

Product Data Sheet

Product Name: S/GSK1349572

Cat. No.: GC17906

Chemical Properties

Cas. No. 1051375-16-6

Chemical Name (4R,12aS)-N-[(2,4-difluorophenyl)methyl]-7-hydroxy-4-methyl-6,8-dioxo-3,4,12,12a-tetrahydro-2H-pyrido[5,6]pyrazino[2,6-b][1,3]oxazine-9-carboxamide

SMILES CC1CCOC2N1C(=O)C3=C(C(=O)C(=CN3C2)C(=O)NCC4=C(C=C(C=C4)F)F)O

Formula $C_{20}H_{19}F_2N_3O_5$

M.Wt 419.4

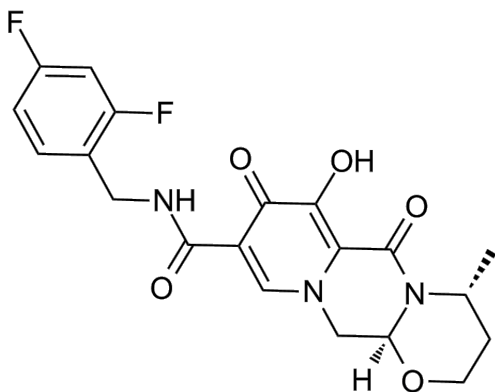
Solubility ≥ 41.9 mg/mL in DMSO

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

Kinase experiment [1]:

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Inhibitory activities

The inhibitory potencies of S/GSK1349572 and was measured in a strand transfer assay using recombinant HIV integrase as previously described. A complex of integrase and biotinylated preprocessed donor DNA-streptavidin-coated Acintillation proximity assay (SPA) beads was formed by incubating 2 μ M purified recombinant integrase with 0.66 μ M biotinylated donor DNA-4 mg/ml streptavidin-coated SPA beads in 25 mM sodium morpholinepropanesulfonic acid (MOPS) (pH 7.2), 23 mM NaCl, and 10 mM MgCl₂ for 5 min at 37°C. These beads were spun down and preincubated with diluted S/GSK1349572 for 60 min at 37°C. Then a 3H-labeled target DNA substrate was added to give a final concentration of 7 nM substrate, and the strand transfer reaction mixture was incubated at 37°C for 25 to 45 min, which allowed for a linear increase in the strand transfer of donor DNA to radiolabeled target DNA. The signal was read using a Wallac MicroBeta scintillation plate reader.

Cell experiment [1]:

Cell lines

MT-4 cells infected with HIV-1 strain IIIB; PBMCs.

Soluble in DMSO > 10 mM. General tips for obtaining a higher concentration:
Preparation method Please warm 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 0.16, 0.8, 4, 20 nM; 4 or 5 days.

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Applications In MT-4 cells, S/GSK1349572 inhibits HIV-1 with EC50 value of 0.71 nM. Also, S/GSK1349572 inhibits HIV-1 in PBMCs and in the PHIV assay with EC50 values of 0.51 and 2.2 nM, respectively. In proliferating IM-9, U-937, MT-4, and Molt-4 cells, S/GSK1349572 exhibits 50% cytotoxic concentrations (CC50) of 4.8, 7.0, 14 and 15 μ M, respectively. In MT-4 cells infected with HIV-1 NL432, S/GSK1349572 inhibits viral replication.

Animal experiment [2]:

Animal models C57BL/6 mice

Dosage form 2.7 mg/kg/day; two weeks; administrated orally.

Applications In C57BL/6 mice, S/GSK1349572 significantly increases serum creatinine, which is consistent with integrase inhibitors competitively inhibiting creatinine secretion.

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]. Kobayashi M, Yoshinaga T, Seki T, et al. In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother, 2011, 55(2): 813-821.

[2]. Eadon MT, Zhang H, Skaar TC, et al. A two-week regimen of high-dose integrase inhibitors does not cause nephrotoxicity in mice. Antivir Chem Chemother, 2015.

Background

S/GSK1349572, also known as dolutegravir, is a novel and potent inhibitor of human

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immunodeficiency virus (HIV) integrase (IN) blocking the strand transfer of integration of the viral genome into the host cell's DNA. It occupies the physical space in the IN active site of the intasome, contacts with the $\beta 4$ - $\alpha 2$ loop of the catalytic core domain, and enters into the pocket vacated by the displaced viral DNA through its extended linker region connecting the metal chelating core the halobenzyl group. S/GSK1349572 exhibits potent anti-HIV activity in peripheral blood mononuclear cells (IC₅₀ = 0.51 nM) *in vitro* and retains activity against raltegravir- and elvitegravir- resistant HIV.

Reference

- [1]. Sherene Min, Ivy Song, Julie Borland, Shuguang Chen, Yu Lou, Tamio Fujiwara, and Stephen C. Piscitelli. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. *ANTIMICROBIAL AGENTS AND CHEMOTHERAPY* 2010; 54(1): 254-258
- [2]. Masanori Kobayashi, Tomokazu Yoshinaga, Takahiro Seki, Chiaki Wakasa-Morimoto, Kevin W. Brown, Robert Ferris, Scott A. Foster, Richard J. Hazen, Shigeru Miki, Akemi Suyama-Kagitani, Shinobu Kawauchi-Miki, Teruhiko Taishi, Takashi Kawasuji, Brian A. Johns, Mark R. Underwood, Edward P. Garvey, Akihiko Sato, and Tamio Fujiwara. In vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. *ANTIMICROBIAL AGENTS AND CHEMOTHERAPY* 2011; 55(2): 813-821
- [3]. Stephen Harem Steven J. Smith, Mathieu Metifiot, Albert Jaxa-Chamiec, Yves Pommier, Stephen H. Hughes, and Peter Cherepanov. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). *Mol Pharmacol* 2011; 80(4): 565-572

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