

产品名称:

**4-(1-isopropyl-2-methyl-1H-imidazol-5-yl)-N-(4-(methylsulfonyl)phenyl)pyrimidin-2-amine**

产品别名: **AZD-5438**

生物活性:							
Description	AZD-5438 is a potent inhibitor of CDK1/2/9 with IC <sub>50</sub> of 16 nM/6 nM/20 nM in cell-free assays. It also inhibits GSK3β, but is less potent to CDK5/6.						
IC <sub>50</sub> & Target [1]	cdk2-cyclin E	cdk2-cyclin A	cdk5-p25	cdk1-cyclin B1	cdk9-cyclin T	cdk6-cyclin D3	
	6 nM (IC <sub>50</sub> )	45 nM (IC <sub>50</sub> )	14 nM (IC <sub>50</sub> )	16 nM (IC <sub>50</sub> )	20 nM (IC <sub>50</sub> )	21 nM (IC <sub>50</sub> )	
	cdk4-cyclin D1	cdk7-cyclin H					
	449 nM (IC <sub>50</sub> )	821 nM (IC <sub>50</sub> )					
In Vitro	AZD5438 potently inhibits the kinase activity of cyclin E-cdk2, cyclin A-cdk2, cyclin B1-cdk1, p25-cdk5, cyclin D3-cdk6, and cyclin T-cdk9 (IC <sub>50</sub> , 6, 45, 16, 21, and 20 nM, respectively). AZD5438 potently inhibits the kinase activity of cyclin E-cdk2, cyclin A-cdk2, cyclin B1-cdk1, p25-cdk5, cyclin D3-cdk6, and cyclin T-cdk9 (IC <sub>50</sub> , 6, 45, 16, 21, and 20 nM, respectively). In common with many other cdk inhibitors, AZD5438 also inhibits the kinase activity of p25-cdk5 and glycogen synthase kinase 3β in vitro (IC <sub>50</sub> , 14 and 17 nM, respectively)[1]. AZD5438 significantly augments cellular radiosensitivity in NSCLC cells. Combined treatment with AZD5438 and irradiation also enhances tumor growth delay, with an enhancement factor ranging from 1.2-1.7[2].						
In Vivo	AZD5438 (50 mg/kg twice daily or 75 mg/kg, p.o.) inhibits human tumor xenograft growth. In vivo, AZD5438 reduces the proportion of actively cycling cells. Further pharmacodynamic analysis of AZD5438-treated SW620 xenografts shows that efficacious doses of AZD5438 (>40% tumor growth inhibition) maintains suppression of biomarkers, such as phospho-pRbSer249/Thr252, for up to 16 hours following a single oral dose[1].						
Solvent&Solubility	<b>In Vitro:</b> <b>DMSO : 100 mg/mL (269.21 mM; Need ultrasonic)</b>						
	<div><div></div><div>Solvent</div><div>Mass</div><div>Concentration</div></div>			1 mg	5 mg	10 mg	
		Preparing		1 mM	2.6921 mL	13.4604 mL	26.9208 mL
		Stock Solutions		5 mM	0.5384 mL	2.6921 mL	5.3842 mL
				10 mM	0.2692 mL	1.3460 mL	2.6921 mL
	<p>*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。</p> <p>储备液的保存方式和期限：-80℃，6 months；-20℃，1 month。 -80℃ 储存时，请在 6 个月内使用，-20℃ 储存时，请在 1 个月内使用。</p> <p><b>In Vivo:</b></p> <p>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 <b>In Vitro</b> 方式配制澄清的储备液，再依次添加助溶剂：</p> <p>——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</p> <p>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</p>						

	<p>Solubility: <math>\geq 2.5</math> mg/mL (6.73 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (6.73 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 400 <math>\mu</math>L PEG300 中, 混合均匀向上述体系中加入 50 <math>\mu</math>L Tween-80, 混合均匀; 然后继续加入 450 <math>\mu</math>L 生理盐水定容至 1 mL。</p> <p>2.请依序添加每种溶剂: 10% DMSO<math>\rightarrow</math> 90% (20% SBE-<math>\beta</math>-CD in saline)</p> <p>Solubility: <math>\geq 2.5</math> mg/mL (6.73 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (6.73 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 20% 的 SBE-<math>\beta</math>-CD 生理盐水中, 混合均匀。</p> <p>3.请依序添加每种溶剂: 10% DMSO <math>\rightarrow</math> 90% corn oil</p> <p>Solubility: <math>\geq 2.5</math> mg/mL (6.73 mM); Clear solution</p> <p>此方案可获得 <math>\geq 2.5</math> mg/mL (6.73 mM, 饱和度未知) 的澄清溶液, 此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例, 取 100 <math>\mu</math>L 25.0 mg/mL 的澄清 DMSO 储备液加到 900 <math>\mu</math>L 玉米油中, 混合均匀。</p>
References	<p>[1]. Byth KF, et al. AZD5438, a potent oral inhibitor of cyclin-dependent kinases 1, 2, and 9, leads to pharmacodynamic changes and potent antitumor effects in human tumor xenografts. Mol Cancer Ther. 2009 Jul;8(7):1856-66. Epub 2009 Jun 9.</p> <p>[2]. Raghavan P, et al. AZD5438, an Inhibitor of Cdk1, 2, and 9, Enhances the Radiosensitivity of Non-Small Cell Lung Carcinoma Cells. Int J Radiat Oncol Biol Phys. 2012 Jul 12.</p>
实验参考:	
Cell Assay	<p>AZD5438 is tested against solid tumor cell lines as previously described. Briefly, cells are incubated for 48 h with AZD5438 at a range of concentrations. At the end of incubation, the cells are pulsed with 5-bromo-2'-deoxyuridine (BrdUrd) and the amount of DNA synthesis is measured. The IC<sub>50</sub> for inhibition of proliferation is specifically determined independently of cell death. Multiple myeloma cell lines are seeded into 96-well plates in RPMI 1640 supplemented with 10% FCS and glutamine and dosed with AZD5438 for 72 h. Cell growth is measured using AlamarBlue and GI<sub>50</sub> values are calculated with reference to pretreatment control values. [1]</p>
Animal Administration	<p>All human tumor xenografts except HX147 are established by s.c. injecting 100 <math>\mu</math>L of tumor cells (between <math>1 \times 10^6</math> and <math>1 \times 10^7</math> cells mixed 1:1 with Matrigel). HX147 tumors are derived from fragment implants (1 mm<sup>3</sup> pieces) from tumors taken from mice initially implanted s.c. with <math>1 \times 10^7</math> cells. These tumor fragments are passaged in mice thrice before implant for antitumor work. Tumors are measured up to three times per week with calipers, tumor volumes are calculated, and the data are plotted as geometric mean for each group versus time, as previously described. Animals are randomized into treatment groups (typically n=10) when tumors reach a mean size of approximately <math>&gt;0.2</math> cm<sup>3</sup> and <math>&gt;0.5</math> cm<sup>3</sup> for mice and rats, respectively. AZD5438 is prepared in hydroxy-propyl-methyl-cellulose. Animals are given either AZD5438 (37.5-75 mg/kg) or vehicle control once or twice daily by oral gavage for appr 3 wk in each case. Tumor volume and percentage tumor growth inhibition (% TGI) are calculated as described previously. Statistical analysis of any change in tumor volume is carried out using a standard t test (P&lt;0.05 is considered to be statistically significant). [1]</p>
	<p>[1]. Byth KF, et al. AZD5438, a potent oral inhibitor of cyclin-dependent kinases 1, 2, and 9, leads to</p>

<b>References</b>	<p><u>pharmacodynamic changes and potent antitumor effects in human tumor xenografts. Mol Cancer Ther. 2009 Jul;8(7):1856-66. Epub 2009 Jun 9.</u></p> <p>[2]. <u>Raghavan P, et al. AZD5438, an Inhibitor of Cdk1, 2, and 9, Enhances the Radiosensitivity of Non-Small Cell Lung Carcinoma Cells. Int J Radiat Oncol Biol Phys. 2012 Jul 12.</u></p>
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源叶生物