# Zorifertinib

**Cat. No.:** HY-18750

**CAS No.:** 1626387-80-1

**Molecular Formula:** $C_{22}H_{23}ClFN_5O_3$

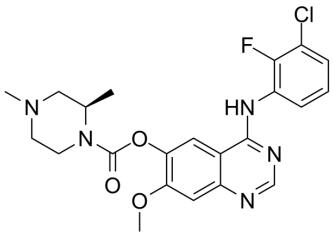
**Molecular Weight:** 459.9

**Target:** EGFR

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

**Storage:**

| | | |
|---|---|---|
| Powder | -20°C | 3 years |
| | 4°C | 2 years |
| In solvent | -80°C | 6 months |
| | -20°C | 1 month |




## SOLVENT & SOLUBILITY

**In Vitro**

DMSO : ≥ 50 mg/mL (108.72 mM)

* "≥" means soluble, but saturation unknown.

**Preparing Stock Solutions**

| Solvent / Mass / Concentration | 1 mg | 5 mg | 10 mg |
|---|---|---|---|
| 1 mM | 2.1744 mL | 10.8719 mL | 21.7439 mL |
| 5 mM | 0.4349 mL | 2.1744 mL | 4.3488 mL |
| 10 mM | 0.2174 mL | 1.0872 mL | 2.1744 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 (5.44 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.44 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.44 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (5.44 mM); Clear solution

## BIOLOGICAL ACTIVITY

**Description**

Zorifertinib (AZD3759) is a potent, orally active, central nervous system-penetrant, EGFR inhibitor. At $K_m$ ATP concentrations, the $IC_{50}$s are 0.3, 0.2, and 0.2 nM for $EGFR^{wt}$, $EGFR^{L858R}$, and $EGFR^{exon\ 19Del}$, respectively[1].

| $IC_{50}$ & Target | EGFR | $EGFR^{L858R}$ | $EGFR^{Exon\ 19\ deletion}$ |
|---|---|---|---|

| | | | |
|---|---|---|---|
| | 0.3 nM ($IC_{50}$) | 0.2 nM ($IC_{50}$) | 0.2 nM ($IC_{50}$) |

**In Vitro**

At 2 mM of ATP concentrations, the $IC_{50}$s are 102, 7.6, and 2.4 nM for $EGFR^{wt}$, $EGFR^{L858R}$, and $EGFR^{exon\ 19Del}$, respectively. Zorifertinib (AZD3759) also inhibits pEGFR in $H838^{wt}$, $H3255^{L858R}$, and $PC\text{-}9^{exon\ 19Del}$ with $IC_{50}$ of 64.5, 7.2, and 7.4 nM, respectively. In cellular phosphorylation studies, Zorifertinib also demonstrates 9-fold inhibition selectivity in EGFR-activating mutant cell lines over EGFR wild-type cell lines (H838 cell line)[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**In Vivo**

Following oral dosing in rats at 2 mg/kg, absorption of Zorifertinib (AZD3759) is rapid with blood $C_{max}$ of 0.58 μM achieved at 1.0 h. Subsequently, blood concentrations of Zorifertinib decline monoexponentially with a mean elimination half-life of 4.3 h, which is close to the same parameter obtained from intravenous dosing of 4.1 h. The bioavailability following an oral dose in rats is 91%. Blood pharmacokinetic parameters of Zorifertinib in male dogs are determined following both a single dose intravenous infusion and oral administration. Following the IV dose in dogs, Zorifertinib blood clearance is determined as 14 mL/min per kg, and the volume of distribution is 6.4 L/kg. Its elimination half-life is 6.2 h. Absorption of Zorifertinib is rapid with blood $C_{max}$ (698 nM) occurring between 0.5 and 1.5 h. The oral bioavailability of Zorifertinib is excellent at 90%. Zorifertinib demonstrated significant dose-dependent antitumor efficacy (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, whereas CP-358774 has a limited effect in this model. At the end of the study, brain tissues are collected for histological assessment. Significantly decreased tumor area is observed by Zorifertinib treatment at the doses of 7.5 and 15 mg/kg. In addition, modulation of pEGFR is detected by a single dose of Zorifertinib at 15 mg/kg 1h after dosing, which confirmed target engagement by Zorifertinib[1].

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## PROTOCOL

**Cell Assay** [1]

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% $CO_2$. Cells are then exposed to concentrations of compounds (e.g., Zorifertinib) ranging from 30 mM to 0.3μM 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 ($GI_{50}$) values are determined using absorbance readings[1].

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**Animal Administration** [1]

Rats[1]

Male Han Wistar rats are orally dosed with the Zorifertinib 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 μL/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.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

## CUSTOMER VALIDATION

- J Pharm Biomed Anal. 2022 Jan 29;211:114626.
- RSC Adv. 2022, 12, 20991-21003.
- Patent. US20220177473A1.

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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.



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