Apixaban

Cat. No.: HY-50667

CAS No.: 503612-47-3

Molecular Formula: $C_{25}H_{25}N_5O_4$

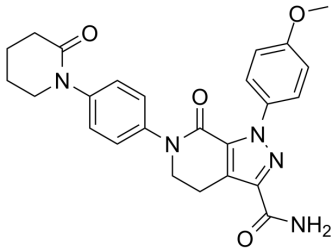
Molecular Weight: 460

Target: Factor Xa

Pathway: Metabolic Enzyme/Protease

Storage:

Powder	-20°C	3 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (108.70 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1739 mL	10.8696 mL	21.7391 mL
	5 mM	0.4348 mL	2.1739 mL	4.3478 mL
	10 mM	0.2174 mL	1.0870 mL	2.1739 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.43 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.43 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Apixaban (BMS-562247-01) is a highly selective, reversible and orally active inhibitor of Factor Xa with K_i of 0.08 nM and 0.17 nM in human and rabbit, respectively[1]. Apixaban is in development for the prevention and treatment of various thromboembolic diseases[2].

IC_{50} & Target

IC50: 0.08 nM (Human Factor Xa), 0.17 nM (Rabbit Factor Xa)

In Vitro

Apixaban (BMS-562247-01) prolongs the clotting times of normal human plasma with the concentrations (EC2x) of 3.6 μM, 0.37 μM, 7.4 μM, and 0.4 μM, which are required respectively to double the prothrombin time (PT), modified prothrombin time (mPT), activated partial thromboplastin time (APTT) and HepTest. Besides, Apixaban shows the highest potency in human and rabbit plasma, but less potency in rat and dog plasma in both the PT and APTT assays[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Apixaban (BMS-562247-01) shows the excellent pharmacokinetics with very low clearance (Cl: 0.02 L/kg/h), and low volume of distribution (Vdss: 0.2 L/kg) in the dogs. Besides, Apixaban also exhibits a moderate half-life (T1/2: 5.8 hours) and good oral bioavailability (F: 58%)[1].

In the arteriovenous-shunt thrombosis (AVST), venous thrombosis (VT) and electrically mediated carotid arterial thrombosis (ECAT) rabbit models, Apixaban produces dose-dependent antithrombotic effects with EC_{50} of 270 nM, 110 nM and 70 nM, respectively[2].

Apixaban significantly inhibits factor Xa activity with IC_{50} of 0.22 μM in rabbit ex vivo[3].

In chimpanzee, Apixaban also shows small volume of distribution (Vdss: 0.17 L/kg), low systemic clearance (Cl: 0.018 L/kg/h), and good oral bioavailability (F: 59%)[4].

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PROTOCOL

Kinase Assay [2]

Purified FXa is obtained after activation with Russell's viper venom followed by affinity chromatography. The resulting FXa is > 95% pure as judged by sodium dodecylsulfate polyacrylamide gel electrophoresis. The substrate affinity values for FXa, expressed as the Michaelis-Menten-Henri constant (K_m), for human, rabbit, rat and dog FXa are determined using the chromogenic substrate S-2765, and are 36, 60, 240 and 70 μM, respectively. The substrate hydrolysis is monitored by measuring absorbance at 405 nm at 25°C for up to 30 min using a SpectraMax 384 Plus plate reader and SoftMax. FXa activity for each substrate and inhibitor concentration pair is determined in duplicate. The K_i values are calculated by non-linear least-squares fitting of the steady-state substrate hydrolysis rates to the equation for competitive inhibition (Equation 1) using GRAFIT, where v equals reactions velocity in OD min−1, Vmax equals maxiumum reaction velocity, S equals substrate concentration, and I equals inhibitor concentration.

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Animal Administration [2]

Briefly, male New Zealand White rabbits are anesthetized with ketamine (50 mg/kg i.m.) and xylazine (10 mg/kg i.m.), and their femoral artery, jugular vein and femoral vein are catheterized. Thrombosis is induced by an arteriovenous (AV)-shunt device containing a silk thread. Blood flowed from the femoral artery via the AV shunt into the opposite femoral vein for 40 min. The shunt is then disconnected and the silk thread covered with thrombus is weighed. As apixaban has an oral bioavailability of < 5% in rabbits (unpublished result), it is administered intravenously for in vivo studies. To achieve a stable plasma level with minimum experimental variability, apixaban, fondaparinux or vehicle is given by a continuous intravenous infusion 1 h prior to shunt placement. The infusion is continued throughout the experiment. Warfarin or vehicle is dosed orally once daily for 4 days. On the fourth day after the last oral dose of warfarin or vehicle, rabbits are anesthetized 1.5 h later, and the treatment effect is evaluated about 2 h postdose. Arterial blood samples for the determination of clotting times or plasma levels are collected 20 min after shunt placement. Plasma levels of apixaban are measured by a specific and sensitive liquid chromatographic mass spectrometry method (LC/MS/MS). In rabbits treated with apixaban, fondaparinux or warfarin, the antithrombotic effects of these agents are expressed as percentage inhibition of thrombus formation based on the treated vs. the corresponding mean vehicle. The ED_{50} value (dose that produced 50% inhibition of thrombus formation) is determined as described below. The apixaban group treatment consists of vehicle (10%N,N-dimethylacetamide; 30% 1,2-propanediol; 60% water) (n=4), and apixaban (mg/kg/h) at 0.03 (n=7), 0.1 (n=7), 0.3 (n=7), 1 (n=7), and 3 (n=3). The fondaparinux group treatment consists of vehicle (saline) (n=6), and fondaparinux (mg/kg/h1) at 0.01 (n=5), 0.03 (n=5), 0.1 (n=5), 0.3 (n=5), and 1 (n=5). The warfarin group treatment consists of vehicle (water) (n=6), and warfarin (mg/kg/day) at 0.1 (n=6), 0.3 (n=6), 1 (n=6), and 3 (n=6).

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Thromb Haemost. 2013 Dec;11(12):2118-27.

- Molecules. 2023 Feb 28.
- Res Pract Thromb Haemost. 2020 Oct 25;4(8):1269-1281.
- Sci Rep. 2020 Jul 6;10(1):11079.
- Int J Lab Hematol. 2020 Apr;42(2):126-133.

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REFERENCES

[1]. Pinto DJ, et al. Discovery of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (apixaban, BMS-562247), a highly potent, selective, efficacious, and orally bioavailable inhibitor of blo

[2]. Wong PC, et al. Apixaban, an oral, direct and highly selective factor Xa inhibitor: in vitro, antithrombotic and antihemostatic studies. J Thromb Haemost. 2008 May;6(5):820-9

[3]. Zhang D, et al. Metabolism, pharmacokinetics and pharmacodynamics of the factor Xa inhibitor apixaban in rabbits. J Thromb Thrombolysis. 2010 Jan;29(1):70-80

[4]. He K, et al. Preclinical pharmacokinetics and pharmacodynamics of apixaban, a potent and selective factor Xa inhibitor. Eur J Drug Metab Pharmacokinet. 2011 Sep;36(3):129-39

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