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3-SUBSTITUTED THIETANE-1,1-DIOXIDES: SYNTHESIS, ANTIDEPRESSANT ACTIVITY, AND IN SILICO PREDICTION OF THEIR PHARMACOKINETIC AND TOXICOLOGICAL PROPERTIES

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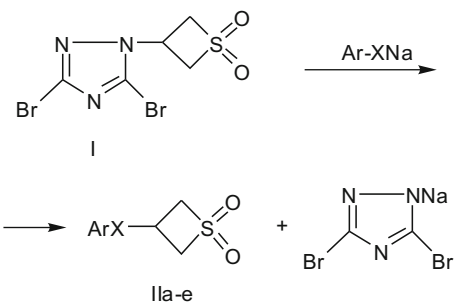
3-Aryloxy- and 3-phenylsulfanylthietane-1,1-dioxides were synthesized by reacting 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazole with sodium phenolates and thiophenolate. The 5-aryloxy- and 5-arenesulfonyl-3-bromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazoles were synthesized via oxidation by H_2O_2 of 5-aryloxy- and 5-phenylsulfanyl-3-bromo-1,2,4-triazoles containing thietane or thietane oxide rings. The 3-substituted thietane-1,1-dioxide **IId** (2 and 20 mg/kg) displayed antidepressant properties in tail-suspension (TST) and forced-swim tests (FST) that were comparable with those of imipramine. Low toxicity risks (mutagenicity, tumorigenicity, irritation, reproductive toxicity) and satisfactory pharmacokinetic characteristics (correspondence to Lipinski's rule of five) were predicted (Osiris Property Explorer, Molinspiration) for it.

Keywords: thietanes, 1,2,4-triazoles, antidepressant activity, prediction, Lipinski's rule of five.

The incidence of psychiatric and behavioral disturbances has increased dramatically in the last decades so that they have become the principal worldwide causes of invalidism and have accounted for over 40 million years of invalidism among people aged from 20 to 29 years [1]. Treatment of depressive disorders is associated with high economic costs. According to WHO predictions, depression will by 2030 be the leading cause of the burden of diseases [2]. However, antidepressants on which pharmacotherapy of depression is based typically have poor clinical efficacies and low safety profiles [3]. Therefore, antidepressants are some of the most thoroughly developed groups of psychotropic agents in the world. In this respect, thietane derivatives that exhibit antidepressant activity are promising [4 – 6]. Therefore, the development of synthetic methods for new 3-aryloxy(sulfanyl)-thietane-1,1,-dioxides and 5-aryloxy(sulfonyl)-3-bromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazoles is crucial.

Previously, it was shown that 3,5-dibromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazole (**I**) reacted with sodium phenolates to eliminate thietane-1,1-dioxide and form 3-aryloxythietane-1,1-dioxides (**IIa-d**) (Scheme 1) [7]. In continuation of this research, the reaction of triazole **I** with sodium mercaptophenolate was studied and resulted in the synthesis of 3-(phenylsulfanyl)thietane-1,1-dioxide (**IIe**) (Scheme 1). The PMR spectrum of **IIe** showed a multiplet for an SCH proton at 3.92 – 4.04 ppm, indicating that the product of thietane-1,1-dioxide elimination had formed.

Scheme 1



IIa-e

R = C_6H_5 (IIa, e), 4-$CH_3C_6H_4$ (IIb), 3,4-$(CH_3)_2C_6H_3$ (IIc), 2-iso-C_3H_7-5-$CH_3C_6H_3$ (IId), X = O (IIa – d), S (IIe).

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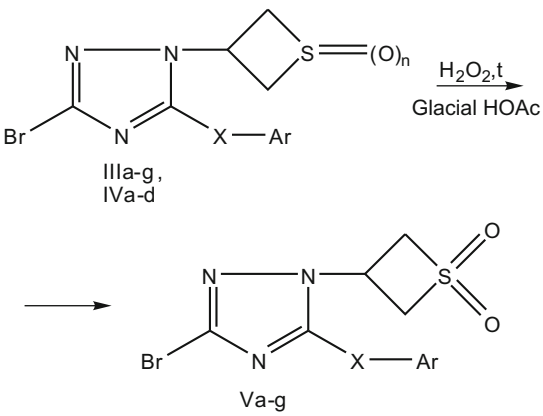
Scheme 2



X = O (IIIa – f, IVa – c, Va – f), S (IIIg), SO (IVd), SO_2 (Vg);
n = 0 (IIIa – g), 1 (IVa – d);
Ar = C_6H_5 (IIIa, g, IVa, d, Va, g), 4-$CH_3C_6H_4$ (IIIb, Vb), 3,4-$(CH_3)_2C_6H_3$ (IIIc, IVb, Vc), 2-iso-C_3H_7-5-$CH_3C_6H_3$ (IIId, Vd), 2,4-$(Cl)_2C_6H_3$ (IIIe, IVc, Ve), naphthyl-1 (IIIe, Ve).

Substituted thietane-1,1-dioxides are usually synthesized via oxidation by H_2O_2 of thietanes or thietane-1-oxides [8]. Therefore, the 5-aryloxy- and 5-phenylsulfonyl-3-bromo-1-(1,1-dioxothietan-3-yl)-1,2,4-triazoles (**Va-g**) were prepared in 33-96% yields via oxidation of thietane-containing triazoles **IIIa-g** and **IVa-d** by 5-10-fold molar excesses of H_2O_2 in glacial HOAc (Scheme 2).

The compositions and structures of the synthesized compounds were confirmed by spectral data (Table 1). IR spectra of **Va-g** contained absorption bands for SO_2 stretching vibrations at ~1139 and 1325 cm^{-1}. This confirmed that the thietane-1,1-dioxide ring had formed. PMR spectra of **Va-g** contained resonances for protons of the thietane-dioxide ring as two multiplets in the ranges 4.7 – 5.0 ppm [$2S(CH)_2$] and 5.3 – 6.1 ppm (NCH) and resonances for the 5-substituent protons.

EXPERIMENTAL CHEMICAL PART

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ (**IIe**) and DMSO-d_6 (**Va-g**) on a Bruker AM-300 instrument at operating frequency 300 MHz for protons and 75 MHz for ^{13}C. IR spectra were taken from KBr pellets on an Infralyum FT-02 spectrometer. Melting points were measured on an SMP11 apparatus. Elemental analyses for C, H, and N agreed with those calculated.

3-(Phenylsulfanyl)thietane-1,1-dioxide (IIe). Metallic Na (0.15 g, 6.6 mmol) was added to anhydrous EtOH (50 mL). When gas bubbles were no longer evolved, mercaptophenol (0.73 g, 6.6 mmol) and triazole **I** (1.99 g, 6 mmol) were added. The mixture was refluxed for 1 h. The solvent was removed in vacuo. The residue was treated with H_2O. The precipitate was filtered off.

General method for synthesizing Va-g.

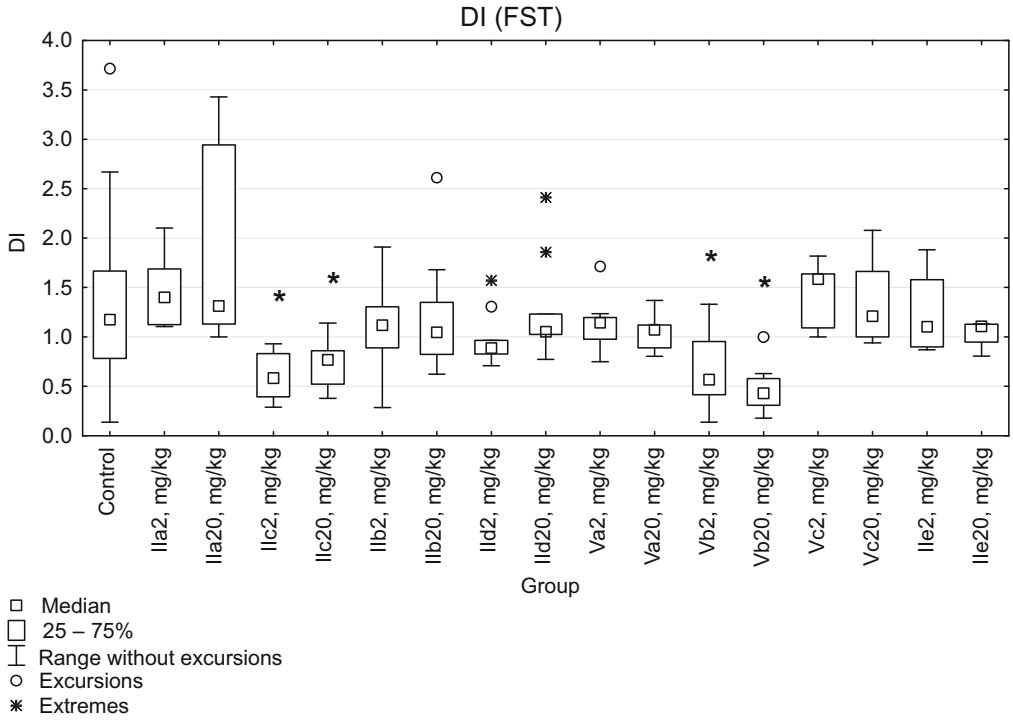


Fig. 1. Influence of synthesized compounds on DI FST. * $p < 0.05$ for Mann—Whitney *U*-criterion as compared with the control.

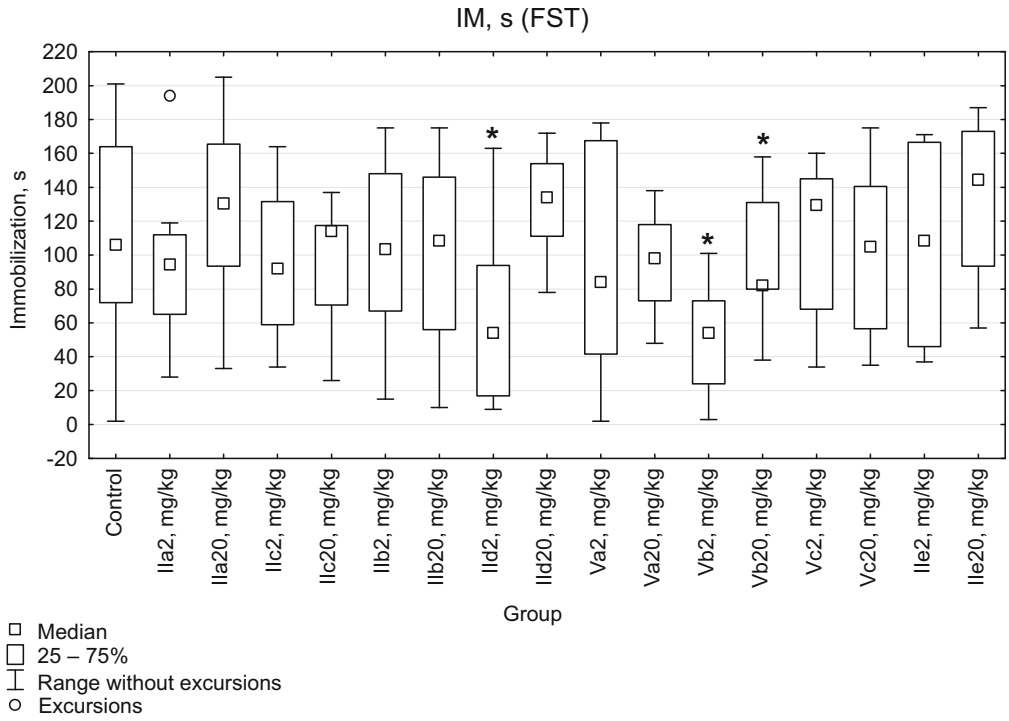


Fig. 2. Influence of synthesized compounds on IM FST (c). * $p < 0.05$ for Mann—Whitney *U*-criterion as compared with the control.

a) A solution of **III** (0.3 mmol) in glacial HOAc (10 mL) was treated with a solution of H_2O_2 (37%, 2.76 g, 30 mmol), refluxed for 0.5 h, and cooled. The resulting precipitate was filtered off and rinsed with H_2O.

TABLE 1. Characteristics of Synthesized Compounds

Compound	mp, °C	Yield, %	PMR and ^{13}C NMR spectra, δ, ppm	IR spectra, ν_{max}, cm^{-1}
IIe	72 – 73 (EtOH)	95	3.92 – 4.04 (m, 1H, SCH), 4.05 – 4.16 [m, 2H, $S(CH)_2$], 4.36 – 4.47 (m, 2H, $S(CH)_2$), 7.34 – 7.41 (m, 5H, CH_{ar})	1213, 1314 and 1480 (C=C)
Va	249 – 250 (BuOH-1)	57[a] 61[b]	4.69 – 4.89 [m, 4H, $2S(CH)_2$], 5.35 – 5.47 (m, 1H, NCH), 7.28 – 7.35 (m, 1H, CH_{ar}), 7.38 – 7.43 (m, 2H, CH_{ar}), 7.45 – 7.51 (m, 2H, CH_{ar})	1142 and 1323 (SO_2); 1292, 1487 and 1528 (C=N, C=C)
Vb	235 – 236 (BuOH-1)	78[a]	2.32 (s, 3H, CH_3), 4.66 – 4.93 [m, 4H, $2S(CH)_2$], 5.32 – 5.48 (m, 1H, NCH), 7.17 – 7.38 (m, 4H, CH_{ar})	1139 and 1326 (SO_2); 1292, 1501 and 1535 (C=N, C=C)
Vc	216 – 217 (BuOH-1)	77[a] 70[b]	2.23 (s, 6H, $2CH_3$), 4.66 – 4.92 [m, 4H, $2S(CH)_2$], 5.34 – 5.45 (m, 1H, NCH), 7.05 – 7.25 (m, 3H, CH_{ar})	1137 and 1324 (SO_2); 1299, 1491 and 1535 (C=N, C=C)
Vd	126 – 128 (hexane)	33[a]	1.15 (e, J 6.8 Hz, 6H, $C(CH_3)_2$), 3.01 – 3.15 (m, 1H, CH), 4.70 – 4.92 [m, 4H, $2S(CH)_2$], 5.38 – 5.50 (m, 1H, NCH), 7.05 – 7.40 (m, 3H, CH_{ar});	1136 and 1328 (SO_2); 1297, 1495 and 1528 (C=N, C=C)
Ve	185 – 187 (BuOH-1)	83[a]	71.15 [$S(CH_2)_2$], 37.15 (NCH), 135.44, 169.74 ($C_{triazole}$), 124.19, 125.94, 128.95, 130.07, 131.54, 156.29 (C_{arom})	1141 and 1330 (SO_2), 1289, 1472 and 1523 (C=N, C=C)
Vf	206 – 208 (BuOH-1)	63[a]	4.81 – 5.01 [m, 4H, $2S(CH)_2$], 5.56 – 5.70 (m, 1H, NCH), 7.75 – 7.72 (m, 4H, CH_{ar}), 7.92 (e, J 7.8 Hz, 1H, CH_{ar}), 8.01 – 8.08 (m, 1H, CH_{ar}), 8.10 – 8.17 (m, 1H, CH_{ar})	1138 and 1322 (SO_2); 1298, 1497 and 1531 (C=N, C=C)
Vg	226 – 227 (EtOH)	96[a] 67[b]	4.76 – 4.90 [m, 4H, $2S(CH)_2$], 5.97 – 6.10 (m, 1H, NCH), 7.69 – 7.79 (m, 2H, CH_{ar}), 7.82 – 7.93 (m, 1H, CH_{ar}), 8.06 – 8.14 (m, 2H, CH_{ar})	1150, 1166 and 1328 (SO_2); 1261 and 1449 (C=N, C=C)

[a] Prepared by method a; [b] prepared by method b.

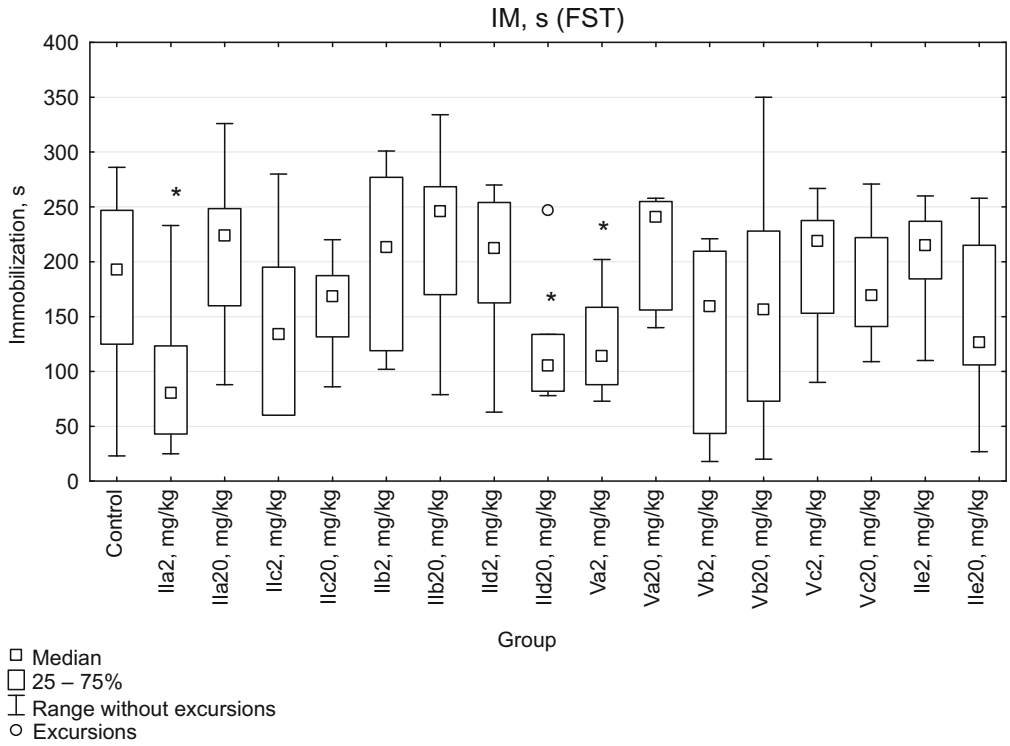


Fig. 3. Influence of synthesized compounds on IM TST (s). * $p < 0.05$ for Mann—Whitney *U*-criterion as compared with the control.

b) A solution of **IV** (3 mmol) in glacial HOAc (20 mL) was treated with a solution of H_2O_2 (37%, 1.38 g, 15 mmol), refluxed for 0.5 h, and cooled. The resulting precipitate was filtered off and rinsed with H_2O.

TABLE 2. Prediction of Toxicity, Drug-likeness, and Drug-score in Osiris Property Explorer and Molinspiration Programs

Compound	Toxicity risks				logP	nON	nOHNH	TPSA	ABC %	Drug-likeness	Drug-score
	Mutagenicity	Tumorigenicity	Irritation	Reproductive							
IIa	(–)	(–)	(–)	(–)	1.22	3	0	43.376	94	– 1.8	0.55
IIb	(–)	(–)	(+)	(–)	1.54	3	0	43.376	94	– 2.93	0.30
IIc	(±)	(±)	(–)	(–)	1.85	3	0	43.376	94	– 4.89	0.30
IId	(–)	(–)	(–)	(–)	2.63	3	0	43.376	94	– 4.81	0.45
IIe	(–)	(–)	(–)	(–)	1.85	2	0	34.142	97	– 2.63	0.50
Va	(–)	(–)	(–)	(±)	2.23	6	0	74.094	83	– 4.87	0.33
Vb	(–)	(–)	(+)	(±)	2.55	6	0	74.094	83	– 5.97	0.19
Vc	(±)	(±)	(–)	(±)	2.85	6	0	74.094	83	– 7.63	0.19
Vd	(–)	(–)	(–)	(±)	3.64	6	0	74.094	83	– 7.53	0.25
Ve	(–)	(–)	(–)	(+)	3.46	6	0	74.094	83	– 2.56	0.19
Vf	(±)	(–)	(–)	(±)	3.41	6	0	74.094	83	– 4.95	0.20
Vg	(–)	(–)	(–)	(±)	0.89	5	0	64.860	87	– 8.18	0.35

Note: (–), no risk; (±), moderate risk; (+), high risk; nON, number of hydrogen acceptors; nOHNH, number of hydrogen donors; TPSA, topological polar surface area; ABC %, percent absorption.

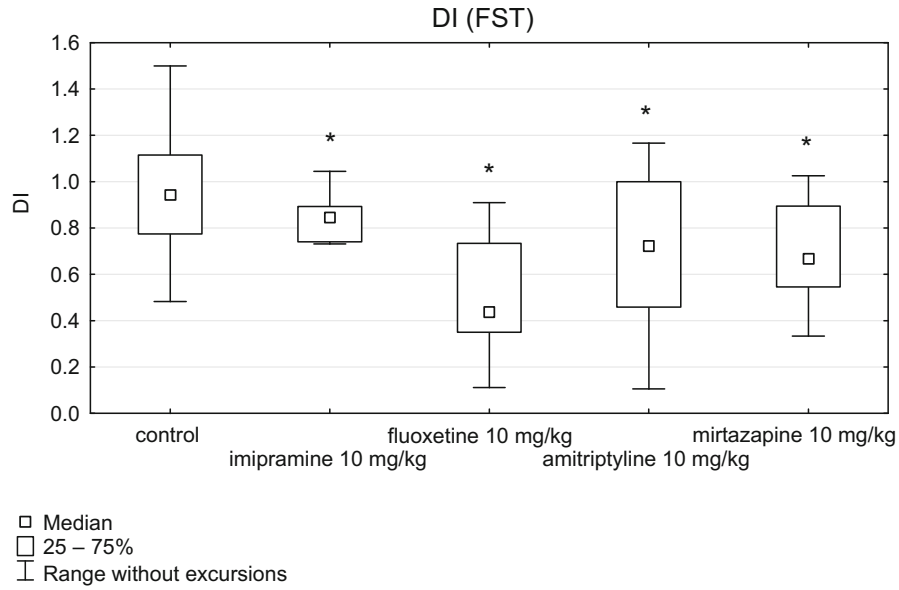


Fig. 4. Influence of antidepressants on immobilization time DI (FST). $^{*}p < 0.05$ for Mann—Whitney *U*-criterion as compared with the control.

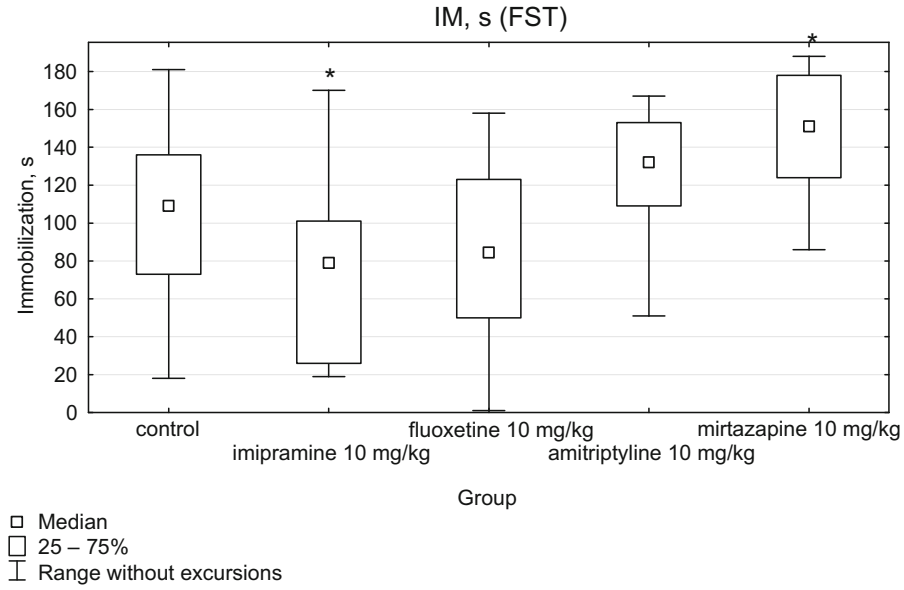


Fig. 5. Influence of antidepressants on immobilization time DI (FST). $^{*}p < 0.05$ for Mann—Whitney *U*-criterion as compared with the control.

EXPERIMENTAL BIOLOGICAL PART

Antidepressant activity of the compounds was assessed in Porsolt forced-swim test (FST) as modified by V. E. Shchetinin [9, 17] and the tail suspension test (TST) [18]. The behavior of mice in the FST was assessed using five types of patterns, i.e., immobilization (IM FST), passive and active swimming, and the number of jumps. The number of periods of passive and active swimming of different length were grouped into four basic ranges (up to 6 sec, from 6 to 18 sec, from 18 to 36 sec, and >36 sec) in order to characterize the swimming rhythms. The depression index (DI FST) was calculated as the ratio of the number of short immobilization periods (<6 sec) to the number of periods of active swimming. The behavior of the mice was recorded for 6 min using a Canon Power Shot A530 digital camera in video mode and for the next 4 min of the test using the BrainTest program [19] to record the aforementioned patterns. Behavior of animals in the TST was assessed for 6 min by counting the total duration of full immobilization periods. The experimental videos were analyzed using the AutoTST 1.0 program (2008).

The experiments used 310 mature non-inbred male mice (18 – 22 g) obtained from SUE Immunopreparat (Ufa). Animals were maintained under vivarium conditions at room temperature with free access to water and food. Compounds were suspended *ex tempore* with Tween-80 in isotonic saline and injected i.p. once at doses of 2 or 20 mg/kg 30 min before the tests. Control mice received equal volumes of isotonic saline with Tween-80. The reference drugs were the antidepressants fluoxetine (0.02 capsules, apo-Fluoxetine, Apotex Inc., Canada), mirtazapine (0.03 tablets, Remeron, MSD Pharmaceuticals Ltd., Russia), imipramine (0.025 pills, melipramine, EGIS Pharmaceuticals PLC, Hungary), and amitriptyline (0.025 tablets, Amitriptyline Grindeks, Latvia), which were injected according to a scheme analogous to that of the compounds at doses of 10 mg/kg.

Results were processed statistically using the Statistica 10.0 software suite (StatSoft, USA). The median (Me) and interquartile interval were calculated. Groups were compared using Kruskal—Wallace one-way dispersion analysis in combination with Newman—Keuls and Dan criteria and the Mann—Whitney *U*-criterion. The normality of the distribution was assessed using the Shapiro—Wilk criterion. Differences were considered statistically significant for $p < 0.05$ [20].

RESULTS AND DISCUSSION

Screening of the synthesized compounds in the TST and FST showed that **IIc** caused statistically significant antidepressant activity by decreasing the DI at doses of 2 and 20 mg/kg by 50.3% ($p = 0.003$) and 35% ($p = 0.014$), respectively, as compared with the control group (Fig. 1). The immobilization time (IM) in both the TST (2 mg/kg, 69.4%; 20 mg/kg, 87.3% as compared with the control) and the FST (2 mg/kg, 86.8%; 20 mg/kg, 107.5%) did not change statistically significantly. IM TST changed statistically significantly for **IIa** and **IIb** by 59.3% (2 mg/kg, $p = 0.003$) and 41.0% (20 mg/kg, $p = 0.019$), respectively.

Compound **IId** reduced IM FST by 49.1% as compared with the control (2 mg/kg, $p = 0.007$) and IM TST by 45.3% (20 mg/kg, $p = 0.044$) (Figs. 2 and 3). Also, DI did not differ statistically significantly from the control value (2 mg/kg, 75.6%, $p = 0.117$; 20 mg/kg, 89.5%, $p = 0.07$) (Fig. 1).

Compound **Vb** at both doses exhibited antidepressant activity. The DI decreased by 51.5% (2 mg/kg, $p = 0.01$) and 63.7% (20 mg/kg, $p = 0.003$) as compared with the control; IM FST, by 49.1% (2 mg/kg, $p = 0.002$) and 22.6% (20 mg/kg, $p = 0.56$). The immobilization time in the TST tended to decrease by 17.4% ($p = 0.127$) and 19% ($p = 0.195$), respectively (Figs. 1 – 3).

The effects of the synthesized compounds were comparable to or greater than those of the traditional antidepressants. Thus, DI FST after administration of the reference drugs decreased by 51.3% for fluoxetine, by 22% for amitriptyline, by 24% for mirtazapine, and by 10% for imipramine whereas the immobilization time after injection of the antidepressants changed in different directions. This agreed with the literature [9] and was related to the pharmacological activity profiles of the drugs (Figs. 4 and 5). Only imipramine reduced statistically significantly IM FST by 27% ($p = 0.045$) whereas mirtazapine increased it by 39% ($p = 0.015$).

A promising direction for safety studies of drug candidates is the *in silico* prediction of their toxicity risks and pharmacokinetic profiles [10]. For this, the synthesized compounds were evaluated using Lipinski's rule of five [11, 12] (drug-likeness).

A compound could become a drug candidate if its molecular mass was <500; log P, <5; number of hydrogen donors, <5 (determined from the sum of OH and NH groups); number of hydrogen acceptors, <10 (determined from the sum of O and N atoms). The numbers of H-bond donors and acceptors and the topological polar surface area (TPSA was used to predict drug transport through the blood—brain barrier or intestinal absorption) [13] were found using the Molinspiration program [14]. The percent absorption (ABC %) was calculated based on the TPSA [15]. Table 2 lists the results.

The Osiris Property Explorer program [16] was used to predict the safety of the compounds. It calculated physicochemical (log P, solubility, molecular mass) and toxic properties (mutagenicity, tumorigenicity, irritation, reproductive toxicity) and the drug-likeness of the molecules. A positive drug-likeness (0.1 – 10) indicated that the molecule contained fragments that are often encountered in drugs. A calculated drug-score coefficient that considered all parameters enabled the potential of the drug candidate to be assessed (0 – 1). Table 2 presents the results.

It was found that the molecular masses of the synthesized compounds were <500. The log P values fell in the range 0.89 – 3.64. The numbers of hydrogen acceptors varied from 2 to 6. This satisfied Lipinski's rule of five. The TSPA and ABC % parameters indicated that the synthesized compounds were possibly highly absorbed.

According to the predictions, the synthesized compounds did not have irritating properties except for **IIb** and **Vb** with 4-methylphenol fragments. Compounds **IIc** and **Vc** with 3,4-dimethylphenol fragments showed moderate risks of mutagenic and tumorigenic effects. Reproductive toxicity was probable for all compounds with 3-bromo-1,2,4-triazole fragments. The drug-likenesses of the compounds were negative, indicating a lack of drugs with structures similar to them.

An overall analysis of the pharmacological screening, toxicological risks, and physicochemical characteristics of the synthesized compounds led to the conclusion that 3-(2-*iso*-propyl-5-methylphenoxy)thietane-1,1-dioxide (**IId**) was the most promising. It exhibited statistically significant antidepressant activity, characteristically lacked toxicity risks, and had a high drug score of 0.45.

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