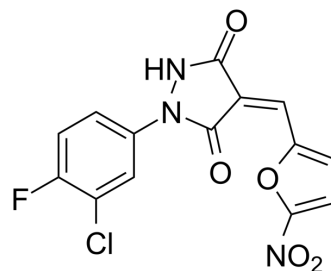


PYZD-4409

Cat. No.:	HY-13297		
CAS No.:	423148-78-1		
Molecular Formula:	C ₁₄ H ₇ ClFN ₃ O ₅		
Molecular Weight:	351.67		
Target:	E1/E2/E3 Enzyme		
Pathway:	Metabolic Enzyme/Protease		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	2 years
		-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 35 mg/mL (99.53 mM)
 * "≥" means soluble, but saturation unknown.

Concentration	Solvent	Mass		
		1 mg	5 mg	10 mg
Preparing Stock Solutions	1 mM	2.8436 mL	14.2179 mL	28.4357 mL
	5 mM	0.5687 mL	2.8436 mL	5.6872 mL
	10 mM	0.2844 mL	1.4218 mL	2.8436 mL

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 (7.11 mM); Clear solution

BIOLOGICAL ACTIVITY

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].

IC₅₀ & 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 LD₅₀ less than 10 μM in 5 of 8 leukemia and myeloma cell lines. In contrast, solid tumor cell lines were less sensitive with an LD₅₀ 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 μ M; 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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Cytotoxicity Assay^[1]

Cell Line:	Myeloma, leukemia, and solid tumor cell lines, primary AML cells and normal hematopoietic cells
Concentration:	10 μ M, 20 μ M, 30 μ M, 40 μ M
Incubation Time:	72 hours
Result:	Induced cell death with a LD ₅₀ less than 10 μ M 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 μ M.

Western Blot Analysis^[1]

Cell Line:	K562 leukemia cells
Concentration:	50 μ M
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 μ M, 10 μ M, 25 μ M
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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male severe combined immunodeficient (SCID) mice with MDAY-D2 murine leukemia cells [1]
Dosage:	10 mg/kg
Administration:	Intraperitoneal injection; daily on alternate days; for 16 days
Result:	Delayed tumor growth and decreased tumor weight without untoward toxicity.

CUSTOMER VALIDATION

- Mol Cell Biol. 2018 Jul 16;38(15). pii: e00024-18.

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REFERENCES

[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.

Caution: Product has not been fully validated for medical applications. For research use only.

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