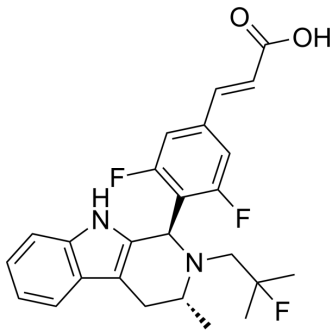
AZD9496

Cat. No.:	HY-12870
CAS No.:	1639042-08-2
Molecular Formula:	$C_{25}H_{25}F_3N_2O_2$
Molecular Weight:	442
Target:	Estrogen Receptor/ERR
Pathway:	Vitamin D Related/Nuclear Receptor
Storage:	4°C, protect from light, stored under nitrogen * In solvent : -80°C, 6 months; -20°C, 1 month (protect from light, stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 104.5 mg/mL (236.43 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	2.2624 mL	11.3122 mL	22.6244 mL
5 mM	0.4525 mL	2.2624 mL	4.5249 mL
10 mM	0.2262 mL	1.1312 mL	2.2624 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 (5.66 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.66 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

AZD9496 is a potent and selective estrogen receptor (ERα) antagonist with an IC_{50} of 0.28 nM. AZD9496 is an orally bioavailable selective oestrogen receptor degrader (SERD).

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 IC_{50} 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 EC_{50} of 0.04 nM[1]. Selectivity of AZD9496 over other tested nuclear hormone receptors is high: androgen receptor (AR), IC_{50}=30 μM; glucocorticoid receptor (GR), IC_{50}=9.2 μM; progesterone receptor (PR), IC_{50}=0.54 μM[2].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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 ICI 182780 control ($P<0.001$) but significantly lower than ICI 47699 ($P=0.001$)[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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Effect of AZD9496, ICI 182780, and ICI 47699 on ERα peptide turnover in MCF-7 cells. Cells are grown in steroid-free conditions in SILAC media containing $^{13}C_6{}^{15}N_4$ 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 ICI 182780 for the time indicated. Data shown is representative of two independent experiments[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cancer Res. 2017 Oct 15;77(20):5602-5613.
- Cell Prolif. 2019 Jul;52(4):e12612.
- Cell Commun Signal. 2019 Aug 14;17(1):94.
- Oncogene. 2018 Aug;37(33):4581-4598.
- Ecotoxicol Environ Saf. 2021 Apr 1;212:111991.

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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.

Caution: Product has not been fully validated for medical applications. For research use only.

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