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SEARCH FOR NEW DRUGS

SYNTHESIS, ANTIDEPRESSANT ACTIVITY, AND PREDICTION OF TOXIC RISKS OF 3-ALKOXY(SULFANYL)THIETANE-1,1-DIOXIDES

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A series of 3-alkyloxy(sulfanyl)thietane-1,1-dioxides were synthesized by reacting 3,5-dibromo-1-(1,1-dioxothietanyl-3)-1,2,4-triazole with sodium alkoxides and thioalkoxides. Compounds **IIa** (2 mg/kg) and **IIh** (6 mg/kg) exhibited antidepressant-like effects at doses equimolar to amitriptyline (10 mg/kg); **IId** (2 mg/kg) and **IIb** (2 and 5.7 mg/kg), effects associated presumably with anxiolytic properties. Prediction of toxic risks, drug-likeness, and physicochemical properties of the molecules using the Osiris DataWarrior and Property Explorer programs showed that the compounds should not have adverse effects on reproductive functions and should not possess oncogenic, mutagenic, and irritant properties.

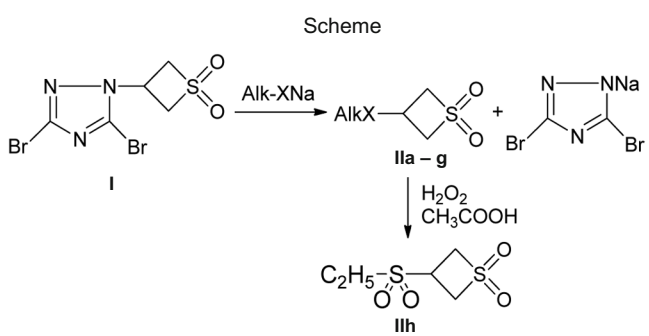
Keywords: 3-substituted thietane-1,1-dioxides, antidepressant activity, forced-swim test, tail-suspension test, open-field test.

Antidepressants are some of the most extensively developed drug classes [1 – 3]. In continuation of discovery research on promising antidepressants among thietane derivatives [4 – 6], we synthesized a series of 3-alkoxy(sulfanyl)thietane-1,1-dioxides and studied their antidepressant activity.

The reaction of 3,5-dibromo-1-(1,1-dioxothietanyl-3)-1,2,4-triazole (**I**) with sodium alkoxides was shown to occur with elimination of the thietane-1,1-dioxide ring and formation of 3-alkoxythietane-1,1-dioxides (**IIa-c**) [7] (Scheme 1). The present article reports reactions of **I** with *tert*-butyl and benzyl alcohols that synthesized 3-alkoxythietane-1,1-dioxides (**IId-f**) (Scheme 1). The reaction of **I** with ethyl mercaptan synthesized the thio-analog of **IIa**, i.e., 3-ethylsulfanylthietane-1,1-dioxide (**IIg**), oxidation of which by H_2O_2 afforded 3-ethylsulfonylthietane-1,1-dioxide (**IIh**) in 52% yield (Scheme 1).

IR spectra of **IId-h** contained absorption bands for SO_2 stretching vibrations in the ranges 1124 – 1159 and 1305 – 1325 cm^{-1}, which confirmed a thietane-1,1-dioxide ring was present. PMR spectra of **IId-h** contained multiplets for thietanedioxide-ring protons in the characteristic regions [8] and for 3-substituent protons. The lack in ^{13}C NMR spectra of **IIg**, **h** of resonances for triazole-ring C atoms and the presence of those for ethyl C atoms also confirmed that the 3-substituted thietane-1,1-dioxides formed.

Scheme



Alk = C_2H_5 (**IIa**, **g**, **h**), *n*-C_3H_7 (**IIb**), i-C_4H_9 (**IIc**), *tert*-C_4H_9 (**IId**), $C_6H_5CH_2$ (**IIe**), 4-$OCH_3C_6H_3CH_2$ (**IIf**), X=O (**IIa – f**), S (**IIg**)

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EXPERIMENTAL CHEMICAL PART

PMR spectra were recorded on Bruker AM-300 and AV-500 spectrometers at operating frequencies 300 and 500.13 MHz, respectively. ^{13}C NMR spectra were recorded on a Bruker AV-500 instrument at operating frequency 125.76 MHz (DEPT90 and DEPT135 modes). The standards were the residual solvent resonances. IR spectra were taken from KBr pellets on an InfraLum FT-02 instrument. Melting points were measured on an SMP30 apparatus. Elemental analyses were performed in a Hekatech Euro 3000 CHNS analyzer and agreed for C, H, and S with those calculated.

3-(*tert*-Butoxy)thietane-1,1-alkoxide (IId). *tert*-Butyl alcohol (15 mL) was treated with metallic Na (0.08 g, 3.3 mmol), heated until gas-bubble evolution ceased, treated with **I** (0.99 g, 3.0 mmol), refluxed for 1 h, and evaporated under vacuum. The residue was worked up with H_2O (10 mL). The precipitate was filtered off and dried. Yield 0.18 g (33%). mp = 97 – 98°C (hexane). PMR spectrum ($CDCl_3$, 500.13 MHz), δ, ppm: 1.21 (s, 9H, $3CH_3$), 4.08 – 4.15 (m, 2H, $S(CH)_2$), 4.29 – 4.36 (m, 2H, $S(CH)_2$), 4.46 – 4.54 (m, 1H, OCH). IR spectrum, ν, cm^{-1}: 1124 and 1315 (SO_2).

3-(Benzyloxy)thietane-1,1-dioxide (IIe). Benzyl alcohol (0.71 g, 6.6 mmol) was treated with metallic Na (0.08 g, 3.3 mmol) and benzene (10 mL), heated until gas-bubble evolution ceased, treated with **I** (0.99 g, 3.0 mmol), refluxed for 4.5 h, and filtered. The filtrate was evaporated under vacuum. The residue was triturated with Et_2O. The precipitate was filtered off and dried. Yield 0.15 g (23%). mp = 70 – 71°C (acetone — hexane). PMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 4.09 – 4.20 (m, 2H, $S(CH)_2$), 4.27 – 4.42 (m, 3H, OCH, $S(CH)_2$), 4.52 (s, 2H, OCH_2), 7.29 – 7.43 (m, 5H, $5H_{ar}$). IR spectrum, ν, cm^{-1}: 1141 and 1314 (SO_2).

3-[(4-Methoxybenzyl)oxy]thietane-1,1-dioxide (IIf) was prepared analogously to **IIe**. Yield 0.21 g (29%). mp = 75 – 76°C (acetone — hexane). PMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 3.82 (s, 3H, OCH_3), 4.08 – 4.16 (m, 2H, $S(CH)_2$), 4.23 – 4.38 (m, 3H, $S(CH)_2$, OCH), 4.45 s (2H, OCH_2), 6.90 (m, 2H, ^3J 6.6 Hz, 3′, 5′ H_{ar}), 7.24 (m, 2H, ^3J 6.7 Hz, 2′, 6′ H_{ar}). IR spectrum, ν, cm^{-1}: 1142 and 1323 (SO_2).

3-Ethylsulfanylthietane-1,1-dioxide (IIg). *tert*-Butyl alcohol (20 mL) was treated with metallic Na (0.11 g, 4.5 mmol), heated until gas-bubble evolution ceased, cooled to room temperature, treated with ethyl mercaptan (0.28 g, 4.3 mmol) and **I** (0.99 g, 3.0 mmol), refluxed for 1 h, and evaporated under vacuum. The residue was worked up with H_2O and extracted with $CHCl_3$. The extract was evaporated. The residue was triturated with hexane. Yield 0.42 g (84%). mp = 53 – 54°C (hexane). PMR spectrum ($CDCl_3$, 500.13 MHz), δ, ppm: 1.28 (t, 3H, ^3J 7.4 Hz, $SCH_2C\underline{H}_3$), 2.62 (g, 2H, ^3J 7.4 Hz, $SC\underline{H}_2CH_3$), 3.59 – 3.69 (m, 1H, SCH), 4.03 – 4.10 (m, 2H, $S(CH)_2$), 4.38 – 4.46 (m, 2H, $S(CH)_2$). ^{13}C NMR spectrum (DMSO-d_6, 125.76 MHz), δ, ppm: 14.42 (CH_3), 22.71 (SCH), 26.80 (SCH_2), 72.01 ($S(CH_2)_2$). IR spectrum, ν, cm^{-1}: 1142 and 1323 (SO_2).

3-Ethylsulfonylthietane-1,1-dioxide (IIh). Glacial HOAc (5 mL) was treated with **IIg** (0.50 g, 3.0 mmol) and H_2O_2 solution (2.76 mL, 30.0 mmol, 37%), refluxed for 0.5 h, and cooled. The resulting precipitate was filtered off, rinsed with H_2O and Et_2O, and dried. Yield 0.31 g (52%). mp = 153 – 154°C (EtOH). PMR spectrum (DMSO-d_6, 500.13 MHz), ppm: 1.21 (t, 3H, ^3J 7.4 Hz, $SCH_2C\underline{H}_3$), 3.22 (q, 2H, ^3J 7.4 Hz, $SC\underline{H}_2CH_3$), 4.36 – 4.63 (m, 5H, SCH, $2S(CH)_2$). ^{13}C NMR spectrum (DMSO-d_6, 125.76 MHz), δ, ppm: 6.37 (CH_3), 38.03 (SCH), 45.49 ($S(O)_2CH_2$), 66.26 ($S(CH_2)_2$). IR spectrum, ν, cm^{-1}, KBr: 1128, 1159, 1305, 1325 (SO_2).

EXPERIMENTAL BIOLOGICAL PART

The experiments used laboratory male white mice (m = 18 – 22 g) that were kept under standard vivarium conditions with free access to water and feed. Animals were handled in compliance with requirements of international recommendations in the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* [9].

3-Substituted thietane-1,1-dioxides were diluted in normal saline, suspended using Tween-80 (1 – 2 drops), and injected i.p. once 30 min before the tests at two doses of 2 mg/kg and equimolar to amitriptyline (10 mg/kg) (**IIa**, 4.8 mg/kg; **IIb**, 5.23; **IIc**, 6.4; **IId**, 5.7; **IIe**, 7.65; **IIf**, 8.77; **IIg**, 6; **IIh**, 6). Control animals received an equal volume of normal saline (0.2 mL/20 g of animal body mass) with Tween-80. The reference drugs were amitriptyline (25-mg tablets, Nycomed Danmark ApS, Denmark) and fluoxetine (Apo-Fluoxetine, 20-mg capsule, Apotex Inc., Canada), which were also suspended with Tween-80, diluted in normal saline, and injected i.p. once at a dose of 10 mg/kg.

Antidepressant activity of the compounds was studied in the forced-swim test (FST) as modified by Shchetinin [10] and the tail-suspension test (TST) [11]. Animal behavior was recorded using a video camera (Panasonic V760) and analyzed using the BrainTest program [12]. The TST evaluated the immobilization time (IT) of animals (IT TST); the FST, the IT (IT FST) and number of immobilization periods, time and number of active swimming periods, floating time, number of jumps, and depression index (DI FST), the calculated ratio of the number of short immobilization periods (sec) to the number of active-swimming periods. The open-field (OF) test was also performed to evaluate the effects of the compounds on the orientation-exploratory activity (OEA), locomotor activity, and emotional anxiety (EA) of the animals [13]. The animal behavior was also recorded using a video camera. The numbers of behavioral patterns, i.e., movement, sniffing, vertical rearing, supported rearing, mink

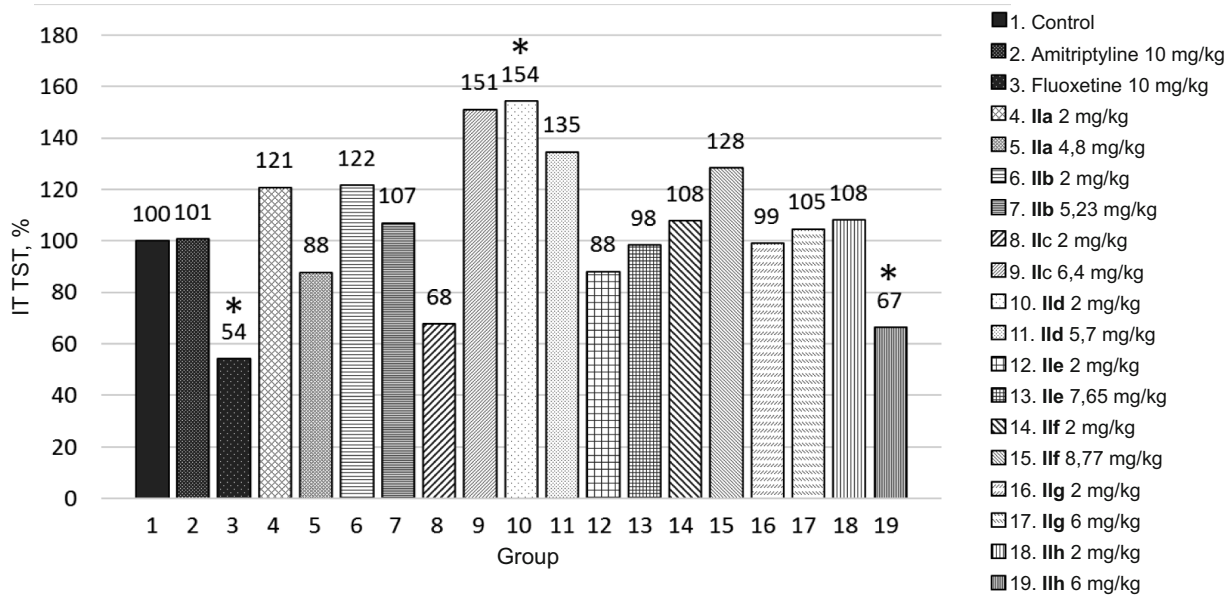

Fig. 1. Effects of **IIa-h** on immobilization time in the tail-suspension test (TST); * $p < 0.05$ for Mann—Whitney *U*-criterion vs. the control group; graphs show group medians expressed in % vs. the control group median.

reflex, grooming, movement in place, and sitting, were recorded. The OEA (total of sniffing, movement, and mink reflex patterns) and EA (total of movement in place, rearing, and supported rearing) were calculated based on these parameters.

Statistical processing of the results used Statistica 8.0 (StatSoft, USA) and Excel 2016 programs (Microsoft Office 365, USA). Variation series were described by calculating basic statistical parameters (median [Me], interquartile range [IQR], mean-square deviation, etc.). Independent sets were compared using nonparametric criteria (Kruskal—Wallis *H*-criterion and Mann—Whitney *U*-criterion) because the dataset did not obey normal distribution laws (evaluated using asymmetry and excess parameters and the Kolmogorov—Smirnov criterion) [14]. The confidence probability for statistical criteria were set at $p < 0.05$ for all analyses.

RESULTS AND DISCUSSION

Figures 1 – 3 summarize the activities of **IIa** – **IIh** in the TST and FST for three series of experiments ($n = 184$). Two reference antidepressants, amitriptyline (nonselective neuronal catecholamine reuptake inhibitor) and fluoxetine (selective neuronal serotonin reuptake inhibitor). Amitriptyline (10 mg/kg) with a single injection 30 min before the test exhibited antidepressant-like activity, reducing the DI by 44% ($p = 0.002$, Fig. 3) and the floating time by 38% ($p = 0.001$) as compared to the control group but increasing the IT FST (by 34%, $p = 0.119$). Fluoxetine (10 mg/kg) did not affect the FST DI and reduced statistically significantly the IT TST by 46% ($p = 0.016$, Fig. 1). This also was consistent with an antidepressant-like effect. Also, the number of jumps decreased (by 53%, $p = 0.00003$).

The screening tests (TST and FST) of the eight compounds found four that were active at one of the doses. A single i.p. injection of ethoxy derivative **IIa** at a dose of 2 mg/kg produced an antidepressant-like effect that was comparable to that of amitriptyline, reducing the DI by 37% ($p = 0.027$, Fig. 3), increasing IT FST by 47% ($p = 0.004$, Fig. 2), and reducing active swimming time by 31% ($p = 0.021$). The activity decreased as the length of the side chain increased, e.g., propoxy- (**IIb**) and *iso*-butoxy-derivatives (**IIc**) did not significantly change the IT (in any test) and DI (Figs. 1 – 3) whereas *tert*-butoxy-derivative **IId** (2 mg/kg) increased IT TST by 54% ($p = 0.005$, Fig. 1).

Introduction of a benzyl substituent into **IIe** and **IIf** caused an inversion of the antidepressant-like effect. The DI increased by 23% ($p = 0.048$) and 40% ($p = 0.011$) for **IIe** (2 mg/kg) and **IIf** (8.77 mg/kg), respectively; IT FST, by 43% ($p = 0.024$, **IIf**, 8.77 mg/kg); floating time, by 20% ($p = 0.048$, **IIe**, 2 mg/kg). Also, the active swimming time decreased by 50% ($p = 0.002$, **IIf**, 8.77 mg/kg); the number of jumps, by 47% ($p = 0.048$, **IIe**, 2 mg/kg) and 65% ($p = 0.009$, **IIf**, 2 mg/kg). Compound **IIf** was characterized by a methoxy group on the benzene ring and was more active than **IIe** (Figs. 1 – 3).

Replacing the O atom in the alkoxy substituent by S caused **IIg** not to affect IT TST, IT FST, and DI (Figs. 1 – 3) and reduced the floating time (by 36%, $p = 0.035$) and number of jumps (by 26%, $p = 0.021$). Oxidation of the S to a sulfone (**IIh**) enhanced the antidepressant-like effect. The DI at a dose of 6 mg/kg diminished by 25% ($p = 0.050$, Fig. 3); IT TST, by 33% ($p = 0.036$, Fig. 1); and IT FST, by 25%

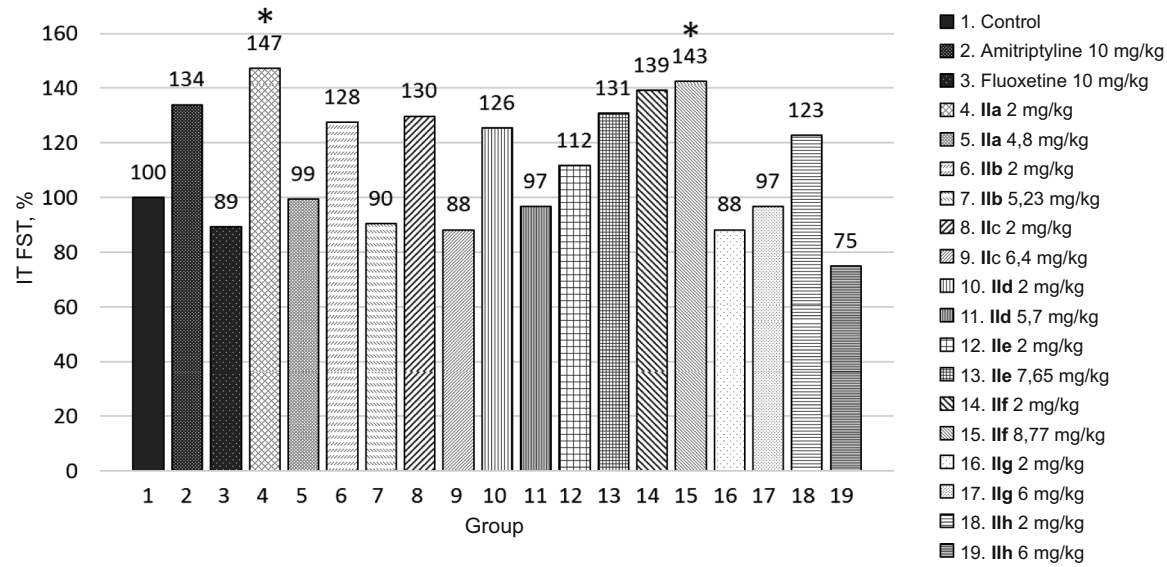

Fig. 2. Effects of **IIa-h** on immobilization time in the forced-swim test (FST); * $p < 0.05$ for Mann—Whitney *U*-criterion vs. the control group; graphs show group medians expressed in % vs. the control group median.

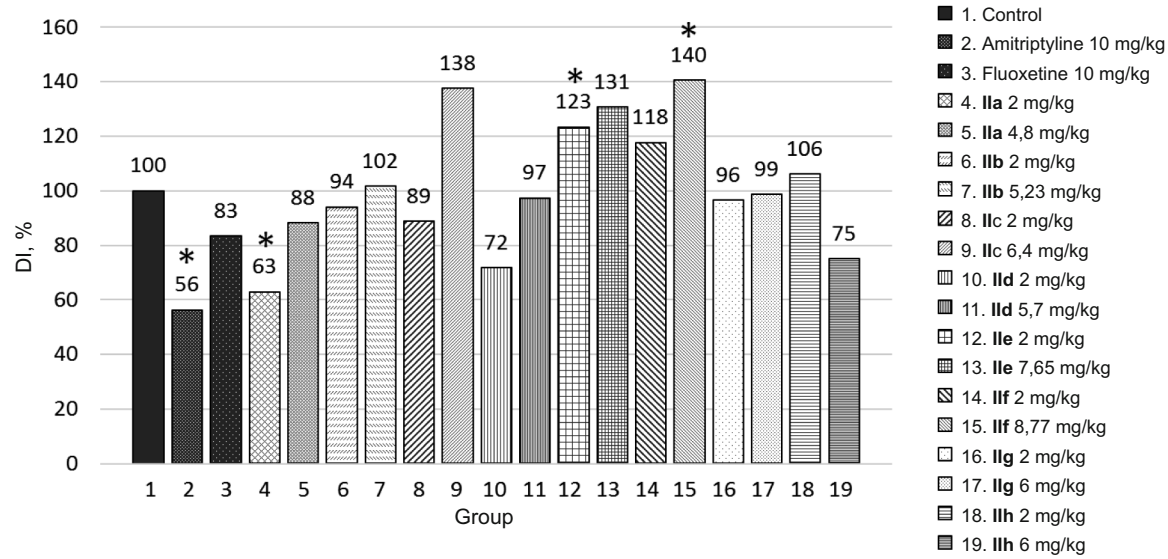

Fig. 3. Effects of **IIa-h** on depression index (DI) in the force-swim test (medians expressed in percent vs. the control group are given); * $p < 0.05$ for Mann—Whitney *U*-criterion vs. the control group; graphs show group medians expressed in % vs. the control group median.

($p = 0.945$, Fig. 2). The floating time decreased (by 53% as compared to the control group, $p = 0.001$). The active swimming time increased slightly (by 38%, $p = 0.368$).

All compounds at analogous doses were studied in OF tests to reveal possible sedative/psychostimulatory activity of the compounds capable of affecting the FST and TST parameters to cause false-positive or false-negative results. For this, three series of experiments were carried out sequentially. The first series studied the activities of **IIg** and **IIh**; the second, **IIa**, **IIb**, and **IId**; the third, **IIc**, **IIe**, and **IIf**.

Compounds **IIa**, **IIb**, and **IId** induced unidirectional changes of the EA in the OF and reduced vertical movements of the animals. Compound **IIb** was the most active. Thus, **IIb** (2 mg/kg) caused statistically significant reductions of EA and OEA [by 45% ($p = 0.01$) and 30% ($p = 0.01$), respectively] and sniffing (by 30%, $p = 0.015$) and supported rearing patterns (by 78%, $p = 0.038$) as compared to the control group. Compound **IIb** at a dose of 5.23 mg/kg reduced statistically significantly OEA (by 20%, $p = 0.021$) and sniffing patterns (by 27%, $p = 0.049$) and did not affect EA (Fig. 4*b*).

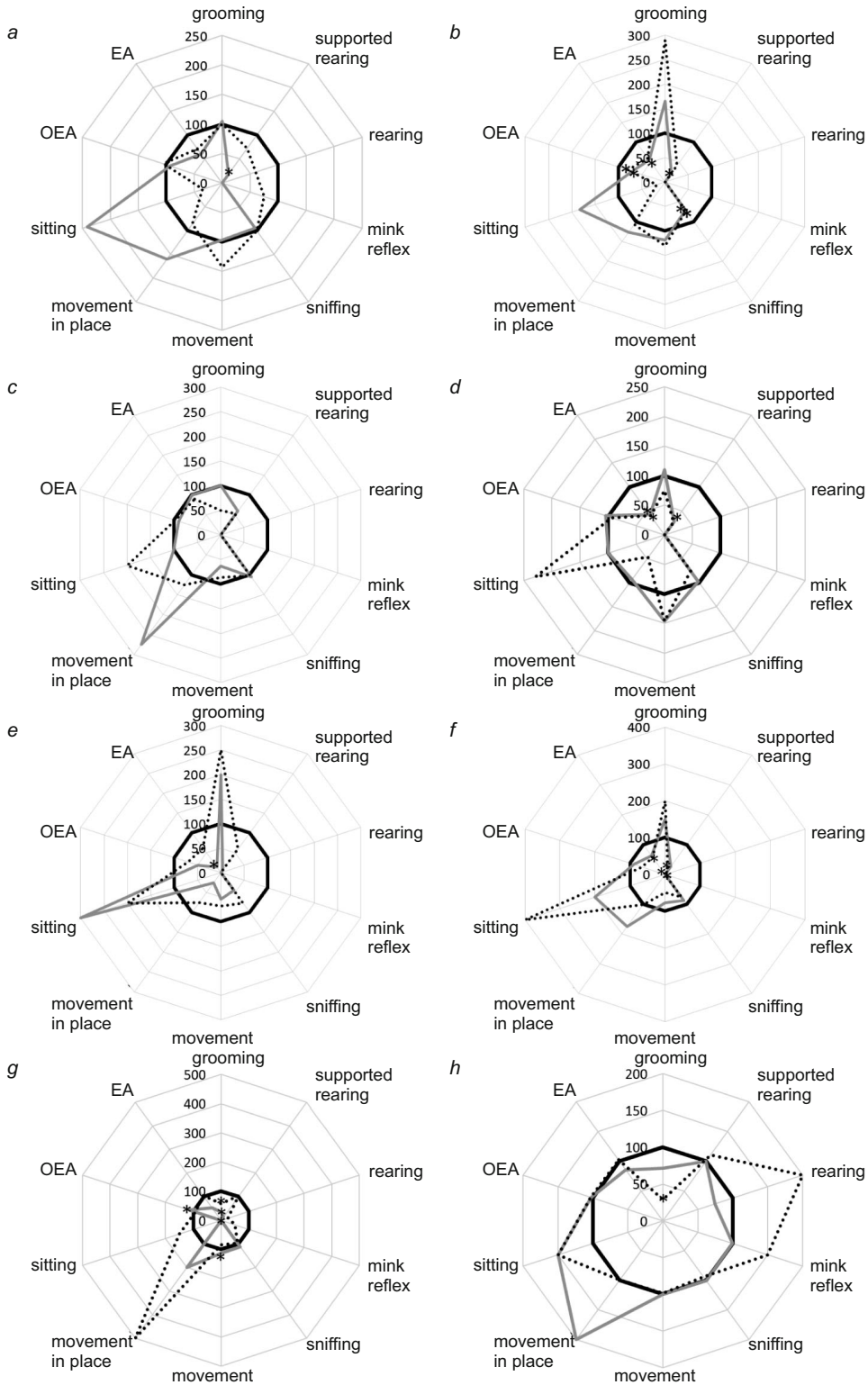

Fig. 4. Effects of **IIa-h** on the open-field (OF) test parameters. Notes: Equimolar doses of **IIa** (*a*), 4.8 mg/kg; **IIb** (*b*), 5.23; **IIc**, (*c*), 6.4; **IId** (*d*), 5.7; **IIe** (*e*), 7.65; **IIf** (*f*), 8.77; **IIg** (*g*), 6; **IIh** (*h*), 6; * $p < 0.05$ for Mann—Whitney *U*-criterion vs. the control group; graphs show medians expressed in % vs. the control group.

Compound **IId** at both doses reduced EA statistically significantly by 58% (2 mg/kg, $p = 0.01$) and 60% (5.7 mg/kg, $p = 0.028$) (Fig. 4*d*); did not affect OEA; and decreased the supported rearing pattern (by 72%, $p = 0.01$, 2 mg/kg). Compound **IIa** at both doses did not affect OEA and horizontal locomotor activity (Fig. 4*a*), tended to decrease EA, and re-

duced significantly the number of supported rearings at a dose of 2 mg/kg (by 82%, $p = 0.015$, Fig. 4*a*).

Compound **IIc** at both doses did not significantly affect the OF parameters although it also tended to reduce vertical movement (Fig. 4*c*).

Benzyl-containing **IIe** (2 mg/kg) and **IIf** (8.77 mg/kg) decreased markedly EA (by 86%, $p = 0.038$) and 43% ($p = 0.011$), respectively (Fig. 4*e* and 4f). Compound **IIf** also decreased statistically significantly vertical locomotor activity (decreased the number of supported rearing, rearing, and mink reflex patterns, Fig. 4*f*).

Compounds containing an S atom had multidirectional activity for all test parameters (OF, TST, FST). Ethylsulfanyl derivative **IIg** was more active in the OF. It at a dose of 2 mg/kg increased OEA (by 14%, $p = 0.015$) and horizontal movement because the movement pattern increased (by 13%, $p = 0.005$) and the sitting pattern decreased (by 100%, $p = 0.038$). Furthermore, **IIg** at both doses reduced the number of grooming patterns (Fig. 4*g*). Ethylsulfonyl derivative **IIh** exhibited antidepressant-like properties in the FST and did not significantly change EA and OEA. However, it at a dose of 6 mg/kg also reduced the number of grooming patterns and tended to increase vertical movement (rearing and mink reflex patterns) (Fig. 4*h*).

The results led to the conclusion that compounds containing a short ethyl group bonded to the thietane-1,1-dioxide ring through an O atom (ethoxy derivative **IIa**, 2 mg/kg) or a sulfonyl group (**IIh**, 6 mg/kg) exhibited antidepressant-like effects [lower DI values and horizontal locomotor activity (movement pattern) in the OF similar to the control]. The effect of **IIa** on the direction and strength was comparable to that of amitriptyline (for DI and IT in the FST); of **IIh**, with fluoxetine (for IT TST). The antidepressant-like activity of **IIh** was dose-dependent with the activities in the TST and FST increasing with increasing dose (Figs. 1 – 3).

Antidepressants with various mechanisms of action had different effects on the FST and TST screening test parameters. This emphasizes the need to use simultaneously both tests to evaluate the primary pharmacological activity of new molecules [15]. Thus, the increased IT FST and lack of TST changes caused by amitriptyline that were found by us were due, on one hand, to its psychosedative activity, which agreed with previously published data [6] and, on the other, to the use of laboratory animals as subjects, for which the behavior under test conditions based on despair paradigms is characteristically variable [16]. Fluoxetine also was active only in the TST, significantly reducing the IT but not affecting the FST parameters. Compound **IIa** (2 mg/kg) had similar effects on the screening test parameters as amitriptyline. However, its effect diminished if the dose was doubled (4.8 mg/kg) with a single injection 30 min before the testing. This suggested a mechanism typical of pharmacy antidepressants that clearly do not affect the IT in screening tests [15]. Conversely, **IIh** manifested dose-dependent antidepressant-like activity characteristic of classical antidepressants, reducing most significantly the IT (TST and FST) and DI at the highest dose.

A comparison of the effects of molecules with the same side-chain length (**IIa** and **IIg**) led to the conclusion that replacing the 3-O atom of the side chain by S (**IIg**) reduced the antidepressant-like activity (TST and FST) and produced activating properties (OF, 2 mg/kg). The OEA and horizontal locomotor activity increased whereas the decision-making time (grooming pattern [17]) and sitting pattern [which correlated with reduced floating time in the FST under the influence of **IIg** (2 mg/kg)] decreased. Oxidation of the S to sulfonyl (**IIh**, 6 mg/kg) produced an antidepressant-like effect with an activating component that manifested as a slight increase of vertical movement and decrease of decision-making time in the OF.

TABLE 1. Prediction of Toxicity, Drug-likeness, and Drug-score in Osiris DataWarrior and Property Explorer Programs

Compound	Toxic risks				clogP	nOH	nOHNH	Lipinski's rule of five obeyed	TPSA	Drug-likeness	Drug-score
	mutagenicity	oncogenicity	irritation	reproduction							
IIa	(-)	(-)	(-)	(-)	– 0.50	3	0	yes	51.75	– 6.41	0.49
IIb	(-)	(-)	(-)	(-)	– 0.05	3	0	yes	51.75	– 4.20	0.50
IIc	(-)	(-)	(-)	(-)	0.17	3	0	yes	51.75	– 3.99	0.50
IId	(-)	(-)	(-)	(-)	0.24	3	0	yes	51.75	– 16.44	0.49
IIe	(-)	(-)	(-)	(-)	0.51	3	0	yes	51.75	– 9.15	0.48
IIf	(-)	(-)	(-)	(-)	0.44	4	0	yes	60.98	– 3.36	0.49
IIg	(-)	(-)	(-)	(-)	0.22	2	0	yes	67.82	– 2.48	0.52
IIh	(-)	(-)	(-)	(-)	– 1.25	4	0	yes	85.04	– 2.38	0.53

Note: (–) is no risk; nOH, number of H acceptors; nOHNH, number of H donors; TPSA, topological polar surface area; c log P, lipophilicity coefficient.

Conversely, compound **IIa** (2 mg/kg) showed antidepressant-like activity in the FST, decreased vertical movement, and did not statistically significantly affect OEA and EA. Apparently, this resulted from its psychosedative properties. Compounds **IIb** and **IId** also exhibited sedative activity by reducing vertical movement and OEA (**IIb** at both doses) and increasing IT TST (**IId**, 2 mg/kg). Both compounds reduced considerably EA (by 45 – 60%), which could indicate potential anxiolytic activity.

Benzyl fragments in the structures led to prodepressant effects. Compounds **IIe** and **IIf** increased the TST and FST parameters (although the activity increased if the side chain lengthened) and decreased EA in the OF (by 75 and 43%, respectively).

Prediction of toxic risks and physicochemical properties and assessment of the drug scores of the synthesized molecules and the similarity of the structures to known drugs (drug-likeness) were studied *in silico* using Lipinski's rule of five [18, 19] and the Osiris DataWarrior [20] and Property Explorer programs [21]. These programs were used to calculate the number of H-bond donors and acceptors, topological polar surface area (TPSA), toxic risks (oncogenicity, mutagenicity, irritation, reproduction), drug-likeness, and drug score. Table 1 presents the results.

The calculated parameters of **IIa** – **h** were found to satisfy Lipinski's rule of five. The molecular masses of the synthesized compounds were <250. The lipophilicity coefficient (c log P) lay in the range from –1.25 to 0.51. The number of H-acceptors was 2 – 4. There were no H-donors. The TPSA values in the range 51.75 – 85.04 indicated that the synthesized compounds penetrated through cell membranes and could cross the blood—brain barrier.

The predicted toxic risks indicated that the synthesized molecules should not have adverse effects on reproduction and should not possess oncogenic, mutagenic, and irritant properties. Drugs of similar structures were unknown for all compounds, which was consistent with the negative drug-likeness parameters.

Thus, pharmacological screening and prediction of toxic risks and physicochemical properties of the studied compounds led to the conclusion that **IIa** and **IIh** were promising molecules with antidepressant activities comparable to that of the reference drugs, no toxic risks, and high drug scores (0.49 – 0.53). Compounds **IId** and **IIb** were also interesting because they reduced EA and probably possessed anxiolytic properties.

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