Product Data Sheet

Product Name: PSI-7409 tetrasodium
Cat. No.: GC33946

Chemical Properties

Cas. No.	1621884-22-7		
SMILES	O[C@@H]([C@@](C)(F)[C@H](N1C(NC(C=C1)=O)=O)O2)[C@H]2COP(O)(OP(OP(O)(O)=O)(O)=O)=O.[4Na]		
Formula	$C_{10}H_{16}FN_2Na_4O_{14}P_3$	M.Wt	592.12
Solubility	Water : ≥ 125 mg/mL (211.11 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	PSI-7409 tetrasodium		

Protocol

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Kinase experiment:

Human DNA polymerase α, β, or γ is assayed in a 10-μL reaction mixture containing 50 mM Tris (pH 7.5), 50 mM NaCl, 3 mU/μL activated calf thymus DNA, a 20 μM concentration of all four natural deoxynucleoside triphosphates, 4 μCi [α-32P]dCTP, 5 mM MgCl2, and increasing concentrations of PSI-7409 (up to 1 mM), D-ddFCTP, or aphidicolin. DNA polymerase α, β, or γ is added to the reaction mixture to give final concentrations of 20, 18, and, 50 μg/mL, respectively. All reactions are run at 37°C and quenched at 30 min by mixing with 1 μL of 0.5 M EDTA. The radiolabeled products are quantified. A nonlinear fit is performed to determine the IC50. The activity of RNA polymerase II is determined in a 25-μL in vitro transcription reaction mixture containing 100 ng of cytomegalovirus (CMV) immediate-early promoter DNA, 400 μM ATP, CTP, and UTP, 16 μM GTP, 10 μCi [α-32P]GTP, 3 mM MgCl2, and various concentrations of PSI-7409 (up to 1 mM), 3'-dCTP, or α-amanitin in transcription buffer (20 mM HEPES [pH 7.9], 100 mM KCl, 0.2 mM EDTA, 0.5 mM DTT, and 20% glycerol). All reactions are run at 30°C and quenched at 60 min by mixing with 125 μL of stop solution (0.3 M Tris-HCl [pH 7.4], 0.3 M sodium acetate, 0.5% SDS, 2 mM EDTA, and 3 μg/mL tRNA). The RNA product is purified. The resulting samples contains 12 μL and the same volume of gel loading dye (98% formamide, 10 mM EDTA, 0.1% xylene cyanol, and 0.1% bromophenol blue) is added. The samples are heated at 90°C for 5 min and loaded onto a 6% polyacrylamide sequencing gel. After running, the gel is exposed to a phosphorscreen, and the product is visualized and quantified by using a phosphorimager[1].

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References:

[1]. Lam AM, et al. PSI-7851, a pronucleotide of beta-D-2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate, is a potent and pan-genotype inhibitor of hepatitis C virus replication. Antimicrob Agents Chemother. 2010 Aug;54(8):3187-96.
[2]. Murakami E, et al. Mechanism of activation of PSI-7851 and its diastereoisomer PSI-7977. J Biol Chem. 2010 Nov 5;285(45):34337-47.

Background

PSI-7409 tetrasodium is an active 5'-triphosphate metabolite of sofosbuvir (PSI-7977), inhibiting HCV NS5B polymerases, with IC50s of 1.6, 2.8, 0.7 and 2.6 μM for GT 1b_Con1, GT 2a_JFH1, GT 3a, and GT 4a NS5B polymerases, respectively.

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PSI-7409 tetrasodium is an active 5'-triphosphate metabolite, inhibiting HCV NS5B polymerases, with IC50s of 1.6, 2.8, 0.7 and 2.6 μM for GT 1b_Con1, GT 2a_JFH1, GT 3a, and GT 4a NS5B polymerases, respectively. PSI-7409 also weakly inhibits human DNA polymerase α, with an IC50 of 550 μM, but shows no inhibition on DNA Pol β and γ[1]. In clone A cells, the levels of PSI-7409 gradually increases to a maximum concentration of about 25 μM over a period of 48 h. PSI-7409 forms at a much faster rate in primary human hepatocytes, achieving a maximum intracellular concentration of ~100 μM at 4 h and remains at that concentration for 48 h[2].

[1]. Lam AM, et al. PSI-7851, a pronucleotide of beta-D-2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate, is a potent and pan-genotype inhibitor of hepatitis C virus replication. Antimicrob Agents Chemother. 2010 Aug;54(8):3187-96. [2]. Murakami E, et al. Mechanism of activation of PSI-7851 and its diastereoisomer PSI-7977. J Biol Chem. 2010 Nov 5;285(45):34337-47.

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