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产品名称：PYZD-4409
产品别名：PYZD-4409

生物活性：		
Description	PYZD-4409 is a specific inhibitor of the ubiquitin-activating enzyme UBA1 with an IC50 of 20 μM (cell-free enzymatic assay). PYZD-4409 induces cell death in malignant cells and preferentially inhibits the clonogenic growth of primary acute myeloid leukemia cells[1].	
IC_{50} & Target	IC50: 20 μM (ubiquitin-activating enzyme UBA1)[1]	
In Vitro	PYZD-4409 (10-40 μM; 72 hours; myeloma, leukemia, and solid tumor cell lines, primary AML cells and normal hematopoietic cells) induces cell death with a **LD_{50}** less than 10 μM in 5 of 8 leukemia and myeloma cell lines. In contrast, solid tumor cell lines were less sensitive with an **LD_{50}** of approximately 15 to 20 μM. PYZD-4409 is preferentially cytotoxic to malignant cells over normal hematopoietic cells[1]. PYZD-4409 (50 μM; 4 hours; K562 leukemia cells) treatment blocks the E1-dependent conjugation of ubiquitin to the E2 enzyme cdc34[1]. PYZD-4409 (0-25 μM; 24 hours; K562 leukemia cells) significantly increases both mRNA and protein levels of Grp78 and Hsp70. In addition, PYZD-4409 increases levels of phospho-JNK and phospho-p38 mitogen-activated protein kinase, which have also been linked to ER stress and the unfolded protein response[1].	
	Cell Cytotoxicity Assay[1]	
	Cell Line:	Myeloma, leukemia, and solid tumor cell lines, primary AML cells and normal hematopoietic cells
	Concentration:	10 μM, 20 μM, 30 μM, 40 μM
	Incubation Time:	72 hours
	Result:	Induced cell death with a **LD_{50}** less than 10 μM in 5 of 8 leukemia and myeloma cell lines. In contrast, solid tumor cell lines were less sensitive with an **LD_{50}** of approximately 15 to 20 μM.
	Western Blot Analysis[1]	
	Cell Line:	K562 leukemia cells
	Concentration:	50 μM
	Incubation Time:	4 hours
	Result:	Blocked the E1-dependent conjugation of ubiquitin to the E2 enzyme cdc34.
	RT-PCR[1]	
	Cell Line:	K562 cells
	Concentration:	0 μM, 10 μM, 25 μM
	Incubation Time:	24 hours
	Result:	Significantly increased both mRNA and protein levels of Grp78 and Hsp70.
In Vivo	PYZD-4409 (10 mg/kg; intraperitoneal injection; daily on alternate days; for 16 days; male severe combined immunodeficient mice) decreases tumor weight and volume without untoward toxicity[1].	
	Animal Model:	Male severe combined immunodeficient (SCID) mice with MDAY-D2 murine leukemia cells[1]
	Dosage:	10 mg/kg

<table>
<tr><td></td><td>Administration:</td><td colspan="4">Intraperitoneal injection; daily on alternate days; for 16 days</td></tr>
<tr><td></td><td>Result:</td><td colspan="4">Delayed tumor growth and decreased tumor weight without untoward toxicity.</td></tr>
<tr><td>Solvent&Solubility</td><td colspan="5">In Vitro:
DMSO : ≥ 35 mg/mL (99.53 mM)
* "≥" means soluble, but saturation unknown.</td></tr>
<tr><td rowspan="4">Preparing Stock Solutions</td><td>Solvent / Mass / Concentration</td><td>1 mg</td><td>5 mg</td><td>10 mg</td></tr>
<tr><td>1 mM</td><td>2.8436 mL</td><td>14.2179 mL</td><td>28.4357 mL</td></tr>
<tr><td>5 mM</td><td>0.5687 mL</td><td>2.8436 mL</td><td>5.6872 mL</td></tr>
<tr><td>10 mM</td><td>0.2844 mL</td><td>1.4218 mL</td><td>2.8436 mL</td></tr>
<tr><td colspan="5">*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°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：
——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 (7.11 mM); Clear solution
此方案可获得 ≥ 2.5 mg/mL (7.11 mM，饱和度未知) 的澄清溶液。
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。</td></tr>
<tr><td>References</td><td colspan="5">[1]. Xu GW, et al. The ubiquitin-activating enzyme E1 as a therapeutic target for the treatment of leukemia and multiple myeloma. Blood. 2010 Mar 18;115(11):2251-9.</td></tr>
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