Product Data Sheet

Product Name: Napsagatran hydrate (Ro 46-6240 hydrate)
Cat. No.: GC34032

Chemical Properties

Cas. No.	159668-20-9		
SMILES	O=C(NC[C@H]1CN(C(N)=N)CCC1)C[C@@H](C(N(C2CC2)CC(O)=O)=O)NS(C3=CC4=CC=CC=C4C=C3)(=O)=O.O		
Formula	$C_{26}H_{36}N_6O_7S$	M.Wt	576.67
Solubility	Soluble in DMSO	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			

Protocol

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Kinase experiment:

Hepatocytes in 12-well plates are preloaded until a maximal intracellular concentration is reached. Measuring the compound efflux at maximal intracellular concentration gives the efflux at steady state. Preload times and compound concentrations are decided from measured uptake data in pilot experiments (Digoxin, 10 μM for 15 minutes; Fexofenadine, 1 μM for 30 minutes; Napsagatran, 10 μM for 30 minutes; and Rosuvastatin, 1 μM for 15 minutes). After preloading, the wells are washed three times in 37°C Krebs-Henseleit buffer with 10 mM HEPES (GIBCO) pH 7.4 (KHL) to ensure that the wells are free from remaining compound. Efflux experiments are started by adding 300 μL KHL (37°C) to each well. Cells are also lysed immediately after washing to determine the initial intracellular concentrations at the start of the experiment. The contribution of ABC-efflux transporter activity to the measured efflux is assayed using 0.5 μM of the inhibitors Elacridar and Fumitremorgin C (FTC)[2].

Animal experiment:

Rabbits[3]The experiment is initiated by a bolus injection followed by infusion of 125I-human fibrinogen. Increase of tracer uptake within 30 min infusion of more than 30% of background value is indicative of onset of thrombus growth and thus, the counts are set to zero and Rabbits receive either Napsagatran a specific thrombin inhibitor (10 μg/kg per min in continuous i.v. infusion) or repetitive i.v. bolus of the monoclonal antiRabbits TF antibody AP-1 (600 μg/kg) at hourly intervals. The placebo-treated Rabbits (control group) receive either saline infused at 1 mL/kg or four boli of an irrelevant IgG Rabbits mAb.

References:

[1]. Pratico D, et al. Interaction of a thrombin inhibitor

and a platelet GP IIb/IIIa antagonist in vivo: evidence thatthrombin mediates platelet aggregation and subsequent thromboxane A2 formation during coronary thrombolysis. J Pharmacol Exp Ther. 1997 Jun;281(3):1178-85.
[2]. Lundquist P, et al. Prediction of in vivo rat biliary drug clearance from an in vitro hepatocyte efflux model. Drug Metab Dispos. 2014 Mar;42(3):459-68.
[3]. Himber J, et al. Inhibition of tissue factor limits the growth of venous thrombus in the rabbit. J Thromb Haemost. 2003 May;1(5):889-95.

Background

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Napsagatran hydrate is a novel and specific thrombin inhibitor.

Napsagatran (Ro 46-6240), the selective thrombin inhibitor, induces a dose-dependent prolongation of the activated partial thromboplastin time (aPTT) and prothrombin time (PT) that is evident 15 min after administration of the bolus of Napsagatran. Napsagatran also reduces the time to reperfusion in a dose-dependent manner and delays or prevents reocclusion[1]. The decreasing intracellular amount and efflux of compound from the cells into the medium is measured. The measured CLint,efflux values are 0.13±0.06, 3.2±0.6, 10.1±2.3, and 110±2.8 for Digoxin, Fexofenadine, Napsagatran, and Rosuvastatin, respectively, thus representing drugs with a >800-fold range of efflux rates[2].

After the first hour of drug administration (from 0 to 60 min), the incorporated radioactivity into thrombi increased from baseline by 73±13, 67±22 and 32±10% in placebo, AP-1 and Napsagatran-treated rabbits, respectively. Statistical analysis confirm that thrombus growth in the placebo and AP-1 treated rabbits is not different. In contrast, reduction of 125I-fibrinogen incorporation by Napsagatran is statistical different from the placebo group ($P<0.01$)[3].

[1]. Pratico D, et al. Interaction of a thrombin inhibitor and a platelet GP IIb/IIIa antagonist in vivo: evidence thatthrombin mediates platelet aggregation and subsequent thromboxane A2 formation during coronary thrombolysis. J Pharmacol Exp Ther. 1997 Jun;281(3):1178-85. [2]. Lundquist P, et al. Prediction of in vivo rat biliary drug clearance from an in vitro hepatocyte efflux model. Drug Metab Dispos. 2014 Mar;42(3):459-68. [3]. Himber J, et al. Inhibition of tissue factor limits the growth of venous thrombus in the rabbit. J Thromb Haemost. 2003 May;1(5):889-95.

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