

Product Data Sheet

Product Name: AZD3759

Cat. No.: GC13143

Chemical Properties

Cas. No. 1626387-80-1

Chemical Name (R)-4-((3-chloro-2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl 2,4-dimethylpiperazine-1-carboxylate

SMILES C1C=CC=CC(NC2=NC=NC3=CC(OC)=C(OC(N4[C@H](C)CN(C)CC4)=O)C=C23)=C1F

Formula $C_{22}H_{23}ClFN_5O_3$

M.Wt 459.9

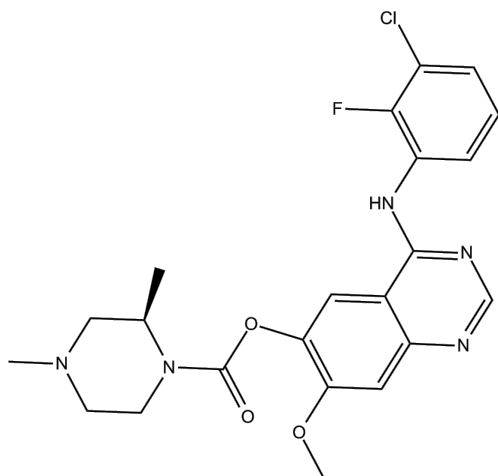
Solubility $\geq 23\text{mg/mL}$ in DMSO

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:** AZD3759 is tested at a single 1 μ M concentration across each of 124 kinases from Millipore kinase panel at an ATP concentration that is within 15 μ M of their corresponding apparent K_m values. The detailed protocols could be obtained from Millipore. In brief, recombinant kinases are incubated within appropriate buffer containing peptide substrate and radiolabelled γ -33P-ATP together with presence or absence of required inhibitor concentration. The reaction is initiated by adding ATP/Mg²⁺ mix. After incubation for 40 minutes at room temperature, the reaction is stopped by adding 3% phosphoric acid solution. A portion of reaction mix is spotted onto P30 filtermat to trap peptide, and washed three times for 5 minutes with phosphoric acid to remove non-specific γ -33P-ATP. The phosphorylated substrate is then measured by scintillation counting, which determined the level of kinase activity inhibition compared to control reactions[1].
- Cell experiment:** Cell proliferation assay is determined by MTS methods. Briefly, cells are seeded in 96-well plates (at a density to allow for logarithmic growth during the 72-hour assay) and incubated overnight at 37°C and 5% CO₂. Cells are then exposed to concentrations of compounds (e.g., AZD3759) ranging from 30 mM to 0.3 μ M for 72 hours. For the MTS endpoint, cell proliferation is measured by the CellTiter AQueous Non-Radioactive Cell Proliferation Assay reagent. Absorbance is measured with a Tecan Ultra instrument. Predose measurements are made, and concentration needed to reduce the growth of treated cells to half that of untreated cells (GI50) values are determined using absorbance readings[1].
- Animal experiment:** Rats[1] Male Han Wistar rats are orally dosed with the AZD3759 at 2 mg/kg in 1% methylcellulose. At 0.25, 0.5, 1, 2, 4 and 7 hour post-dose, cerebral spinal fluid (CSF) is collected from cisterna magna, and blood samples (>60 μ L/time point/each site) are collected via cardiac puncture, into separate EDTA coagulated tubes, and then immediately diluted with 3-fold volume of water. Brain tissue is harvested and homogenized in 3x volume of 100 mM phosphate buffered saline (pH7.4). All samples are stored at -70°C prior to LC/MS/MS analysis.

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References:

[1]. Zeng Q, et al. Discovery and Evaluation of Clinical Candidate AZD3759, a Potent, Oral Active, Central Nervous System-Penetrant, Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor. J Med Chem. 2015 Oct 22;58(20):8200-15.

Background

AZD3759 is a potent and oral active inhibitor of EGFR (IC_{50} = 7.0-7.7 nM) with antineoplastic activity.

EGFR (epidermal growth factor receptor) is a cell-surface receptor tyrosine kinase. The receptor activation leads to dimerization and tyrosine autophosphorylation. It induces a cascade of downstream cellular responses such as modification in gene expression, cell proliferation and cytoskeletal rearrangement etc.

AZD3759 shows equally potent inhibitory effect on cell phosphorylation or proliferation in EGFR-activating mutant cell lines (PC-9 and H3255) in the range of 7.0–7.7nM. In cellular phosphorylation assays, AZD3759 also exhibits 9-fold inhibition selectivity in EGFR-activating

mutant cell lines over EGFR wild-type cell lines (H838). [1]

In brain metastasis mouse model, AZD3759 demonstrates prominent antitumor efficacy in a dose dependent manner (~78% tumor growth inhibition at 7.5 mg/kg qd and tumor regression at 15 mg/kg qd, respectively, 4 weeks after treatment, with <20% body weight loss). In addition, at the doses of 7.5 and 15 mg/k, AZD3759 significantly decreases tumor area in the brain tissue collected from the same mouse model. [1]

Reference:

Zeng Q, Wang J, Cheng Z et al. Discovery and Evaluation of Clinical Candidate AZD3759, a Potent, Oral Active, Central Nervous System-Penetrant, Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor. J Med Chem. 2015 Oct 22;58(20):8200-15

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