# Napsagatran hydrate

**Cat. No.:** HY-15759A

**CAS No.:** 159668-20-9

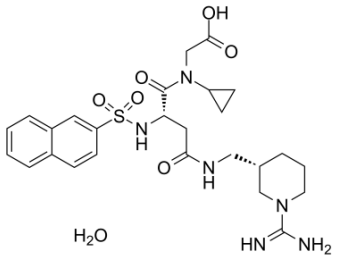
**Molecular Formula:** $C_{26}H_{36}N_6O_7S$

**Molecular Weight:** 576.67

**Target:** Thrombin

**Pathway:** Metabolic Enzyme/Protease

**Storage:** Please store the product under the recommended conditions in the Certificate of Analysis.



## BIOLOGICAL ACTIVITY

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| **Description** | Napsagatran hydrate is a novel and specific thrombin inhibitor. |
| **$IC_{50}$ & Target** | Thrombin[1] |
| **In Vitro** | 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 $CL_{int,efflux}$ 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].<br>MCE has not independently confirmed the accuracy of these methods. They are for reference only. |
| **In Vivo** | 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 $^{125}$I-fibrinogen incorporation by Napsagatran is statistical different from the placebo group ($P<0.01$)[3].<br>MCE has not independently confirmed the accuracy of these methods. They are for reference only. |

## PROTOCOL

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| **Kinase Assay** [2] | 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].<br>MCE has not independently confirmed the accuracy of these methods. They are for reference only. |

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| **Animal Administration** [3] | Rabbits[3]<br>The experiment is initiated by a bolus injection followed by infusion of $^{125}$I-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.<br>MCE has not independently confirmed the accuracy of these methods. They are for reference only. |

## 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.





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