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ORIGINAL ARTICLE

In vitro and *in vivo* studies of the novel antithrombotic agent BAY 59-7939—an oral, direct Factor Xa inhibitor

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Summary. BAY 59-7939 is an oral, direct Factor Xa (FXa) inhibitor in development for the prevention and treatment of arterial and venous thrombosis. BAY 59-7939 competitively inhibits human FXa (K_i 0.4 nM) with > 10 000-fold greater selectivity than for other serine proteases; it also inhibited prothrombinase activity (IC_{50} 2.1 nM). BAY 59-7939 inhibited endogenous FXa more potently in human and rabbit plasma (IC_{50} 21 nM) than rat plasma (IC_{50} 290 nM). It demonstrated anticoagulant effects in human plasma, doubling prothrombin time (PT) and activated partial thromboplastin time at 0.23 and 0.69 μM, respectively. *In vivo*, BAY 59-7939 reduced venous thrombosis (fibrin-rich, platelet-poor thrombi) dose dependently (ED_{50} 0.1 mg kg^{-1} i.v.) in a rat venous stasis model. BAY 59-7939 reduced arterial (fibrin- and platelet-rich) thrombus formation in an arteriovenous (AV) shunt in rats (ED_{50} 5.0 mg kg^{-1} p.o.) and rabbits (ED_{50} 0.6 mg kg^{-1} p.o.). Slight inhibition of FXa (32% at ED_{50}) reduced thrombus formation in the venous model; to affect arterial thrombosis in the rat and rabbit, stronger inhibition of FXa (74%, 92% at ED_{50}) was required. Calculated plasma levels in rabbits at the ED_{50} were 14-fold lower than in the rat AV shunt model, correlating with the 14-fold lower IC_{50} of FXa inhibition in rabbit compared with rat plasma; this may suggest a correlation between FXa inhibition and antithrombotic activity. Bleeding times in rats and rabbits were not significantly affected at antithrombotic doses (3 mg kg^{-1} p.o., AV shunt). Based on these results, BAY 59-7939 was selected for clinical development.

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Introduction

Anticoagulants in current clinical use comprise the vitamin K antagonists—such as warfarin—heparins (including low-molecular-weight heparins), and parenterally administered direct thrombin inhibitors. Warfarin can be administered orally; however, its major drawbacks include the need for monitoring—because of a narrow therapeutic window and large inter- and intraindividual variability in dose–response—a slow onset and offset of action, and extensive food and drug interactions [1–3]. Heparins have a rapid onset of action, but must be administered parenterally. Despite recent developments, there is still an unmet need for safe, oral anticoagulants for both short- and long-term use.

Factor Xa (FXa) has emerged as a particularly promising target for effective anticoagulation because it acts at the convergence point of the intrinsic and extrinsic coagulation pathways. FXa catalyzes the conversion of prothrombin to thrombin; one molecule of FXa results in the generation of more than 1000 thrombin molecules [4]. Thus, inhibiting FXa may block this burst of thrombin generation, thereby diminishing thrombin-mediated activation of coagulation and platelets.

Recent research has focused on the identification of small-molecule FXa inhibitors with good oral bioavailability and predictable pharmacokinetics. An oral, direct FXa inhibitor that does not require routine coagulation monitoring would offer significant advantages over current therapies. BAY 59-7939 belongs to a new class of small-molecule, active-site-directed FXa inhibitors. It is a non-basic compound with high oral bioavailability in rats and dogs (60–86%) [5]. Currently, BAY 59-7939 is in clinical development for the prevention and treatment of thromboembolic disorders.

We report the *in vitro* properties of BAY 59-7939, its antithrombotic efficacy in animal models of arterial and venous thrombosis, and its effect on hemostasis—the pharmacological profile on which BAY 59-7939 was chosen for clinical development.

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Materials and methods

Agents

BAY 59-7939 (5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide; Mr = 435.89 g mol^{-1}; Fig. 1) was synthesized by Bayer HealthCare AG (Wuppertal, Germany). Human, rat, and rabbit purified FXa, thrombin, and plasmin were obtained from Kordia (Leiden, The Netherlands); Factor XIa (FVIIa) from Calbiochem® (Schwalbach, Germany); trypsin and urokinase from Sigma (Taufkirchen, Germany); activated protein C (APC) from Haemochrom Diagnostica (Essen, Germany); Factor VIIa (FVIIa), Factor IXaβ (FIXaβ), FX, and prothrombin from Enzyme Research Laboratories (Swansea, UK); tissue factor from American Diagnostica Inc. (Stanford, USA). Chromogenic substrates (chromozym TH, X, U, trypsin, and plasmin) were from Roche Diagnostics (Mannheim, Germany); S 2366™ from Chromogenix Instrumentation Laboratory (Bubendorf, Switzerland); and Pefachrome® FXa from Pentapharm (Basel, Switzerland). Fluorogenic substrates (I-1100 and H-D-Phe-Pro-Arg-6-amino-1-naphthalene-benzylsulfonamide·H_2O) were from Bachem (Bubendorf, Switzerland); Russell's viper venom (RVV) from Pentapharm; Neoplastin® Plus (thromboplastin) and PTT-Reagent from Roche Diagnostics; hirudin (Refludan®) from Aventis (Strasbourg, France). Xylazine (Rompun®) was from Bayer HealthCare, ketamine (Ketavet®) from Pharmacia & Upjohn (Karlsruhe, Germany), and pentobarbital-Na (Nembutal®) from Richter Pharma (Wels, Austria).

In vitro *studies*

Enzyme assays The activity of BAY 59-7939 against purified serine proteases was measured using chromogenic or fluorogenic substrates in 96-well microtiter plates at 25 °C. The enzymes were incubated with BAY 59-7939 or its solvent, dimethyl sulfoxide (DMSO), for 10 min. The reactions were initiated by the addition of the substrate, and the color or fluorescence was monitored continuously at 405 nm using a Spectra Rainbow Thermo Reader (Tecan, Crailsheim, Germany), or at 630/465 nm using a SPECTRAfluor plus (Tecan), respectively, for 20 min (if not otherwise stated).

Enzymatic activity was analyzed in the following buffers (final concentrations): human FXa (0.5 nM), rabbit FXa (2 nM), rat FXa (10 nM), or urokinase (4 nM) in 50 mM Tris–HCl buffer, pH 8.3, 150 mM NaCl, and 0.1% bovine serum albumin (BSA); Pefachrome FXa (50–800 μM) or chromozym U (250 μM) with thrombin (0.69 nM), trypsin (2.2 nM), or plasmin (3.2 nM) in 0.1 μM Tris–HCl, pH 8.0, and 20 mM $CaCl_2$; chromozym TH (200 μM), chromozym plasmin (500 μM), or chromozym trypsin (500 μM) with FXIa (1 nM) or APC (10 nM) in 50 mM phosphate buffer, pH 7.4, 150 mM NaCl; and S 2366 (150 or 500 μM) with FVIIa (1 nM) and tissue factor (3 nM) in 50 mM Tris–HCl buffer, pH 8.0, 100 mM NaCl, 5 mM $CaCl_2$ and 0.3% BSA, H-D-Phe-Pro-Arg-6-amino-1-naphthalene-benzylsulfonamide·H_2O (100 μM) and measured for 3 h as described previously [6]. The FIXaβ/FX assay, comprising FIXaβ (8.8 nM) and FX (9.5 nM) in 50 mM Tris–HCl buffer, pH 7.4, 100 mM NaCl, 5 mM $CaCl_2$ and 0.1% BSA, was started by the addition of I-1100 (50 μM), and measured for 60 min.

The inhibitory constant (K_i) against FXa was calculated according to the Cheng–Prusoff equation ($K_i = IC_{50}/1 + [S]/K_m$), where [S] is the substrate concentration, and K_m is the Michaelis–Menten constant. K_m was determined from a Lineweaver–Burk plot. The IC_{50} was the amount of inhibitor required to diminish the initial velocity of the control by 50%.

Prothrombinase assay The effect of BAY 59-7939 on prothrombinase activity was measured via thrombin generation, as described previously with some modifications [7]. Briefly, human FXa (0.025 nM) was incubated in 10 mM HEPES buffer, pH 7.4, 2 mM $CaCl_2$ and washed human platelets (1×10^7 mL^{-1}) for 10 min at 37 °C. The reaction was initiated by adding prothrombin (1 μM) and BAY 59-7939 or DMSO. After 20 min, 20-μL aliquots were diluted with 160 μL buffer, and thrombin activity was measured using 20 μL chromozym TH (500 μM).

FXa activity in plasma Human, rat, or rabbit plasma (45 μL) was mixed with 5 μL hirudin (10 μg mL^{-1}), 5 μL BAY 59-7939 or DMSO, and 50 μL RVV (human, 0.7 mU mL^{-1}; rat/rabbit, 3.5 mU mL^{-1}), dissolved in 50 μM $CaCl_2$ at 37 °C. Chromozym X (50 μL; 600 μM) was added after 15 min. The increase in optical density was measured at 37 °C, as described above.

Coagulation assays Activated partial thromboplastin time (aPTT) and prothrombin time (PT) were measured using commercially available kits. BAY 59-7939 or DMSO (3 μL) were added to 100 μL platelet-poor plasma (PPP) and incubated for 10 min at 37 °C. Clotting times were measured in a coagulometer (Biomatic 4000; Sarstedt, Nümbrecht, Germany), in accordance with the manufacturer's instructions (final volume 303 μL). Anticoagulant activity was defined as the concentration required to double the plasma clotting times [CT_2 (μM)].

Plasma preparation Human blood was collected by venipuncture from healthy subjects who had not been medicated during the last 10 days. Rabbit blood was obtained by puncture of the A. carotis, and rat blood was withdrawn from the abdominal aorta under anesthesia. Blood was collected into plastic tubes containing 1/10 volume of 3.8% trisodium citrate. PPP was obtained by immediate centrifugation at 2500 *g* for 10 min at 4 °C, and stored at – 20 °C.

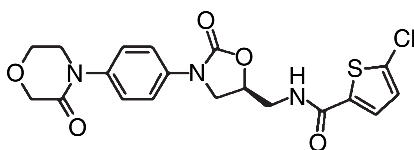

Fig. 1. Chemical structure of BAY 59-7939 (5-chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide).

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In vivo *studies*

Animals and anesthetics Fasted, male Wistar rats (HsdCpb:WU) were anesthetized by intraperitoneal injection of xylazine and ketamine (12 and 50 mg kg^{-1}, respectively); in the bleeding-time model, pentobarbital-Na (60 mg kg^{-1}) was used. Fasted, female New Zealand White rabbits (Esd:NZW) were anesthetized by intramuscular administration of xylazine and ketamine (5 and 40 mg kg^{-1}, respectively). All procedures were conducted in accordance with the German Animal Protection Act (Deutsches Tierschutzgesetz).

Rat venous stasis model Thrombus formation was induced in anesthetized rats ($n = 10$ per dose group) as described previously, with minor modifications [8]. The abdominal vena cava was exposed and two loose sutures (8–10 mm apart) were placed below the left renal venous branch. BAY 59-7939 dissolved in polyethylene glycol/H_2O/glycerol (996 g/100 g/60 g), or vehicle was given by intravenous (i.v.) bolus injection into a tail vein 15 min before thrombus induction. Thromboplastin (0.5 mg kg^{-1}) was injected into a femoral vein and, after 15 s, the proximal and distal sutures were tied. Fifteen minutes later, the ligated segment was removed, the thrombus withdrawn and weighed. Blood samples were obtained by cardiac puncture immediately before thrombus removal.

Arteriovenous shunt model in rats and rabbits An arteriovenous (AV) shunt in anesthetized rats and rabbits was performed as described previously, with minor modifications [8–10]. The right common carotid artery and the left jugular vein were cannulated with two 100-mm-long, saline-filled catheters. In rats ($n = 10$ per dose group), the polyethylene catheters (PE-60; Becton Dickinson, Sparks, MD, USA) were connected with a 30-mm-long polyethylene tube (PE-160; Becton Dickinson) containing a rough nylon thread (40 × 0.15 mm), folded into a double string. In rabbits ($n = 6$ per dose group), polyurethane vein catheters (outside diameter 2.1 mm; Braun, Melsungen, Germany) were connected with a 40-mm-long polyethylene tube (PE-240; Becton Dickinson), containing a rough nylon thread (60 × 0.15 mm), folded into a double string. BAY 59-7939, dissolved in solutol/ethanol/H_2O [40%/10%/50% (v/v/v)], or vehicle was given orally 90 min before the shunt was opened for 15 min. The nylon thread was then withdrawn and weighed. Blood samples were withdrawn from the carotid artery just after thrombus removal.

Rat tail-bleeding model BAY 59-7939 ($n = 10$ per dose group) or vehicle was given orally 90 min before the tails of anesthetized rats were transected 2 mm from the tip and vertically immersed in saline at 37 °C. The time until continuous blood flow ceased for > 30 s was measured, with a maximum observation time of 10 min (longer bleeding times were assigned a value of 10 min).

Rabbit ear-bleeding model Ear-bleeding time (EBT) was determined in anesthetized rabbits ($n = 5$ per dose group), as described previously [11]. A standardized 3-mm-long incision was made at different sites of the right ear in each animal 90 and 105 min after administration of oral BAY 59-7939 or vehicle. Blood from the incision was removed with filter paper every 30 s. The time until the bleeding stopped was measured.

Statistical analysis

Student's *t*-test (one-way ANOVA) was used for unpaired data, with a statistical significance level of $P < 0.05$. Data are expressed as mean ± SEM. IC_{50} values were calculated using Graph Pad Prism, version 3.02 (Graph Pad Software Inc., San Diego, CA, USA). ED_{50} values were calculated by linear regression analysis using Excel 97 (Microsoft®).

Results

In vitro *studies*

Enzyme assays BAY 59-7939 inhibited human FXa concentration dependently, with a K_i of 0.4 ± 0.02 nM (Fig. 2). It is a competitive inhibitor of the amidolytic activity of FXa, as demonstrated by Lineweaver–Burk analysis (Fig. 3). At concentrations up to 20 μM, BAY 59-7939 did not affect related serine proteases; selectivity was more than 10 000-fold greater for FXa (Table 1). BAY 59-7939 showed a similar affinity to purified human and rabbit FXa (IC_{50} 0.7 ± 0.01 and 0.8 ± 0.01 nM, respectively), but was less potent against purified rat FXa (IC_{50} 3.4 nM; Table 2).

Prothrombinase assay To determine whether BAY 59-7939 was an effective inhibitor of FXa complexed with Factor Va and Ca^{2+} on a phospholipid membrane, we reconstituted the prothrombinase complex on platelets. The generation of thrombin was inhibited concentration-dependently, with an IC_{50} of 2.1 ± 0.4 nM, as measured in an amidolytic assay (Fig. 2).

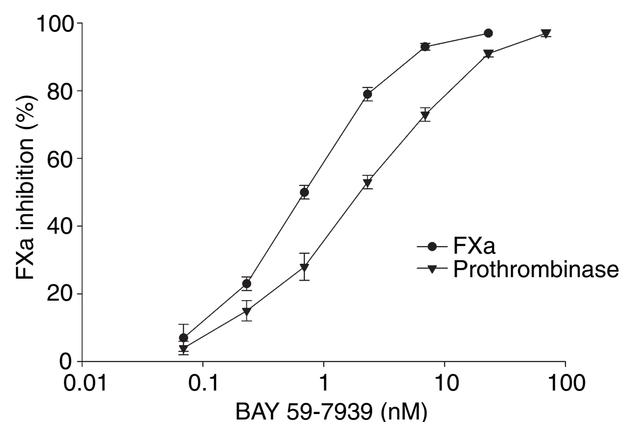

Fig. 2. Effect of BAY 59-7939 on purified human free Factor Xa (FXa) using a chromogenic substrate of FXa (●), and on prothrombinase activity on platelet surfaces using prothrombin as substrate (measuring generated thrombin; ▼). Each value represents the mean ± SEM of five measurements in triplicate.

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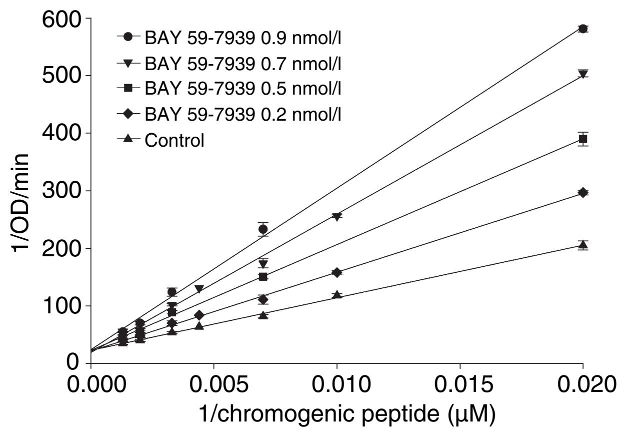

Fig. 3. Kinetic analysis of the inhibitory effect of BAY 59-7939 on Factor Xa (FXa). Lineweaver–Burk plots of the activity of 0.5 nM FXa against a chromogenic substrate in the absence or presence of 0.2, 0.5, 0.7, and 0.9 nM BAY 59-7939. Results are mean ± SD.

Table 1 Human protease selectivity profile of BAY 59-7939

Inhibition of	Concentration (nM)
Factor Xa	$K_i = 0.4 \pm 0.02$
Factor VIIa, Factor IXa, Factor XIa, thrombin, activated protein C, plasmin, urokinase, trypsin	$IC_{50} > 20\ 000$

Table 2 Effect of BAY 59-7939 on inhibition of human, rabbit, and rat Factor Xa (FXa) in buffer, plasma FXa, and the concentrations required to double the prothrombin time (PT) and activated partial thromboplastin time (aPTT) *in vitro* (CT_2)

Species	FXa (buffer) IC_{50} (nM)	FXa (plasma) IC_{50} (nM)	PT CT_2 (µM)	APTT CT_2 (µM)
Human	0.7 ± 0.01	21 ± 1.0	0.23 ± 0.02	0.69 ± 0.09
Rabbit	0.8 ± 0.01	21 ± 2.0	0.12 ± 0.01	1.97 ± 0.49
Rat	3.4 ± 0.02	290 ± 20.0	0.30 ± 0.02	2.09 ± 0.19

Results expressed as mean ± SEM.

FXa activity in plasma In plasma, endogenous human and rabbit FXa, generated by RVV, was inhibited to a similar extent by BAY 59-7939 (IC_{50} 21 ± 0.001 and 21 ± 0.002 nM, respectively), whereas 14-fold higher concentrations were required in rat plasma (IC_{50} 290 ± 0.02 nM; Table 2).

Plasma clotting times BAY 59-7939 prolonged PT and aPTT concentration dependently; the PT assay was more sensitive than aPTT. In the PT assay, anticoagulant activity was greatest in the rabbit (CT_2 0.12 ± 0.01 µM), followed by human (CT_2 0.23 ± 0.02 µM), and then rat (CT_2 0.30 ± 0.02 µM; Table 2). In the aPTT assay, BAY 59-7939 was most potent in human plasma (CT_2 0.69 ± 0.09 µM) and less effective in rabbit and rat plasma (CT_2 1.97 ± 0.49 and 2.09 ± 0.19 µM, respectively).

In vivo *studies*

Rat venous stasis model In a venous thrombosis model, thrombi were obtained by employing a combination of stasis and injection of thromboplastin. BAY 59-7939, administered by i.v. bolus before thrombus induction, reduced thrombus formation (ED_{50} 0.1 mg kg^{-1}), inhibited FXa, and prolonged PT (Fig. 4A–C) dose dependently. PT and FXa were affected slightly at the ED_{50} (1.8-fold increase and 32% inhibition, respectively). At 0.3 mg kg^{-1} (dose leading to almost complete inhibition of thrombus formation), BAY 59-7939 moderately prolonged PT (3.2 ± 0.5-fold) and inhibited FXa activity (65 ± 3%).

Rat AV-shunt model Thrombosis was induced by exposure of a thrombogenic surface in an AV shunt. To evaluate its potential oral efficacy, BAY 59-7939 was given orally before blood was circulated in the shunt. BAY 59-7939 reduced thrombus formation dose dependently (ED_{50} 5.0 mg kg^{-1}; Fig. 5A). It also had a dose-dependent effect on

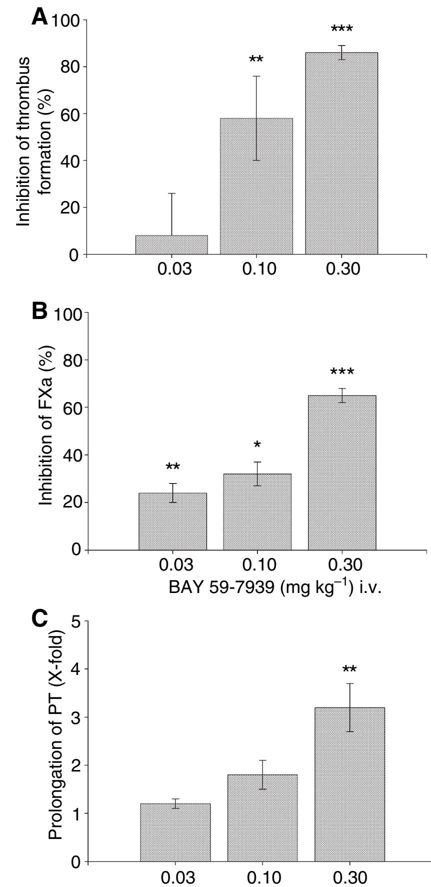

Fig. 4. Effect of BAY 59-7939 in a rat venous stasis model. BAY 59-7939 or the appropriate vehicle was given by i.v. bolus injection 15 min before thrombus induction. (A) Inhibition of thrombus formation. (B) Inhibition of endogenous Factor Xa (FXa) after activation by Russell's viper venom. (C) Prolongation of prothrombin time (PT). Blood samples were withdrawn by cardiac puncture immediately after removal of the thrombus. Results are mean ± SEM of 10 animals. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

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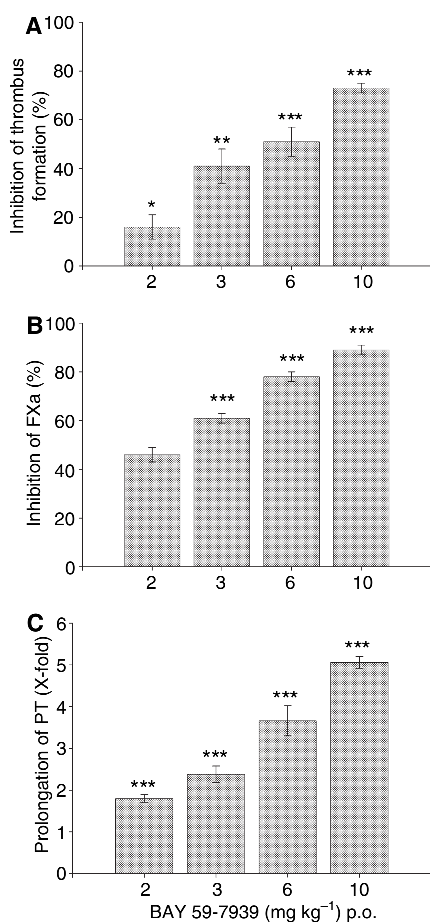

Fig. 5. Effect of BAY 59-7939 in a rat arteriovenous (AV)-shunt model. BAY 59-7939 or vehicle was given orally 90 min before blood was circulated in the shunt. (A) Inhibition of thrombus formation. (B) Inhibition of endogenous Factor Xa (FXa) after activation by Russell's viper venom. (C) Prolongation of prothrombin time (PT). Blood samples were withdrawn from the carotid artery catheter just after thrombus removal. Results are mean ± SEM of six animals. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

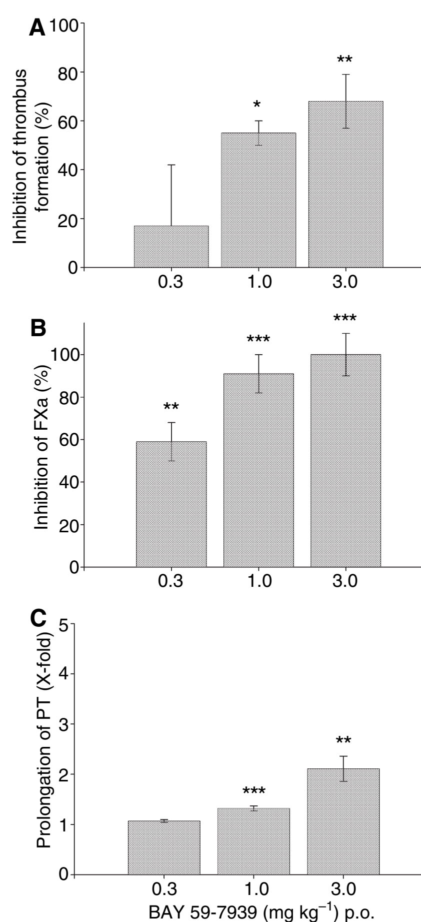

Fig. 6. Effect of BAY 59-7939 in a rabbit arteriovenous (AV)-shunt model. The extracorporeal circulation was opened 90 min after oral administration of BAY 59-7939 or vehicle. (A) Inhibition of thrombus formation. (B) Inhibition of endogenous Factor Xa (FXa) after activation by Russell's viper venom. (C) Prolongation of prothrombin time (PT). Blood samples were withdrawn from the carotid artery catheter just after removal of the thrombus. Each value represents the mean ± SEM of six animals. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

FXa activity and PT (Fig. 5B,C); at the ED_{50}, BAY 59-7939 inhibited FXa by 74% and prolonged PT 3.2-fold, as calculated from the dose–response curves.

Rabbit AV-shunt model Oral BAY 59-7939, given before opening the shunt, inhibited thrombus formation dose dependently (ED_{50} 0.6 mg kg^{-1}; Fig. 6A). It also had a dose-dependent effect on FXa activity and PT (Fig. 6B,C); at the ED_{50}, FXa was almost completely inhibited (92%), but PT was prolonged only slightly (1.2-fold), as calculated from the dose–response curves.

Rat tail-bleeding model Tail-bleeding time was evaluated at the antithrombotic-effective oral dose (minimal dose preventing thrombus formation in AV shunt model) of 3 mg kg^{-1} and multiples thereof. Bleeding time was not different from baseline at the antithrombotic-effective dose of BAY 59-7939 (Table 3). At doses greater than the ED_{50} (6 and 10 mg kg^{-1}), there was a dose-dependent, moderate prolongation of approximately 2- and 3-fold, respectively.

Rabbit ear-bleeding model EBT was assessed at 90 and 105 min in the same animal after oral administration of BAY 59-7939. At all doses tested, there was no significant increase of EBT, even at multiples of the ED_{50} in the AV-shunt model (Table 3).

Table 3 Effect of BAY 59-7939 on rat tail-transection bleeding time and rabbit ear-bleeding time measured 90 and 105 min after oral administration

	Prolongation of bleeding time (X-fold)		
		Ear-bleeding time, rabbit	
BAY 59-7939 (mg kg^{-1}) p.o.	Tail-bleeding time, rat	t = 90 min	t = 105 min
0.3	ND	1.4 ± 0.7	1.0 ± 0.5
1.0	ND	1.7 ± 0.9	1.1 ± 0.5
3.0	1.0 ± 0.1	1.6 ± 0.8	1.3 ± 0.7
6.0[a]	2.1 ± 0.2*	ND	ND
10.0[a]	2.7 ± 0.2***	ND	ND

ND, Not determined. $*P < 0.05$; $***P < 0.001$. Results are expressed as mean ± SEM. [a]Bleeding did not stop within the observation time of 10 min in two of 10 rats.

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