产品名称：**AZD9496**
产品别名：**AZD9496**

生物活性：

Description	AZD9496 is a potent and selective estrogen receptor (**ERα**) antagonist with an **IC_{50}** of 0.28 nM.
IC_{50} & Target	IC50: 0.28 nM (ERα antagonism), 0.14 nM (ERα downregulation), 0.82 nM (ERα binding)[1]
In Vitro	The potency of AZD9496 with IC50 of 0.82 nM, 0.14 nM, and 0.28 nM in ERα binding, downregulation, and antagonism, respectively. AZD9496 significantly inhibits MCF-7 cell growth with EC50 of 0.04 nM[1]. Selectivity of AZD9496 over other tested nuclear hormone receptors is high: androgen receptor (AR), IC50=30 μM; glucocorticoid receptor (GR), IC50=9.2 μM; progesterone receptor (PR), IC50=0.54 μM[2].
In Vivo	Significant tumor growth inhibition is observed as low as 0.5 mg/kg dose in the estrogen-dependent MCF-7 xenograft model, where this effect is accompanied by a dose-dependent decrease in PR protein levels, demonstrating potent antagonist activity. Combining AZD9496 with PI3K pathway and CDK4/6 inhibitors lead to further growth-inhibitory effects compared with monotherapy alone. AZD9496, given once daily orally at 5 and 25 mg/kg produced statistically significant increases in uterine weight compared with the fulvestrant control (P<0.001) but significantly lower than tamoxifen (P=0.001)[1]. AZD9496 is also tested in a long-term estrogen deprived model (LTED), using the HCC-1428 LTED cell line that grows in the absence of estrogen and is thought to best represent a model of aromatase inhibition. AZD9496 shows significant activity, with a dose of 5 mg/kg giving tumor regressions in this model[2].

Solvent&Solubility

In Vitro:

DMSO : ≥ 104.5 mg/mL (236.17 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.2600 mL	11.3002 mL	22.6004 mL
	5 mM	0.4520 mL	2.2600 mL	4.5201 mL
	10 mM	0.2260 mL	1.1300 mL	2.2600 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: ≥ 2.5 mg/mL (5.65 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (5.65 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 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: 2.5 mg/mL (5.65 mM); Suspended solution; Need ultrasonic 此方案可获得 2.5 mg/mL (5.65 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 25.0 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]. Weir HM, et al. AZD9496: An Oral Estrogen Receptor Inhibitor That Blocks the Growth of ER-Positive and ESR1-Mutant Breast Tumors in Preclinical Models. Cancer Res. 2016 Jun 1;76(11):3307-18. [2]. De Savi C, et al. Optimization of a Novel Binding Motif to (E)-3-(3,5-Difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)acrylic Acid (AZD9496), a Potent and Orally Bioavailable Selective Estrogen Receptor Downregulator and Antagonist. J Med Chem. 2015 Oct 22;58(20):8128-40.

实验参考：

Cell Assay	Effect of AZD9496, Fulvestrant, and Tamoxifen on ERα peptide turnover in MCF-7 cells. Cells are grown in steroid-free conditions in SILAC media containing 13C615N4 L-arginine to label ERα peptide as “heavy” (blue line) and then switched to grow in media containing unlabeled L-arginine to label newly synthesized protein as “normal” (red line) with 0.1% DMSO, 300 nM Tamoxife, 100 nM AZD9496, or 100 nM Fulvestrant for the time indicated. Data shown is representative of two independent experiments[1].
Animal Administration	Mice[1] In vivo efficacy of AZD9496 in MCF-7 xenograft model. MCF-7 xenografts, grown in male SCID mice, are dosed daily with either PEG/captisol (vehicle) or AZD9496 (0.02, 0.1, 0.5, 10, and 50 mg/kg, p.o., q.d.). Tumor growth is measured by caliper at regular intervals and mean tumor volumes plotted for each dosed group.
References	[1]. Weir HM, et al. AZD9496: An Oral Estrogen Receptor Inhibitor That Blocks the Growth of ER-Positive and ESR1-Mutant Breast Tumors in Preclinical Models. Cancer Res. 2016 Jun 1;76(11):3307-18. [2]. De Savi C, et al. Optimization of a Novel Binding Motif to (E)-3-(3,5-Difluoro-4-((1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)phenyl)acrylic Acid (AZD9496), a Potent and Orally Bioavailable Selective Estrogen Receptor Downregulator and Antagonist. J Med Chem. 2015 Oct 22;58(20):8128-40.