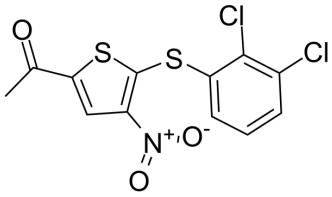
P005091

Cat. No.:	HY-15667
CAS No.:	882257-11-6
Molecular Formula:	$C_{12}H_7Cl_2NO_3S_2$
Molecular Weight:	348.22
Target:	Deubiquitinase
Pathway:	Cell Cycle/DNA Damage
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

1-Methyl-2-pyrrolidinone : 100 mg/mL (287.17 mM; Need ultrasonic)
DMSO : 25 mg/mL (71.79 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.8717 mL	14.3587 mL	28.7175 mL
5 mM	0.5743 mL	2.8717 mL	5.7435 mL
10 mM	0.2872 mL	1.4359 mL	2.8717 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 4% NMP >> 3% Tween-80 >> 20% PEG400 >> 73% ddH2O
   Solubility: 8 mg/mL (22.97 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (7.18 mM); Suspended solution; Need ultrasonic and warming
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (7.18 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	P005091 is a selective and potent inhibitor of ubiquitin-specific protease 7 (USP7) with an EC_{50} of 4.2 μM.
IC_{50} & Target	EC50: 4.2 μM (USP7)
In Vitro	P005091 is a trisubstituted thiophene with dichlorophenylthio, nitro, and acetyl substituents mediating anti-USP7 activity. P005091 exhibits potent, specific, and selective deubiquitylating activity against USP7. In contrast, P005091 does not inhibit

	other DUBs or other families of cysteine proteases tested (EC_{50} > 100 mM). P005091 inhibits the labeling of USP7 with HA-UbVME in a concentration-dependent manner. USP7-mediated cleavage of high molecular weight polyubiquitin chains is inhibited in a dose-dependent manner by P005091. Moreover, P005091 inhibits USP7- but not USP2- or USP8-mediated cleavage of poly K48-linked ubiquitin chains. USP7 inhibition by P005091 induces HDM2 polyubiquitylation and accelerates degradation of HDM2. P005091 inhibits USP7 deubiquitylating activity, without blocking proteasome activity in MM Cells. P005091 inhibits growth in MM cells and overcomes bortezomib-resistance. P005091 induces a dose-dependent decrease in viability of various MM cell lines, including those that are resistant to conventional therapies dexamethasone (Dex) (MM.1R), doxorubicin (Dox-40), or melphalan (LR5) (IC_{50} range 6-14 μM). P005091 overcomes bone marrow stromal cell-induced growth of MM Cells. P005091 decreases HDM2 and HDMX, as well as upregulated p53 and p21 levels. Overall, P005091-induced cytotoxicity is mediated in part via HDM2-p21 signaling axis and although p53 is upregulated in response to P005091 treatment, the cytotoxic activity of P005091 is not dependent on p53[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In animal tumor model studies, P005091 is well tolerated, inhibits tumor growth, and prolongs survival. Combining P005091 with lenalidomide, HDAC inhibitor SAHA, or dexamethasone triggers synergistic anti-MM activity[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Recombinant enzymes in 20 mM Tris-HCl (pH 8.0), 2 mM $CaCl_2$, and 2 mM β-mercaptoethanol are incubated with dose ranges of P005091 for 30 min in a 96-well plate before the addition of Ub-PLA2 and NBD C6-HPC or Ub-EKL and EKL substrate. The liberation of a fluorescent product within the linear range of the assay is monitored using a Perkin Elmer Envision fluorescence plate reader. Vehicle (2% [v/v] DMSO) and 10 mM N-ethylmaleimide (NEM) are included as controls. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	For the animal study, P005091 is dissolved in 4% NMP(N-methyl-2-Pyrrolidone), 4% Tween-80, and 92% Milli-Q water at a final concentration of 2 mg/mL. The human plasmacytoma xenograft model is performed as previously described. CB-17 SCID-mice are subcutaneously inoculated with MM.1S, ARP-1, or RPMI-8226 cells in 100 μL of serum free RPMI-1640 medium. When tumors are measurable (100-180 mm^3), mice are randomized into treatment groups. In the SCID-hu model, human fetal bone grafts are subcutaneously implanted into SCID mice. Four weeks after bone implantation, INA-6 cells are injected directly into the fetal bone implant in SCID mice; and as a measure of tumor burden, mouse sera samples are analyzed for shIL-6R by ELISA. Upon detection of shIL-6R, mice are treated with vehicle or P005091, and mouse serum is analyzed for alterations in shIL-6R levels. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Commun. 2023 Feb 9;14(1):731.
- Theranostics. 2022 May 16;12(9):4348-4373.
- EMBO J. 2022 Jul 11;e108791.
- J Exp Clin Cancer Res. 2019 Nov 15;38(1):468.
- EBioMedicine. 2024 Jan 9:100:104961.

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REFERENCES

[1]. Chauhan D, et al. A small molecule inhibitor of ubiquitin-specific protease-7 induces apoptosis in multiple myeloma cells and overcomes bortezomib resistance. Cancer Cell. 2012 Sep 11;22(3):345-58.

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