

Product Data Sheet

Product Name: AV-412 free base

Cat. No.: GC35436

Chemical Properties

Cas. No. 451492-95-8

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

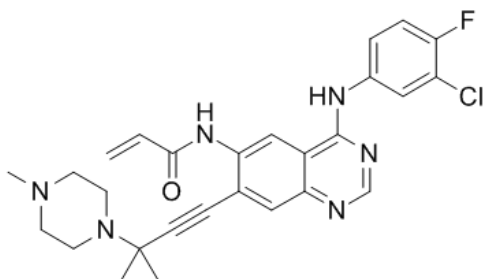
Formula C27H28ClFN6O M.Wt 507

Solubility DMSO: ≥ 50 mg/mL (98.62 mM) Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Caution: Product has not been fully validated for medical applications. For research use only.

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- Kinase experiment:** 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 MnCl₂, 10 mM Mg acetate, 0.1 mg/mL poly(Glu, Tyr) 4:1, [³²P-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 experiment:** 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 ³H-thymidine incorporation during this period is measured[1].
- Animal experiment:** 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 receptor and ErbB2 tyrosine kinase inhibitor. Cancer Sci. 2007 Dec;98(12):1977-84.

Background

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AV-412 free base (MP-412 free base) is an EGFR inhibitor with IC₅₀s of 0.75, 0.5, 0.79, 2.3, 19 nM for EGFR, EGFR L858R, EGFR T790M, EGFR L858R/T790M and ErbB2, respectively. EGFR|0.75 nM (IC₅₀)|ErbB2|19 nM (IC₅₀)|EGFR L858R|0.51 nM (IC₅₀)|EGFR L858R/T790M|2.3 nM (IC₅₀)|EGFR T790M|0.79 nM (IC₅₀)

AV-412 inhibits autophosphorylation of EGFR and ErbB2 with IC₅₀ of 43 and 282 nM, respectively. AV-412 also inhibits epidermal growth factor (EGF)-dependent cell proliferation with an IC₅₀ 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 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].

[1]. Suzuki T, et al. Pharmacological characterization of MP-412 (AV-412), a dual epidermal growth factor receptor and ErbB2 tyrosine kinase inhibitor. Cancer Sci. 2007 Dec;98(12):1977-84.

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