产品名称：Dolutegravir (sodium)
产品别名：Dolutegravir sodium；S/GSK1349572 sodium

生物活性：

Description

Dolutegravir sodium (S/GSK1349572 sodium) is a highly potent and orally bioavailable HIV integrase strand transfer inhibitor with an IC_{50} of 2.7 nM for HIV-1 integrase-catalyzed strand transfer. Dolutegravir sodium (S/GSK1349572 sodium) inhibits HIV-1 viral replication with an IC_{50} of 0.51 nM in peripheral blood mononuclear cells. Dolutegravir sodium (S/GSK1349572 sodium) retains a high potency against the HIV-1 Y143R, N155H, and G140S/Q148H mutants (EC_{50}=3.6-5.8 nM) [1][2].

IC_{50} & Target

IC50: 2.7 nM (HIV-1 integrase)[1]

In Vitro

The EC_{50} of Dolutegravir (S/GSK1349572) against HIV-1 is 0.51 nM in PBMCs, 0.71 nM in MT-4 cells, and 2.2 nM in the PHIV assay, which uses a pseudotyped self-inactivating virus. The 50% cytotoxic concentrations (CC_{50}) for Dolutegravir in proliferating IM-9, U-937, MT-4, and Molt-4 cells are 4.8, 7.0, 14, and 15 μM, respectively. In unstimulated and stimulated PBMCs, the CC_{50} are 189 μM and 52 μM, respectively. Based on the EC_{50} of Dolutegravir against HIV-1 in PBMCs (i.e., 0.51 nM), this translates to a cell-based therapeutic index of at least 9,400[1].

In Vivo

Following a single intravenous (IV) administration of Dolutegravir, the plasma clearance is low in rats (0.23 mL/min/kg) and monkeys (2.12 mL/min/kg). The half-lives in the rat and monkey are similar, approximately 6 h, and the steady-state volume of distribution (V_{ss}) is low. Following oral administration, Dolutegravir is rapidly absorbed with a high oral bioavailability when administered as a solution to fasted male rats and a single monkey (75.6 and 87.0%, respectively). Dolutegravir exposure (C_{max} and AUC) increased with increasing dose following oral administration of a suspension to non-fasted rats up to 250 mg/kg and non-fasted monkeys up to 50 mg/kg, although the increase is less than proportional[2].

Solvent&Solubility

In Vitro:

DMSO : ≥ 4.5 mg/mL (10.20 mM)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2657 mL	11.3286 mL	22.6572 mL
5 mM	0.4531 mL	2.2657 mL	4.5314 mL
10 mM	0.2266 mL	1.1329 mL	2.2657 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

References

[1]. Kobayashi M, et al. In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother. 2011 Feb;55(2):813-21.

[2]. Moss L, et al. The comparative disposition and metabolism of dolutegravir, a potent HIV-1 integrase inhibitor, in mice, rats, and monkeys. Xenobiotica. 2015 Jan;45(1):60-70.

[3]. Hare S, et al. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). Mol Pharmacol. 2011 Oct;80(4):565-72.

实验参考：	
Cell Assay	In vitro growth inhibition (cytotoxicity) studies are conducted with S/GSK1349572 (0.16, 0.8, 4, and 20 nM) in proliferating human leukemic and lymphomic cell lines (IM-9, U-937, MT-4, and Molt-4) as well as in stimulated and unstimulated human PBMCs. ATP levels are quantified by using the CellTiter-Glo luciferase reagent to measure the ability of a compound to inhibit cell growth as an indicator of the compound's potential for cytotoxicity[1].
Animal Administration	For rat and monkey PK studies, Dolutegravir is administered as the free acid or the sodium salt. All doses are presented in terms of the free acid. Dolutegravir is administered by intravenous (IV) short-term (within 2 min) bolus (1 mg/kg) to three male rats and two male monkeys. For single oral administration, Dolutegravir as a solution (5 mg/kg) is administered to three fasted male rats and two fasted male monkeys. Dolutegravir is administered as single oral doses of 5, 50, 100, and 250 mg/kg to non-fasted male rats (n=2/dose level) and 3, 10, and 50 mg/kg to non-fasted female monkeys. For intravenous administration, blood samples are collected from rats (0.2 mL via jugular vein cannula) and monkeys (approximately 0.2 or 0.5 mL via saphenous vein in a hindlimb) into Na_2EDTA-treated syringes at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h. For oral administration, samples are collected at 0.25 (rats only), 0.5, 1, 2, 4, 6 [rats (solution and suspension) and monkey (solution only)], 8, and 24 h. Following collection, the blood is immediately put on wet ice and then centrifuged within an hour at 1740 g for 10 min at 4°C to obtain plasma. All samples are stored at approximately -20°C or colder prior to analysis by using a method based on protein precipitation and LC-MS/MS analysis. [2]
References	[1]. Kobayashi M, et al. In Vitro antiretroviral properties of S/GSK1349572, a next-generation HIV integrase inhibitor. Antimicrob Agents Chemother. 2011 Feb;55(2):813-21. [2]. Moss L, et al. The comparative disposition and metabolism of dolutegravir, a potent HIV-1 integrase inhibitor, in mice, rats, and monkeys. Xenobiotica. 2015 Jan;45(1):60-70. [3]. Hare S, et al. Structural and functional analyses of the second-generation integrase strand transfer inhibitor dolutegravir (S/GSK1349572). Mol Pharmacol. 2011 Oct;80(4):565-72.