

Product Data Sheet

Product Name: Siramesine hydrochloride

Cat. No.: GC15222

Chemical Properties

Cas. No. 224177-60-0

Chemical Name 1'-(4-(1-(4-fluorophenyl)-1H-indol-3-yl)butyl)-3H-spiro[isobenzofuran-1,4'-piperidine] hydrochloride

SMILES FC1=CC=C(N2C=C(C3=CC=CC=C32)CCCCN4CCC5(C6=CC=CC=C6CO5)CC4)C=C1.Cl

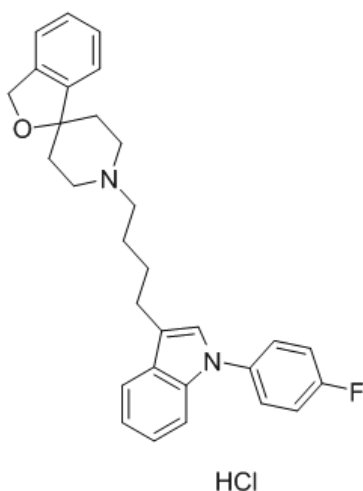
Formula $C_{30}H_{32}ClFN_2O$ M.Wt 491.04

Solubility >49.1mg/mL in DMSO Storage Desiccate 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]:

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Cell lines HaCaT cell

Preparation Method Cells were plated onto a 24-well plate at 0.5×10^5 cells per well and grown overnight before the experiment. Siramesine was dissolved in DMSO to make a 20mM stock solution, which was then diluted in complete culture medium to the final concentrations used. Inhibitors and antioxidants were applied 2 hours before the Siramesine treatment. After the cells were incubated with the diluted celecoxib for 8 hours, cell viability, cysteine aspartic acid protease activity, and cathepsin activity were measured. The integrity of lysosomal and mitochondrial membranes was determined by flow cytometry.

Reaction
Conditions 5–40 μ M; 8 hours

Applications Siramesine can induce rapid cell death in a number of cell lines at concentrations above 20 μ M. In HaCaT cells, cell death was accompanied by caspase activation, rapid loss of mitochondrial membrane potential (MMP), cytochrome c release, cardiolipin peroxidation and typical apoptotic morphology.

Animal experiment [2]:

Animal models C57/bl6 mice

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Examined the effect of the sigma-2 receptor agonist Siramesine on cocaine-associated locomotion, Pavlovian learning, and reward neurocircuitry using electrophysiology recordings and in vivomicrodialysis.

1. Siramesine and BD 1063 was dissolved in saline using 1% Tween80 and subsequent sonication for 10min.
2. Mice received either saline, Siramesine (0.3 or 1mg/kg) 10 or 60 min before an acute 15mg/kg cocaine injection. Subsequently, the movement behavior of the

Preparation Method animals were monitored for 30min.

3. Administered Siramesine (0.1, 0.3, or 1mg/kg) 60min prior to the cocaine training sessions to acquisition of Cocaine-Associated Place Preference.
4. Siramesine (1.75µM in 0.001% Tween 80) was bath applied to test the effect on spontaneous and evoked excitatory postsynaptic currents (EPSCs).
5. The mice were injected with 0.3mg/kg of cilazapride and then 15mg/kg of cocaine. Subsequently, the dopamine levels in the striatum were detected through in vivo microdialysis technique.

Dosage form 0.1, 0.3, and 1mg/kg/day for 3 days; i.p.

Applications Via in vivomicrodialysis, Siramesine significantly decreased cocaine-evoked dopamine release in the striatum of freely moving mice.

References:

- [1] Cesen MH, Repnik U, Turk V, Turk B. Siramesine triggers cell death through destabilisation of mitochondria, but not lysosomes. Cell Death Dis. 2013 Oct 3;4(10):e818.
- [2] Klawonn AM, Nilsson A, Rådberg CF, Lindström SH, Ericson M, Granseth B, Engblom D, Fritz M. The Sigma-2 Receptor Selective Agonist Siramesine (Lu 28-179) Decreases Cocaine-Reinforced Pavlovian Learning and Alters Glutamatergic and Dopaminergic Input to the Striatum. Front Pharmacol. 2017 Oct 10;8:714.

Background

Siramesine hydrochloride is an effective sigma-2 receptor agonist. Siramesine has an annanometer-

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level affinity for the sigma-2 receptor ($IC_{50} = 0.12nM$), and its selectivity for the sigma-2 receptor is 140 times that of the sigma-1 receptor ($IC_{50} = 17nM$) [1]. The sigma-2 receptor is highly expressed in various rapidly proliferating cancer cells and is considered a biomarker of cancer cells [2]. Siramesine triggers cell death through mitochondrial instability rather than lysosomes, showing effective anti-cancer activity [3].

In vitro, Siramesine (0-15 μ M) treatment of cultures containing glioblastoma stem cell-like spheres (GSS) for 24 hours reduced sphere formation, indicating its inhibitory effect on tumor stem cell properties [4]. The lysosomal destabilizing drug Siramesine (with a concentration higher than 20 μ M) can induce rapid cell death in many cell lines. In HaCaT cells, the concentration of Siramesine that induces significant cell death within 8 hours is within the range of 20-30 μ M, and 90% of the cells die after treatment with a concentration of 40-50 μ M of Siramesine. And Siramesine at concentrations greater than 25 μ M reduces the mitochondrial membrane potential (MMP) of HaCaT cells within 15 minutes [1].

In vivo, In C57 mice with cocaine-enhanced behavior, the sigma-2 receptor agonist Siramesine (0.1, 0.3, and 1mg/kg/d; i.p.) significantly reduced the dopamine release induced by cocaine in the striatum of freely moving mice, which may have therapeutic potential for treating cocaine relapse [5]. 24 hours before the test, Siramesine (1mg/kg/d; i.p.) combined with MEM (as well as AMA) administration could shorten the immobility time of rats. The combined treatment of Siramesine and AMA is not affected by progesterone nor by BD 1047 (a new sigma antagonist with preferential affinity for the sigma 1 site) [6].

References:

- [1] Česen MH, Repnik U, Turk V, Turk B. Siramesine triggers cell death through destabilisation of mitochondria, but not lysosomes. *Cell Death Dis.* 2013 Oct 3;4(10):e818.
- [2] Huang Y S, Lu H L, Zhang L J, et al. Sigma-2 receptor ligands and their perspectives in cancer diagnosis and therapy[J]. *Medicinal research reviews*, 2014, 34(3): 532-566.
- [3] Bhatti I. The lysosomotropic agent siramesine induces cell death in prostate cancer cells and synergizes with the tyrosine kinase inhibitor lapatinib[J]. 2024.
- [4] Jensen S S, Petterson S A, Halle B, et al. Effects of the lysosomal destabilizing drug siramesine on glioblastoma in vitro and in vivo[J]. *BMC cancer*, 2017, 17: 1-16.
- [5] Klawonn AM, Nilsson A, Rådberg CF, Lindström SH, Ericson M, Granseth B, Engblom D, Fritz M.

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The Sigma-2 Receptor Selective Agonist Siramesine (Lu 28-179) Decreases Cocaine-Reinforced Pavlovian Learning and Alters Glutamatergic and Dopaminergic Input to the Striatum. Front Pharmacol. 2017 Oct 10;8:714.

[6] Skuza G, et al. The synergistic effect of selective sigma receptor agonists and uncompetitive NMDA receptor antagonists in the forced swim test in rats. J Physiol Pharmacol. 2006 Jun;57(2):217-29.

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