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SEARCH FOR NEW DRUGS

SYNTHESIS AND ANTIDEPRESSANT ACTIVITY OF THIETANE-CONTAINING 4-(2-OXO-2-PHENYLETHYL)-1*H*-1,2,4-TRIAZOL-4-IUM BROMIDES

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Thietane-containing 4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromides were synthesized by quaternization of thietanyltriazoles with phenacyl bromides. The starting thietanyltriazoles were obtained by the reaction of 1,2,4-triazoles and 2-chloromethylthiirane followed by oxidation of 1-(thietan-3-yl)-1,2,4-triazole to 1-(1-oxidotheitan-3-yl)-1,2,4-triazole and 1-(1,1-dioxidothietan-3-yl)-1,2,4-triazole. The structures of the synthesized compounds were confirmed by IR, PMR, and ^{13}C and ^{15}N NMR spectroscopy. An *in vivo* study of the antidepressant activity revealed the promising compound 1-(1,1-dioxidothietan-3-yl)-4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromide (**IXa**), which statistically significantly reduced the duration of immobilization in the forced swimming test by 44% as compared to the control group. Compound **IXa** is a low-toxic substance (class 4 toxicity) with a high bioavailability predicted according to *in silico* calculations.

Keywords: 1,2,4-triazole, thietane, antidepressant activity, SwissADME, GUSAR-online.

Depression and anxiety disorders are the principal causes of global incidence of diseases and cause enormous economic harm on society [1]. Many patients do not achieve remission and recovery because existing antidepressants are not effective enough [2]. Therefore, the development of new more effective antidepressants, including those directed at new therapeutic targets, is an important thrust of psychopharmacology [3].

1,2,4-Triazole derivatives (trazodone and nefazodone) and 3-substituted thietane-1,1-dioxides have characteristic antidepressant effects [4 – 9]. Potent antidepressant properties were observed by us in recent research on 1,24-triazole derivatives containing a thietane ring [10 – 12].

Several psychotropic agents contain oxophenylalkyl moieties in their structures. Antidepressant activity was found for bupropion (an inhibitor of neuronal reverse uptake of noradrenaline and dopamine) [13] and the atypical neuroleptic roluperidone, which was proposed for treating schizophrenia (antagonist of $5HT_{2A}$- and σ2-receptors) and

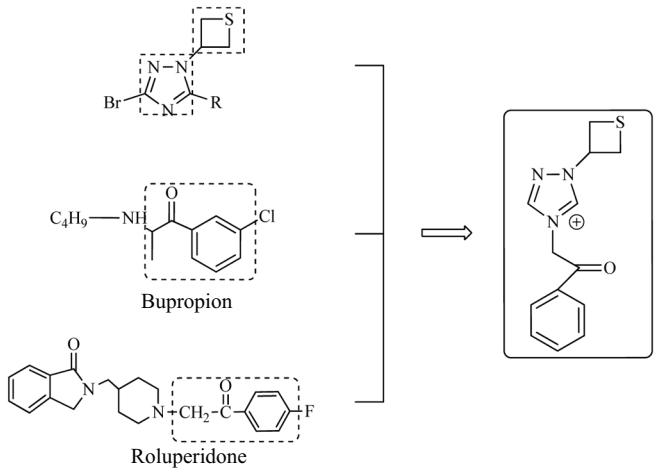

Fig. 1. Design of potential antidepressants.

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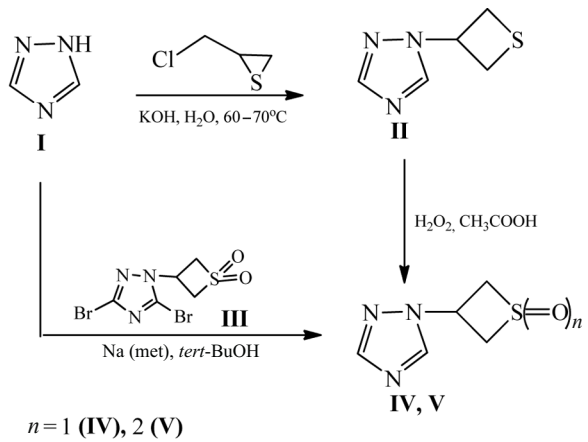
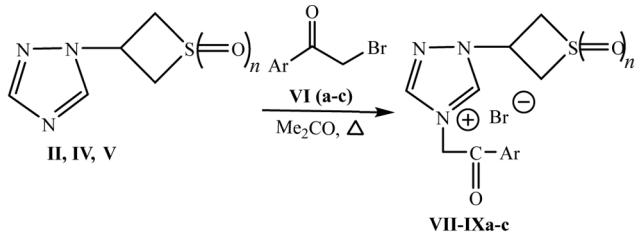
Scheme 1



n = 1 **(IV),** 2 **(V)**

Scheme 2



n = 0 (**II, VII**)
1 (**IV, VIII**)
2 (**V, IX**)
Ar = Ph (**a**), 4-BrC_6H_4 (**b**), 4-$NO_2C_6H_4$ (**c**)

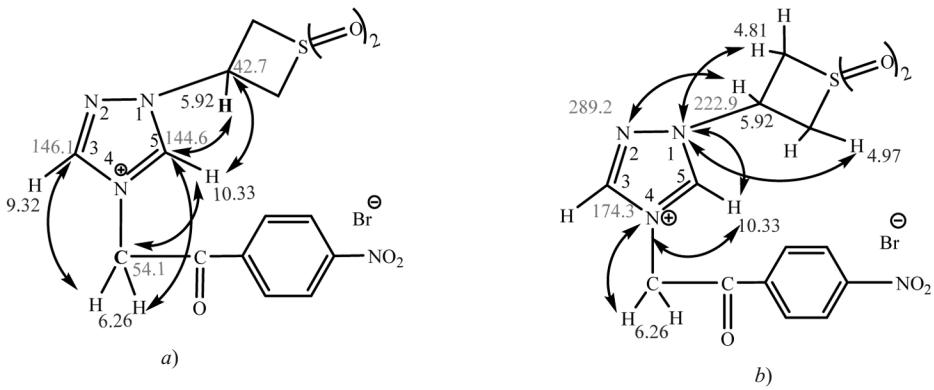
several other neurodegenerative disorders [14]. A combination of 1,2,4-triazole, thietane, and a 2-oxo-2-phenylethyl substituent was used by us in the present article to design new potential antidepressants (Fig. 1).

The target thietane-containing 4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromides were synthesized in two steps from 1,2,4-triazole. The first step produced the starting 1-thietanyl-1,2,4-triazoles **II**, **IV**, and **V**. The reaction of triazole (**I**) with 2-chloromethylthiirane in H_2O in the presence of KOH formed asymmetric 1-(thietan-3-yl)-1,2,4-triazole (**II**) in 39% yield (Scheme 1). The structure of **II** was confirmed by the presence in the PMR spectrum of two singlets for the triazole-ring protons at 7.95 and 8.11 ppm and characteristic resonances of the thietane-ring protons [15].

Oxidation of **II** by H_2O_2 (two-fold molar excess) produced 1-(1-oxothietan-3-yl)-1,2,4-triazole (**IV**) in 13% yield (Scheme 1). The PMR and ^{13}C NMR spectra of sulfoxide **IV** were consistent with the formation of *cis*- and *trans*-isomers in a 1:5 ratio [16, 17]. The PMR spectrum showed two resonances of $S(CH)_2$ groups of the *cis*-isomer at ~3.9 and 4.8 ppm; of the *trans*-isomer, at ~3.6 and 3.9 ppm. The NCH proton of the *trans*-isomer was sterically close to the S=O oxygen atom. Its multiplet was shifted to weak field by 1.14 ppm as compared to the multiplet of the *cis*-isomer. The ^{13}C NMR spectrum of **IV** contained resonances for the NCH carbon atom of the *cis*-isomer at 42.7 ppm; of the *trans*-isomer, at 51.4 ppm. The IR spectrum of **IV** exhibited a characteristic absorption for the vS=O vibration at 1063 $cm^{(1}$ [18].

Oxidation of **II** by H_2O_2 (10-fold molar excess) produced 1-(1,1-dioxothietan-3-yl)-1,2,4-triazole (**V**) in 41% yield (Scheme 1). Compound **V** was also synthesized by dioxothietanylation of 1,2,4-triazole by the literature method [19]. Samples of **V** did not depress the melting point of mixtures. Their IR and PMR spectra agreed fully.

The second step involved quaternization of the starting compounds by phenacyl bromides. Usually, quaternization of 1-substituted 1,2,4-triazoles uses prolonged heating with alkylating agents in Me_2CO or MeCN [20]. Triazoles **II**, **IV**, and **V** were reacted with an equimolar amount of phenacyl bromides **VIa-c** in Me_2CO under reflux for 4 – 13 h (Scheme 2) to form thietane-containing 4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromides (**VII-IXa-c**) in 11 – 53% yields. PMR spectra of **VII-IXa-c** gave resonances for phenacyl methylene protons at 6.1 – 6.3 ppm and for phenyl aromatic protons at 7.6 – 8.5 ppm. The triazole ring proton resonances were shifted to weak field by 1 – 2 ppm as com-



a) *b*)

Fig. 2. Principal correlations in $^1H(^{13}C$-a) and $^1H(^{15}N$ HMBC spectra-b) of **IXc**.

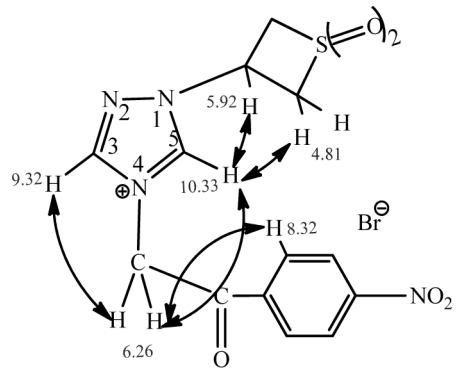


Fig. 3. Principal correlations in NOESY spectrum of **IXc**.

pared to the those of the starting compounds. ^{13}C NMR spectra of **VII-IXa-c** showed weak-field resonances at 188 – 190 ppm for the C=O groups. Sulfoxides **VIIIa-c**, like the starting compound **IV**, were dominated by the *trans*-isomer. The yields of **VIIa-c** did not increase if the reactions of **II** with the phenacyl bromides were performed with microwave activation.

Two-dimensional (2D) HMBC, HSQC, and NOESY spectra of **IXc** were recorded for unambiguous confirmation of the quaternization of the N^4-position.

The 2D $^1H(^{13}C$ HMBC spectrum of **IXc** established that the protons of the CH_2CO(moiety in the N^4-position were coupled to C^3 and C^5 of the triazole ring (Fig. 2*a*). The 2D $^1H–^{15}N$ HMBC spectrum of **IXc** showed coupling of N^4 with the CH_2CO(protons and the triazole H_5 proton (Fig. 2*b*).

The 2D NOESY spectrum of **IXc** exhibited cross peaks between the CH_2CO(protons and triazole-ring protons H^3 and H^5 (Fig. 3). The formation of quaternization products at the N^4-position agreed with the literature [20].

IR spectra of **VII-IXa-c** contained absorption bands for νC=O vibrations in the range 1682 – 1706 cm^{-1}. IR spectra of sulfoxides **VIIIa-c** contained a characteristic absorption band for νS=O at 1074 – 1078 cm^{-1}; of sulfones **IXa-c**, two absorption bands for νSO_2 groups at ~1143 and 1327 cm^{-1}.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded from KBr pellets on an InfraLUM FT-02 FT spectrometer (Russia). PMR and ^{13}C NMR spectra were taken on a Bruker AM-300 pulsed spectrometer (USA) at operating frequency 300.13 MHz (^1H) for **II** and **V** and on a Bruker Avance III pulsed spectrometer (USA) at operating frequency 500.13 MHz (^1H) and 125.47 MHz (^{13}C) for the other compounds. Chemical shifts in PMR and ^{13}C NMR spectra were given vs. residual solvent resonances of $CDCl_3$ (7.26 ppm for ^1H and 77.0 ppm for ^{13}C) and DMSO-d_6 (2.50 ppm for ^1H and 39.5 ppm for ^{13}C). ^{13}C NMR spectra were edited based on DEPT-90 and DEPT-135 experiments. 2D $^1H–^{13}C$ HMBC, $^1H–^1H$ NOESY, and $^1H–^{15}N$ HMBC spectra of **IXc** were recorded using standard multi-pulse sequences embedded in the instrument software. Chemical shifts in ^{15}N NMR spectra were given in ppm vs. liquid NH_3 external standard.

Elemental analyses for C, H, N, and S were performed on a Hekatech Euro3000 analyzer (Germany) and agreed satisfactorily with those calculated. Melting points were measured on a Stuart SMP30 apparatus (Great Britain). The course of reactions and purity of synthesized compounds were monitored by TLC on Sorbfil PTSKh-P-A-UF plates using $CHCl_3$–EtOH (9:1, v/v). Spots were detected in UV light and in a chamber with I_2 vapor.

GC-MS spectra of **II**, **IV**, and **V** were recorded using a gas chromatograph with an Agilent MSD 5977B mass-selective detector (USA). The carrier gas was He (1.0 mL/min). The electron-impact ionizing potential was 70 eV. The chromatographic separation used an HP-5ms quartz capillary column (30 m × 0.25 mm × 0.25 μm). The injected sample volume for all measurements was 1 μL. The vaporizer and interface temperatures were 130°C for **II**; 170°C, **IV**; and 200°C, **V**. The analysis time was 30 min. The scanned mass range was 40 – 500 *m*/*z*. Experimental data were recorded and processed using Qualitative Analysis 10.0 software.

Microwave syntheses were performed in a CEM Discover SP monomodal microwave system (USA) at operating frequency 2.45 GHz. The reactions occurred in a 35-mL vessel with a special lid. The reaction temperature was monitored by an inbuilt IR sensor on the external vessel surface.

Compound **III** was prepared by the literature method [21]; phenacyl bromides **VIa-c**, as before [22]. Commercially available reagents were used in the work.

1-(Thietan-3-yl)-1,2,4-triazole (II). A solution of KOH (2.62 g, 24 mmol) in H_2O (20 mL) was treated with triazole (**I**, 1.38 g, 20 mmol), heated to 60 – 70°C, and treated with 2-chloromethylthiirane (1.34 g, 24 mmol). The reaction mixture was stirred for 1 h, cooled, and extracted with $CHCl_3$ (2 × 15 mL). The $CHCl_3$ extract was filtered through a layer of silica gel. The filtrate was evaporated under vacuum. The oily residue was purified by reprecipitation from an Me_2CO solution of hexane (2:1, v/v) and dried. Yield: 1.10 g (39%), yellow oil. PMR spectrum ($CDCl_3$), δ, ppm: 3.28 – 3.50 (m, 2H, $S(CH)_2$), 3.84 – 4.13 (m, 2H, $S(CH)_2$), 5.53 – 5.73 (m, 1H, NCH), 7.95 (s, 1H, H_{tr}), 8.11 (s, 1H, H_{tr}). Found, *m*/*z*: 141.0 [M^+]. Calc., *m*/*z*: 141.0 [M^+]. $C_5H_7N_3S$.

1-(1-Oxothietan-3-yl)-1,2,4-triazole (IV). Compound **II** (2.60 g, 20 mmol) in glacial HOAc (35 mL) was treated with H_2O_2 solution (37.7%, 1.36 g, 40 mmol). The reaction mixture was held for 2 h at room temperature, neutralized with NH_3 solution to pH 7 – 8, and extracted with $CHCl_3$ (3 × 25 mL). The $CHCl_3$ extract was evaporated under vacuum to dryness. The residue was triturated with hexane. The precipitate was filtered off, rinsed with H_2O, and dried. Yield: 0.40 g (13%), white powder, mp 99 – 101°C (*i*-PrOH–hexane, 1:1). IR spectrum, ν_{max}, cm^{-1}: 1063 (S=O), 1186, 1276 (C-N), 1503 (C=N), 2950 – 3108 (C-H). PMR spectrum, $CDCl_3$, δ, ppm: 3.63 – 3.68 (m, 2H, $S(CH)_2$) –

trans, 3.90 – 3.95 (m, 2H, $S(CH)_2$) – *cis* and *trans*, 4.17 – 4.21 (m, 2H, $S(CH)_2$) – *cis*, 4.75 – 4.81 (m, 1H, NCH) – *cis*, 5.87 – 5.92 (m, 1H, NCH) – *trans*, 8.02 (s, 1H, H_{tr}) – *cis* and *trans*, 8.13 (s, 1H, H_{tr}) – *trans*, 8.15 (s, 1H, H_{tr}) – *cis*. ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 42.7 (NCH) – *cis*, 51.4 (NCH) – *trans*, 57.1 ($S(CH_2)_2$) – *trans*, 59.5 ($S(CH_2)_2$) – *cis*, 142.2 (CH_{tr}) – *cis*, 142.7 (CH_{tr}) – *trans*, 152.9 (CH_{tr}) – *cis*, 153.2 (CH_{tr}) – *trans*. Ratio of *cis*- and *trans*-isomers 1:5. Found, *m*/*z*: 157.0 [M^+]. Calc., *m*/*z*: 157.0 [M^+]. $C_5H_7N_3O_2S$.

1-(1,1-Dioxothietan-3-yl)-1,2,4-triazole (V). Compound **II** (2.86 g, 20 mmol) in glacial HOAc (30 mL) was treated with H_2O_2 solution (30%, 6.80 g, 200 mmol), refluxed for 1 h, cooled, and neutralized with NH_3 solution to pH 9 – 10. The resulting precipitate was filtered off, rinsed with H_2O, and dried. Yield 1.41 g (41%), white powder, mp 187 – 188°C (EtOH). IR spectrum, ν_{max}, cm^{-1}: 1141, 1325 (SO_2), 1173, 1280 (C-N), 1508 (C=N), 2973 – 3099 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 4.61 – 4.74 (m, 2H, $S(CH)_2$), 4.75 – 4.91 (m, 2H, $S(CH)_2$), 5.42 – 5.55 (m, 1H, NCH), 8.12 (s, 1H, H_{tr}), 8.73 (s, 1H, H_{tr}). Found, *m*/*z*: 173.0 [M^+]. Calc., *m*/*z*: 173.0 [M^+]. $C_5H_7N_3O_2S$.

General method for synthesis of thietane-containing 4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromides (VII-IXa-c)

A. A solution of **II** (5 mmol) in Me_2CO (25 mL) was treated with phenacyl bromide (**VIa-c**, 5 mmol). The mixture was refluxed for 13 h and cooled. The resulting precipitate was filtered off, rinsed with Et_2O, and dried.

Compounds **VIII-IXa-c** were prepared analogously with refluxing for 4 h for **VIIIa-c** and for 9 h for **IXa-c**.

B. A reaction vessel was charged with a solution of **II** (0.28 g, 2 mmol) in Me_2CO (10 mL), treated with phenacyl bromide (**VIa-c**, 2 mmol), sealed, placed into a microwave oven at 80°C and power 100 W for 60 min with dynamic control, and cooled. The resulting precipitate was filtered off, rinsed with Et_2O, and dried.

4-(2-Oxo-2-phenylethyl)-1-(thietan-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (VIIa). Yield: A. 0.53 g (31%), B. 0.20 (29%), white powder, mp 160 – 161°C (*i*-PrOH(hexane, 1:1). IR spectrum, ν_{max}, cm^{-1}: 1169, 1232 (C-N), 1572, 1599 (C=C, C=N), 1706 (C=O), 3037 – 3082 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 3.49 – 3.52 (m, 2H, $S(CH)_2$), 3.89 – 3.94 (m, 2H, $S(CH)_2$), 6.14 (s, 2H, CH_2), 6.17 – 6.20 (m, 1H, NCH), 7.63 – 7.66 (m, 2H, H_{arom}), 7.76 – 7.79 (m, 1H, H_{arom}), 8.06 – 8.09 (m, 2H, H_{arom}), 9.24 (s, 1H, H_{tr}); 10.16 (s, 1H, H_{tr}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 32.7 ($S(CH_2)_2$), 54.3 (CH_2CO), 56.6 (NCH), 128.7 (CH_{arom}), 129.7 (CH_{arom}), 133.8 (C_{arom}), 135.3 (CH_{arom}), 143.3 (CH_{tr}), 146.3 (CH_{tr}), 190.7 (CO). $C_{13}H_{14}BrN_3OS$.

4-[2-(4-Bromophenyl)-2-oxoethyl]-1-(thietan-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (VIIb). Yield: A. 0.75 g (45%), B. 0.23 (24%), white powder, mp 178 – 180°C (EtOH). IR spectrum, ν_{max}, cm^{-1}: 1161, 1235 (C-N), 1569, 1599 (C=C, C=N), 1694 (C=O), 3004 – 3031 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 3.49 – 3.54 (m, 2H, $S(CH)_2$), 3.91 – 3.94 (m, 2H, $S(CH)_2$), 6.13 (s, 2H, CH_2), 6.18 – 6.21 (m, 1H, NCH), 7.89 (d, 2H, J 8.5 Hz, H_{arom}), 8.01 (d, 2H, J 8.5 Hz, H_{arom}), 9.24 (s, 1H, H_{tr}), 10.16 (s, 1H, H_{tr}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 32.2 ($S(CH_2)_2$), 53.8 (CH_2CO), 56.2 (NCH), 128.9 (C_{arom}), 130.2 (CH_{arom}), 132.3 (CH_{arom}), 132.4 (C_{arom}), 142.8 (CH_{tr}), 145.8 (CH_{tr}), 189.6 (CO). $C_{13}H_{13}Br_2N_3OS$.

4-[2-(4-Nitrophenyl)-2-oxoethyl]-1-(thietan-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (VIIc). Yield: 0.23 g (12%), B. 0.11 (14%), white powder, T_{dec} 207°C (EtOH). IR spectrum, ν_{max}, cm^{-1}: 1151, 1227 (C-N), 1348, 1524 (NO_2), 1569, 1599 (C=C, C=N), 1704 (C=O), 3028 – 3082 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 3.49 – 3.52 (m, 2H, $S(CH)_2$), 3.89 – 3.94 (m, 2H, $S(CH)_2$), 6.17 – 6.22 (m, 3H, NCH, CH_2), 8.29 (d, 2H, J 8.7 Hz, H_{arom}), 8.45 (d, 2H, J 8.8 Hz, H_{arom}), 9.24 (s, 1H, H_{tr}), 10.16 (s, 1H, H_{tr}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 32.6 ($S(CH_2)_2$), 54.7 (CH_2CO), 56.7 (NCH), 124.7 (CH_{arom}), 130.2 (CH_{arom}), 138.5 (C_{arom}), 143.3 (CH_{tr}), 146.3 (CH_{tr}), 151.1(C_{arom}), 189.2 (CO). $C_{13}H_{13}BrN_4O_3S$.

1-(1-Oxothietan-3-yl)-4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromide (VIIIa). Yield 0.20 g (11%), white powder, mp 155 – 157°C (EtOH – hexane, 2:5). IR spectrum, ν_{max}, cm^{-1}: 1074 (S=O), 1186, 1241 (C-N), 1572, 1601 (C=C, C=N), 1700 (C=O), 3043 – 3082 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 3.66 – 3.67 (m, 2H, $S(CH)_2$) – *cis*, 3.78 – 3.83 (m, 2H, $S(CH)_2$) – *trans*, 4.01 – 4.05 (m, 2H, $S(CH)_2$) – *trans*, 4.35 – 4.39 (m, 2H, $S(CH)_2$) – *cis*, 5.53 – 5.68 (m, 1H, NCH) – *cis*, 6.17 – 6.20 (s, 2H, CH_2) – *cis* and *trans*, 6.30 – 6.33 (m, 1H, NCH) – *trans*, 7.64 – 7.67 (m, 2H, H_{arom}), 7.78 – 7.81 (m, 1H, H_{arom}), 8.07 – 8.09 (m, 2H, H_{arom}), 9.29 – 9.32 (m, 1H, H_{tr}), 10.18 – 10.22 (m, 1H, H_{tr}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 45.9 (NCH) – *cis*, 54.0 (CH_2CO), 54.1 (NCH) – *trans*, 55.8 ($S(CH_2)_2$) – *cis*, 58.4 ($S(CH_2)_2$) – *trans*, 128.3 (CH_{arom}), 129.2 (CH_{arom}), 133.4 (C_{arom}), 134.8 (CH_{arom}), 143.2 (CH_{tr}) – *cis*, 143.8 (CH_{tr}) – *trans*, 146.2 (CH_{tr}) – *cis*, 146.3 (CH_{tr}) – *trans*, 190.3 (CO). Ratio of *cis*- and *trans*-isomers 1:5. $C_{13}H_{14}BrN_3O_2S$.

4-[2-(4-Bromophenyl)-2-oxoethyl]-1-(1-oxothietan-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (VIIIb). Yield 0.67 g (32%), white powder, T_{dec} 182°C (Me_2CO). IR spectrum, ν_{max}, cm^{-1}: 1078 (S=O), 1175, 1237 (C-N), 1572, 1601 (C=C, C=N), 1682 (C=O), 3043 – 3082 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 3.65 – 3.71 (m, 2H, $S(CH)_2$) – *cis*, 3.77 – 3.83 (m, 2H, $S(CH)_2$) – *trans*, 4.00 – 4.05 (m, 2H, $S(CH)_2$) – *trans*, 4.35 – 4.39 (m, 2H, $S(CH)_2$) – *cis*, 5.52 – 5.59 (m, 1H, NCH) – *cis*, 6.17 (s, 2H, CH_2), 6.29 – 6.35 (m, 1H, NCH) – *trans*, 7.89 (d, 2H, J 8.6 Hz, H_{arom}), 8.01 (d, 2H, J 8.7 Hz, H_{arom}), 9.31 (s, 1H, H_{tr}) – *cis* and *trans*, 10.21 (s, 1H, H_{tr}) – *trans*, 10.28 (s, 1H, H_{tr}) – *cis*. ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 45.9 (NCH) – *cis*, 53.9 (CH_2CO), 54.1 (NCH) – *trans*, 55.8 ($S(CH_2)_2$) – *cis*, 58.4 ($S(CH_2)_2$) – *trans*, 128.9 (C_{arom}), 130.2 (CH_{arom}), 132.3

(CH_{arom}), 132.4 (C_{arom}), 143.6 (CH_{tr}) – *cis*, 143.8 (CH_{tr}) – *trans*, 146.1 (CH_{tr}) – *cis*, 146.3 (CH_{tr}) – *trans*, 189.7 (CO). Ratio of *cis*- and *trans*-isomers 1:4. $C_{13}H_{13}Br_2N_3O_2S$.

4-[2-(4-Nitrophenyl)-2-oxoethyl]-1-(1-oxothietan-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (VIIIc). Yield 1.06 (53%), white powder, T_{dec} 169°C (*i*-PrOH(H_2O, 10:1). IR spectrum, ν_{max}, cm^{-1}: 1074 (S=O), 1167, 1219 (C-N), 1350, 1522 (NO_2), 1572, 1601 (C=C, C=N), 1700 (C=O), 3043 – 3082 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 3.66 – 3.72 (m, 2H, $S(CH)_2$) – *cis*, 3.78 – 3.84 (m, 2H, $S(CH)_2$) – *trans*, 4.01 – 4.06 (m, 2H, $S(CH)_2$) – *trans*, 4.36 – 4.41 (m, 2H, $S(CH)_2$) – *cis*, 5.54 – 5.61 (m, 1H, NCH) – *cis*, 6.25 (s, 2H, CH_2), 6.31 – 6.37 (m, 1H, NCH) – *trans*, 8.31 – 8.33 (m, 2H, H_{arom}), 8.46 (d, 2H, J 8.9 Hz, H_{arom}), 9.14 (s, 1H, H_{tr}) – *cis* and *trans*, 10.22 (s, 1H, H_{tr}) – *trans*, 10.29 (s, 1H, H_{tr}) – *trans*. ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 45.9 (NCH) – *cis*, 54.1 (NCH) – *trans*, 54.4 (CH_2CO), 55.8 ($S(CH_2)_2$) – *trans*, 58.4 ($S(CH_2)_2$) – *cis*, 124.2 (CH_{arom}), 129.8 (CH_{arom}), 138.0 (C_{arom}), 143.8 (CH_{tr}) – *cis* and *trans*, 146.1 (CH_{tr}) – *cis*, 146.3 (CH_{tr}) – *trans*, 150.7 (C_{arom}), 189.6 (CO). Ratio of *cis*- and *trans*-isomers 1:5. $C_{13}H_{13}BrN_4O_4S$.

1-(1,1-Dioxothietan-3-yl)-4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromide (IXa). Yield 0.30 g (16%), white powder, mp 189 – 190°C (EtOH). IR spectrum (ν_{max}, cm^{-1}): 1143, 1329 (SO_2), 1186, 1227 (C-N), 1569, 1587 (C=C, C=N), 1695 (C=O), 3007 – 3067 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 4.77 – 4.81 (m, 2H, $S(CH)_2$), 4.94 – 4.99 (m, 2H, $S(CH)_2$), 5.91 – 5.93 (m, 1H, NCH), 6.21 – 6.23 (m, 2H, CH_2) 7.63 – 7.66 (m, 2H, H_{arom}), 7.76 – 7.79 (m, 1H, H_{arom}), 8.07 – 8.08 (m, 2H, H_{arom}), 9.33 – 9.35 (m, 1H, H_{tr}), 10.33 – 10.37 (m, 1H, H_{tr}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 43.1 (NCH), 54.5 (CH_2CO), 71.4 ($S(CH_2)_2$), 128.2 (CH_{arom}), 129.1 (CH_{arom}), 133.3 (C_{arom}), 134.7 (CH_{arom}), 144.5 (CH_{tr}), 146.1 (CH_{tr}), 190.1 (CO). $C_{13}H_{14}BrN_3O_3S$.

4-[2-(4-Bromophenyl)-2-oxoethyl]-1-(1,1-dioxothietan-3-yl)-1*H*-1,2,4-triazol-4-ium bromide (IXb). Yield 1.07 g (47%), white powder, T_{dec} 193°C (*i*-BuOH(H_2O, 10:1). IR spectrum (ν_{max}, cm^{-1}): 1143, 1325 (SO_2), 1173, 1216 (C-N), 1569, 1596 (C=C, C=N), 1697 (C=O), 3007 – 3067 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 4.76 – 4.80 (m, 2H, $S(CH)_2$), 4.94 – 4.99 (m, 2H, $S(CH)_2$), 5.62 – 5.66 (m, 1H, NCH), 6.13 (s, 2H, CH_2), 7.81 – 7.86 (m, 2H, H_{arom}), 7.98 – 8.05 (m, 2H, H_{arom}), 9.12 (s, 1H, H_{tr}), 9.46 (s, 1H, H_{tr}). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 41.6 (NCH), 56.1 (CH_2CO), 71.4 ($S(CH_2)_2$), 121.4 (CH_{arom}), 125.1 (CH_{arom}), 129.2 (C_{arom}), 130.6 (CH_{tr}), 132.6 (CH_{tr}), 138.2 (C_{arom}), 190.9 (CO). $C_{13}H_{13}Br_2N_3O_2S$.

1-(1,1-Dioxothietan-3-yl)-4-[2-(4-nitrophenyl)-2-oxoethyl]-1*H*-1,2,4-triazol-4-ium bromide (IXc). Yield 0.88 g (42%), white powder, T_{dec} 195°C (*n*-PrOH(H_2O, 10:1). IR spectrum, ν_{max}, cm^{-1}: 1143, 1326 (SO_2), 1184, 1227 (C-N), 1390, 1550 (NO_2), 1569, 1596 (C=C, C=N), 1706 (C=O), 3007 – 3067 (C-H). PMR spectrum (DMSO-d_6), δ, ppm: 4.79 – 4.83 (m, 2H, $S(CH)_2$), 4.95 – 5.00 (m, 2H, $S(CH)_2$), 5.90 – 5.96 (m, 1H, NCH), 6.26 (s, 2H, CH_2), 8.32 (d, 2H, J 8.8 Hz, $H^{2.6}{}_{arom}$), 8.47 (d, 2H, J 8.8 Hz, $H^{3.5}{}_{arom}$), 9.32 (s, 1H, $H^{3}{}_{tr}$), 10.33 (s, 1H, $H^{5}{}_{tr}$). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 42.7 (NCH), 54.1 (CH_2CO), 70.9 ($S(CH_2)_2$), 124.2 ($CH^{3.5}{}_{arom}$), 129.8 ($CH^{2.6}{}_{arom}$), 138.0 ($C^{1}{}_{arom}$), 144.6 ($CH^{5}{}_{tr}$), 146.1 ($CH^{3}{}_{tr}$), 150.7 ($C^{4}{}_{arom}$), 189.6 (CO). ^{15}N NMR spectrum (DMSO-d_6), δ, ppm: 174.3 ($N^{4}{}_{tr}$), 222.9 ($N^{1}{}_{tr}$), 289.2 ($N^{2}{}_{tr}$), 368.7 (NO_2). $C_{13}H_{13}BrN_4O_4S$.

EXPERIMENTAL BIOLOGICAL PART

Antidepressant activity. The antidepressant activity of synthesized **VIIa, b**, **VIIIa**, and **IXa, b** was evaluated using outbred white male mice and the behavioral tail suspension test (TST) [23], forced swimming test (FST) [24], and open-field test (OF) [25]. Experimental animals (20 – 24 g) were kept under vivarium conditions on a balanced diet according to GOST R 50258 – 92. All studies were conducted according to requirements of the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* (ETS No. 123, 1986) [26] and Decision No. 81 of the Council of the Eurasian Economic Commission of Nov. 3, 2016, *On Approval of Good Laboratory Practice Rules of the Eurasian Economic Union in the Field of Drug Circulation* [27].

The tested compounds were dissolved in normal saline and administered in doses equimolar to fluoxetine (10 mg/kg) once intraperitoneally (i.p.) 30 min before testing, by analogy to the scheme for administering the reference drug fluoxetine (10 mg/kg, Fluoxetine, 20-mg capsules, Promed, RF). The behavior of the animals in the TST, FST, and OF was recorded on a video camera and analyzed using the BrainTest program [28]. The total duration of immobilization (DI) was determined in the TST; DI, in the FST; duration of active and passive swimming, in the FST with calculation of the chronobiological index of depression (ID) as the ratio of the number of short immobilization periods (duration sec) to the number of active swimming periods. The number of patterns of grooming, rearing, supported rearing, stretch-attend posture, sniffing, movement, motion in place, and sitting was recorded in the OF. The emotional anxiety parameters (EA, i.e., the sum of patterns of sniffing, movement, and stretch-attend posture) and orientation-exploratory activity (OEA, i.e., the sum of patterns of motion in place, rearing, and supported rearing) were calculated.

The *in vivo* acute toxicity (LD_{50}) of **IXa** was estimated by the method of Deichmann and LeBlanc [29]. The compound was injected once i.p. to outbred white male mice ($n = 6$). The lowest dose causing a lethal outcome was determined.

Results were statistically analyzed using the Statistica 13.3 program (TIBCO Software, Inc., USA). The nature of the distribution was evaluated. The basic parameters of the descriptive statistics (median, interquartile interval, mini-

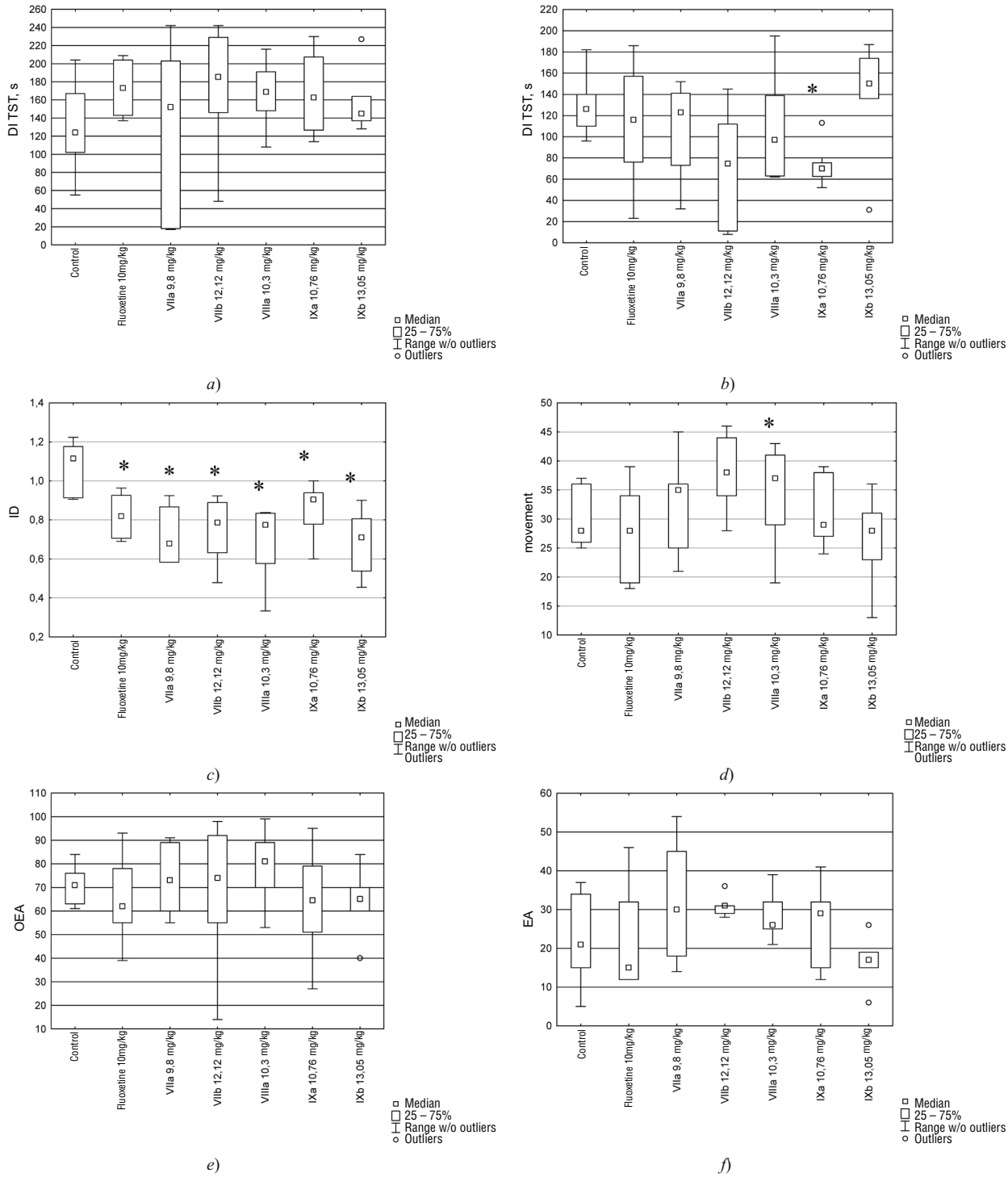


Fig. 4. Effects of **VIIa, b**, **VIIIa**, **IXa, b** on DI in TST-a), DI in TST-b), and ID in FST-c), and number of movements-d), orientation-exploratory activity-e), and emotional anxiety-f) in OF test. Note: medians of groups and interquartile interval ± minimum – maximum are given in the graphs; * $p < 0.05$ for the Mann(Whitney *U*-criterion as compared to the control group.

mum – maximum, root-mean-square deviation, outliers) were estimated and compared using the Kruskal(Wallis and Mann(Whitney criteria [30]. The statistical significance level was taken as 0.05.

RESULTS AND DISCUSSION

Fluoxetine (10 mg/kg) showed an antidepressant effect in the FST, reducing the ID by 27% ($p = 0.011$) vs. the con-

trol group (Fig. 4*c*) and did not affect the DI in the TST and FST (Fig. 4*a* and 4b).

All tested compounds also reduced the ID in the FST by 19 – 39% ($p < 0.05$, Fig. 4*c*) and did not change the TST DI (Fig. 4*a*) as compared to the control. Also, **IXa** statistically significantly reduced the FST DI by 44% vs. the control group ($p = 0.003$, Fig. 4*b*).

Only **VIIIa** significantly increased the number of movements in the OF test (by 32%, $p = 0.043$, Fig. 4*d*) as compared to the control group. It did not affect the EA and OEA. The other compounds did not affect these parameters (Fig. 4*e* and 4f). This was indicative of the manifestation by them in the screening tests of a true antidepressant effect.

The results led to the conclusion that the amount of active swimming and the number of jumps (151% → 193% → 214%, $p > 0.05$ for all compared pairs[2]) tended to increase as the degree of oxidation of the sulfur increased (**VIIa → VIIIa → IXa**). The ID in this series increased insignificantly (61% → 69% → 81%, $p > 0.05$ for all compared pairs).

Introduction of a Br atom onto the benzene ring increased the number of jumps → 50% → 175%, $p = 0.043$) only in the series of thietanes → **VIIa → VIIb**) while the reverse dependence was observed in the series of thietane dioxides → **IXa → IXb**), i.e., the jumps → 81% → 64%, $p = 0.08$), amount of active swimming → 214% → 109%, $p = 0.045$), and DI → 56% → 119%, $p = 0.045$) of the animals tended to decrease.

The increased number of movements without effects on the number of jumps and amount of active swimming of the mice under the influence of **VIIIa** (by 32% as compared to the control, $p = 0.043$) led to the conclusion that the antidepressant activity of the compound was associated with psychoactive action and was not a consequence of psychostimulatory activity.

Thus, introduction of a Br atom on the benzene ring nullified the psychoactive effect of the thietane-dioxide ring. However, it was noteworthy that the strength of the antidepressant effect did not depend on the degree of oxidation of the sulfur or on the presence of a Br atom on the benzene ring.

The new compounds were analyzed according to Lipinski's rule of five and the Veber rule using the SwissADME web resource [31] to reveal compounds capable after *in vivo* testing of providing a drug candidate.

The molecular masses of the synthesized compounds were <500 g/mol. The structures of **VII-IXa-c** did not contain H-bond donors. The number of acceptors was ≤10. The compounds contained ≤10 rotating bonds. The topological polar surface area (TPSA) was ≤140 Å^2, which led to the

[2] Values expressed in percent of the control value taken as 100%.

TABLE 1. Prognosis of *in silico* Physicochemical Parameters and Acute Toxicity and Agreement with Lipinski's Rule of Five and Veber Rule of **VII-IXa-c**

Compound	Parameter								
	MM, g/mol	RB[a]	HBA[b]	HBD[c]	TPSA[d], A^2	Lipophilicity, Log$P_{o/w}$	by Lipinski	by Veber	LD_{50} of rat-i.p.), mg/kg
VIIa	340.24	4	2	0	64.07	– 1.81	+		240.60 class 4
VIIb	419.13	4	2	0	64.07	– 4.87	+	+	480.60e class 4
VIIc	385.24	5	4	0	109.89	– 4.21	+	+	527.30e class 4
VIIIa	356.24	4	3	0	75.05	– 4.34	+	+	320.00 class 4
VIIIb	435.13	4	3	0	75.05	– 4.46	+	+	228.40e class 4
VIIIc	401.24	5	5	0	120.87	– 4.57	+	+	288.20e class 4
IXa	372.24	4	4	0	81.29	– 5.55	+	+	492.90 class 4
IXb	451.13	4	4	0	81.29	– 5.72	+	+	535.70e class 4
IXc	417.24	5	6	0	127.11	– 6.63	+	+	494.30e class 4

Note: number of bonds capable of free rotation-a); number of H-bond acceptors-b); number of H-bond donors-c); topological polar surface area-d), compound fell outside the applicability range of the models.

conclusion that **VII-IXa-c** agreed with Lipinski's and Veber's rules. Therefore, they probably had high peroral bioavailability (Table 1). The GUSAR-online web resource was used for a preliminary assessment of the acute toxicity [32]. A calculation of the toxicity upon i.p. administration to rats showed that the synthesized compounds fell in class 4 toxicity (low-toxic compounds) according to the GOST 12.1.007–76 classification [33, 34] (Table 1).

The LD_{50} value of the most promising compound (**IXa**) was determined *in vivo* to confirm the calculated acute toxicities. The value was 1000 mg/kg, which corresponded to class 4 toxicity.

Thus, further preclinical studies of 1-(1,1-dioxothietan-3-yl)-4-(2-oxo-2-phenylethyl)-1*H*-1,2,4-triazol-4-ium bromide (**IXa**) are promising based on an overall evaluation of the pharmacological screening, acute toxicity, and *in silico* calculation of its pharmacokinetic parameters.

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