# PYZD-4409

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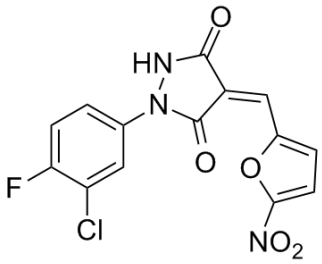
| **Cat. No.:** | HY-13297 |
| **CAS No.:** | 423148-78-1 |
| **Molecular Formula:** | $C_{14}H_7ClFN_3O_5$ |
| **Molecular Weight:** | 351.67 |
| **Target:** | E1/E2/E3 Enzyme |
| **Pathway:** | Metabolic Enzyme/Protease |
| **Storage:** | Powder -20°C 3 years<br>4°C 2 years<br>In solvent -80°C 6 months<br>-20°C 1 month |




## SOLVENT & SOLUBILITY

**In Vitro**

DMSO : ≥ 35 mg/mL (99.53 mM)

* "≥" means soluble, but saturation unknown.

| Preparing Stock Solutions | Mass / Solvent / Concentration | 1 mg | 5 mg | 10 mg |
|---|---|---|---|---|
| | 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 $IC_{50}$ 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].

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

Cell Cytotoxicity Assay[1]

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| 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]

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| 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]

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| 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].

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

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| 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. |

## 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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