AZD9496

Cat. No.: HY-12870
CAS No.: 1639042-08-2
Molecular Formula: C₂₅H₂₅F₃N₂O₂
Molecular Weight: 442.47
Target: Estrogen Receptor/ERR
Pathway: Others
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 (236.17 mM)
H₂O: < 0.1 mg/mL (insoluble)
* “≥” means soluble, but saturation unknown.

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Solvent Mass</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mM</td>
<td>2.2600 mL</td>
<td>11.3002 mL</td>
<td>22.6004 mL</td>
<td></td>
</tr>
<tr>
<td>5 mM</td>
<td>0.4520 mL</td>
<td>2.2600 mL</td>
<td>4.5201 mL</td>
<td></td>
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<tr>
<td>10 mM</td>
<td>0.2260 mL</td>
<td>1.1300 mL</td>
<td>2.2600 mL</td>
<td></td>
</tr>
</tbody>
</table>

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 (5.65 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.65 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description
AZD9496 is a potent and selective estrogen receptor (ERα) antagonist with an IC₅₀ of 0.28 nM. AZD9496 is an orally bioavailable selective oestrogen receptor degrader (SERD).

IC₅₀ & 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 ICI 182780 control (P<0.001) but significantly lower than ICI 47699 (P=0.001). 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.

**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.

**Animal Administration [1]**

Mice

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.

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**REFERENCES**

