

Product Data Sheet

Product Name: SR9011 hydrochloride

Cat. No.: GC37676

Chemical Properties

Cas. No. 2070014-94-5

SMILES O=C(N1CC(CN(CC2=CC=C(Cl)C=C2)CC3=CC=C([N+])([O-])=O)S3)CC1)NCCCCC.[H]Cl

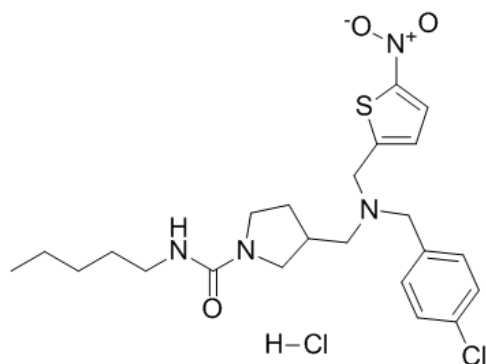
Formula $C_{23}H_{32}Cl_2N_4O_3S$ M.Wt 515.5

Solubility DMSO: ≥ 32 mg/mL (62.08 mM) 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

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

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Cell experiment: MCF10A, MDA-MB-231, MCF-7, MDA-MB-361, SKBR3, BT474 cells are plated in 6-well plates one day before treatment. The MTT cell proliferation assays are performed. Briefly, 3×10^3 to 5×10^3 cells per well are plated in 96-well plates. Twenty-four hours later, cells are treated with SR9011 (0, 2, 4, 6, 8 and 10 μ M) or DMSO. Seventy-two hours after treatment, the cells are labeled with 1.2 mM MTT and incubated for 4 hours. DMSO is then added and readings are taken on a plate reader at 540 nm[2].

Animal experiment: Mice[1] For circadian gene expression experiments male C57BL6 mice (8-10 weeks of age) are either maintained on a L:D (12h:12h) cycle or on constant darkness. At circadian time (CT) 0 animals are administered a single dose of 100 mg/kg SR9011 (i.p.) and groups of animals (n=6) are sacrificed at CT0, CT6, CT12 and CT18. Gene expression is determined by real time QPCR.

References:

- [1]. Solt LA, et al. Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. Nature. 2012 Mar 29;485(7396):62-8.
- [2]. Wang Y, et al. Anti-proliferative actions of a synthetic REV-ERB α / β agonist in breast cancer cells. Biochem Pharmacol. 2015 Aug 15;96(4):315-22.

Background

SR9011 hydrochloride is a REV-ERB α / β agonist with IC₅₀s of 790 nM and 560 nM for REV-ERB α and REV-ERB β , respectively. IC₅₀: 790 nM (Rev-ErbB α), 560 nM (Rev-ErbB β)[1]

SR9011 dose-dependently increases the REV-ERB-dependent repressor activity assessed in HEK293 cells expressing a chimeric Gal4 DNA Binding Domain (DBD) - REV-ERB ligand binding domain (LBD) α or β and a Gal4-responsive luciferase reporter (REV-ERB α IC₅₀=790 nM, REV-ERB β IC₅₀=560 nM). SR9011 potently and efficaciously suppresses transcription in a cotransfection assay using full-length REV-ERB α along with a luciferase reporter driven by the Bmal1 promoter (SR9011 IC₅₀=620 nM). SR9011 suppresses the expression of BMAL1 mRNA in HepG2 cells in a

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REV-ERB α/β -dependent manner[1] SR9011 suppresses proliferation of the breast cancer cell lines regardless of their ER or HER2 status. SR9011 appears to pause the cell cycle of the breast cancer cells prior to M phase. Cyclin A (CCNA2) is identified as a direct target gene of REV-ERB suggesting that suppression of expression of this cyclin by SR9011 may mediate the cell cycle arrest. Treatment with SR9011 results in an increase in cells in the G0/G1 phase and a decrease of cells in S and G2/M phase suggesting that activation of REV-ERB may be resulting in decreased transition from G1 to S phase and/or from S to G2/M phase[2].

SR9011 displays reasonable plasma exposure, thus, the expression of REV-ERB responsive genes is examined in the liver of mice treated with various doses of SR9011 for 6-days. The plasminogen activator inhibitor type 1 gene (Serpine1) is a REV-ERB target gene and displays dose-dependent suppression of expression in response to SR9011. The cholesterol 7 α -hydroxylase (Cyp7a1) and sterol response element binding protein (Srebp1) genes have also been shown to be responsive to REV-ERB and are dose-dependently suppressed with increasing amounts of SR9011. After 12 days in D:D conditions mice are injected with a single dose of SR9011 or vehicle at CT6 (peak expression of Rev-erb α). Vehicle injection causes no disruption in circadian locomotor activity. However, administration of a single dose of SR9011 results in loss of locomotor activity during the subject dark phase. Normal activity returns the next circadian cycle, consistent with clearance of the drugs in less than 24h. The SR9011-dependent decrease in wheel running behavior in the mice under constant darkness conditions is dose-dependent and that the potency (ED₅₀=56 mg/kg) is similar to the potency of SR9011-mediated suppression of a REV-ERB responsive gene, Srebf1, in vivo (ED₅₀=67mg/kg)[1].

[1]. Solt LA, et al. Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. Nature. 2012 Mar 29;485(7396):62-8. [2]. Wang Y, et al. Anti-proliferative actions of a synthetic REV-ERB α/β agonist in breast cancer cells. Biochem Pharmacol. 2015 Aug 15;96(4):315-22.

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