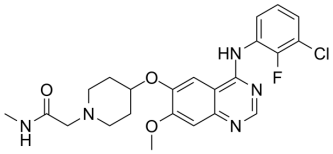
Molecular Weight: 473.93

Target: EGFR

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

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 (69.63 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1100 mL	10.5501 mL	21.1002 mL
5 mM	0.4220 mL	2.1100 mL	4.2200 mL
10 mM	0.2110 mL	1.0550 mL	2.1100 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.28 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.28 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.28 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Sapitinib (AZD-8931) is a reversible, ATP competitive EGFR inhibitor of with IC_{50}s of 4, 3 and 4 nM for EGFR, ErbB2 and ErbB3 in cells, respectively.

IC_{50} & Target

EGFR	ErbB2	HER3
4 nM (IC_{50})	3 nM (IC_{50})	4 nM (IC_{50})

In Vitro	AZD8931 shows potent inhibitory effect on erbB2 in the ligand-independent MCF-7 cl24 cells, with IC_{50} of 59 nM[1]. AZD8931 (1 μM) has no significant effect on EGFR expression level, but significantly inhibits phosphorylation of Akt in a time- and dose-dependent manner in both SUM149 and FC-IBC-02 cells. AZD8931 (0.01, 0.1, 1, or 2 μM) inhibits proliferation and induces apoptosis in human IBC cells[2]. At the cellular level, AZD8931 inhibits EGF-stimulated phosphorylation of EGFR in the KB cell line (IC_{50}: 4 nM) and heregulin-stimulated phosphorylation of HER2 (IC_{50}: 3 nM) and HER3 (IC_{50}: 4 nM) in the MCF-7 cell line. However, AZD8931 exhibits no CYP P450 inhibition (IC_{50} > 10 μM against 1A2, 2C9, 2C19, 2D6, and 3A4)[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	AZD8931 (6.25-50 mg/kg, p.o.) significantly inhibits BT474c (breast), Calu-3 (NSCLC), LoVo (colorectal), FaDu (SCCHN), and PC-9 (NSCLC) tumor xenograft growth. AZD8931 is active in xenograft tumor models responsive to EGFR inhibition alone (LoVo and PC-9) or EGFR or erbB2 inhibition (BT474c, Calu-3, and FaDu). AZD8931 causes pharmacodynamic changes in proliferation and apoptosis markers in human tumor xenograft models[1]. AZD8931 (25 mg/kg, p.o.) significantly inhibits the growth of SUM149 and FC-IBC-02 cells in vivo in SCID mice[2]. AZD8931 displays favorable oral pharmacokinetics in rat and dog (low clearance and good bioavailability) and low human hepatocyte turnover (Clint < 4.5 μL/min/106 cells). In nude mouse after oral administration at 50 mg/kg, AZD8931 shows improved exposure, and at at 100 mg/kg oral dose once daily, it shows potent tumor growth inhibition activity in the LoVo mouse xenograft model[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cells are incubated for 96 h with a suitable range of concentrations of drug to ensure accurate estimation of the inhibitor concentration required to give 50% growth inhibition (GI_{50}; typically between 0.001-10 μM). Viable cell number is determined by 4 h of incubation with MTS Colorimetric Assay reagent and absorbance measured at 490 nm on a spectrophotometer. Each experiment is carried out in triplicate for each drug concentration and data are presented as geometric means. Sensitivity groupings of GI_{50} data are <1 μM, 1 to 7 μM, and >7 μM. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Swiss nude (nu/nu genotype) and severe combined immunodeficient mice are used. AZD8931, GW572016, and ZD1839 are suspended in a 1% (v/v) solution of polyoxyethylenesorbitan monooleate (Tween 80) in deionized water. Animals are given AZD8931 (6.25-50 mg/kg), GW572016 (100 mg/kg), ZD1839 (100-150 mg/kg), or vehicle control once (qd) or twice daily (bid) by oral gavage. The duration of each study is determined by tumor growth characteristics, with studies ending once tumors reach ~1 cm^3. Tumor volume and percentage tumor growth inhibition are calculated and statistical analysis of any change in tumor volume is carried out using a standard t test (P value of lower then 0.05 is considered to be statistically significant). 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. 2023 May 29;42(6):112570.
- J Transl Med. 2021 Jan 23;19(1):43.
- Mol Cancer Res. 2019 Jan;17(1):20-29.
- Molecules. 2023 Mar 2.

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REFERENCES

[1]. Hickinson DM, et al. AZD8931, an equipotent, reversible inhibitor of signaling by epidermal growth factor receptor, ERBB2 (HER2), and ERBB3: a unique agent for simultaneous ERBB receptor blockade in cancer. Clin Cancer Res. 2010 Feb 15;16(4):1159-69.

[2]. Mu Z, et al. AZD8931, an equipotent, reversible inhibitor of signaling by epidermal growth factor receptor (EGFR), HER2, and HER3: preclinical activity in HER2 non-amplified inflammatory breast cancer models. J Exp Clin Cancer Res. 2014 May 30;33:47.

[3]. Barlaam B, et al. Discovery of AZD8931, an Equipotent, Reversible Inhibitor of Signaling by EGFR, HER2, and HER3 Receptors. ACS Med Chem Lett. 2013 May 31;4(8):742-6.

[4]. Wang R, et al. Endothelial Cells Promote Colorectal Cancer Cell Survival by Activating the HER3-AKT Pathway in a Paracrine Fashion. Mol Cancer Res. 2018 Aug 21. pii: molcanres.0341.2018.

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