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EFFICACY OF 4-(2-(4-NITROPHENYL)-2-OXOETHYL)-1-(THIETANE-3-YL)-1H-1,2,4-TRIAZOL-4 BROMIDE IN THE RAT MODEL OF INFERIOR VENA CAVA THROMBOSIS

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Abstract

Introduction. According to WHO, acute disorders of cerebral circulation are anticipated to become a predominant contributor to the global disease burden by 2030. The comprehensive management of vascular depression entails not only the use of antidepressants but also fundamental interventions. The development of a novel molecule based on thietane-containing heterocycles, merging the attributes of an antidepressant and an antiplatelet agent, holds promise for enhancing therapeutic efficacy in patients with acute cerebrovascular accidents through multimodal action.

Objective is to conduct a preclinical assessment of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4-th bromide concerning model thrombosis in rats.

Materials and Methods. The investigation involved the evaluation of thrombosis processes and the haemostasis system in rats subjected to complete occlusion of the inferior vena cava within 24 hours post-thrombosis induction. Techniques employed included thromboelastography, Born aggregometry, standard clotting assays to appraise the coagulation facet of haemostasis, and morphological examinations.

Results. The results demonstrate that 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4-th bromide mitigates thrombosis mass, restores platelet hyper aggregation, and counters hypercoagulation observed in acute inferior vena cava thrombosis in rats. Comparative analysis with reference drugs substantiates the superior effectiveness of the chosen compound in thrombosis prevention.

Conclusion. The preclinical investigation of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4-th bromide unveils a fusion of established antidepressant and antithrombotic activities, laying groundwork for further drug development endeavours.

Key words: antithrombotic activity, haemostasis system, pharmacological activity, thietane-containing heterocycles.

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ЭФФЕКТИВНОСТЬ 4-(2-(4-НИТРОФЕНИЛ)-2-ОКСОЭТИЛ)-1-(ТИЕТАН-3-ИЛ)-1Н-1,2,4-ТРИАЗОЛ-4-ИЯ БРОМИДА НА МОДЕЛИ ТРОМБОЗА НИЖНЕЙ ПОЛОЙ ВЕНЫ У КРЫС

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Резюме

Введение. По прогнозам ВОЗ, к 2030 году острые нарушения мозгового кровообращения будут занимать лидирующие позиции среди причин бремени болезней в глобальном масштабе. Комплексная терапия сосудистой депрессии включает не только антидепрессанты, но и базисные средства для коррекции последствий нарушений мозгового кровотока, в том числе с антиагрегантной активностью. В этой связи разработка новой молекулы на основе тиетансодержащих гетероциклов, сочетающей в себе свойства антидепрессанта и антиагреганта, позволит качественно усилить эффективность терапии пациентов с острым нарушением мозгового кровообращения за счет мультимодального действия.

Цель работы. Провести доклиническую оценку 4-(2-(4-нитрофенил)-2-оксоэтил)-1-(тиетан-3-ил)-1н-1,2,4-триазол-4-ия бромида в отношении модельного тромбоза у крыс.

Материалы и методы. Изучены процессы тромбообразования и система гемостаза крыс, подвергшихся полной окклюзии нижней полой вены на первые сутки после тромбоза. Проводились тромбоэластография, агрегатометрия по Born, стандартные клоттинговые тесты по оценке коагуляционного звена гемостаза и морфологические исследования.

Результаты. Установлено, что 4-(2-(4-нитрофенил)-2-оксоэтил)-1-(тиетан-3-ил)-1н-1,2,4-триазол-4-ия бромида снижает массивность тромбоза, нормализует показатели гиперагрегации тромбоцитов и гиперкоагуляции, возникающие при остром тромбозе нижней полой вены у крыс. Сопоставление с препаратами сравнения подтверждает высокую эффективность выбранного соединения в качестве средства профилактики тромбоза.

Заключение. Таким образом, в результате доклинических исследований 4-(2-(4-нитрофенил)-2-оксоэтил)-1-(тиетан-3-ил)-1н-1,2,4-триазол-4-ия бромида установлено сочетание ранее определенной антидепрессивной и антитромботической активности, что может послужить основой для дальнейшей разработки лекарственных препаратов.

Ключевые слова: антитромботическая активность, производные 3-замещенных тиетанов, система гемостаза, фармакологическая активность.

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Introduction

By 2030, acute cerebral vascular accidents (ACVA) are projected to emerge as a leading cause of global disease burden, according to WHO forecasts [1, 2]. A hallmark manifestation of vascular brain damage is the onset of depressive disorders, which accompany both acute and chronic disorders of cerebral circulation. This depressive state not only diminishes the patient's quality of life but also complicates the treatment of underlying vascular diseases, elevating the risks of stroke and mortality [3]. Epidemiological data indicate that one in every three stroke survivors experiences a clinically significant decrease in mood [4]. Combining antidepressants with fundamental methods of correcting impaired cerebral blood flow can notably augment their therapeutic efficacy, enhancing cognitive functions and alleviating behavioural and psychological symptoms [5, 6]. However, the effectiveness of antidepressants in treating vascular depression tends to be somewhat lower compared to conventional depression. Moreover, a greater severity of accompanying cognitive disorders serves as a predictive factor for an inadequate response to therapy. Consequently, the comprehensive management of vascular depression encompasses not only antidepressants but also basic interventions to rectify the consequences of cerebral blood flow disorders, including those with antiplatelet activity [7]. In this context, the development of a novel molecule based on thietane-containing heterocycles, amalgamating the attributes of an antidepressant and an antiplatelet agent, promises to significantly enhance therapy effectiveness for ACVA patients through its multimodal action. The synthesis of analogues and derivatives of established drugs represents a contemporary trend in the realm of new drug development. Earlier investigations targeting potential antiplatelet agents among newly synthesised 3-substituted thietanes have revealed pronounced antiplatelet activity in select compounds of this series in vitro [8]. This paper delineates the therapeutic and prophylactic efficacy findings of 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazol-4-bromide [4] (referred to as compound I) and drugs utilised in clinical practice concerning diurnal thrombosis of the inferior vena cava in rats.

Materials and Methods

Experimental procedures adhered to the guidelines outlined in the "Guidelines for the preclinical study of new pharmacological substances". The study involved 84 adult male rats of white non-linear strain, aged between 3.5 and 4.0 months. The animals were housed under standard vivarium conditions with a temperature of 21 ± 1.5 °C, humidity ranging from 57 % to 60 %, and exposed to natural lighting. Prior to experimentation, the rats underwent a 24-hour fasting period with continuous access to water [9]. All experimental protocols complied with the International Recommendations of the European Convention for the Protection of Vertebrates for Experimental Animals, the regulations of laboratory practices during preclinical studies in the Russian Federation, and adhered to the Ministry of Health and Social Development of Russia Order No. 708n dated 23.08.2010, known as the "Rules of Laboratory Practice" (GLP). Ethical approval for the study was obtained from the ethics committee of the Bashkir State Medical University (protocol No. 2, dated November 12, 2020).

Rats were stratified into specific experimental groups, each comprising 20 individuals: intact rats, sham-operated rats (subjected solely to anaesthesia and median laparotomy), saline-treated rats, rats treated with pentoxifylline, rats treated with acetylsalicylic acid, rats treated with sodium enoxaparin, and rats treated with compound I. Considering the principle of chemical similarity and the potential application of compound I in depression management associated with cerebral circulation disorders, 3,7-dimethyl-1-(5-oxohexyl)xanthine was selected as an analogue drug at this stage of the study ("Pentoxifylline," JSC "Dalkhimpharm," Russia) [10].

Intravenous administration of the test substance and comparator drugs was conducted one hour prior to modelling thrombosis of the inferior vena cava, following established protocols [11]. Dosages were equimolar to the dose of pentoxifylline, which suppresses platelet aggregation in intact rats by 50 % with intravenous administration (ED50 = 40.0 mg/kg). The control group received an appropriate volume of sterile 0.9 % sodium chloride solution (500 ml infusion solution, B. Brown Medical, Russia, series N 22530629, valid until: 06.2024).

Following the conclusion of the experiments, the efficacy of preventive measures was assessed by measuring the masses of blood clots and evaluating haemostasis system indicators. Under general anaesthesia, blood samples were collected from the jugular vein through venesection [12]. A 3.8 % sodium citrate solution (stabiliser) was used for venous blood collection.

Platelet aggregation function was assessed using the Born method [13] on an aggregometer "AT-02" (LLC "NPF Meditsina-Technika," Russia). Adenosine diphosphate (ADP) at a concentration of 20 μg/ml and collagen at 5 mg/ml were employed as inducers of platelet aggregation at various stages of the study.

The effect on the coagulation component of haemostasis (activated partial thromboplastin time (APTT),

prothrombin time (PT), fibrinogen levels), D-dimer levels, and antithrombin III (ATIII) activity were measured using an automated selective haemostasis analyser STA-Compact (F. Hoffmann-La Roche Ltd., France) with original reagent kits manufactured by Roche Diagnostics (F. Hoffmann-La Roche Ltd., France) [14].

Thromboelastography was performed using a TEG 5000 device (Haemoscope Corporation, USA) to analyse thromboelastograms, determining parameters such as clotting tendency (R), platelet and fibrinogen functional activity (MA, Angle), fibrinolysis activity (CLT), and physicomechanical properties of clots (G) [15, 16].

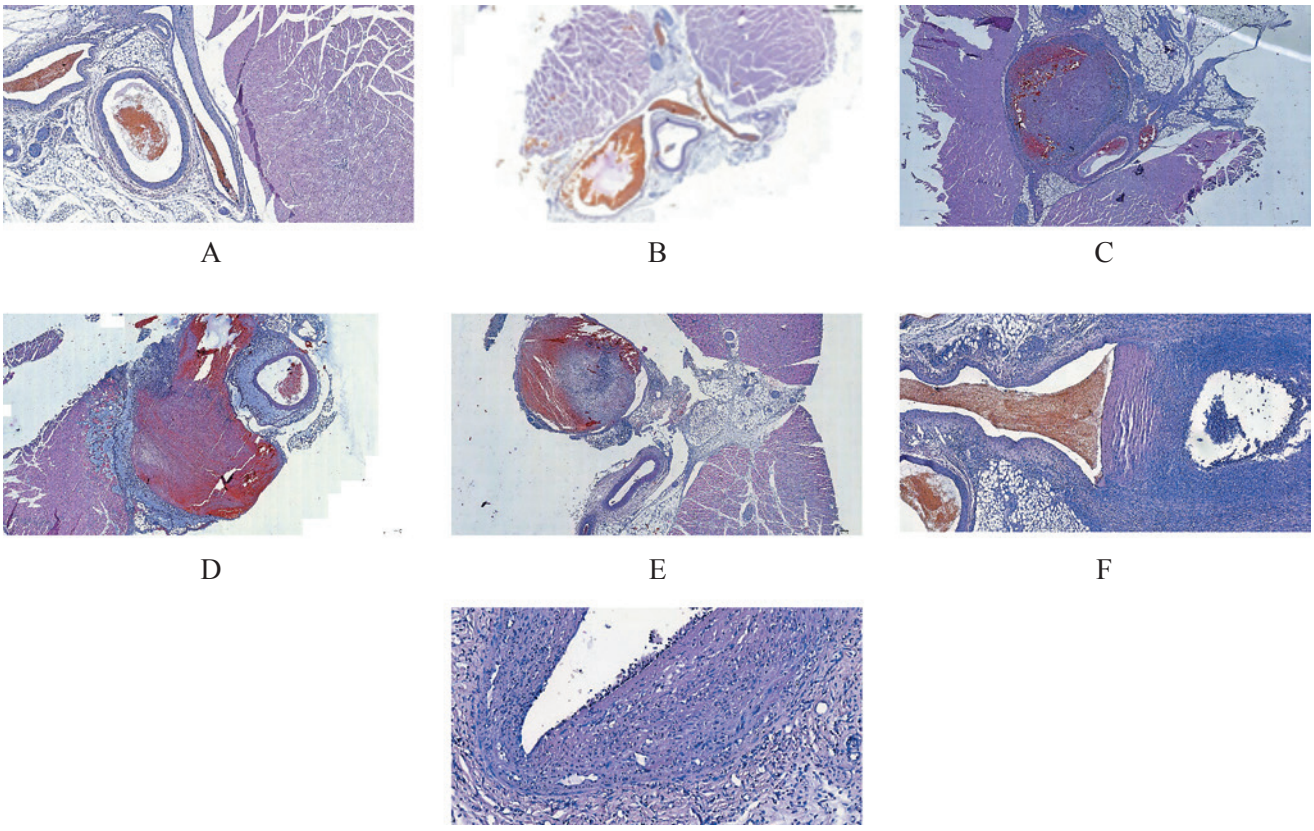
Under general anaesthesia, rats underwent surgical access to the abdominal cavity to extract formed thrombi from the inferior vena cava. Thrombus mass was measured immediately post-extraction, with dry thrombus mass determined after 7 days of drying at 37 °C.

Post-experiment, tissue sampling was conducted for morphological studies. Cross-sections of the substance were incised at intervals of 0.5 cm, with fragments featuring visible thrombosis of the inferior vena cava selected for histological processing. Tissues were fixed in 10 % buffered neutral formalin, underwent standard histological treatment, embedded in paraffin, and sectioned to a thickness of 4 microns for staining with haematoxylin-eosin.

To mitigate the uncontrolled influence of local temperature on chemical and biochemical processes, all laboratory procedures were performed under infrared monitoring of local temperature dynamics using a ThermoTracer TH9100XX thermal imager (NEU, USA), with ambient temperatures maintained between 24–25 °C. Temperature range for thermal imaging camera was set at 25–36 °C [17–19].

Comparison drugs used in the experiments included: pentoxifylline (solution for injection 20 mg/ml-5 ml, JSC "Borisovsky Plant of medicines" (Belarus, Borisov), series N 290918, valid until: 08.2023), acetylsalicylic acid (Pharmaceutical factory Shandong Xinhua Pharmaceutical Co., LTD, China, series N 10L18, valid until: 06.2024), and enoxaparin sodium ("Kleksan"®, solution for injection 40 mg/ml-1 ml, Sanofi-Aventis France, France, series N 5LM42, valid until 11.2023).

Statistical analysis of study results was performed using the Statistica 10.0 statistical package (StatSoft Inc, USA). Normality of data distribution was assessed using the Shapiro-Wilk criterion. Descriptive statistics were presented as median and interquartile interval. Analysis of variance was conducted using the Kraskel-Wallis criterion (for independent observations) and Friedman test (for repeated observations), with a critical significance level set at $p < 0.05$ [20].



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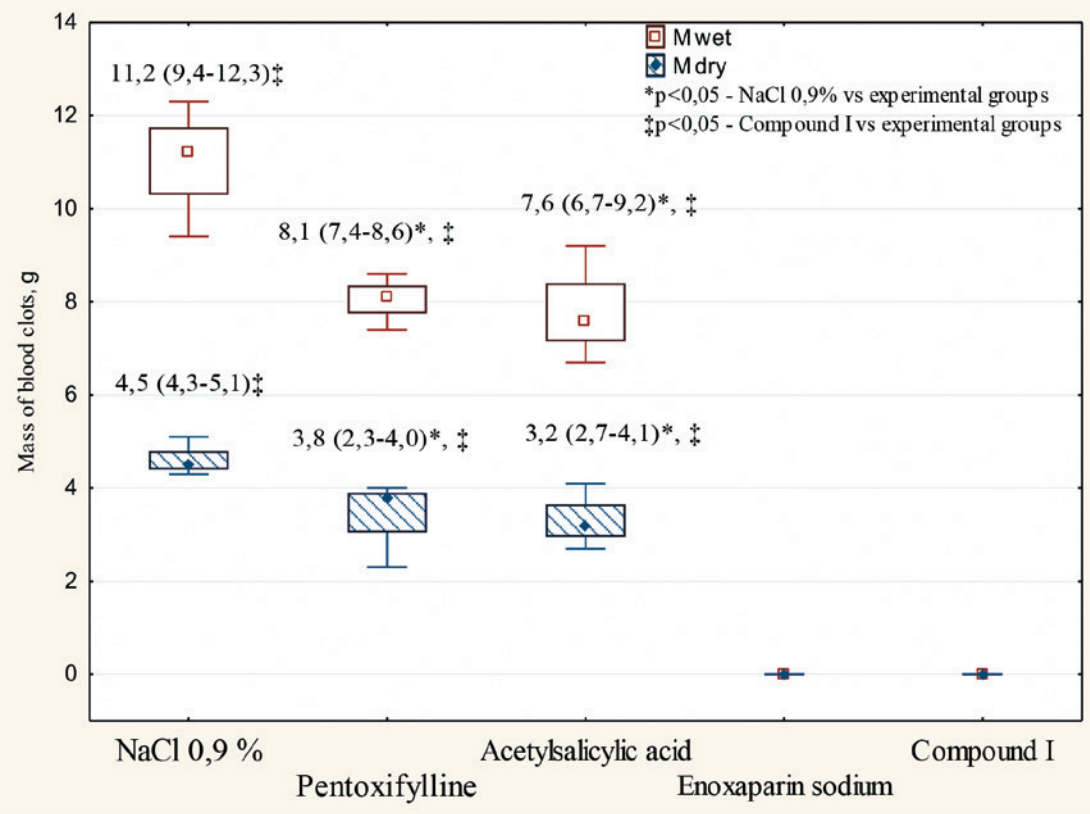

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Figure 1. Sections of the inferior vena cava of the intact rats (A) and group of falsely operated rats (B), Saline Solution group (C), Pentoxifylline (D), Acetylsalicylic acid (E), Enoxaparin sodium (F) and Compound I (G) and results of weighing blood clots from the inferior vena cava (H):

A, B — Transverse section microphotos represented by the inferior vena cava, aorta, nerve bundles, and surrounding soft tissues, Stained Hematoxylin-Eosin. ×20; C–D — Transverse section of the inferior vena cava and aorta. Venous-type vessel with mixed thrombus of layered architecture and foci of organisation. Intima is thickened due to mucoid swelling, media is represented by 2–3 layers of smooth myocytes, adventitia is made by fibrous connective tissue. Particularly, Figure D shows pronounced perivascular plasmatic tissue impregnation, Stained Hematoxylin-Eosin. ×50; E–F — there is visually thickened wall of the inferior vena cava. In the vicinity there is an enlarged lymphoid nodocity with purulent cells in the centre. Stained Hematoxylin-Eosin. ×20. Figure G show the wall of the vena cava with residual agglutinated platelets and leukocytes along the intima of the vessel. No thrombotic masses are visualised in the lumen, Stained Hematoxylin-Eosin. ×200.

Рис. 1. Срезы нижней полой вены интактных крыс (A), группы ложнооперированных крыс (B), группы физиологического раствора (C), пентоксифиллина (D), ацетилсалициловой кислоты (E), эноксапарина натрия (F), соединения I (G) и результаты взвешивания тромбов нижней полой вены (H):

A, B — микрофотографии поперечного сечения, представленные нижней полой веной, аортой, нервными пучками и окружающими мягкими тканями, окрас гематоксилин-эозин ×20; C–D — поперечный срез нижней полой вены и аорты. Сосуд венозного типа со смешанным тромбом слоистой архитектуры и очагами организации. Интима утолщена за счет слизистой оболочки, медия представлена 2–3 слоями гладких миоцитов, адвентиция представлена волокнистой соединительной тканью. В частности, на рисунке D показана выраженное периваскулярное плазматическое пропитывание ткани, окрас гематоксилин-эозин. ×50; E-F — визуально утолщена стенка нижней полой вены. Рядом — увеличенный лимфоидный узелок с гнойными клетками в центре. Окрас гематоксилин-эозин ×20. На рисунке G представлена стенка полой вены с остаточными агглютинированными тромбоцитами и лейкоцитами по интиме сосуда. В просвете тромботические массы не визуализируются. Окрас гематоксилин-эозин, x200.

Results

The study revealed that in the group of falsely operated rats, no blood clot formation occurred in the intact inferior vena cava. Median values of fresh and dry blood clot masses in rats treated with saline solution were 11.2 g and 4.5 g, respectively (Table 1). Treatment with acetylsalicylic acid and pentoxifylline significantly reduced the mass of fresh blood clots by 1.5 times ($p < 0.05$) compared to the control. Administration of sodium enoxaparin or compound I effectively prevented blood clot formation under conditions of complete occlusion, as no thrombosis was observed upon visual examination of the inferior vena cava.

Macroscopic assessments were corroborated by histological examinations. On the first day of the experiment, histological analysis in the control groups revealed parietal thrombosis of the inferior vena cava accompanied by interstitial tissue oedema (Figure 1). Conversely, no blood clots were detected in rats treated with compound I or enoxaparin sodium.

D-dimer levels in the saline solution group increased significantly to 6.4 μg/ml ($p < 0.05$), while antithrombin III (ATIII) activity decreased by 31.5 % ($p < 0.05$) compared to intact rats, reflecting increased consumption in the thrombosis area. Pentoxifylline and acetylsalicylic acid reduced ATIII activity by an average of 20.4 % ($p < 0.05$) relative to intact rats, with D-dimer levels comparable to the saline solution group. Conversely, D-dimer and ATIII levels in the enoxaparin sodium and compound I groups corresponded to those of intact animals.

Platelet aggregation normalisation to intact levels was observed with pentoxifylline, acetylsalicylic acid, and enoxaparin sodium treatments. Compound I significantly reduced platelet aggregation by 1.3 times ($p < 0.05$) compared to intact animals for ADP and collagen.

Thromboelastography of rats in the physiological control group indicated haemostasis system activation towards coagulation system and fibrinolysis activation (Table 2). Platelet functional activity, represented by maximum amplitude (MA), increased by 1.3 times ($p < 0.05$), while the coagulation enzymatic component (R) decreased by 2.2 times ($p < 0.05$). The clotting potential index (CI) was 3.6 ($p < 0.05$), indicative of pronounced hypercoagulation. Clot strength remained consistent with control values.

Thromboelastography data for pentoxifylline and acetylsalicylic acid demonstrated effective correction

Table 1. Indicators of antithrombotic activity of compound I and comparison drugs in the simulation of inferior vena cava thrombosis in rats, Me [0.25–0.75]

Таблица 1. Показатели антитромботической активности соединения I и препаратов сравнения при моделировании тромбоза нижней полой вены у крыс, Me [0,25–0,75]

№	Group	ADP, mm	Collagen, mm	AT (III), %	D-dimers, μg/ml
1	Intact rats	44,8 (43,9–54,2)	44,1 (42,7–46,9)	96,1 (94,8–97,1)	2,3 (1,8–2,5)
2	A group of falsely operated rats	46,5‡ (43,2–56,9)	43,4‡ (40,2–44,8)	95,9 (94,8–98,2)	2,8 (2,3–2,9)
3	NaCl 0,9 %	67,4*, ‡ (58,2–71,9)	64,5*, ‡ (59,2–71,8)	65,8*, ‡ (64,4–77,1)	6,4*, ‡ (5,8–6,6)
4	Pentoxifylline	47,8‡ (46,3–54,1)	42,9‡ (40,8–44,5)	76,5*, ‡ (74,7–80,5)	6,3*, ‡ (5,9–6,8)
5	Acetylsalicylic acid	48,2‡ (45,1–52,6)	43,6‡ (38,7–45,9)	76,8*, ‡ (73,1–78,4)	5,7*, ‡ (5,5–6,2)
6	Enoxaparin sodium	42,8‡ (41,4–49,1)	42,4‡ (40,3–45,6)	96,2 (93,7–97,1)	2,7 (2,5–2,9)
7	Compound I	36,8* (34,6–38,5)	37,4* (34,3–39,4)	94,9 (93,8–96,9)	3,3 (2,2–4,0)

Note: *p < 0,05 — group of intact rats vs experimental groups, ‡p < 0,05 — compound I vs experimental groups. M is the mass of blood clots.

of hypercoagulation and platelet hyper aggregation induced by thrombosis, returning values to those of intact animals. Enoxaparin sodium treatment led to parameters indicative of decreased coagulation component activity, with lengthened K and R parameters ($p < 0.05$) and reduced MA ($p < 0.05$). Compound I prophylactic administration normalised thromboelastography parameters, decreasing MA by 46.9 % ($p < 0.05$) compared to the saline solution group and by 31.0 % ($p < 0.001$) compared to intact rats. Coagulation index (CI) values indicated a shift towards hypo coagulation and its value lies in range of -0.8/-1.3.

Discussion

The emergence of organic depression in recent years, often linked with vascular brain diseases, necessitates a multimodal approach to treating patients with cerebral circulatory disorders. This approach involves not only antidepressants but also antiplatelet agents. The development of novel drugs based on thietane-containing heterocycles, with both antiaggregational and antidepressant properties, represents a contemporary trend in pharmacology due to their broad pharmacological activity and high safety profile. Notably, some newly synthesised 3-substituted thietanes have exhibited significant antiaggregational activity in vitro [13].

In this study, 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4-bromide (compound I), possessing antidepressant activity, demonstrated notable antithrombotic efficacy in a rat model of inferior vena cava thrombosis. Both therapeutic and prophylactic administrations of compound I resulted in substantial reductions in platelet aggregation and improvements in thromboelastography parameters compared to pentoxifylline, acetylsalicylic acid, and enoxaparin sodium. Considering its chemical structure affinity, it is plausible to hypothesise that compound I's antiplatelet activity may be akin to other xanthine derivatives, potentially involving platelet adenosine receptors and cyclic AMP concentration regulation [21]. However, further investigations employing recep-

Table 2. Evaluation of the effectiveness of compound I and comparison drugs to prevent thrombosis of the inferior vena cava according to thromboelastography, Me [0.25–0.75]

Таблица 2. Оценка эффективности соединения I и препаратов сравнения для профилактики тромбоза нижней полой вены по данным тромбоэластографии, Me [0,25–0,75]

Indicator	Control (intact)	S. NaCl 0,9 %	Pentoxifylline	Acetylsalicylic acid	Enoxaparin sodium	Compound I
R, min	12,1 (10,8–13,3)	5,6* (4,5–7,1)	12,7 (10,2–14,1)‡	11,4 (9,7–13,2)‡	6,7 (6,1–7,5)*	7,4 (6,8–7,7)
K, m	4,5 (4,2–5,7)	5,2 (3,3–6,1)	5,6 (5,2–6,4)	4,7 (4,3–5,7)	6,8* (6,3–7,4)	4,6 (4,1–5,9)
Angle, deg	44,2 (42,1–45,8)	71,2* (71,4–75,4)	42,3 (41,0–44,9)	44,8 (41,5–46,9)	38,5 (37,2–42,1)	42,3 (39,6–43,4)
MA, mm	56,1 (52,4–57,9)	72,8*, ‡ (69,4–73,5)	52,4‡ (49,6–54,1)	55,1‡ (49,1–57,3)	52,9‡ (49,7–54,7)	38,7* (31,6–41,5)
G, dyne/ cm^2	6,2 (5,8–6,5)	6,3‡ (5,7–7,1)	5,4‡ (5,1–7,2)	6,1‡ (5,4–7,1)	3,6* (3,3–4,7)	4,3* (3,7–4,8)
CL30, %	92,8 (88,4–94,5)	100,0 (100,0–100,0)	95,3 (91,4–98,2)	91,4 (89,5–93,1)	86,5 (84,4–92,3)	82,7 (81,6–91,4)
LY30, %	28,7 (27,3–30,5)	84,1* (83,7–93,5)	28,5 (27,5–32,1)‡	25,2 (21,6–27,4)	32,7 (29,8–34,1)	28,7 (27,5–30,4)
CLT, min	46,2 (44,5–47,1)	27,5*, ‡ (23,4–28,4)	46,4‡ (45,2–49,4)	45,8‡ (44,2–47,7)	30,2* (23,2–38,1)	31,4* (29,6–33,1)
CI	0,4 (0,2–0,7)	3,6*, ‡ (2,8–4,1)	0,5‡ (0,4–0,6)	0,4‡ (0,3–0,6)	- 1,2‡ (-1,0/-1,4)	-1,2 (-0,8/-1,3)

Note: *p < 0,05 — group of intact rats vs experimental groups, ‡p < 0,05 — compound I vs experimental groups. M is the mass of blood clots.

tor tropicity determination techniques are warranted to elucidate the precise mechanism of action.

Conclusion

Intravenous administration of compound I effectively prevented thrombosis in our experiment, surpassing comparison drugs in key haemostasis system markers. These findings suggest that 4-(2-(4-nitrophenyl)-2-oxoethyl)-1-(thietane-3-yl)-1H-1,2,4-triazole-4-bromide holds promise as a highly effective antithrombotic agent.

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