

产品名称:

1-(2-((S)-piperidin-3-ylcarbamoyl)-5-(3-fluorophenyl)thiophen-3-yl)urea

产品别名: **AZD-7762**

生物活性:

Description	AZD-7762 is a potent ATP-competitive checkpoint kinase (Chk) inhibitor in with an IC ₅₀ of 5 nM for Chk1.				
IC ₅₀ & Target	Chk1	Chk2			
	5 nM (IC ₅₀)	5 nM (IC ₅₀)			
In Vitro	AZD-7762 (AZD7762) is an equally potent inhibitor of Chk1 and Chk2 in vitro. AZD-7762 potently inhibits Chk1 and Chk2, abrogates DNA damage-induced S and G ₂ checkpoints, enhances the efficacy of NSC 613327 and SKF 104864A, and modulates downstream checkpoint pathway proteins. AZD-7762 potently inhibits Chk1 phosphorylation of a cdc25C peptide with an IC ₅₀ of 5 nM as measured by a scintillation proximity assay. The K _i for AZD-7762 is determined to be 3.6 nM. Kinetic characterization suggests that AZD-7762 binds in the ATP-binding site of Chk1 and is thought to compete directly for ATP binding in a reversible manner. AZD-7762 is shown to abrogate the G ₂ arrest induced by Camptothecin with an average EC ₅₀ of 10 nM (n=12) and maximal abrogation in the range of 100 nM[1].				
In Vivo	In the rat H460-DNp53 xenograft study, AZD-7762 (AZD7762) potentiates the antitumor activity of NSC 613327 in a dose-dependent manner by a decrease in %T/C with increasing dose (48% and 32%, 10 and 20 mg/kg AZD-7762, respectively). In the mouse xenograft study in combination with CPT-11, SW620 established tumors are treated with vehicle, CPT-11 alone, AZD-7762 alone, or AZD-7762 in combination with CPT-11. AZD-7762 dosed alone shows insignificant antitumor activity, whereas CPT-11 alone displays striking and significant activity (%T/C with increasing dose is 9 and 1, respectively). In combination with AZD-7762, %T/C increases significantly to -66% and -67%, respectively[1]. AZD7762 combination with CX-5461 induces cancer cell death of Tp53-null (Tp53-/-) Eμ-Myc lymphoma cells in vitro and in vivo[2].				
Solvent&Solubility	In Vitro: DMSO : 100 mg/mL (275.92 mM; Need ultrasonic)				
		Solvent Concentration	Mass		
	Preparing Stock Solutions	1 mM	2.7592 mL	13.7961 mL	27.5923 mL
		5 mM	0.5518 mL	2.7592 mL	5.5185 mL
		10 mM	0.2759 mL	1.3796 mL	2.7592 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℃, 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。				
	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 (6.90 mM); Clear solution				

	<p>此方案可获得 ≥ 2.5 mg/mL (6.90 mM, 饱和度未知) 的澄清溶液。</p> <p>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。</p> <p>2.请依序添加每种溶剂: 10% DMSO\rightarrow 90% (20% SBE-β-CD in saline)</p> <p>Solubility: ≥ 2.5 mg/mL (6.90 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.90 mM, 饱和度未知) 的澄清溶液。</p> <p>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。</p> <p>3.请依序添加每种溶剂: 10% DMSO \rightarrow90% corn oil</p> <p>Solubility: ≥ 2.5 mg/mL (6.90 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.90 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 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中, 混合均匀。</p>
References	<p>[1]. Zabludoff SD, et al. AZD7762, a novel checkpoint kinase inhibitor, drives checkpoint abrogation and potentiates DNA-targeted therapies. <i>Mol Cancer Ther.</i> 2008 Sep;7(9):2955-66.</p> <p>[2]. Quin J, et al. Inhibition of RNA polymerase I transcription initiation by CX-5461 activates non-canonical ATM/ATR signaling. <i>Oncotarget.</i> 2016 Aug 2;7(31):49800-49818.</p>
实验参考:	
Cell Assay	<p>SW620 (5.5×10^3 per well) or MDA-MB-231 (5×10^3 per well) cells are seeded in 96-well plates and incubated overnight. Cells are dosed for 24 h with a 9-point titration of NSC 613327 ranging from 0.01 to 100 nM with or without a constant dose of AZD-7762 (300 nM). Control wells are dosed with vehicle alone (0.1% DMSO) or 300 nM AZD-7762. After 24 h, medium is removed and AZD-7762 alone is added back to the wells treated previously with AZD-7762 for an additional 24 h. Cells are then incubated in drug-free medium for an additional 72 h. The effect on cell proliferation is determined by MTS assay[1].</p>
Animal Administration	<p>Mice and Rats[1]</p> <p>Male NCr mice and male rnu rats are used. For xenograft models in mice, tumor cells are harvested, pelleted by centrifugation for 5 min, and resuspended in sterile PBS. Cells (3×10^3-6×10^6) are implanted s.c. into the right flank of the mice in a volume of 0.1 to 0.2 mL using a 25-gauge needle. Tumors are allowed to grow to the designated size of 100 to 200 mm³ before the administration of compound. For xenograft models in rats, Cells are harvested, pelleted by centrifugation for 5 min, and resuspended in 50% sterile PBS and 50% Matrigel. Rats receive a 5 Gy whole-body radiation dose 5 days before cell implantation to improve tumor growth. H460-DNp53 cells (1×10^7) are implanted s.c., into the right flank of the rats in a volume of 0.2 mL using a 25-gauge needle. Tumors are allowed to grow to the designated size of 100 to 200 mm³ before the administration of AZD-7762. AZD-7762 (10 and 20 mg/kg) is administered by i.v. injection via the tail vein. Cyclic schedules are used and treatment ranged from three to five cycles. Each cycle includes administration of a standard agent (NSC 613327 or CPT-11) every 3 days follow by delivery of AZD-7762. Tumor volumes are measured with electronic calipers and calculated.</p> <p>Mice [2]</p> <p>C57Bl/6 mice are intravenously injected with 2×10^5 Eμ-Myc B-lymphoma cells in PBS and treated</p>

	<p>with pharmacological inhibitors from 8 days post-injection. Treatment of mice is continued until an ethical end-point is reached; hunched posture, ruffled fur, enlarged lymph nodes, laboured breathing, weight loss greater than 20% of start body weight and limited mobility or paralysis.</p> <p>AZD7762 is delivered intraperitoneally in 10.3% -hydroxypropyl-β-cyclodextrin in 0.9% saline at 20 mg/kg daily on weekdays.</p>
References	<p>[1]. <u>Zabludoff SD, et al. AZD7762, a novel checkpoint kinase inhibitor, drives checkpoint abrogation and potentiates DNA-targeted therapies. Mol Cancer Ther. 2008 Sep;7(9):2955-66.</u></p> <p>[2]. <u>Quin J, et al. Inhibition of RNA polymerase I transcription initiation by CX-5461 activates non-canonical ATM/ATR signaling. Oncotarget. 2016 Aug 2;7(31):49800-49818.</u></p>



源叶生物