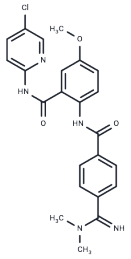
Data Sheet (Cat.No.T4341)

TargetMol

Betrixaban

Chemical Properties



CAS No. : 330942-05-7

Formula: C23H22ClN5O3

Molecular Weight: 451.91

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	Betrixaban (PRT054021) is a non-vitamin K oral anticoagulant whose action is driven by the competitive and reversible inhibition of the factor Xa [1]. It was selected among all lead compounds due to its low hERG channel affinity while sustaining its factor Xa inhibition capacity [3]. Betrixaban, now developed by Portola Pharmaceuticals Inc., is prescribed as a venous thromboembolism (VTE) prophylactic for adult patients with moderate to severe restricted motility or with other risks for VTE [2]. VTE can be manifested as deep vein thrombosis or pulmonary embolism and it is a leading cause of preventable death in hospitalized patients [4].
Targets(IC50)	Factor Xa
In vitro	In patch clamp hERG assays, Betrixaban has IC50 of 8.9 μM. The plasma kallikrein IC50 and Ki values for Betrixaban are 6.3 μM and 3.5 μM respectively. Betrixaban (hERG Ki 1.8 μM) exhibits significantly lower hERG activity than all the others (hERG Ki?0.5 μM)
In vivo	Dosed at 0.5 mg/kg IV and 2.5 mg/kg PO, Betrixaban has bioavailability of 51.6% in dog; dosed at 0.75 mg/kg IV and 7.5 mg/kg PO, Betrixaban has bioavailability of 58.7% in monkey[1]. Both Betrixaban and Apixa-ban-mediated whole-blood INR increases are similarly reversed by r-Antidote. After i.v. infusion of the three fXa inhibitors (each admin¬istered individually) for 30 min, the total plasma concentrations of rivaroxaban, Betrixaban and apixaban are 1.4±0.4 μM (mean±s.d.), 0.2±0.01 μM and 1.4±0.3 μM, respectively, and the percentages of unbound inhibitor are 2.2%±0.8% (mean±s.d.), 40% ±7.2% and 1.5%±0.3%, respectively. After administration of r-Antidote, the total plasma concentrations of the inhibitors increased to 1.9±0.09 μM, 2.0±0.4 μM and 4.2±0.7 μM, respectively, and the percentage of unbound inhibitor declined to 0%, 0.3%±0.1% and 0.05%±0.02%, respectively. Therefore, for each of the three inhibitors, correction of prothrombin time by r-Antidote to near-normal values is associated with a reduction in the free fraction of the inhibitor[2].
Kinase Assay	To measure the inhibition of fXa activity by direct fXa inhibitors and the reversal of its inhibitory effect by r-Antidote, purified human plasma fXa (3 nM) (Haematologic Technologies), varying concentrations of inhibitor (0, 2.5, 5.0 and 7.5 nM) and r-Antidote are added to the assay buffer (20 mM Tris, 150 mM NaCl, 5 mM Ca2+ and 0.1% BSA, pH 7.4). After incubation at room temperature for 30 min, 100 μM Spectrozyme-fXa is added to the mixture, and the initial rate of sub?strate cleavage is monitored continuously for 5 min at 405 nm in a 96-well plate reader. The initial velocity of product formation as a function of inhibitor and r-Antidote concentrations is analyzed by Dynafit to estimate the

Kinase Assay	binding affinity of r-Antidote to each inhibitor[2]. .
Animal Research	Whole-blood INR values (mean±s.d.) in rats infused with Betrixaban (1 mg/kg per hour) or vehicle and then treated with either vehicle or r-Antidote by i.v. bolus (6 mg) over 5 min plus infusion (9 mg/h) for up to 90 min. Circles, vehicle+vehicle; squares, Betrixaban + vehicle; triangles, Betrixaban + r-Antidote. *P≤0.02 compared to the r-Antidote treatment group determined by unpaired two-tailed t test. Whole-blood INR values (mean±s.d.) in rats infused with Apixaban (0.5 mg per kg body weight h?1) or vehicle and then treated with either vehicle or r-Antidote by i.v. bolus (6 mg) over 5 min plus infusion (6 mg/h) for up to 90 min. Circles, vehicle + vehicle; squares, apixaban + vehicle; triangles, apixaban+r-Antidote. *P≤0.01 compared to the r-Antidote treatment group determined by unpaired two-tailed t test.

Solubility Information

Solubility	DMSO: 22.73 mg/mL (50.3 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+90% Saline: < 2.27 mg/mL (5.02 mM),Lower concentrations may be soluble, but exact solubility limit is unknown. 10% DMSO+40% PEG300+5% Tween 80+45% Saline: 2.27 mg/mL (5.02 mM),Solution. *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	2.2128 mL	11.0641 mL	22.1283 mL
5 mM	0.4426 mL	2.2128 mL	4.4257 mL
10 mM	0.2213 mL	1.1064 mL	2.2128 mL
50 mM	0.0443 mL	0.2213 mL	0.4426 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

Zhang P, et al. Discovery of Betrixaban (PRT054021), N-(5-chloropyridin-2-yl)-2-(4-(N,N-dimethylcarbamimidoyl) benzamido)-5-methoxybenzamide, a highly potent, selective, and orally efficacious factor Xa inhibitor. Bioorg Med Chem Lett. 2009 Apr 15;19(8):21

Lu G, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med. 2013 Apr;19(4):446-51.

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