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产品名称：AZD-9291 (mesylate)
产品别名：奥斯替尼甲磺酸盐；Osimertinib mesylate

生物活性：

Description

Osimertinib mesylate (AZD-9291 mesylate) is an irreversible and mutant selective EGFR inhibitor with IC_{50}s of 12 and 1 nM against $EGFR^{L858R}$ and $EGFR^{L858R/T790M}$, respectively.

IC_{50} & Target

$EGFR^{L858R/T790M}$	$EGFR^{L858R}$
1 nM (IC_{50})	12 nM (IC_{50})

In Vitro

Osimertinib (AZD-9291) shows similar potency to early generation tyrosine kinase inhibitor (TKIs) in inhibiting EGFR phosphorylation in EGFR cells harboring sensitising EGFR mutants including PC-9 (ex19del), H3255 (L858R) and H1650 (ex19del), with mean IC_{50} values ranging from 13 to 54 nM for Osimertinib. Osimertinib (AZD-9291) also potently inhibits phosphorylation of EGFR in T790M mutant cell lines (H1975 (L858R/T790M), PC-9VanR (ex19del/T790M), with mean IC_{50} potency less than 15 nM[1].

In Vivo

The tumor-bearing mice are treated with Osimertinib (AZD-9291) (5 mg/kg/day) for one to two weeks. Within days of treatment, 5 of 5 C/L858R mice displays nearly 80% reduction in tumor volume by magnetic resonance imaging MRI after therapy with Osimertinib, while 5 of 5 mice treated with vehicle shows tumor growth[1]. Osimertinib (AZD-9291) demonstrates improved rat PK, reduced hERG affinity, and improved IGF1R margins relative to the previously described compounds, and so this compound is selected for further investigation. Osimertinib (AZD-9291) also offers an additional degree of broader chemical and profile diversity when compared to the previously described lead compounds. Upon dosing Osimertinib (AZD-9291) in three efficacy models, The comparable efficacy is observed at relatively low doses (10 mg/kg per day). The excellent efficacy is also observed when Osimertinib (AZD-9291) is dosed at 5 mg/kg per day[2].

Solvent&Solubility

In Vitro:

DMSO : 20 mg/mL (33.57 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6787 mL	8.3933 mL	16.7867 mL
	5 mM	0.3357 mL	1.6787 mL	3.3573 mL
	10 mM	0.1679 mL	0.8393 mL	1.6787 mL

*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。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

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 In Vitro 方式配制澄清的储备液，再依次添加助溶剂：

——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

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

	Solubility: ≥ 2 mg/mL (3.36 mM); Clear solution 此方案可获得 ≥ 2 mg/mL (3.36 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 20.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline) Solubility: ≥ 2 mg/mL (3.36 mM); Clear solution 此方案可获得 ≥ 2 mg/mL (3.36 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 20.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。
References	[1]. Cross DA, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014 Sep;4(9):1046-61. [2]. Finlay MR, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistancemutations that spares the wild type form of the receptor. J Med Chem. 2014 Oct 23;57(20):8249-67.

实验参考：

Cell Assay	PC-9 cells are seeded into T75 flasks (5×10^5 cells/flask) in RPMI growth media and incubated at 37°C, 5% CO_2. The following day the media is replaced with media supplemented with a concentration of EGFR inhibitor equal to the EC_{50} concentration predetermined in PC-9 cells. Media changes are carried out every 2-3 days and resistant clones allowed to grow to 80% confluency prior to the cells being trypsinised and reseeded at the original seeding density in media containing twice the concentration of EGFR inhibitor. Dose escalations are continued until a final concentration of 1.5 μM ZD1839, 1.5 μM BIBW 2992, 1.5 μM WZ4002 or 160 nM Osimertinib (AZD-9291) are achieved[1].
Animal Administration	Mice[1] The $EGFR^{L858R}$ and $EGFR^{L858R+T790M}$ mice (male and female) are used. Osimertinib (AZD-9291) is suspended in 1% Polysorbate 80 and administered via oral gavage once daily at the doses of 7.5 mg/kg and 5 mg/kg, respectively. Mice are imaged weekly at the Vanderbilt University Institute of Imaging Science. For immunoblot analysis, mice are treated for eight hours with drug as described before dissection and flash freezing of the lungs. Lungs are pulverized in liquid nitrogen before lysis. Rats[2] The male RccHan:WIST rats (10-week-old) are received a single oral dose of Osimertinib (200 mg/kg). Blood glucose levels are measured using an Accuchek Active meter.
References	[1]. Cross DA, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014 Sep;4(9):1046-61. [2]. Finlay MR, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistancemutations that spares the wild type form of the receptor. J Med Chem. 2014 Oct 23;57(20):8249-67.