Dolutegravir

Cat. No.: HY-13238

CAS No.: 1051375-16-6

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

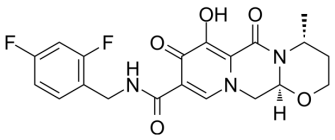
Molecular Weight: 419.38

Target: HIV Integrase; HIV

Pathway: Metabolic Enzyme/Protease; Anti-infection

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 10 mg/mL (23.84 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3845 mL	11.9224 mL	23.8447 mL
	5 mM	0.4769 mL	2.3845 mL	4.7689 mL
	10 mM	0.2384 mL	1.1922 mL	2.3845 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.62 mg/mL (6.25 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (5.96 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.96 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.96 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Dolutegravir (S/GSK1349572) 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 (S/GSK1349572) inhibits HIV-1 viral replication with an IC_{50} of 0.51 nM in peripheral blood mononuclear cells. Dolutegravir 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	HIV-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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2020 Feb 14;367(6479):806-810.
- Int J Antimicrob Agents. 2019 Dec;54(6):814-819.
- J Infect Dis. 2022 Sep 19;jiac386.
- J Neuroimmune Pharmacol. 2019 Jul 23;10.1007/s11481-019-09862-1.
- Life Sci. 9 September 2022, 120948.

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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]. 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.

[3]. 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.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA