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SEARCH FOR NEW DRUGS

SYNTHESIS AND HYPOTENSIVE ACTIVITY OF PYRIMIDINE-2,4-(1H,3H)-DIONE DERIVATIVES CONTAINING THIETANE RINGS WITH SULFUR IN VARIOUS OXIDATION STATES

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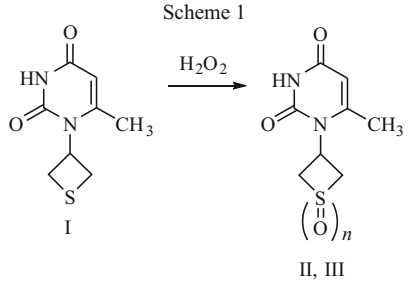
Oxo- and dioxothietane derivatives of 6-methyl-1-(thietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione were synthesized by oxidation. *N*-Alkylation and CH-aminomethylation produced 3-alkyl- and 5-aminomethyl-substituted 6-methyl-1-(thietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione, 6-methyl-1-(1-oxothietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione, and 1-(1,1-dioxothietan-3-yl)-6-methylpyrimidine-2,4-(1*H*,3*H*)-dione. The synthesized compounds showed hypotensive activity. Compounds causing pronounced, prolonged, and dose-dependent hypotensive effects that were comparable with those of reference drugs nebivolol (2 mg/kg), lisinopril (10 mg/kg), and amlodipine (1 mg/kg) were discovered.

Keywords: thietanepyrimidine-2,4-(1*H*,3*H*)-dione, oxidation, N-alkylation, CH-aminomethylation, hypotensive activity.

Many clinical hypotensive drugs are insufficiently effective, produce slowly a clinically significant reduction of arterial pressure (AP), and have limitations because of side effects or a reduction in the quality of life. These limit significantly their clinical application [1 – 3]. The discovery and development of new highly effective and non-toxic hypotensive drugs with prolonged action is a critical problem of modern pharmacology and pharmaceutical chemistry. Therefore, the goal of the present work was to discover compounds with hypotensive activity among pyrimidine-2,4-(1*H*,3*H*)-dione derivatives with thietane, oxo-, and dioxothietane rings.

The starting material was 6-methyl-1-(thietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (**I**), which was synthesized by the literature method [4]. Oxidation of **I** in glacial HOAc by a two-fold excess of H_2O_2 produced 6-methyl-1-(1-oxothietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (**II**); by a 10-fold excess of H_2O_2, 1-(1,1-dioxothietan-3-yl)-6-methylpyrimidine-2,4-(1*H*,3*H*)-dione (**III**) (Scheme 1).

Scheme 1



n = 1 (II), 2 (III).

^{13}C NMR spectra confirmed that the oxothietane and dioxothietane rings formed. Spectra of **II** and **III** showed shifts in different directions for the thietane C atoms. Resonances for the C atoms of $S(CH_2)_2$ were shifted to weak field by 22.4 and 34.8 ppm, respectively, whereas the resonance for the C atom of NCH was shifted to strong field by 4.8 and 15.9 ppm compared with the unoxidized thietane ring. This was explained by the electron-accepting influence of the oxidized S atom. The spectra also contained resonances for the C atoms of pyrimidine-2,4-(1*H*,3*H*)-dione.

IR spectra of **II** and **III** showed bands for C=O, C=C, C–N, and N–H stretching vibrations of the pyrimidine moi-

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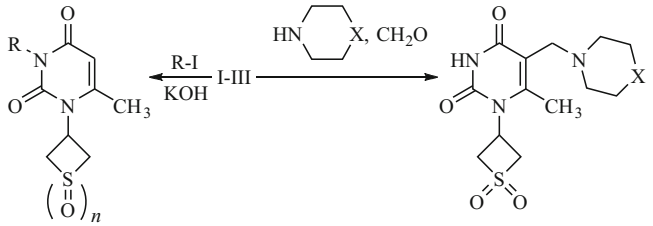
ety in addition to bands for S=O stretching vibrations at 1089 cm^{-1} (**II**) and asymmetric and symmetric SO_2 stretching vibrations at 1312 and 1154 cm^{-1} (**III**). This was consistent with an oxothietane and dioxothietane ring, respectively,

3-Alkyl-substituted **IV** – **VI** were synthesized via reaction of equimolar amounts of **I** or **II**, alkylhalides, and NaOH in DMF (Scheme 2).

Scheme 2



R = C_2H_5 (IV, VI); *n*-C_4H_9 (V);
n = 0 (I, IV, V); 1 (II, VI); 2 (III, VII, VIII);
X = O (VII); CH_2 (VIII).

Aminomethylation of **III** by formaldehyde and secondary cyclic amines in refluxing Me_2CO produced 5-aminomethyl-substituted 1-(1,1-dioxothietan-3-yl)-6-methylpyrimidine-2,4-(1*H*,3*H*)-diones (**VII**, **VIII**) (Scheme 2).

IR spectra of **VII** and **VIII** contained bands for N–H, C=O, C=C, C–N, and SO_2 stretching vibrations in the characteristic regions and absorption at 1455 and 1441 cm^{-1} that was due to CH_2–C^5=C^6, which was missing in starting **III**. This confirmed their structure as C-5 Mannich bases in the amine form.

The PMR spectrum of **VII** also confirmed that the 5-aminomethyl derivative formed. A broad singlet for the pyrimidine N^3H proton, a singlet for the 5-CH_2 protons, and resonances for the morpholine protons in the characteristic regions were observed. The ^{13}C NMR spectrum of **VIII** showed resonances for the 6-methyldioxothietanylpyrimidine-2,4-(1*H*,3*H*)-dione C atoms in addition to resonances for the 5-CH_2 C atom and the piperidine ring.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded from KBr pellets on an Infralyum FT-02 instrument. PMR and ^{13}C NMR spectra were recorded on Bruker AM-300 (300 MHz for ^1H; 75 MHz for ^{13}C) and Bruker Avance III (500 MHz for ^1H; 125 MHz for ^{13}C) instruments. The solvent was deuterated DMSO; internal standard, TMS. The purity of the synthesized compounds was confirmed by TLC on Silufix plates using BuOH:HOAc (glacial):H_2O (4:1:2). Detection used UV light and I_2 vapor in a humid chamber. Elemental analyses of the synthesized compounds agreed with those calculated.

6-Methyl-1-(1-oxothietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (II). A solution of **I** (2.0 g, 10 mmol) in glacial HOAc (36 mL) was treated with H_2O_2 (37.7%, 1.8 g, 20 mmol), left for 1 h, and neutralized with NH_4OH solution (25%) to pH 7 with cooling in ice. The precipitate was filtered off and dried. Yield 1.5 g (70%). Mp 234 – 235°C (DMF). R_f 0.33. $C_8H_{10}N_2O_3S$. IR spectrum, ν_{max}, cm^{-1}: 1089 (S=O), 1428 (C-N), 1607 (C=C), 1639 (C^4=O), 1737 (C^2=O), 2944 (N-H). ^{13}C NMR spectrum (75 MHz, DMSO-d_6) δ, ppm: 17.98 (6-CH_3), 42.24 ($C^3_{thiet.}$), 54.50 ($C^{2.4}_{thiet.}$), 98.48 (C^5), 150.87 (C^6), 152.07 (C^2), 162.37 (C^4).

1-(1,1-Dioxothietan-3-yl)-6-methylpyrimidine-2,4-(1*H*,3*H*)-dione (III). A solution of **I** (2.0 g, 10 mmol) in glacial HOAc (36 mL) was treated with H_2O_2 (37.7%, 9.02 g, 100 mmol) and left for 24 h. The precipitate was filtered off and dried. Yield 1.97 g (80%). Mp 247 – 248°C (H_2O). R_f 0.00. $C_8H_{10}N_2O_4S$. IR spectrum, ν_{max}, cm^{-1}: 1154, 1312 (SO_2), 1414 (C-N), 1617 (C=C), 1638 (C^4=O), 1741 (C^2=O), 3083 (N-H). ^{13}C NMR spectrum (125 MHz, DMSO-d_6) δ, ppm: 18.06 (6-CH_3), 31.13 ($C^3_{thiet.}$), 66.89 ($C^{2.4}_{thiet.}$), 98.50 (C^5), 151.08 (C^6), 152.24 (C^2), 162.83 (C^4).

6-Methyl-1-(thietan-3-yl)-3-ethylpyrimidine-2,4-(1*H*,3*H*)-dione (IV) was synthesized by the literature method [5].

3-Butyl-6-methyl-1-(thietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (V) was synthesized by the literature method [5].

6-Methyl-1-(1-oxothietan-3-yl)-3-ethylpyrimidine-2,4-(1*H*,3*H*)-dione (VI). KOH (1 g, 18 mmol) and **II** (3.21 g, 15 mmol) were dissolved in H_2O (5 mL), treated with DMF (60 mL) and ethyliodide (18 mmol), stirred at 40 – 50°C for 5 h, and evaporated to dryness in vacuo. The residue was treated with $CHCl_3$ (60 mL), refluxed, and filtered. The filtrate was evaporated. Yield 3.09 g (71%). Mp 166 – 168°C dec. (1-pentanol). R_f 0.61. $C_{10}H_{14}N_2O_3S$. IR spectrum, ν_{max}, cm^{-1}: 1032, 1061 (S=O), 1422 (C-N), 1655 (C^4=O, C=C), 1701 (C^2=O).

1-(1,1-Dioxothietan-3-yl)-6-methyl-5-(morpholin-4-ylmethyl)pyrimidine-2,4-(1*H*,3*H*)-dione (VII). A suspension of **III** (1.47 g, 6 mmol) in Me_2CO (40 mL) was treated with formaldehyde solution (5.4 mL, 33.7%, 60 mmol) and morpholine (1.57 g, 18 mmol), refluxed for 3 h, and cooled. The resulting precipitate was filtered off, washed with H_2O, and dried. Yield 1.36 g (69%). Mp 202 – 203°C (1-BuOH). R_f 0,17. $C_{13}H_{19}N_3O_5S$. IR spectrum, ν_{max}, cm^{-1}: 1137, 1322 (SO_2), 1455 (NH_2-C^5=C^6), 1412 (C-N), 1634 (C=C), 1638 (C^4=O), 1713 (C^2=O), 3160 (N-H). PMR spectrum ^1H (300 MHz, DMSO-d_6) δ, ppm: 11,28 (br.s, 1H, N^3H), 5,69 – 5,57 (m, 1H, NCH), 4,97 – 4,90 [m, 2H, $S(CH)_2$], 4,31 – 4,23 [m, 2H, $S(CH)_2$], 3,51 [t, 4H, J 4,5 Hz, $O(CH_2)_2$], 3,12 (s, 2H, 5-CH_2), 2,33 [t, 4H, J 4,0 Hz, $N(CH_2)_2$], 2,16 (s, 3H, 6-CH_3).

1-(1,1-Dioxothietan-3-yl)-6-methyl-5-(piperid-1-ylmethyl)pyrimidine-2,4-(1*H*,3*H*)-dione (VIII) was prepared analogously to **VII** from **III**. Yield 1.35 g (69%). Mp 206 – 207°C (1-PrOH). R_f 0.15. $C_{14}H_{21}N_3O_4S$. IR spectrum, ν_{max}, cm^{-1}: 1139, 1320 (SO_2), 1441 (CH_2-C^5=C^6), 1635 (C^4=O, C=C), 1715 (C^2=O), 3074 (N-H). ^{13}C NMR spectrum (125 MHz, DMSO-d_6) δ, ppm: 15.99 (6-CH_3), 23.94 ($C^{4'}_{piper}$), 25.52 ($C^{3',5'}_{piper}$), 31.44 ($C^3_{thiet.}$), 51.83 (5-CH_2),

53.60 ($C^{2',6'}_{piper}$), 60.81 ($C^{2.4}_{thiet.}$), 105.37 (C^5), 150.34 (C^6), 151.07 (C^2), 163.27 (C^4).

EXPERIMENTAL BIOLOGICAL PART

Mature female white laboratory rats (280 – 320 g, 3.5 – 4 months old) were obtained from Rappolovo Laboratory Animal Nursery, RAMS, and were housed under standard vivarium conditions with natural lighting and fed a full-ration balanced diet (GOST R 50258-92).

The study was performed according to RF Ministry of Health and Social Development Order No. 708 of Aug. 23, 2010 "On Approval of Laboratory Practice Rules," GOST R-53434-2009 "Principles for Laboratory Practice," and the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (1986).

Systolic arterial pressure (SAP) and cardiac contraction frequency (CCF) were measured using an IITC29 non-invasive blood pressure system (IITC Life Science Inc., USA). For this, animals were placed in a holder. A cuff with an integrated photosensor was wrapped around the tail, filled with air (10 – 15 mm Hg above the expected AP), and slowly depressurized. The SAP and CCF were recorded automatically on a PC connected to the device. The initial readings were the values recorded before administering the compounds.

Screening of the thietane-, oxothietane-, and dioxothietanepyrimidine-2,4-(1*H*,3*H*)-dione derivatives for hypotensive activity used 54 animals. The SAP and CCF were recorded after injecting the test compounds into a tail vein. Nine groups were composed of six animals each. Group 1 was the control, which received i.v. DMSO solution (50%, 0.3 mL/100 g mass). Groups 2 – 9 received i.v. the test compounds (**I-VIII**) at a dose of 1/30 of the molecular weight (6.6, 7.1, 7.7, 7.5, 8.5, 8.0, 10, and 10 mg/kg). The solvent was DMSO solution (50%). The readings were recorded 30, 60, and 90 min after injecting the compounds.

The dose—effect (hypotensive) relationship was studied using orally administered **II**. Its duration of action was compared with standards. Seven groups of six animals each were formed. Group 1 was the control [intact animals that received starch paste (2%, 0.2 mL/100 g mass)]. Group 2 received **II** at a dose of 7.1 mg/kg; group 3, **II** (14.2 mg/kg); group 4, **II** (28.4 mg/kg); group 5, nebilet (2 mg/kg); group 6, diroton (10 mg/kg); and group 7, normodipine (1 mg/kg). Selective â$_1$-adrenoreceptor blocker nebivolol (nebilet, Berlin-Chemie AG, Germany), ACE inhibitor lisinopril (diroton, Gedeon-Richter, Hungary), and Ca^{2+}-channel inhibitor amlodipine (normodipine, Gedeon-Richter, Hungary) were used as reference drugs. The compounds at the studied doses and the reference drugs were suspended in starch paste (2%) and administered orally. The parameters were recorded for 1-h intervals at 8 and 24 h after administration using an IITC 29 non-invasive blood pressure system (IITC Life Science Inc., USA). The initial readings were the values recorded before administering the compounds.

The results were processed statistically using Microsoft Excel 2007 and the Student pairing criterion.

TABLE 1. Effect of Thietane-, Oxothietane-, and Dioxothietanepyrimidine-2,4-(1*H*,3*H*)-dione Derivatives on SAP After i.v. Injection (n = 6)

Compound, dose		Initial	30 min	60 min	90 min
Control, 50% DMSO solution, 0.3 mL/100 g	$M \pm S$	122.1 ± 6.8	124.3 ± 5.5	122.3 ± 2.5	122.9 ± 2.6
	%	…	1.8	0.2	0.6
I, 6.6 mg/kg	$M \pm S$	128.2 ± 1.4	126.9 ± 15.5	122.2 ± 16.8	120.9 ± 15.9
	%	…	– 1.0	– 4.6	– 5.7
II, 7.1 mg/kg	$M \pm S$	126.7 ± 1.7	120.1 ± 7.9*	114.3 ± 20.6*	107.7 ± 13.9 *
	%	…	– 5.2	– 9.7	– 15.0
III, 7.7 mg/kg	$M \pm S$	130.7 ± 9.4	120.2 ± 7.7*	117.9 ± 2.0*	114.7 ± 6.6 *
	%	…	– 8.0	– 9.8	– 12.2
IV, 7.5 mg/kg	$M \pm S$	130.3 ± 7.3	123.8 ± 4.6	118.8 ± 8.4	126.7 ± 5.5
	%	…	– 5.0	– 8.9	– 2.8
V, 8.5 mg/kg	$M \pm S$	129.1 ± 6.2	124.9 ± 5.8*	127.7 ± 8.7	126.0 ± 6.7
	%	…	– 3.3	– 1.1	– 2.4
VI, 8.0 mg/kg	$M \pm S$	128.2 ± 7.8	124.0 ± 10.7	119.6 ± 12.2	120.9 ± 15.8
	%	…	– 3.3	– 6.7	– 5.7
VII, 10 mg/kg	$M \pm S$	129.8 ± 2.9	122.6 ± 5.4*	115.6 ± 5.5*	105.1 ± 3.6 *
	%	…	– 5.6	– 11.0	– 19.0
VIII, 10 mg/kg	$M \pm S$	125.9 ± 7.0	124.4 ± 5.4	122.4 ± 8.2	120.1 ± 6.6
	%	…	– 1.1	– 2.7	– 4.6

* Statistically significant compared with the control ($p < 0.05$).

RESULTS AND DISCUSSION

Screening of the thietanepyrimidine-2,4-(1*H*,3*H*)-dione derivatives for hypotensive activity found that those derivatives containing an unoxidized thietane ring did not affect the SAP and increased the CCF by at most 10% (**V**) or exhibited weak hypotensive effects and reduced the SAP from 1.0 to 8.9% (**I**, **IV**) with the CCF increasing by 10% and decreasing by 8.5%, respectively. Compounds **II**, **III**, and **VII**, which contained thietane-1-oxide or thietane-1,1-dioxide rings, decreased the SAP most significantly, by a maximum at 90 min of 15, 12.2, and 19%, respectively, compared with the initial readings. They did not noticeably affect the CCF. However, introducing an alkyl moiety into the 3-position of oxothietanepyrimidine-2,4-(1*H*,3*H*)-dione (**VI**) or an N-methylenepiperidine into the 5-position of the dioxothietane derivative (**VIII**) decreased significantly the hypotensive effect without affecting the CCF. The SAP and CCF did not change in the control group (Table 1).

Next, the hypotensive activity of the most active compounds was studied using oral administration. Compound **VII** (20 mg/kg) reduced the SAP by a maximum of 10.5% at 6 h. The SAP was restored to the initial value by 24 h. Orally administered compound **III** (15.4 mg/kg) had slightly less pronounced hypotensive activity than that administered i.v. The SAP decreased by a maximum of 11% relative to the initial value. However, the effect was persistent. The SAP remained reduced by 10% at 24 h. Compound **II** (14.2 mg/kg)

TABLE 2. Comparative Effects of Thietane-, Oxothietane-, and Dioxothietanepyrimidine-2,4-(1*H*,3*H*)-dione Derivatives and Standards on SAP After Oral Administration to Rats ($n = 6$)

Compound, dose		Initial	1 h	2 h	3 h	4 h	5 h	6 h	8 h	24 h
Control	$M \pm S$	127.7 ± 3.6	128.6 ± 2.1	127.0 ± 3.2	130.2 ± 3.7	128.4 ± 2.3	129.2 ± 1.4	127.9 ± 2.0	128.6 ± 1.9	128.8 ± 1.6
	%	…	0.7	– 0.5	2.0	0.6	1.2	0.2	0.7	0.9
II, 14.2 mg/kg	$M \pm S$	125.9 ± 1.2	121.1 ± 2.9	116.6 ± 7.0*	112.3 ± 6.5*	113.7 ± 5.5*	113.5 ± 9.7*	111.0 ± 11.3*	110.8 ± 4.0	108.9 ± 3.6#&
	%	…	– 3.8	– 7.4	– 10.8	– 9.7	– 9.8	– 11.8	– 12.0	– 13.5
III, 15.4 mg/kg	$M \pm S$	124.9 ± 4.3	120.4 ± 3.7*	117.8 ± 3.2*	115.9 ± 5.4*	114.1 ± 5.4*	114.6 ± 3.4*	112.7 ± 4.9*	111.0 ± 5.5	111.9 ± 3.7#
	%	…	– 3.6	– 5.7	– 7.2	– 8.6	– 8.3	– 9.8	– 11.1	– 10.4
VII, 20 mg/kg	$M \pm S$	126.1 ± 4.7	123.4 ± 3.0	123.8 ± 1.7	119.1 ± 3.1	118.6 ± 3.4	115.9 ± 3.4*	112.9 ± 4.2*	113.9 ± 4.0	121.4 ± 3.3
	%	…	– 2.1	– 1.9	– 5.6	– 6.0	– 8.1	– 10.5	– 9.7	– 3.7
Normodipine, 1 mg/kg	$M \pm S$	125.0 ± 1.2	125.7 ± 1.5	124.8 ± 3.0*	118.9 ± 2.2*	115.1 ± 4.7*	112.1 ± 5.7*	111.4 ± 5.1*	109.2 ± 5.9	120.8 ± 2.7
	%	…	0.5	– 0.2	– 4.9	– 7.9	– 10.3	– 10.8	– 12.6	– 3.4
Diroton, 10 mg/kg	$M \pm S$	129.2 ± 0.7	124.0 ± 6.0	118.9 ± 1.8*	115.4 ± 2.2*	113.3 ± 0.9*	107.4 ± 3.9*	106.2 ± 2.8*	106.1 ± 3.1	120.9 ± 0.7
	%	…	– 4.0	– 8.0	– 10.7	– 12.3	– 16.9	– 17.8	– 17.9	– 6.4
Nebivolol, 2 mg/kg	$M \pm S$	128.2 ± 2.4	119.1 ± 4.8*	118.0 ± 2.6*	115.3 ± 3.5*	112.7 ± 1.2*	106.7 ± 3.1*	105.0 ± 2.5*	103.7 ± 2.7	118.9 ± 8.1
	%	…	– 7.1	– 8.0	– 10.1	– 12.1	– 16.8	– 18.1	– 19.2	– 7.3

* statistically significant compared with the control ($p < 0.05$); # statistically significant compared to the animal group that received reference normodipine ($p < 0.05$); & statistically significant compared to the animal group that received reference diroton ($p < 0.05$).

TABLE 3. Dose – Effect Relationship of 6-Methyl-1-(1-oxothietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (**II**) for SAP After Oral Administration to Rats ($n = 6$)

Compound, dose		Initial	1 h	2 h	3 h	4 h	5 h	6 h	8 h	24 h
Control	$M \pm S$	127.7 ± 3.6	128.6 ± 2.1	127.0 ± 3.2	130.2 ± 3.7	128.4 ± 2.3	129.2 ± 1.4	127.9 ± 2.0	128.6 ± 1.9	128.8 ± 1.6
	%	…	0.7	– 0.5	2.0	0.6	1.2	0.2	0.7	0.9
7.1 mg/kg	$M \pm S$	126.7 ± 1.0	126.7 ± 2.3	125.3 ± 2.8	121.1 ± 3.5	120.9 ± 6.2	120.2 ± 0.8	121.9 ± 0.5	121.4 ± 1.5	121.9 ± 2.4
	%	…	0.0	– 1.1	– 4.4	– 4.6	– 5.1	– 3.8	– 4.1	– 3.8
14.2 mg/kg	$M \pm S$	125.9 ± 1.2	121.1 ± 2.9	116.6 ± 7.0*	112.3 ± 6.5*	113.7 ± 5.5*	113.5 ± 9.7*	111.0 ± 11.3*	110.8 ± 4.0	108.9 ± 3.6
	%	…	– 3.8	– 7.4	– 10.8	– 9.7	– 9.8	– 11.8	– 12.0	– 13.5
28.4 mg/kg	$M \pm S$	127.3 ± 2.5	124.7 ± 0.3	122.0 ± 1.7	120.1 ± 0.7	118.6 ± 1.8	116.9 ± 2.4	115.3 ± 3.4	113.9 ± 6.0	116.8 ± 3.9
	%	…	– 2.1	– 4.2	– 5.7	– 6.9	– 8.2	– 9.4	– 10.6	– 8.3

* statistically significant compared with the control ($p < 0.05$).

had the most pronounced and prolonged hypotensive activity in these tests. The SAP decreased gradually and continuously and showed no tendency to return to the initial level by 24 h (Table 2). The AP decreased by a maximum of 12.6% after 8 h and practically returned to the initial value 1 d after administration for the group that received normodipine reference drug (1 mg/kg). The AP was lower than the initial levels by 17.9 and 19.2% after 8 h and by 6.4 and 7.3% after 24 h for animals that received lisinopril (10 mg/kg) and nebilet (2 mg/kg) (Table 2).

The dose – effect relationship study for oral administration showed that **II** (7.1 mg/kg) exhibited weak hypotensive activity with a maximum at 5 h. The AP decreased by 5.1% and by 3.8% after 24 h relative to the initial values. Doubling the dose (14.2 mg/kg) enhanced the hypotensive activity of **II**. Starting at 1 h, the AP decreased by 3.8%; at 5 h, 9.8%; and at 8 h, 12%. The AP remained reduced by 13.5% at 24 h after administration. However, it remained at the initial level in the control group. Increasing the dose further to 28.4 mg/kg did not increase the hypotensive activity of **II**. The AP decreased by 10.6% at 8 h and by 8.3% after 1 d (Table 3). The test compounds and reference drugs had practically no effect on the CCF.

Thus, newly synthesized 6-methyl-1-(1-oxothietan-3-yl)pyrimidine-2,4-(1*H*,3*H*)-dione (**II**) administered orally at a dose of 7.1 mg/kg reduced AP by 15% compared with the initial level. Orally administered **II** reduced the AP most significantly at a dose of 14.2 mg/kg with an effect comparable to those of amlodipine, lisinopril, and nebivolol. However, its duration of action was better than theirs (Table 2). Thus, **II** was recommended for further research.

The similarity of the chemical structures of this series of compounds and antihypertensive drugs, in particular, the á-adrenoceptor antagonist urapidil, prompted us to study their hypotensive activity. It can be supposed that **II** exhibits adreno-blocking activity, which will be the subject of further research.

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