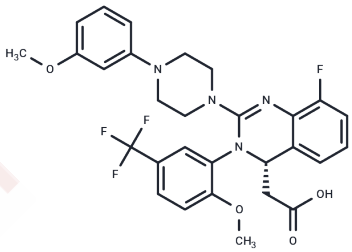
Data Sheet (Cat.No.T5396)

TargetMol

Letermovir

Chemical Properties



CAS No. : 917389-32-3

Formula: C29H28F4N4O4

Molecular Weight: 572.55

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	Letermovir (AIC246) (AIC246) is a novel anti-CMV compound (EC50: about 5 nM in fibroblast cells). It targets the pUL56 subunit of the viral terminase complex.
Targets(IC50)	HCV Protease,Virus Protease
In vitro	The inhibitory potency of Letermovir surpasses ganciclovir (GCV) by more than 400-fold with respect to EC50s (mean, ~4.5 nM versus ~2 μM) and by more than 2,000-fold with respect to EC90 values (mean, ~6.1 nM versus ~14.5 μM). NHDF monolayers showed no microscopically apparent cytotoxic effects at Letermovir concentrations of <33 μM when observed during antiviral assays [1]. Letermovir is remarkably specific for human cytomegaloviruses since no significant activity was noted against any other herpesvirus tested. The EC50s obtained for RCMV and MCMC indicated that no (RCMV) or only a very low-level (MCMV, 4.51 μM) Letermovir sensitivity could be detected even for rodent cytomegaloviruses [2].
In vivo	Letermovir treatment led to a dose-dependent reduction of the HCMV titer in transplanted cells compared to that of the placebo-treated control group using the mouse xenograft model. Statistical analysis revealed significant antiviral effects for the 10-, 30-, and 100-mg/kg/day treatment groups of Letermovir as well as for the 100-mg/kg/day VGCV control group [1]. The incidence of prophylaxis failure with letermovir, as compared with placebo, was 48% versus 64% at a daily letermovir dose of 60 mg, 32% at a dose of 120 mg, and 29% at a dose of 240 mg. Kaplan-Meier time-to-onset profiles for prophylaxis failure showed a significant difference in the comparison of letermovir at a dose of 240 mg per day with placebo [3].
Cell Research	Briefly, 96-well microtiter plates were seeded with 1.5 × 10^4 cells/well and incubated overnight. Drugs were added to the wells in 3-fold serial dilutions starting from 0.33 mM (the DMSO concentration was kept constant at 0.66% throughout the whole plate). After a 7-day incubation period, alamarBlue solution was added to each well and the fluorescence signal was measured using a SpectraFluor Plus fluorescence reader. The relative fluorescence units of treated wells were expressed as percentages of untreated cell control wells and plotted against the logarithm of drug concentrations. Drug concentrations reducing cell viability by 50% (CC50s) were determined from dose-response curves. The assays were performed at least three times with duplicate samples. CC50 values were used to calculate the selectivity index (SI = CC50/EC50) for individual substances [1].

Animal Research	Briefly, Gelfoam hemostyptic gelatin devices were cut aseptically into 1-cm2 pieces. These implants were soaked in NHDF cell culture growth medium (GM), and sponges were brought to 37°C in a CO2 incubator. NHDF cells were infected with cell-free HCMV strain Davis at an MOI of 0.03. After 4 h, cells were collected by trypsinization followed by centrifugation at room temperature for 10 min at 800 × g. Cells were resuspended in GM and counted using a hemocytometer. Each Gelfoam implant was seeded with a suspension of 1 × 10^6 infected cells by pipetting the cells onto the sponges. Human cells were allowed to adhere to the collagen sponges for at least 3 to 4 h at 37°C. To enhance vascularization of the implant, 250 ng recombinant human basic fibroblast growth factor was pipetted onto each implant 1 h prior to transplantation. Mice (18 to 25 g body weight) were anesthetized, and the Gelfoam sponges were implanted subcutaneously in the dorsoscapular area. After transplantation, mice were randomized and grouped in ~10 animals per treatment group. Starting 4 h after transplantation, mice were treated once daily with the indicated compounds for nine consecutive days. Drugs were applied per os by oral gavage. Total administration volume was 10 ml/kg. Mice were sacrificed after 9 days of treatment, and the Gelfoam implants were removed and digested with collagenase at 37°C. After 2 to 3 h, human cells were recovered by centrifugation and resuspended in GM. Subsequently, the isolated cell suspensions were serially diluted and mixed with uninfected NHDF indicator cells and PFU were determined by plaque assays. Virus titers determined from isolated cells are given as PFU/ml [1].

Solubility Information

Solubility	Ethanol: 2 mg/mL (3.49 mM),Sonication is recommended. DMSO: 70 mg/mL (122.26 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 2 mg/mL (3.49 mM),Sonication is recommended. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	1.7466 mL	8.7329 mL	17.4657 mL
5 mM	0.3493 mL	1.7466 mL	3.4931 mL
10 mM	0.1747 mL	0.8733 mL	1.7466 mL
50 mM	0.0349 mL	0.1747 mL	0.3493 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Lischka P, et al. In vitro and in vivo activities of the novel anticytomegalovirus compound AIC246. Antimicrob Agents Chemother. 2010 Mar;54(3):1290-7.
Marschall M, et al. In vitro evaluation of the activities of the novel anticytomegalovirus compound AIC246 (letermovir) against herpesviruses and other human pathogenic viruses. Antimicrob Agents Chemother. 2012 Feb; 56(2):1135-7.
Chemaly RF, et al. Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation.N Engl J Med. 2014 May 8;370(19):1781-9.