**产品名称：1H-Indole-5-carbonitrile, 2-hydroxy-3-[5-(4-morpholinylmethyl)-2-pyridinyl]-**
**产品别名：AZD1080**

## 生物活性：

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| **Description** | AZD1080 is a potent and selective GSK3 inhibitor. AZD1080 inhibits recombinant human GSK3α and GSK3β with pKi (IC50) of 8.2 (6.9 nM) and 7.5 (31 nM), respectively. | | | | |
| **$IC_{50}$ & Target** [1] | GSK-3α | GSK-3β | cdk5 | cdk2 | cdk1 |
| | 8.2 (pKi) | 7.5 (pKi) | 6.4 (pKi) | 5.9 (pKi) | 5.7 (pKi) |
| **In Vitro** | AZD1080 shows selectivity against cdk2 (pKi=5.9; 1150 nM; 37-fold), cdk5 (pKi=6.4; 429 nM; 14-fold), cdk1 (pKi=5.7; 1980 nM; 64-fold) and Erk2 (pKi< 5; >10 μM; >323-fold). AZD1080 (at 10 μM) is also evaluated for pan-kinase selectivity and showed good overall selectivity versus 23 kinases, as well as against 65 different receptors, enzymes and ion channels in MDS Pharma screen (< 50% effect at 10 μM AZD1080). Concentration-dependent inhibition of tau phosphorylation is observed for AZD1080 (IC50=324 nM) and the non-selective reference GSK3 inhibitor LiCl (IC50=1.5 mM) indicating that AZD1080 is several orders of magnitude more potent than LiCl[1]. | | | | |
| **In Vivo** | The pharmacokinetic analysis in blood after oral administration revealed that AZD1080 has a good oral bioavailability in rats (15-24%) with a half-life of 7.1 h, making AZD1080 attractive for further in vivo testing. The subchronic (3 days) oral treatment with AZD1080 at 4 or 15 μmol/kg significantly blocked the MK-801-induced memory deficit (AZD1080 vs. MK-801, $p<0.05$ at 4 μmol/kg and $p<0.01$ at 15 μmol/kg) in mice, raising the hypothesis that longer treatment may be required to prime the synapses to function effectively[1]. | | | | |
| **Solvent&Solubility** | ***In Vitro:*** **DMSO : 21.35 mg/mL (63.85 mM; Need ultrasonic and warming)** | | | | |
| | **Preparing Stock Solutions** | **Solvent / Mass / Concentration** | **1 mg** | **5 mg** | **10 mg** |
| | | 1 mM | 2.9907 mL | 14.9535 mL | 29.9070 mL |
| | | 5 mM | 0.5981 mL | 2.9907 mL | 5.9814 mL |
| | | 10 mM | 0.2991 mL | 1.4953 mL | 2.9907 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。<br>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：<br>——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<br>Solubility: ≥ 2.5 mg/mL (7.48 mM); Clear solution<br>此方案可获得 ≥ 2.5 mg/mL (7.48 mM，饱和度未知) 的澄清溶液。<br>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。 | | | | |

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| | 2.请依序添加每种溶剂： 10% DMSO→ 90% (20% SBE-β-CD in saline)<br>Solubility: ≥ 2.5 mg/mL (7.48 mM); Clear solution<br>此方案可获得 ≥ 2.5 mg/mL (7.48 mM，饱和度未知) 的澄清溶液。<br>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]. Georgievska B, et al. AZD1080, a novel GSK3 inhibitor, rescues synaptic plasticity deficits in rodent brain and exhibits peripheral target engagement in humans. J Neurochem. 2013 May;125(3):446-56. |

**实验参考：**

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| **Animal Administration** | Mice[1]<br>A total of 161 male C57BL/6 mice, 8-12 weeks of age, are used. The animals are kept in conventional housing (3-5 mice per cage) and fed standard rodent chew and tap water ad libitum. Typically 9-12 mice are included in each experimental group and 2-4 mice in the satellite groups (for determination of compound exposure in plasma and brain, see below). AZD1080 (4.0 or 15 μmol/kg) or vehicle (water with 0.5% ascorbic acid, 0.01% EDTA, pH 2.0) is administered by oral gavage (10 mL/kg) acutely or subchronically (twice daily) for 3 days. The training trial is performed at 1.5, 3, or 5 h after final administration with AZD1080. To disrupt learning, the mice received subcutaneous administration of MK-801 (0.1 or 0.15 mg/kg; (+)-MK.801 hydrogen maleate) or vehicle (saline) 30 min before the training trial.<br>Rats[1]<br>A total of 71 adult male Sprague-Dawley rats (250-300 g) are used. The rats receive an acute dose of AZD1080 (1, 3 or 10 μmol/kg) or vehicle (water with 0.5% ascorbic acid, 0.01% EDTA, pH 2.0) via oral gavage (dosing volume 5 mL/kg). At 1, 2, 3, 6, or 24 h after administration the rats are anesthetized and blood, from abdominal aorta, is sampled in heparin micro tainer tubes. Peripheral blood mononuclear cells (PBMC) are isolated from the blood samples. Separate blood samples are obtained for plasma processing and subsequent bioanalysis. |
| **Kinase Assay** | The GSK3β, Cdk2, and Cdk5 Ki's are determined using scintillation proximity assays and kinetic analyses. The GSK3α assay is performed for the GSK3β assay. The KM value of ATP used to calculate the Ki value for GSKα is 10 μM. Inhibition of Cdk1 is performed. The KM value of ATP used to calculate the Ki value is 51 μM. Erk2 activity is determined using an Ser/Thr kinase SPA kit, p42 MAPK kinase (20 U/well), and biotinylated MBP. The KM value of ATP used to calculate the Ki value is 71 μM[1]. |
| **References** | [1]. Georgievska B, et al. AZD1080, a novel GSK3 inhibitor, rescues synaptic plasticity deficits in rodent brain and exhibits peripheral target engagement in humans. J Neurochem. 2013 May;125(3):446-56. |