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SEARCH FOR NEW DRUGS

SYNTHESIS AND BIOLOGICAL ACTIVITY OF ETHYL 2-[8-ARYLMETHYLIDENEHYDRAZINO-3-METHYL-7-(1-OXOTHIETAN-3-YL)XANTH-1-YL]ACETATES

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Ethyl 2-[8-Arylmethylidenehydrazino-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]acetates (**IV**) were synthesized via reactions of ethyl 2-[8-hydrazino-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]acetic acid (**III**) with various benzaldehydes and acetophenones. The structures of the compounds were elucidated using IR and NMR spectroscopy and elemental analysis. The antiplatelet, anticoagulation, antioxidant, and anti-inflammatory activities were assessed *in vitro* and in laboratory animals to identify promising compounds exhibiting antiplatelet (hydrazone **IVd**) and antioxidant properties (hydrazone **IVb**). Both **IVb** and **IVd** according to *in silico* calculations were characterized by the absence of toxic risks (mutagenicity, oncogenicity, reproductive toxicity, local irritation) and had acceptable topological polar surface area so that they were promising.

Keywords: oxothietanylxanthines; arylmethylidenehydrazines; antiplatelet, anticoagulant, antioxidant, anti-inflammatory activity; Lipinski's rule of five.

Previous research by us on the synthesis of thietanylxanthines showed that they were promising building blocks for chemical modification of the 1- and 8-positions to produce new biologically active molecules [1, 2]. Xanthylhydrazones exhibited broad spectra of biological activity such as anti-inflammatory, analgesic, and antioxidant [3, 4]. However, hydrazine derivatives of thietane-containing 2-(xanth-1-yl)-acetic acids are still practically unstudied with respect to both chemistry and pharmacology. Therefore, the goals of the present work were to synthesize ethyl 2-[8-arylmethylidenehydrazino-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]-acetates, to predict their toxic risks, and to assess preliminarily their biological activities.

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Ethyl 2-[8-bromo-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]acetate (**II**) was synthesized in 80% yield (Scheme 1) via oxidation of starting ester **I** [9] by H_2O_2 in HOAc. Weak-field shifts in the ^{13}C NMR spectrum by up to 55.2 ppm of resonances for the thietane-oxide ring $S(CH_2)_2$ of **II** confirmed that the sulfoxide had formed.

Ester **II** reacted with an excess of hydrazine hydrate (Scheme 1) at the xanthine 8-position to form ethyl 2-[8-hydrazino-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]acetate (**III**), the structure of which was confirmed by two singlets at 4.48 and 8.59 ppm in the PMR spectrum for the hydrazine NH_2 and NH protons and a triplet at 1.20 ppm and quartet at 4.13 for the ethoxy group.

Arylmethylidenehydrazines **IVa-j** were synthesized in good yields via reactions of **III** with aromatic aldehydes and ketones (Scheme 1). The compositions and structures of **IVa-j** were confirmed by NMR and IR spectroscopy. Thus, the appearance at weak field in PMR spectra of **IVa-j** of resonances for aromatic protons and a singlet for the azomethine proton at 7.8 – 8.4 ppm (HC=N, **IVa-e**) or for the

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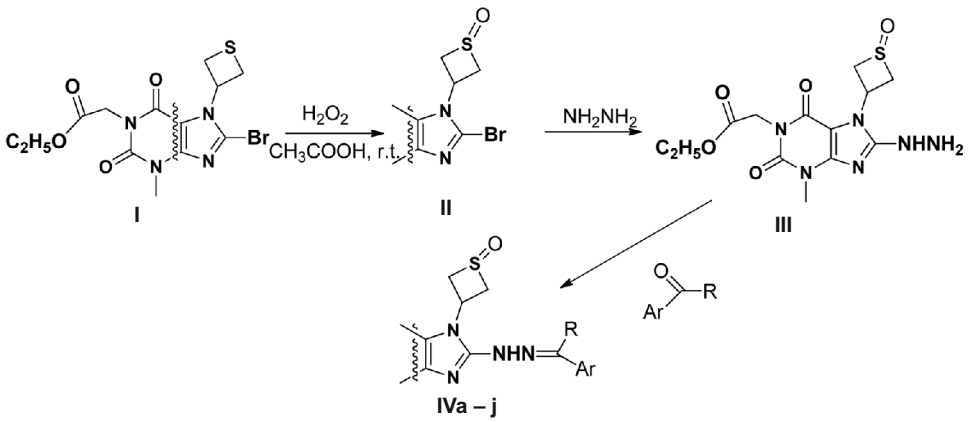
Scheme 1



R = H (**a** – **e**), CH_3 (**f** – **j**);

Ar = C_6H_4-4-N$(CH_3)_2$ (**a**), C_6H_4-4-OCH_3 (**b**), C_6H_4-2-OH (**c**), C_6H_3-2-OH, 5-Br (**d**), C_6H_3-4-OH, 3-OCH_3 (**e**), C_6H_5 (**f**), C_6H_4-4-NO_2 (**g**), C_6H_4-4-NH_2 (**h**), C_6H_4-4-OH (**i**), C_6H_4-4-Br (**j**)

methyl protons at 2.3 – 2.4 ppm (CH_3C=N, **IVf-j**) indicated that the arylmethylidene derivatives had formed.

EXPERIMENTAL CHEMICAL PART

IR spectra were taken from KBr pellets on an Infralum-FT-02 spectrometer. Melting points were measured on an SMP 30 apparatus. NMR spectra were recorded on a Bruker DRX-500 spectrometer at operating frequency 500.13 (^{1}H) and 125.76 MHz (^{13}C). Solvent resonances were used as internal standards. Elemental analyses for C, H, N, and S agreed with those calculated.

Ethyl 2-[8-bromo-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]acetate (II). Compound **I** (4.80 g, 12 mmol) was dissolved with heating in glacial HOAc (100 mL). The solution was cooled to 20°C, treated with a solution of H_2O_2 (33%, 2.48 g, 24 mmol), held at 20 – 25°C for 1.5 h, neutralized with NH_3 solution to pH 7.0, and held at 5°C for 10 – 12 h. The resulting precipitate was filtered off, rinsed with H_2O, and dried. Yield 4.00 (80.0%); mp 212 – 213°C (PrOH-2). IR spectrum, ν, cm^{-1}: 1062.6 (S=O), 1211.1, 1228.5, 1369.2, 1390.4, 1533.2, 1608.4 (C=C, C=N), 1662.4, 1708.6, 1743.4 (C=O). PMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 1.29 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$), 3.42 – 3.48 (m, 2H, $S(CH)_2$), 3.56 (s, 3H, CH_3), 4.23 (q, 2H, J 7.2 Hz, $CH_3\underline{CH_2}$), 4.25 – 4.31 (m, 2H, $S(CH)_2$), 4.76 (s, 2H, NCH_2), 6.46 – 6.54 (m, 1H, NCH). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 14.1 ($CH_2\underline{C}H_3$), 30.2 (N-CH_3), 42.6 (N-CH_2), 52.8 (N-CH), 55.2 ($S(CH_2)_2$), 61.8 ($\underline{C}H_2CH_3$), 108.5 (C_5), 128.6 (C_8), 150.4 (C_4), 151.1 (C_2), 153.5 (C_6), 169.2 (C=O).

Ethyl 2-[8-hydrazino-3-methyl-7-(1-oxothietan-3-yl)-xanth-1-yl]acetate (III). A solution of **II** (0.42 g, 1 mmol) in *i*-BuOH (16 mL) was treated with a solution of hydrazine hydrate (64.3%, 0.15 g, 3 mmol), refluxed for 1 h, and cooled. The resulting precipitate was filtered off, rinsed with *i*-BuOH and H_2O, and dried. Yield 0.22 g (48.0%); mp 213.8 – 216.5°C (EtOH). IR spectrum, ν, cm^{-1}: 1026.0 (S=O), 1213.0, 1376.9, 1421.3, 1488.8, 1533.2, 1560.2, 1614.1 (C=C, C=N), 1648.9, 1691.3, 1747.2 (C=O). 3255.3, 3322.8 (N-H). PMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 1.20 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$), 3.28 – 3.34 (m, 2H, $S(CH)_2$), 3.40 (s, 3H, CH_3), 3.95 – 4.03 (m, 2H, $S(CH)_2$), 4.13 (q, 2H, J 7.1 Hz, $CH_3\underline{CH_2}$), 4.48 (br. s, 2H, NH_2), 4.60 (s, 2H, NCH_2), 6.21 – 6.31 (m, 1H, NCH), 8.59 (br.s, 1H, NH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.5 ($CH_2\underline{C}H_3$), 30.0 (N-CH_3), 42.4 (N-CH_2), 48.6 (N-CH), 55.9 ($S(CH_2)_2$), 61.4 ($\underline{C}H_2CH_3$), 102.2 (C_5), 150.9 (C_4), 151.1 (C_2), 152.6 (C_6), 156.4 (C_8), 168.9 ($CH_2\underline{C}$=O).

Ethyl 2-[8-hydrazino-3-methyl-7-(1-oxothietan-3-yl)-xanth-1-yl]acetate hydrochloride (III·HCl). A hot solution of **III** (0.30 g, 0.8 mmol) in *i*-PrOH (8 mL) was treated with HCl in EtOH to pH 2.0 and cooled. The resulting precipitate was filtered off, rinsed with *i*-PrOH, and dried. Yield 0.25 g (77.0%); mp 180.4 – 180.7°C (*i*-PrOH–hexane). IR spectrum, ν, cm^{-1} (KBr): 1001.9 (SO), 1211.8, 1449.3, 1538.6, 1608.4 (C-C, C=C, N=C), 1653.7, 1701.0, 1746.2 (C=O), 2669.0, 3120.3, 3320.9, 3544.6 (N^+H_3, N-H).

General method for synthesizing ethyl 2-[8-arylmethylidenehydrazino-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]acetates (IVa-j). Hydrazine **III** (0.30 g, 0.8 mmol) in *i*-PrOH (40 mL) was treated with a carbonyl compound (1 mmol) and conc. HCl (1 drop). The solution was refluxed for 2 h and cooled. For **IVa** and -**b**, addition of conc. HCl was not required. The resulting precipitate was filtered off, rinsed with H_2O, and dried.

Ethyl 2-[8-(4-dimethylaminophenylmethylidene)hydrazino-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]acetate (IVa). Yield 0.30 g (76.4%); mp (dec.) 235.7°C (*i*-PrOH–H_2O, 1:0.1). IR spectrum, ν, cm^{-1} (KBr): 1018.2 (S=O), 1207.2, 1356.4, 1488.8, 1523.5, 1610.3, 1635.4

(C=C, C=N), 1657.7, 1697.1, 1749.1 (C=O), 2829.1 – 3016.2 (N-H). PMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 1.30 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$), 3.00 (s, 6H, $N(CH_3)_2$), 3.43 – 3.50 (m, 2H, $S(CH)_2$), 3.52 (s, 3H, CH_3), 4.24 (q, 2H, J 7.1 Hz, $CH_3\underline{CH_2}$), 4.30 – 4.38 (m, 2H, $S(CH)_2$), 4.77 (s, 2H, NCH_2), 6.62 – 6.74 (m, 2H, H_{arom}7.02 – 7.12 (m, 1H, NCH), 7.52 (d, 2H, J 8.6 Hz, H_{arom}), 7.88 (s, 1H, N=CH), 9.28 (br.s, 1H, NH). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 14.2 ($CH_2\underline{C}H_3$), 30.1 (N-CH_3), 40.3 ($N(CH_3)_2$), 42.4 (N-CH_2), 49.8 (N-CH), 56.4 ($S(CH_2)_2$), 61.6 (CH_2CH_3), 103.5 (C_5), 112.1 (C_{arom}), 128.7 (CH_{arom}), 146.8 (HC=N), 150.4 (C_4), 150.9 (C_2), 151.1 (C_6), 153.3 (C_8), 168.6 ($CH_2\underline{C}$=O).

Ethyl 2-{8-[2-(4-methoxybenzylidene)hydrazino]-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl}acetate (IVb). Yield 0.26 g (66.7%); mp 230.5 – 232.5°C (*i*-PrOH). IR spectrum, ν, cm^{-1} (KBr): 1016.3 (S=O), 1207.2, 1251.6, 1392.4, 1531.2, 1608.4, 1635.4 (C=C, C=N), 1652.7, 1699.0, 1749.1 (C=O), 3143.4, 3218.6 (N-H). PMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 1.30 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$); 3.44 – 3.50 (m, 2H, $S(CH)_2$); 3.54 (s, 3H, N-CH_3); 3.82 (s, 3H, O-CH_3); 4.24 (q, 2H, J 7.1 Hz, CH_3CH_2); 4.32 – 4.40 (m, 2H, $S(CH)_2$); 4.77 (s, 2H, NCH_2); 6.90 (d, 2H, J 8.6 Hz, H_{arom}); 6.92 – 7.02 (m, 1H, NCH); 7.59 (d, 2H, J 8.6 Hz, H_{arom}); 7.97 (s, 1H, N=CH); 9.78 (br.s, 1H, NH). ^{13}C NMR spectrum ($CDCl_3$, 125 MHz), δ, ppm: 14.2 ($\underline{CH_3}CH_2$); 30.2 (N-CH_3); 42.5 (N-CH_2); 49.6 (N-CH); 55.4 (O-CH_3); 56.4 ($S(CH_2)_2$); 61.7 ($CH_3\underline{CH_2}$); 103.4 (C_5); 114.3 (CH_{arom}); 126.0 (C_{arom}); 128.8 (CH_{arom}); 146.0 (HC=N); 150.2 (C_4); 151.0 ($C_{2,6}$); 153.4 (C_8); 161.4 (C_{arom}); 168.6 ($CH_2\underline{C}O$).

Ethyl 2-{8-[2-(2-hydroxybenzylidene)hydrazino]-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl}acetate (IVc). Yield 0.37 g (99%); mp 255.5 – 256.7°C (DMF–H_2O, 1:0.4). IR spectrum, ν, cm^{-1} (KBr): 1039.5 (SO), 1203.38, 1344.2, 1430.9, 1475.3, 1490.7, 1583.3, 1635.4 (C-C, C=C, N=C), 1700.9, 1747.1 (C=O), 2950.6 – 3143.4 (N-H, OH). PMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 1.19 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$,); 3.35 – 3.43 (m, 5H, $S(CH)_2$, N-CH_3); 4.03 – 4.10 (m, 2H, $S(CH)_2$); 4.13 (q, 2H, J 7.1 Hz, $CH_3\underline{CH_2}$); 4.60 (s, 2H, NCH_2); 6.51 – 6.60 (m, 1H, NCH); 6.84 – 6.82 (m, 2H, H_{arom}); 7.21 – 7.26 (m, 1H, H_{arom}); 7.57 (d, 1H, J 7.7 Hz, H_{arom}); 8.42 (s, 1H, N=CH); 10.70 (s, 1H, NH); 11.67 (s, 1H, OH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.5 ($\underline{C}H_3CH_2$); 30.0 (N-CH_3); 42.6 (N-CH_2); 49.6 (N-CH); 56.1 ($S(CH_2)_2$); 61.4 ($\underline{C}H_2CH_3$); 102.9 (C_5); 116.73 (CH_{arom}); 119.78 (C_{arom}); 119.8 (CH_{arom}); 128.3 (CH_{arom}); 131.3 (CH_{arom}); 144.4 (C=N); 150.4 (C_4); 150.9 (C_2); 151.1 (C_6); 153.0 (C_8); 157.1 (C_{arom}); 168.8 ($CH_2\underline{C}O$).

Ethyl 2-{8-[2-(5-bromo-2-hydroxybenzylidene)hydrazino]-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl}acetate (IVd). Yield 0.34 g (76.8%); mp (dec.) 260.5°C (DMF–H_2O, 1:0.8). IR spectrum, ν, cm^{-1} (KBr): 1031.7 (SO), 1216.9, 1429.0, 1483.0, 1577.5, 1618.0 (C-C, C=C, N=C), 1650.8, 1702.8, 1735.6 (C=O), 2985.3 – 3205.1 (N-H, OH). PMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 1.19 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$,); 3.33 – 3.40 (m, 2H, $S(CH)_2$); 3.42 (s, 3H, N-CH_3); 4.02 – 4.10 (m, 2H, $S(CH)_2$); 4.13 (q, 2H, J 7.1 Hz, $CH_3\underline{CH_2}$); 4.61 (s, 2H, NCH_2); 6.46 – 6.56 (m, 1H, NCH); 6.87 (d, 1H, J 8.7 Hz, H_{arom}); 7.38 (dd, 1H, J 8.7 Hz, ^{4}J 2.5 Hz, H_{arom}); 7.77 (d, 1H, ^{4}J 2.3 Hz, H_{arom}); 8.38 s (1H, N=CH); 10.90 s (1H, NH); 11.78 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.5 ($\underline{C}H_3CH_2$); 30.1 (N-CH_3); 42.6 (N-CH_2); 49.5 (N-CH); 56.1 ($S(CH_2)_2$); 61.4 ($CH_3\underline{C}H_2$); 102.9 (C_5); 111.1 (C_{arom}); 119.0 (CH_{arom}); 122.2 (C_{arom}); 129.8 (CH_{arom}); 133.5 (CH_{arom}); 142.3 (C=N); 150.9 (C_4); 151.0 (C_2); 153.1 (C_6); 156.2 (C_8); 162.8 (C_{arom}); 168.8 ($CH_2\underline{C}O$).

Ethyl 2-{8-[2-(4-hydroxy-3-methoxybenzylidene)hydrazino]-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl}acetate (IVe). Yield 0.34 g (84.2%); mp (dec.) 244.8 – 245.5°C (DMF–H_2O, 1:1). IR spectrum, ν, cm^{-1} (KBr): 1025.9 (SO), 1224.6, 1288.3, 1394.3, 1517.73, 1623.7 (C-C, C=C, N=C), 1654.6, 1685.6, 1747.2 (C=O), 2966.0, 3216.7 (N-H, OH). PMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 1.19 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$,); 3.35 – 3.43 (m, 5H, $S(CH)_2$, N-CH_3); 3.81 (s, 3H, O-CH_3); 4.04 – 4.17 (m, 4H, $S(CH)_2$, $CH_3\underline{CH_2}$); 4.60 (s, 2H, NCH_2); 6.80 (d, 1H, J 8.1 Hz, H_{arom}); 6.94 – 7.06 (m, 2H, NCH, H_{arom}); 7.27 (s 1H, H_{arom}); 8.00 (s, 1H, N=CH); 9.48 (s, 1H, NH), 11.58 (s, 1H, OH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.5 ($\underline{C}H_3CH_2$); 30.1 (N-CH_3); 42.6 (N-CH_2); 50.2 (N-CH); 56.1 (O-CH_3); 56.3 ($S(CH_2)_2$); 61.4 ($CH_3\underline{C}H_2$); 102.9 (C_5); 108.73 (CH_{arom}); 115.87 (CH_{arom}); 122.12 (CH_{arom}); 125.89 (C_{arom}); 145.26 (İC=N); 148.60 (C_{arom}); 149.18 (C_4); 150.72 (C_2); 150.94 (C_6); 151.07 (C_{arom}); 152.82 (C_8); 168.8 ($CH_2\underline{C}O$).

Ethyl 2-{3-methyl-7-(1-oxothietan-3-yl)-8-[2-(1-phenylethylidene)hydrazino]xanth-1-yl}acetate (IVf). Yield 0.25 g (66.1%); mp 249.7 – 250.7°C (DMF–H_2O, 1:1). IR spectrum, ν, cm^{-1} (KBr): 1031.7 (SO), 1207.2, 1361.5, 1519.7 (C-C, C=C, N=C), 1645.0, 1685.5, 1702.6, 1743.4 (C=O), 2923.6 – 3031.6 (N-H). PMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 1.20 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$); 2.38 (s, 3H, C-CH_3); 3.30 – 3.40 (m, 2H, $S(CH)_2$); 3.42 (s, 3H, N-CH_3); 4.04 – 4.18 (m, 4H, $S(CH)_2$, $CH_3\underline{CH_2}$); 4.63 (s, 2H, NCH_2); 6.70 – 6.81 (m, 1H, NCH); 7.35 – 7.46 (m, 3H, H_{arom}); 7.80 (d, 2H, J 6.2 Hz, H_{arom}); 10.57 (s, 1H, NH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.5 ($\underline{C}H_3CH_2$); 14.8 (C-$\underline{C}H_3$); 30.2 (N-CH_3); 42.6 (N-CH_2); 50.6 (N-CH); 56.3 ($S(CH_2)_2$); 61.4 ($\underline{C}H_2CH_3$); 103.3 (C_5); 126.5 (CH_{arom}); 129.0 (CH_{arom}); 129.6 (CH_{arom}); 138.3 (C_{arom}); 150.7 (C_4), 151.0 (C_2); 151.5 (C_6); 152.1 (C=N); 153.2 (C_8); 168.8 ($CH_2\underline{C}O$).

Ethyl 2-(3-methyl-8-{2-[1-(4-nitrophenyl)ethylidene]-hydrazino}-7-(1-oxothietan-3-yl)xanth-1-yl)acetate (IVg). Yield 0.30 g (72.5%); mp (dec.) 255.0°C (DMF). IR spectrum, ν, cm^{-1} (KBr): 1031.7 (SO), 1201.5, 1489.5, 1619.0 (C-C, C=C, N=C), 1337.4, 1516.1 (NO_2), 1657.2, 1695.4, 1758.9 (C=O), 3165.8 – 3270.4 (N-H). PMR spectrum

(DMSO-d_6, 500 MHz), δ, ppm: 1.22 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$,); 2.44 (s, 3H, C-CH_3); 3.38 – 3.47 (m, 5H, $S(CH)_2$, N-CH_3); 4.04 – 4.12 (m, 2H, $S(CH)_2$); 4.15 (q, 2H, J 7.1 Hz, $CH_3\underline{CH_2}$); 4.65 (s, 2H, NCH_2); 6.69 – 6.80 (m, 1H, NCH); 8.05 (d, 2H, J 8.7 Hz, H_{arom}); 8.26 (d, 2H, J 8.7 Hz, H_{arom}); 10.86 (s, 1H, NH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.0 ($\underline{C}H_3CH_2$); 14.1 (C-$\underline{C}H_3$); 29.7 (N-CH_3); 42.1 (N-CH_2); 50.1 (N-CH); 55.8 ($S(CH_2)_2$); 61.0 ($CH_3\underline{C}H_2$); 103.1 (C_5); 123.7 (CH_{arom}); 127.0 (CH_{arom}); 144.0 (C_{arom}); 147.3 (C_{arom}); 148.1 (C_4); 150.0 (C_2); 150.5 (C_6); 150.9 (C=N); 152.8 (C_8); 168.3 ($CH_2\underline{C}O$).

Ethyl 2-(8-{2-[1-(4-aminophenyl)ethylidene]hydrazino}-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl)acetate (IVh). Yield 0.18 g (46.0%); mp (dec.) 215.0°C (DMF–H_2O, 1:0.9). IR spectrum, ν, cm^{-1} (KBr): 1024.0 (SO), 1205.3, 1344.2, 1490.7, 1519.7, 1618.0 (C-C, C=C, N=C), 1652.7, 1700.9, 1756.9 (C=O), 2877.3 – 3023.9 (N-H, NH_2). PMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 1.20 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$); 2.43 (s, 3H, C-CH_3); 3.35 – 3.46 (m, 5H, $S(CH)_2$, N-CH_3); 4.02 – 4.19 (m, 4H, $S(CH)_2$, $CH_3\underline{CH_2}$); 4.63 (s, 2H, NCH_2); 6.68 – 6.79 (m, 1H, NCH); 8.04 (d, 2H, J 8.9 Hz, H_{arom}); 8.24 (d, 2H, J 8.8 Hz, H_{arom}); 10.84 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.5 ($\underline{C}H_3CH_2$); 14.6 (C-$\underline{C}H_3$); 30.2 (N-CH_3); 42.6 (N-CH_2); 50.6 (N-CH); 56.3 ($S(CH_2)_2$); 61.4 ($CH_3\underline{C}H_2$); 103.6 (C_5); 124.1 (CH_{arom}); 127.5 (CH_{arom}); 144.4 (C_{arom}); 147.8 (C_{arom}); 148.6 (C_4); 150.5 (C_2); 151.0 (C_6); 151.3 (C=N); 153.3 (C_8); 168.8 ($CH_2\underline{C}O$).

Ethyl 2-(8-{2-[1-(4-hydroxyphenyl)ethylidene]hydrazino}-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl)acetate (IVi). Yield 0.29 g (74.2%); mp 265.0 – 266.8°C (DMF). IR spectrum, ν, cm^{-1} (KBr): 1012.5 (SO), 1215.0, 1396.2, 1416.2, 1518.9, 1610.3 (C-C, C=C, N=C), 1655.2, 1704.8, 1748.2 (C=O), 3120.3, 3184.0 (N-H, OH). PMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 1.20 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$); 2.31 (s, 3H, C-CH_3); 3.29 – 3.39 (m, 2H, $S(CH)_2$), 3.41 (s, 3H, N-CH_3); 4.02 – 4.10 (m, 2H, $S(CH)_2$); 4.13 (q, 2H, J 7.1 Hz, $CH_3\underline{CH_2}$); 4.62 (s, 2H, NCH_2); 6.72 – 6.82 (m, 3H, NCH, H_{arom}); 7.64 (d, 2H, J 8.6 Hz, H_{arom}); 9.75 (s, 1H, NH), 10.41 (s, 1H, OH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.5 ($\underline{C}H_3CH_2$); 14.6 (C-$\underline{C}H_3$); 30.1 (N-CH_3); 42.6 (N-CH_2); 50.6 (N-CH); 56.3 ($S(CH_2)_2$); 61.4 ($CH_3\underline{C}H_2$); 103.1 (C_5); 115.69 (CH_{arom}); 128.0 (CH_{arom}); 129.1 (C_{arom}); 150.7 (C_4); 151.0 (C_2); 152.0 (C_6); 152.40 (C=N); 153.1 (C_8); 159.1 (C_{arom}); 168.8 ($CH_2\underline{C}O$).

Ethyl 2-(8-{2-[1-(4-bromophenyl)ethylidene]hydrazino}-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl)acetate (IVj). Yield 0.35 g (79.0%); H_{arom} 255.0°C (DMF). IR spectrum, ν, cm^{-1} (KBr): 1025.1 (SO), 1218.0, 1378.9, 1484.3, 1522.2, 1644.9 (C-C, C=C, N=C), 1652.7, 1702.3, 1748.6 (C=O), 3023.7 (N-H). PMR spectrum (DMSO-d_6, 500 MHz), δ, ppm: 1.20 (t, 3H, J 7.1 Hz, $\underline{CH_3}CH_2$,); 2.36 (s, 3H, C-CH_3); 3.33 – 3.40 (m, 2H, $S(CH)_2$); 3.42 (s, 3H, N-CH_3); 4.02 – 4.10 (m, 2H, $S(CH)_2$); 4.13 (q, 2H, J 7.1 Hz, $CH_3\underline{CH_2}$); 4.63 (s, 2H, NCH_2); 6.67 – 6.77 (m, 1H, NCH); 7.60 (d, 2H, J 8.5 Hz, H_{arom}); 7.74 (d, 2H, J 8.5 Hz, H_{arom}); 10.62 (s, 1H, NH). ^{13}C NMR spectrum (DMSO-d_6, 125 MHz), δ, ppm: 14.5 ($\underline{C}H_3CH_2$); 14.6 (C-$\underline{C}H_3$); 30.2 (N-CH_3); 42.6 (N-CH_2); 50.6 (N-CH); 56.3 ($S(CH_2)_2$); 61.4 ($CH_3\underline{C}H_2$); 103.3 (C_5); 123.0 (C_{arom}); 128.5 (CH_{arom}); 132.9 (CH_{arom}); 137.5 (C_{arom}); 150.2 (C_4); 150.6 (C_2); 150.97 (C_6); 151.9 (C=N); 153.2 (C_8); 168.8 ($CH_2\underline{C}O$).

Toxicities and pharmacological activities (drug-likeness) of the synthesized compounds were predicted using the Osiris DataWarrior program [5]. The drug-likeness was selected based on a confirmation of the potential of the series, a bioavailability assessment of the most promising compounds, and identification of promising derivatives.

EXPERIMENTAL BIOLOGICAL PART

Experiments were conducted according to Good Laboratory Practice requirements of the Eurasian Economic Union for handling drugs.

Antiplatelet and anticoagulant activity were assessed *in vitro* using blood from 70 healthy male donors aged 18 – 24 years. The study was approved by the Ethics Committee, Bashkir State Medical University, Ministry of Health of Russia (No. 2 dated Oct. 17, 2012). Informed consent was obtained from all participants before collecting blood.

Effects of the compounds on platelet aggregation was studied using the Born method [6] on an AT-02 aggregometer (NPF Medtekh, Russia). Antiplatelet activity of the synthesized compounds and reference drugs was evaluated at a final concentration of 10^{-3} M after incubation for 5 min. The aggregation inductors were adenosine diphosphate (ADP) at a concentration of 20 ìg/mL and collagen at a concentration of 5 mg/mL (Tekhnologiya-Standart, Russia). Effects of the compounds on the maximum amplitude of aggregation (MA), aggregation rate, and time to reach MA during ADP-induced platelet aggregation were studied. The latent period of aggregation was evaluated in a collagen-induced platelet aggregation test. The reference drugs were pentoxifylline (Pentoxifylline, 20 mg/mL, solution for injection, 5-mL ampuls; Dal?khimfarm OAO, Russia) based on a chemical likeness principle and acetylsalicylic acid (powder drug substance; Shandong Xinhua Pharmaceutical Co., Ltd., China).

Anticoagulant activity was determined using clotting tests [7] on a Solar CGL 2110 turbidimetric hemocoagulometer (Solar ZAO, Belarus). The final concentration of the tested compounds and reference drug was 5×10^{-4} g/mL. The activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen concentration were studied according to A. Clauss. The reference drug was heparin sodium (5000 IU/mL, solution for injection, 1-mL ampuls, Sintez OAO, Russia).

Antioxidant activity of the compounds was evaluated *in vitro* using chemiluminescence (CL) in simple model sys-

tems with initiation of 1) formation of reactive oxygen species (ROS) (model I); 2) lipid peroxidation (LPO) (model II); and 3) generation of ROS by phagocytes (model III) [8, 9]. The tested compounds and reference drug ascorbic acid (powder drug substance, Hebei Welcome Pharmaceutical Co., Ltd., China) were added to a final concentration of 10^{-3} M. Chemiluminescence was recorded on a KhLM-003 chemiluminometer (Russia). CL intensity was measured from the emission light sum and flash activity.

Anti-inflammatory activity of the compounds was determined in 24 non-inbred male white mice (20 – 30 g). Test animals were kept under vivarium conditions with natural lighting at 22 – 24°C, 40 – 50% relative humidity, and free access to water and feed. Test compounds were injected once i.p. as suspensions with Tween-80 at a dose equimolar to the reference drug dose (diclofenac sodium, 10 mg/kg; voltaren, 25 mg/mL of solution for i.v. administration; Novartis, Switzerland). Controls received an equivalent volume of normal saline (0.9%). Acute inflammation of the right paw of the mice was induced by subplantar injection under the plantar fascia of formalin solution (0.05 mL, 1%) 30 min after injection of the test compounds [7, 10]. Anti-inflammatory activity was measured from the mass difference of inflamed (right) and healthy (left) paws 4 h after formalin injection.

Statistical analysis used the Statistica 10.0 program suite (StatSoft Inc., USA). A check for normal distributions was made using the Shapiro—Wilk criterion. The median, 25 and 75 percentiles, and minima and maxima were calculated to describe variational series. A one-factor dispersion analysis (if the collected data obeyed normal distribution rules and scatters of all sets were equal; *F*-criterion) or Kruskal—Wallis test (if the collected data did not obey normal distribution rules; *H*-criterion) was performed. The critical significance level p for statistical criteria was 0.05.

RESULTS AND DISCUSSION

The MA values of ester **II** and hydrazones **IVa**, **-d**, **-e**, **-f**, **-h**, and **-i** in the ADP-induced platelet aggregation test were

TABLE 1. Effects of **II**, **IVa**, **-b**, and **d-i** and Reference Drugs on Platelet Aggregation and Plasma Hemostasis System, Me (25 – 75%)

Compound	Latent period, % of control	Maximum amplitude, % of control	Aggregation rate, % of control	Time to reach MA, % of control	APTT, % of control
	collagen-induced aggregation	ADP-induced aggregation			
II	+ 6.3 (5.9 – 8.1)$^{+,\#}$	– 15.4 (11.4 – 17.8)$^{*,+}$	– 8.1 (6.5 – 10.3)$^{+}$	– 25.4 (23.1 – 30.2)$^{**,++,\#\#}$	6.9 (6.2 – 8.5)*
IVa	– 23.3 (20.1 – 27.9)$^{**,++,\#\#}$	– 17.2 (13.4 – 19.3)$^{*,+}$	– 29.3 (27.6 – 30.1)$^{**,\#}$	– 17.9 (15.4 – 20.3)$^{**,++,\#\#}$	9.2 (8.7 – 11.6)*
IVb	– 11.3 (9.8 – 12.4)$^{*,++,\#}$	– 8.9 (7.7 – 9.1)$^{*,++,\#}$	– 1.6 (1.4 – 2.3)$^{++,\#}$	+ 13.5 (11.3 – 15.4)$^{*,+}$	9.3 (8.8 – 10.5)*
IVd	– 12.2 (10.4 – 13.5)$^{*,++,\#}$	– 13.1 (12.5 – 14.3)$^{*,+}$	+ 1.1 (0.6 – 1.3)$^{++,\#}$	+ 29.9 (22.4 – 30.1)$^{**,\#}$	4.6 (3.8 – 6.2)*
IVe	+ 1.3 (1.1 – 2.3)$^{+}$	– 15.9 (13.4 – 16.7)$^{*,+}$	– 23.2 (22.1 – 26.7)$^{**,+,\#}$	– 8.8 (7.6 – 9.3)$^{++,\#}$	4.7 (2.5 – 7.3)*
IVf	– 13.3 (10.2 – 15.4)$^{*,++,\#}$	– 15.9 (13.4 – 16.5)$^{*,+}$	– 19.9 (15.6 – 17.3)$^{*,+,\#}$	– 14.6 (10.6 – 15.3)$^{*,++,\#\#}$	5.6 (5.4 – 7.2)*
IVg	– 14.5 (10.2 – 19.7)$^{*,++,\#}$	– 9.6 (8.3 – 10.4)$^{++,\#}$	– 2.9 (2.1 – 4.3)$^{++,\#}$	– 21.2 (17.8 – 23.4)$^{**,++,\#\#}$	10.3 (7.7 – 11.4)*
IVh	– 2.3 (1.2 – 3.4)$^{+}$	– 13.8 (10.5 – 16.3)$^{*,+}$	– 38.5 (36.5 – 40.1)$^{**,\#}$	– 24.8 (22.1 – 26.7)$^{**,++,\#\#}$	9.3 (9.1 – 11.8)*
IVi	+ 11.1 (9.3 – 12.4)$^{*,+,\#\#}$	– 15.4 (13.2 – 17.6)$^{*,+}$	– 21.4 (19.4 – 22.3)$^{**,+,\#}$	– 32.6 (30.1 – 35.6)$^{**,++,\#\#}$	8.4 (7.1 – 10.2)*
Pentoxifylline	+ 32.4 (28.7 – 35.6)**	– 48.4 (42.7 – 56.5)**	– 34.9 (28.7 – 39.6)**	+ 32.1 (27.6 – 32.4)**	–
Acetylsalicylic acid	– 2.1 (1.1 – 2.6)	– 13.7 (10.8 – 16.4)*	– 10.5 (7.6 – 12.3)*	+ 10.5 (8.7 – 13.4)*	–
Heparin sodium	–	–	–	–	20.3 (19.7 – 21.4)*

* $p \le 0.05$; ** $p \le 0.001$ vs. the control; $^{+}$ $p \le 0.05$; $^{++}$ p 0.001 vs. pentoxifylline; $^{\#}$ p 0.05; $^{\#\#}$ $p \le 0.001$ vs. acetylsalicylic acid; data statistically significant vs. heparin sodium ($p \le 0.05$), $n = 6$.

TABLE 2. Effects of **II**, **III**, **IVa**, **-b**, **-e**, and **-f** and Reference Drug on Chemiluminescence in Model Systems for Generating Reactive Oxygen Species (**I**), Lipid Peroxidation (**II**), and Blood Macrophage Activity (**III**)

Compound	Model	Light sum	Flash
II	I	+ 35.7 (30.9 – 47.1)$^{*, \alpha}$	– 9.6 (7.7 – 12.1)$^{\alpha}$
	II	– 24.1 (19.2 – 26.1)$^{*, \beta}$	– 14.4 (10.1 – 18.3)$^{\beta}$
	III	– 33.0 (29.4 – 36.5)$^{*, \gamma}$	– 28.5 (25.9 – 36.9)$^{*, \gamma}$
III · HCl	I	+ 18.4 (16.3 – 19.2)$^{*, \alpha}$	+ 4.32 (4.30 – 4.35)$^{**, \alpha}$
	II	+ 43.8 (42.6 – 44.1)$^{**, \beta}$	+ 10.21 (9.7 – 11.3)$^{**, \beta}$
	III	+ 18.4 (16.3 – 19.2)$^{*, \gamma}$	+ 4.32 (4.30 – 4.35)$^{**, \gamma}$
IVa	I	+ 79.8 (74.2 – 83.1)$^{**, \alpha}$	+ 19.9 (14.6 – 20.3)$^{*, \alpha}$
	II	– 4.6 (3.9 – 5.7)$^{\beta}$	– 14.1 (12.3 – 16.5)$^{\beta}$
	III	+ 65.8 (60.8 – 70.3)**	+ 51.5 (47.9 – 55.4)$^{**, \gamma}$
IVb	I	– 23.5 (21.3 – 27.4)$^{*, \alpha}$	– 34.2 (30.5 – 38.7)$^{**, \alpha}$
	II	– 59.5 (54.2 – 63.2)$^{**, \beta}$	– 29.2 (26.3 – 31.5)$^{**, \beta}$
	III	+ 17.4 (10.7 – 20.3)$^{\#}$	+ 14.3 (13.8 – 15.1)$^{*, \#}$
IVe	I	+ 47.4 (40.5 – 51.4)$^{**, \alpha}$	+ 26.1 (25.4 – 27.1)$^{**, \alpha}$
	II	– 12.4 (10.3 – 14.5)$^{\beta}$	– 12.1 (10.5 – 14.7)$^{\beta}$
	III	+ 17.7 (15.9 – 17.9)$^{\gamma}$	+ 15.4 (11.4 – 19.3)$^{\gamma}$
IVf	I	– 13.9 (12.3 – 16.1)$^{\alpha}$	– 17.2 (15.4 – 19.3)$^{*, \alpha}$
	II	– 30.7 (25.6 – 33.8)$^{*, \beta}$	– 28.6 (22.4 – 30.4)$^{**, \beta}$
	III	+ 10.1 (7.9 – 11.5)$^{\gamma}$	+ 21.4 (21.1 – 33.4)$^{**, \gamma}$
Ascorbic acid	I	– 84.5 (79.3 – 87.1)**	– 91.7 (82.3 – 95.2)**
	II	– 78.1 (70.4 – 82.4)**	– 86.8 (80.3 – 92.1)**
	III	+ 73.1 (66.7 – 75.2)**	+ 98.7 (94.8 – 100.3)**

Values are given as differences in % between test and control groups; medians and interquartile intervals from six measurements are given; * $p \le 0.05$, ** $p \le 0.001$ vs. the control; $^{\alpha}$ $p \le 0.05$, $^{\beta}$ $p \le 0.05$, $^{\gamma}$ $p \le 0.05$ are statistically significant differences vs. ascorbic acid for models I, II, and III, respectively.

comparable to that of acetylsalicylic acid but significantly (by 3.7 – 2.8 times) less than that of pentoxifylline. The MA was statistically significantly reduced by **IVb** and **-g** as compared to acetylsalicylic acid and pentoxifylline (Table 1). The platelet aggregation rate was significantly less for hydrazones **IVa**, **-e**, **-f**, **-h**, and **-i** than for acetylsalicylic acid but greater than for pentoxifylline (except for **IVh**). The times to reach the MA for **II**, **IVa**, **-e**, and **-i** were less than those for the reference drugs ($p < 0.05$) and the controls ($p < 0.05$) except for **IVe**. Compounds **IVb** and **-d** increased this parameter as compared to acetylsalicylic acid and pentoxifylline (by 13.5 and 29.9%, respectively).

The latent period in the collagen-induced aggregation test increased only for **IVi**. However, its duration was considerably shorter than for pentoxifylline ($p < 0.05$). The other tested compounds shortened significantly the latent period as compared to the control except for **II** and **IVe**, which were inactive.

All compounds caused significant hypocoagulation, increased the APTT by 4.6 – 10.3% vs. the control, and did not affect the fibrinogen concentration and PT. The effects of the tested compounds were significantly inferior to those of heparin, which increased APTT by 20.3%.

Thus, compound **IVd** of the tested molecules had an antiplatelet effect that was comparable to acetylsalicylic acid for the aggregation MA, surpassed it for the time to reach the MA, and was most promising for further studies. However, the antiplatelet activity of **IVd** was inferior to that of pentoxifylline, like the other compounds (**II**, **IVa**, **-b**, **-e**, and **-i**).

The antioxidant activities of **II**, **III·HCl**, **IVa**, **-b**, **-e**, and **-f** in the three model systems were equally effective for ROS generation (Table 2). Ester **II** reduced significantly LPO and ROS generation by phagocytes (by 24.1 and 33.0%, respectively; $p < 0.05$). However, it had pro-oxidant activity for ROS generation in model system I (by 35.7%, $p < 0.05$).

Compounds **IVa** and **-e** did not affect LPO activity (model system II) although they increased ROS generation in model system I (79.8 and 47.4%, $p < 0.001$). Compound **IVa** also increased the microbicidal properties of phagocytes (65.8%, $p < 0.001$).

Hydrazone **IVb** had targeted action like that of ascorbic acid. However, its antioxidant activity was lower. It reduced ROS generation (by 23.5%, $p < 0.05$) and LPO intensity (by 59.5%, $p < 0.001$) and stimulated insignificantly microbicidal activity of phagocytes (by 17.4%, $p < 0.05$). Hydrazone **IVf** decreased LPO intensity by 30.7% ($p < 0.05$).

The tested compounds did not exhibit anti-inflammatory activity *in vivo* in the formalin edema test of male mouse hind paws.

The toxicities and physicochemical properties of the synthesized compounds predicted by the Osiris DataWarrior program were evaluated using Lipinski's rule of five [11]. Ester **II** and hydrazones **IVb**, **-d**, **-f**, **-h**, and **-j** were found to be potentially nontoxic compounds, i.e., should not have mutagenic, oncogenic, and local irritating action and were characterized by reproductive toxicity. Hydrazine **III** and

TABLE 3. Prediction of Toxicity, "Drug-likeness", and Agreement with Lipinski's Rule of Five of Synthesized Compounds in the Osiris DataWarrior Program

Compound	Toxic risks				Drug-likeness	CLogP (≤ 5)	NOH (0…10)	NOHNH (0…5)	Mm (≤ 500)	RotB (0…10)	TPSA (≤ 170 A^2)
	mutagenicity	oncogenicity	Irritating action	reproductive toxicity							
II	(–)	(–)	(–)	(–)	– 4.87	– 0.18	9	0	419.26	5	121.02
III	(–)	(+)	(–)	(–)	– 5.80	– 0.819	11	2	370.39	6	159.07
IVa	(–)	(+)	(–)	(–)	– 0.81	2.30	12	1	501.57	9	148.65
IVb	(–)	(–)	(–)	(–)	– 1.01	2.33	12	1	488.52	9	154.64
IVc	(–)	(–)	(–)	(–)	– 1.06	2.05	12	2	474.50	8	165.64
IVd	(–)	(–)	(–)	(–)	– 2.85	2.78	12	2	553.39	8	165.64
IVe	(–)	(±)	(–)	(–)	– 0.99	1.98	13	2	504.52	9	174.87
IVf	(–)	(–)	(–)	(–)	– 1.51	2.34	11	1	472.53	8	145.41
IVg	(–)	(–)	(–)	(–)	– 6.47	1.25	14	1	517.52	9	191.23
IVh	(–)	(–)	(–)	(–)	– 1.50	1.66	12	2	487.54	8	171.43
IVi	(–)	(–)	(+)	(±)	– 1.48	1.99	12	2	488.52	8	165.64
IVj	(–)	(–)	(–)	(–)	– 3.30	3.06	11	1	551.42	8	145.41

Note: (–) is the lack of risk; (±), moderate risk level; (+), high risk level; nOH, number of H acceptors; nOHNH, number of H donors; Drug-likeness, drug similarity level; RotB, number of rotating bonds; TPSA, topological polar surface area.

arylmethylidenehydrazines **IVa** and -**e** could exhibit oncogenic activity whereas arylmethylidenehydrazine **IVi** could possess irritating effects and have reproductive toxicity (Table 3).

Lipinski's rule of five was fully satisfied only by ester **II**. The other compounds did not satisfy the number of H acceptors (nOH, >10) and/or molecular mass (MM, >500). However, the increased number of H acceptors for the tested compounds (nOH = 11 – 14) and MM values (up to 553) were not critical and are often found for drugs used in medicine.

Furthermore, most synthesized compounds had topological polar surface area (TPSA) <170 $Å^2$. Therefore, they should penetrate well through cell membranes (Table 3). The drug-likeness of the synthesized compounds had negative values, indicating a lack of drugs of similar structure.

Thus, the pharmacological screening results, *in silico* calculations of toxic risks, and physicochemical properties found that the synthesized ethyl 2-[8-arylmethylidenehydrazino-3-methyl-7-(1-oxothietan-3-yl)xanth-1-yl]acetates were a promising class for discovery of new biologically active compounds capable of exhibiting antiplatelet, anticoagulant, and antioxidant activity. Hydrazones **IVd** (antiplatelet activity) and **IVb** (antioxidant activity) were potentially promising, lacked characteristic toxic risks, and had acceptable TPSA.

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