

Product Data Sheet

Product Name: Sephin1
Cat. No.: GC12498

Chemical Properties

Cas. No. 13098-73-2

Chemical Name (E)-2-(2-chlorobenzylidene)hydrazinecarboximidamide

SMILES C1C=CC=CC=C1/C=N/NC(N)=N

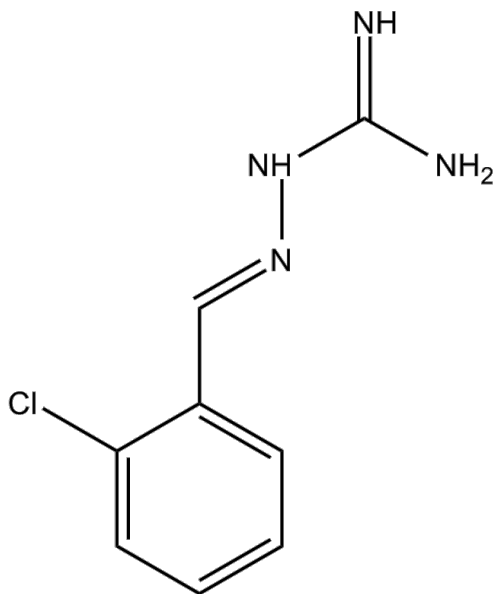
Formula $C_8H_9ClN_4$ M.Wt 196.64

Solubility $\geq 7.75\text{mg/mL}$ in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice. All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

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

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Cell lines HeLa and 293T cells

Limited solubility. General tips for obtaining a higher concentration: Please warm Preparation method the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Reaction Conditions 6 h

Applications Sephin1 selectively disrupts the PPP1R15A-PP1c complex but leave the related PPP1R15B-PP1c complex unaffected. Thus Sephin1 prolongs eIF2a phosphorylation after stress, delays translation recover and attenuates expression of stress genes such as pro-apoptotic protein-CHOP.

Animal experiment [1]:

Animal models SOD1 mice SOD1G93A in C57BL/6J

Dosage form 5 mg/kg

Applications The progressive weight loss of SOD1 mutant mice and their motor deficits are almost completely prevented by 5 mg/kg of Sephin1 once a day, without adverse effects on weight gain or motor performance of wild-type mice. Sephin1 also prevents the motor deficits of SOD1 mutant mice that associated with motor neuron loss.

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Other notes Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

1. Das I, Krzyzosiak A, Schneider K et al. Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit. Science. 2015 Apr 10;348(6231):239-42.

Background

Sephin1 is a selective inhibitor of stress-induced PPP1R15A and targets disease associated with accumulation of misfolded protein. [1]

PPP1R15A is a regulator subunit of protein phosphatase 1 and regulates stress-induced eIF2 α (α subunit of eukaryotic translation initiation factor 2). It brings PP1 (serine/threonine-protein phosphatase) to dephosphorylate eIF2 α . Phosphorylation of eIF2 α reduces protein synthesis and prevents the accumulation of misfolded protein in ER (endoplasmic reticulum). Thus inhibiting PPP1R15A prolongs the phosphorylation of eIF2 α , and benefits the treatment for protein misfolding disease. [1]

In cells treated with 5 μ m Sephin1 for 6 hours, Sephin1 specifically disrupted the PPP1R15A-PP1c complex without affecting PPP115B-PP1c complex. As a consequence, Sephin1 prolonged eIF2 α phosphorylation in HeLa cells after stress (*2.5 μ g/ml tunicamycin treatment) and delayed translational recovery. Sephin1 rescued cell from cytotoxic ER stress* in wild-type cell but not the PPP1R15A mutant cell. [1]

In mice administrated orally with 1-5mg/kg Sephin1 for given time, Sephin1 exhibited no adverse effects on rotarod performances, total body weight gain or memory. Treating MPZ (Deletion of serine 63 of myelin protein zero) mutant mice with 1mg/kg orally twice a day, prevented the molecular, morphological and motor defects. Oral treatment of 5 mg/kg of Sephin1 once a day, prevented motor deficits, motor neuron loss and the molecular defects in SOD1 (Mutant and misfolding-prone superoxide dismutase 1) mutant mice. [1]

Reference:

[1].Das I, Krzyzosiak A, Schneider K, Wrabetz L, D'Antonio M, Barry N, Sigurdardottir A, Bertolotti A.

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