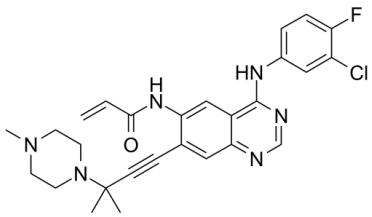
Data Sheet

Product Name:	AV-412 (free base)
Cat. No.:	CS-2402
CAS No.:	451492-95-8
Molecular Formula:	C27H28ClFN6O
Molecular Weight:	507.00
Target:	EGFR
Pathway:	JAK/STAT Signaling; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 50 mg/mL (98.62 mM)



BIOLOGICAL ACTIVITY:

AV-412 free base (MP-412 free base) is an **EGFR** inhibitor with **IC_{50}**s of 0.75, 0.5, 0.79, 2.3, 19 nM for EGFR, $EGFR^{L858R}$, $EGFR^{T790M}$, $EGFR^{L858R/T790M}$ and ErbB2, respectively. IC50 & Target: IC50: 0.75 nM (EGFR), 0.5 nM ($EGFR^{L858R}$), 0.79 nM ($EGFR^{T790M}$), 2.3 nM ($EGFR^{L858R/T790M}$), 19 nM (ErbB2)[1] **In Vitro:** AV-412 inhibits autophosphorylation of EGFR and ErbB2 with IC_{50} of 43 and 282 nM, respectively. AV-412 also inhibits epidermal growth factor (EGF)-dependent cell proliferation with an IC_{50} of 100 nM. AV-412 abrogates EGFR signaling in the gefitinib-resistant H1975 cell line, which harbors a double mutation of L858R and T790M in EGFR[1]. **In Vivo:** In animal studies using cancer xenograft models, AV-412 (30 mg/kg) demonstrates complete inhibition of tumor growth of the A431 and BT-474 cell lines, which overexpress EGFR and ErbB2, respectively. AV-412 suppresses autophosphorylation of EGFR and ErbB2 at the dose corresponding to its antitumor efficacy. When various dosing schedules are applied, AV-412 shows significant effects with daily and every-other-day schedules, but not with a once-weekly schedule, suggesting that frequent dosing is preferable for this compound. Furthermore, AV-412 shows a significant antitumor effect on the ErbB2-overexpressing breast cancer KPL-4 cell line, which is resistant to gefitinib[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]Recombinant intracellular kinase domains of EGFR, $EGFR^{L858R}$, $EGFR^{T790M}$, $EGFR^{L858R/T790M}$, and purified EGFR from A431 cell membranes are used. Kinase reactions are carried out in 8 mM MOPS (pH 7.0), 0.2 mM ethylenediaminetetraacetic acid (EDTA), 10 mM $MnCl_2$, 10 mM Mg acetate, 0.1 mg/mL poly(Glu, Tyr) 4:1, [γ^{33}P-ATP], and 5–10 mU of enzyme, except that 250 μM of the GGMEDIYFEFMGGKKK peptide substrate is used for $EGFR^{T790M}$. Phosphorylation is initiated by the addition of ATP and is allowed to proceed for 40 min at room temperature. The reaction is stopped by the addition of 3% phosphoric acid, then aliquots of the reaction mixture are spotted onto a filtermat. After rinsing to remove peptides bound non-specifically, the filter is scintillation counted [1]. **Cell Assay:** AV-412 is dissolved in DMSO[1].[1]To test the effects of AV-412 on growth factor-dependent cell proliferation, A431 and A7r5 cells are cultured for 24 h at 37°C in the presence of 1 ng/mL epidermal growth factor and 50 ng/mL platelet-derived growth factor, respectively. The ^{3}H-thymidine incorporation during this period is measured[1]. **Animal Administration:** AV-412 is suspended in 0.5% aqueous gum tragacanth solution[1].[1]Mice: For studies examining the dosing schedule in relation to efficacy against TE-8 tumors, AV-412 is administered either once daily, every other day, or once per week for 2 weeks. Mice are killed 1 day after the final treatment, and the tumors are dissected and weighed. For evaluation of tumor phosphorylation, tumor-bearing mice are given a single administration of AV-412 and tumors are dissected 4 h later[1].

References:

[1]. Suzuki T, et al. Pharmacological characterization of MP-412 (AV-412), a dual epidermal growth factor receptorand ErbB2 tyrosine kinase inhibitor. Cancer

Sci. 2007 Dec;98(12):1977-84.

CAIndexNames:

2-Propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-methyl-3-(4-methyl-1-piperazinyl)-1-butyn-1-yl]-6-quinazolinyl]-

SMILES:

O=C(C=C)NC1=CC2=C(NC3=CC=C(C(Cl)=C3)F)N=CN=C2C=C1C#CC(C)(C)N(CC4)CCN4C

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