

产品名称: **AZD3759**

产品别名: **AZD3759**

生物活性:

Description	AZD3759 is a potent, oral active, central nervous system-penetrant, <b>EGFR</b> inhibitor. At $K_m$ ATP concentrations, the $IC_{50}$ s are 0.3, 0.2, and 0.2 nM for EGFR <sup>wt</sup> , EGFR <sup>L858R</sup> , and EGFR <sup>exon 19Del</sup> , respectively.				
IC <sub>50</sub> & Target	EGFR	EGFR <sup>L858R</sup>	EGFR <sup>Exon 19 deletion</sup>		
	0.3 nM (IC <sub>50</sub> )	0.2 nM (IC <sub>50</sub> )	0.2 nM (IC <sub>50</sub> )		
In Vitro	At 2 mM of ATP concentrations, the $IC_{50}$ s are 102, 7.6, and 2.4 nM for EGFR <sup>wt</sup> , EGFR <sup>L858R</sup> , and EGFR <sup>exon 19Del</sup> , respectively. AZD3759 also inhibits pEGFR in H838 <sup>wt</sup> , H3255 <sup>L858R</sup> , and PC-9 <sup>exon 19Del</sup> with IC <sub>50</sub> of 64.5, 7.2, and 7.4 nM, respectively. In cellular phosphorylation studies, AZD3759 also demonstrates 9-fold inhibition selectivity in EGFR-activating mutant cell lines over EGFR wild-type cell lines (H838 cell line) [1].				
In Vivo	Following oral dosing in rats at 2 mg/kg, absorption of AZD3759 is rapid with blood $C_{max}$ of 0.58 $\mu$ M achieved at 1.0 h. Subsequently, blood concentrations of AZD3759 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 AZD3759 in male dogs are determined following both a single dose intravenous infusion and oral administration. Following the IV dose in dogs, AZD3759 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 AZD3759 is rapid with blood $C_{max}$ (698 nM) occurring between 0.5 and 1.5 h. The oral bioavailability of AZD3759 is excellent at 90%. AZD3759 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 erlotinib had 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 AZD3759 treatment at the doses of 7.5 and 15 mg/kg. In addition, modulation of pEGFR is detected by a single dose of AZD3759 at 15 mg/kg 1h after dosing, which confirmed target engagement by AZD3759 [1].				
Solvent&Solubility	<b>In Vitro:</b>  <b>DMSO : <math>\geq</math> 50 mg/mL (108.72 mM)</b>  <b>H<sub>2</sub>O : &lt; 0.1 mg/mL (insoluble)</b>  * ">" means soluble, but saturation unknown.				
	<div>Preparing Stock Solutions</div>	<div>Solvent / Mass / Concentration</div>	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
	<p>*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液。一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。</p> <p>储备液的保存方式和期限 -80℃, 6 months; -20℃, 1 month。 -80℃ 储存时，请在 6 个月内使用，-20℃ 储存时，请在 1 个月内使用。</p> <p><b>In Vivo:</b></p> <p>请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 <b>In Vitro</b> 方式配制澄清的储备液，再依次添加助溶剂：</p> <p>——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现</p>				

	<p>用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶</p> <p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: <math>\geq 2.5</math> mg/mL (5.44 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (5.44 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 400 <math>\mu</math>L PEG300 中，混合均匀向上述体系中加入 50 <math>\mu</math>L Tween-80，混合均匀；然后继续加入 450 <math>\mu</math>L 生理盐水定容至 1 mL。</p> <p>2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-<math>\beta</math>-CD in saline) Solubility: 2.5 mg/mL (5.44 mM); Suspended solution; Need ultrasonic</p> <p>此方案可获得 2.5 mg/mL (5.44 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 20% 的 SBE-<math>\beta</math>-CD 生理盐水水溶液中，混合均匀。</p> <p>3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: <math>\geq 2.5</math> mg/mL (5.44 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (5.44 mM, 饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例，取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 玉米油中，混合均匀。</p>
References	<p>[1]. <a href="#">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.</a> 2015 Oct 22;58(20):8200-15.</p>
实验参考：	
Cell Assay	<p>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<sub>2</sub>. Cells are then exposed to concentrations of compounds (e.g., AZD3759) ranging from 30 mM to 0.3<math>\mu</math>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 (GI<sub>50</sub>) values are determined using absorbance readings [1].</p>
Animal Administration	<p>Rats[1]</p> <p>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 (&gt;60 <math>\mu</math>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.</p>
	<p>AZD3759 is tested at a single 1 <math>\mu</math>M concentration across each of 124 kinases from Millipore kinase panel at an ATP concentration that is within 15 <math>\mu</math>M of their corresponding apparent K<sub>m</sub> values. The detailed protocols could be obtained from Millipore. In brief, recombinant kinases are incubated within appropriate buffer containing peptide substrate and radiolabelled <math>\gamma</math>-<sup>33</sup>P-ATP together with presence or absence of required inhibitor concentration. The reaction is initiated by adding</p>

<b>Kinase Assay</b>	ATP/Mg <sup>2+</sup> 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 $\gamma$ - <sup>33</sup> P-ATP. The phosphorylated substrate is then measured by scintillation counting, which determined the level of kinase activity inhibition compared to control reactions [1].
<b>References</b>	[1]. <u>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.</u>



源叶生物