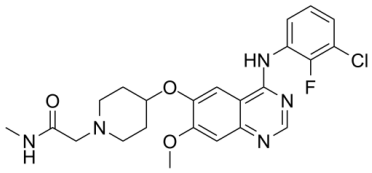
Data Sheet

Product Name:	Sapitinib
Cat. No.:	CS-3951
CAS No.:	848942-61-0
Molecular Formula:	C23H25ClFN5O3
Molecular Weight:	473.93
Target:	EGFR
Pathway:	JAK/STAT Signaling; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 33 mg/mL (69.63 mM)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 4 nM (EGFR), 3 nM (ErbB2), 4 nM (ErbB3)[1] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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. **Animal Administration:** Sapitinib is suspended in a 1% (v/v) solution of polyoxyethylenesorbitan monooleate (Tween 80) in deionized water.[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).

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.

CAIndexNames:

1-Piperidineacetamide, 4-[[4-[(3-chloro-2-fluorophenyl)amino]-7-methoxy-6-quinazolinyl]oxy]-N-methyl-

SMILES:

O=C(CN1CCC(OC2=CC3=C(NC4=CC=CC(Cl)=C4F)N=CN=C3C=C2OC)CC1)NC

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