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SYNTHESIS AND ANTIDEPRESSANT ACTIVITY OF 4-ALKYL-5-BROMO-2,4-DIHYDRO-2-(THIETAN-3-YL)-1,2,4-TRIAZOL-3-ONES

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A series of 4-alkyl-5-bromo-2,4-dihydro-2-(thietan-3-yl)-1,2,4-triazol-3-ones (**IIa-g**) were synthesized by reacting 5-bromo-2,4-dihydro-2-(thietan-3-yl)-1,2,4-triazol-3-one (**I**) with alkyl halides and dimethyl sulfate. The structures of the synthesized compounds were confirmed by IR, PMR, and ^{13}C NMR spectroscopic data. The antidepressant activity of the synthesized compounds in non-inbred male mice was investigated using tail-suspension and forced-swim tests. Compounds **I** and **IIa,c**,**f,g** after a single intraperitoneal injection produced antidepressant effects in screening tests and did not cause sedative and/or psychostimulatory effects in the open-field test. Compound **I** produced an antidepressant effect comparable to that of fluoxetine, had low toxicity (class IV toxicity), and was superior to fluoxetine in therapeutic index and strength of the antidepressant effect after a course of administration. The calculated physicochemical properties and toxic risks showed that all synthesized compounds complied fully with Lipinski's rule of five. The calculated drug score and absence of predicted toxic risks for the most active compound **I** suggested that it was promising for creating a new pharmaceutical substance with antidepressant activity.

Keywords: 1,2,4-triazole, thietane, alkylation, antidepressant activity, forced-swim test, tail-suspension test.

Greater than 30 antidepressants are currently available worldwide [1] and are used to treat a broad spectrum of diseases, e.g., recurrent unipolar depression, which is one of the leading global causes of invalidism and occupies 13th place among all incidents of illness and injury [2]. However, a significant patient cohort does not achieve remission and cure because existing antidepressants are insufficiently effective [3]. Therefore, the development of new more effective antidepressants including those directed at new therapeutic targets is an important direction in psychopharmacology [4].

1,2,4-Triazole is a favored structure in medicinal chemistry [5]. It is featured in drugs with antifungal, antiviral, antitumor, antiaggregant, hypoglycemic, anticonvulsant, anxiolytic, and antidepressant activity [6]. Antidepressant activity is characteristic mainly of 1,2,4-triazol-3-one derivatives such as trazodone, nefazodone, and etoperidone (Fig. 1).

Trazodone was widely used to treat depression in many countries starting in the 1960s. It is considered an ideological precursor of modern generation IV multimodal antidepressants (such as vilazodone and vortioxetine) [7]. The effectiveness of trazodone is comparable to that of other antidepressants although it can be effective for depression and anxiety disorders resistant to other drugs because of its complexity and multifunctional receptor mechanism of action (5-HT$_{1A}$ agonist, 5-HT$_{2A/C}$ and α1-adrenoreceptor antagonist, serotonin transporter inhibitor) [7]. The search for trazodone analogs continues to this day [8, 9] (Fig. 1).

Derivatives of the four-membered S-containing heterocycle thietane were discovered by us in previous studies to be promising candidates with antidepressant activity [10 – 12]. The combination of a 1,2,4-triazol-3-one and a thietane in a single molecule was employed in the present work to design new potential antidepressants (Fig. 2).

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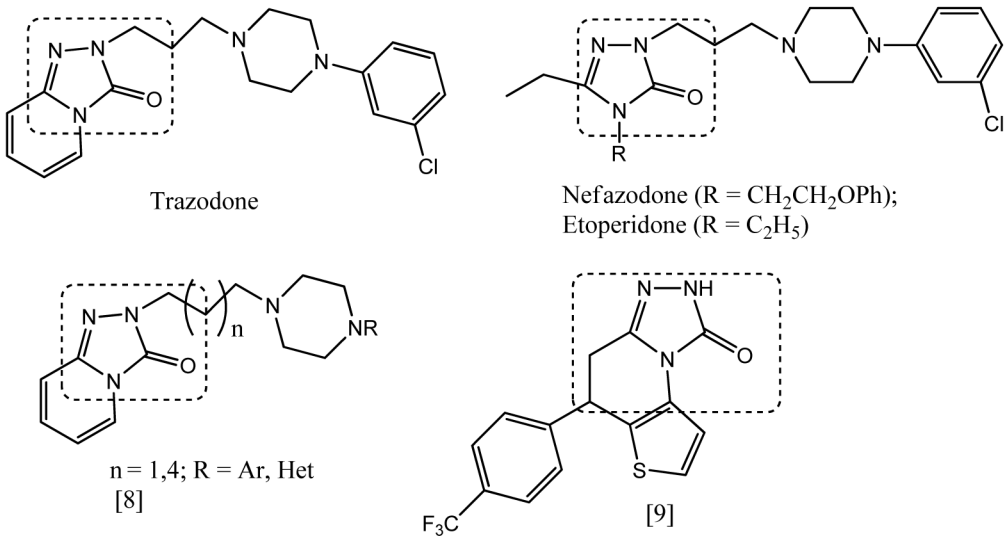


Fig. 1. Triazolone derivatives with antidepressant activity.

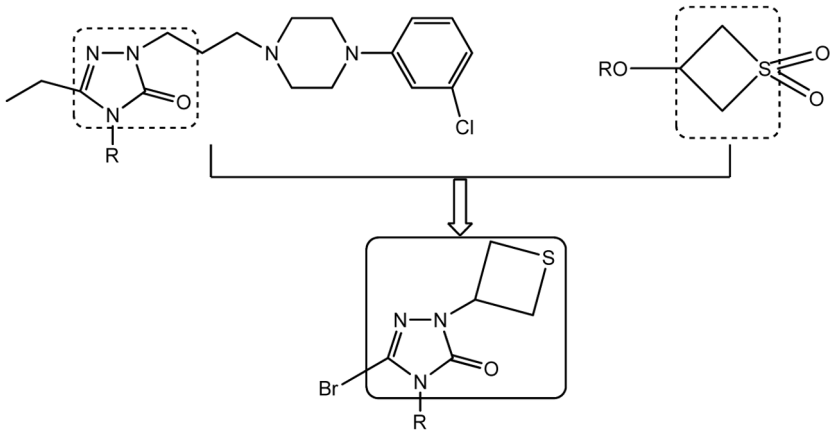
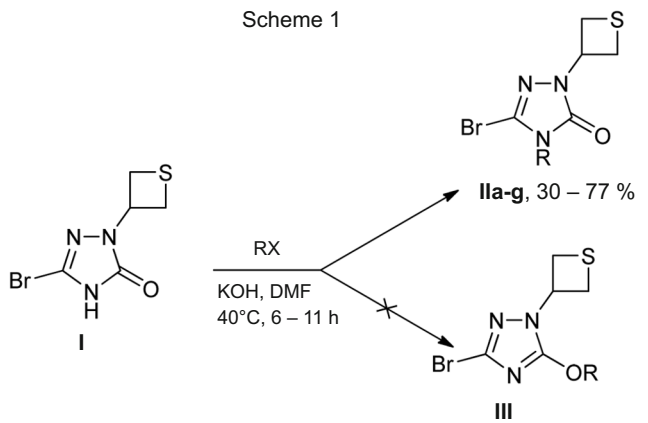


Fig. 2. Design of potential antidepressants.

Scheme 1



R = CH_3 (**a**), C_2H_5 (**b**), n-C_3H_7 (**c**), n-C_4H_9 (**d**), n-C_6H_{13} (**e**), $CH_2C_6H_5$ (**f**), CH_2CH_2Br (**g**); X = OSO_3CH_3, I, Br, Cl.

Starting 5-bromo-2,4-dihydro-2-(thietan-3-yl)-1,2,4-triazol-3-one (**I**) was synthesized by the literature method [13]. Thietane-containing 1,2,4-triazol-3-one **I** reacted with alkyl halides and dimethyl sulfate in the presence of KOH solution in DMF at 40ºC. A two-fold molar excess of the alkylating agent was used for 1,2-dibromoethane to avoid the reaction of both Br atoms. The reactions gave 30 – 77% yields of the *N*-alkylation products, i.e., 4-alkyl-5-bromo-2,4-dihydro-2-(thietan-3-yl)-1,2,4-triazol-3-ones (**IIa**-**g**). Products from *O*-alkylation, i.e., 5-alkoxy-3-bromo-1-(thietan-3-yl)-1,2,4-triazoles (**IIIa**-**g**) were not observed (Scheme 1).

PMR spectra of **IIa**-**g** contained three multiplets for the thietane-ring protons and resonances for protons of the 4-alkyl substituents. The *N*-alkylation was confirmed by comparing PMR spectra of *N*-substituted triazolone **IIb** and the isomeric *O*-substituted triazole **IIIb**, which was reported

before [14]. The quartet for the CH_2 protons of the ethyl substituent of **IIb** was shifted to strong field by 0.73 ppm as compared to the analogous resonances for 5-ethoxytriazole **IIIb**. ^{13}C NMR spectra of **IIc, e**,**g** showed NCH_2 resonances at ~44 ppm while the OCH_2 resonances were usually observed at ~60 – 70 ppm [15].

The formation of the *N*-alkylation products was also confirmed by the presence in IR spectra of **IIa-g** of absorption bands for C=O stretching vibrations at ~1690 cm^{-1}.

EXPERIMENTAL CHEMICAL PART

PMR spectra were recorded in $CDCl_3$ on Bruker AM-300 and Bruker AV-500 instruments at operating frequencies 300 and 500.13 MHz, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ (DEPT90, DEPT135 modes) on a Bruker AV-500 instrument at operating frequency 125.76 MHz. The internal standards were residual solvent resonances (7.26 ppm for ^1H, 77.0 ppm for ^{13}C). IR spectra were recorded from KBr pellets on an InfraLUM FT-02 instrument. Melting points were measured on an SMP30 apparatus. Elemental analyses were performed on a Euro3000 CHNS analyzer (Hekatech) and agreed with those calculated for C, H, N, and S.

5-Bromo-2,4-dihydro-4-methyl-2-(thietan-3-yl)-1,2,4-triazol-3-one (IIa). A solution of KOH (0.14 g, 2.50 mmol) in H_2O (2.5 mL) was treated with triazolone **1** (0.59 g, 2.50 mmol), DMF (5 mL), and dimethyl sulfate (0.32 g, 2.50 mmol); stirred at 40°C for 7 h; cooled; and poured into H_2O (50 mL). The resulting precipitate was filtered off, rinsed with H_2O, and dried. Yield 0.40 g (63%). mp = 145 – 147°C (hexane–EtOH). PMR spectrum (300 MHz), δ, ppm: 3.27 (s, 3H, CH_3), 3.18 – 3.33 (m, 2H, $S(CH)_2$), 3.87 – 4.03 (m, 2H, $S(CH)_2$), 5.46 – 5.60 (m, 1H, NCH). PMR spectrum, ν, cm^{-1}: 1285; 1389; 1434; 1537 (C=N, C-N); 1684 (C=O).

5-Bromo-2,4-dihydro-2-(thietan-3-yl)-4-ethyl-1,2,4-triazol-3-one (IIb). A solution of KOH (0.34 g, 6.00 mmol) in H_2O (5 mL) was treated with triazolone **I** (1.18 g, 5.00 mmol), DMF (10 mL), and ethyl iodide (0.94 g, 6.00 mmol); stirred at 40°C for 6 h; cooled; and poured into H_2O (50 mL). The resulting precipitate was filtered off, rinsed with H_2O, and dried. Yield 0.40 g (30%). mp = 122 – 124°C (hexane–EtOH). PMR spectrum (300 MHz), δ, ppm: 1.31 (t, 3H, ^3J 7.2 Hz, CH_3), 3.19 – 3.31 (m, 2H, $S(CH)_2$), 3.74 (q, 2H, ^3J 7.2 Hz, CH_2), 3.88 – 4.00 (m, 2H, $S(CH)_2$), 5.45 – 5.64 (m, 1H, NCH). IR spectrum, ν, cm^{-1}: 1229; 1386; 1458; 1527 (C=N, C-N); 1686 (C=O).

5-Bromo-2,4-dihydro-4-*n*-propyl-2-(thietan-3-yl)-1,2,4-triazol-3-one (IIc) was prepared analogously to **IIb**. Yield 0.87 g (63%). mp = 131 – 133°C (hexane). PMR spectrum (500 MHz), δ, ppm: 0.95 (t, 3H, ^3J 7.5 Hz, CH_3), 1.65 – 1.75 (m, 2H, CH_2), 3.22 – 3.27 (m, 2H, $S(CH)_2$), 3.61 (t, 2H, ^3J 7.4 Hz, CH_2), 3.88 – 3.97 (m, 2H, $S(CH)_2$), 5.49 – 5.58 (m, 1H, NCH). PMR spectrum ^{13}C, δ, ppm: 11.0 (CH_3), 22.1 (CH_2), 33.7 ($S(CH_2)_2$), 44.7 (CH_2), 50.8 (NCH), 122.5 (C_5); 151.3 (C_3). IR spectrum, ν, cm^{-1}: 1212; 1389; 1458; 1527(C=N, C-N); 1703 (C=O).

5-Bromo-4-*n*-butyl-2,4-dihydro-2-(thietan-3-yl)-1,2,4-triazol-3-one (IId) was prepared analogously to **IIb**. Yield 0.75 g (51%). mp = 107 – 109°C (hexane). PMR spectrum (300 MHz), δ, ppm: 0.94 (t, 3H, ^3J 7.3 Hz, CH_3), 1.27 – 1.42 (m, 2H, CH_2), 1.58 – 1.71 (m, 2H, CH_2), 3.19 – 3.30 (m, 2H, $S(CH)_2$), 3.64 (t, 2H, ^3J 7.4 Hz, CH_2), 3.88 – 3.98 (m, 2H, $S(CH)_2$), 5.45 – 5.61 (m, 1H, NCH). IR spectrum, ν, cm^{-1}: 1198; 1389; 1463; 1529 (C=N, C-N); 1693 (C=O).

5-Bromo-4-*n*-hexyl-2,4-dihydro-2-(thietan-3-yl)-1,2,4-triazol-3-one (IIe). A solution of KOH (0.17 g, 3.00 mmol) in H_2O (2.5 mL) was treated with triazolone **I** (0.59 g, 2.50 mmol), DMF (5 mL), and hexyl iodide (0.63 g, 3.00 mmol) and stirred at 40°C for 7 h. More KOH (0.08 g, 1.50 mmol) in H_2O (1 mL) and hexyl iodide (0.32 g, 1.50 mmol) were added 3 h after the start of the reaction. The mixture was stirred for 4 h, cooled, and poured into H_2O (50 mL). The resulting precipitate was filtered off, rinsed with H_2O, and dried. Yield 0.52 g (65%). mp = 118 – 120°C (hexane). PMR spectrum (500 MHz), δ, ppm: 0.84 – 0.93 (m, 3H, CH_3), 1.25 – 1.38 (m, 6H, $3CH_2$), 1.61 – 1.72 (m, 2H, CH_2), 3.20 – 3.29 (m, 2H, $S(CH)_2$), 3.63 (t, 2H, ^3J 7.5 Hz, CH_2), 3.88 – 3.98 (m, 2H, $S(CH)_2$), 5.48 – 5.58 (m, 1H, NCH). PMR spectrum ^{13}C, δ, ppm: 14.0 (CH_3), 22.4 (CH_2), 26.1 (CH_2), 28.7 (CH_2), 31.2 (CH_2), 33.7 ($S(CH_2)_2$), 43.3 (CH_2), 50.8 (NCH), 122.2 (C_5); 151.3 (C_3). IR spectrum, ν, cm^{-1}: 1344; 1391; 1461; 1532 (C=N, C-N); 1699 (C=O).

4-Benzyl-5-bromo-2,4-dihydro-2-(thietan-3-yl)-1,2,4-triazol-3-one (IIf) was prepared analogously to **IIe**. Yield 0.50 g (60%). mp = 118 – 120°C (hexane–EtOH). PMR spectrum ($CDCl_3$, 300 MHz), δ, ppm: 3.18 – 3.32 (m, 2H, $S(CH)_2$), 3.86 – 4.02 (m, 2H, $S(CH)_2$), 4.82 (s, 2H, CH_2), 5.47 – 5.64 (m, 1H, NCH), 7.18 – 7.48 (m, 5H, H_{arom}). IR spectrum, ν, cm^{-1}: 1188, 1345, 1380, 1525 (C=N, C=C, C-N); 1693 (C=O).

5-Bromo-4-(2-bromoethyl)-2,4-dihydro-2-(thietan-3-yl)-1,2,4-triazol-3-one (IIg). A solution of KOH (0.62 g, 11.00 mmol) in H_2O (5 mL) was treated with triazolone **I** (2.60 g, 11.00 mmol), DMF (10 mL), and 1,2-dibromoethane (4.13 g, 22.00 mmol); stirred at 40°C for 6 h; cooled; and poured into H_2O (100 mL). The resulting precipitate was filtered off, rinsed with H_2O, and dried. Yield 2.91 g (77%). mp = 120 – 122°C (EtOH). PMR spectrum ($CDCl_3$, 500 MHz), δ, ppm: 3.24 – 3.28 (m, 2H, $S(CH)_2$), 3.59 (t, 2H, ^3J 6.6 Hz, CH_2Br), 3.91 – 3.96 (m, 2H, $S(CH)_2$), 4.06 (t, 2H, ^3J 6.7 Hz, NCH_2), 5.49 – 5.57 (m, 1H, NCH). PMR spectrum ^{13}C ($CDCl_3$, 125.76 MHz), δ, ppm: 27.3 (CH_2), 33.6 ($S(CH_2)_2$), 44.3 (CH_2), 50.9 (NCH), 122.0 (C_5); 150.8 (C_3). IR spectrum, ν, cm^{-1}: 1149, 1386, 1439, 1528 (C=N, C-N); 1693 (C=O).

EXPERIMENTAL BIOLOGICAL PART

The experiments used 280 non-inbred male white mice (22 – 24 g) obtained from a laboratory animal nursery (filial of Mikrogen, MH RF, Ufa). All animals were accommodated under standard vivarium conditions with natural lighting and a full-ration balanced diet (GOST 33215-2014) [16] in compliance with International Recommendations of the *European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes* (1997).

Screening for antidepressant activity used tail-suspension (TST) [17] and forced-swim tests (FST) [18] in which the total duration of immobilization (TDI) and also the biorhythm depression index (DI) in the FST were evaluated. The open-field test (OF) was used to exclude false-positive and false-negative results [19]. Behavior was analyzed using the BrainTest computer program [20]. The tested compounds and fluoxetine (Apo-Fluoxetine, 20 mg capsules; Apotex Inc., Canada) were administered once i.p. 30 min before testing at doses of 2 and 10 mg/kg, respectively. The compounds and reference drug were suspended immediately before administration in Tween-80 (1 – 2 drops) and diluted with normal saline for administration in a volume of 0.4 mL per 20 g

TABLE 1. Effects on TST and FST Parameters of **I**, **IIa-g**, and Fluoxetine after a Single Administration

Series	Group	Parameter	TDI, s, TST	TDI, s, FST	DI, FST
I	Control	*n*	50	50	50
		Me (*IQR*)	106.5 (75.5, 167.5)	109.5 (82.0, 144.8)	0.96 (0.79, 1.11)
	I 2 mg/kg	*n*	16	16	16
		Me (*IQR*)	75.0 (62.0, 173.8)	87.6 (0.0, 106.0)	0.80 (0.58, 1.00)
		p	0.35	0.02	0.05
	IIb 2 mg/kg	*n*	8	8	8
		Me (*IQR*)	152.5 (142.5, 190.5)	145.0 (127.8, 168.2)	0.77 (0.70, 1.10)
		p	0.03	0.04	0.43
	IIc 2 mg/kg	*n*	8	8	8
		Me (*IQR*)	136.0 (115.2, 166.5)	126.5 (119.5, 140.2)	0.74 (0.66, 0.90)
		p	0.63	0.31	0.04
	IId 2 mg/kg	*n*	8	8	8
		Me (*IQR*)	170.0 (160.0, 188.8)	132.0 (115.8, 166.8)	0.72 (0.38, 0.98)
		p	0.001	0.23	0.08
	IIe 2 mg/kg	*n*	8	8	8
		Me (*IQR*)	119.0 (110.0, 158.0)	124.5 (93.8, 140.0)	0.89 (0.75, 0.98)
		p	0.55	0.93	0.31
	IIf 2 mg/kg	*n*	7	7	7
		Me (*IQR*)	159.0 (107.5, 186.5)	125.0 (111.0, 138.0)	0.68 (0.53, 0.78)
		p	0.24	0.79	0.001
	IIa 2 mg/kg	*n*	8	8	8
		Me (*IQR*)	136.5 (117.2, 149.2)	71.5 (48.8, 118.0)	0.38 (0.26, 0.52)
		p	0.33	0.11	< 0.001
	IIg 2 mg/kg	*n*	8	8	8
		Me (*IQR*)	146.5 (64.5, 179.0)	76.5 (71.2, 91.0)	1.23 (0.95, 1.32)
		p	0.80	0.03	0.16
II	Control	*n*	8	8	8
		Me (*IQR*)	138.5 (75.5, 166.5)	126.0 (103.2, 153.0)	0.91 (0.80, 0.99)
	Fluoxetine	*n*	8	8	8
		Me (*IQR*)	127.5 (89.0, 137.0)	72.5 (55.0, 111.5)	0.58 (0.39, 0.74)
		p	0.72	0.04	0.001

Note. Here and in Tables 2 and 3: *n*, number of observations; *Me*, median; *IQR*, interquartile range; *p*, Mann–Whitney criterion; TDI, total duration of immobilization; DI, depression index.

of body mass. Control animals received i.p. an equivalent volume of normal saline with Tween-80 (1 – 2 drops).

Acute toxicity (LD_{50}) was determined using the Litchfield–Wilcoxon method [21] as modified by Prozorovskii [22]. Compound **I** was administered at doses of 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mg/kg once i.p. to non-inbred male mice.

The range of therapeutic doses of **I** was studied by administering once i.p. at doses of 1/4000 (0.2 mg/kg), 1/2000 (0.4), 1/400 (2), 1/200 (4), 1/100 (8), 1/24 (35), 1/12 (70), and 1/6 (140) of LD_{50} 30 min before the FST and TST. Antidepressant activity of **I** was also assessed using a 14-day course of daily i.p. administration at doses of 2 and 7.6 mg/kg (equimolar to 10 mg/kg of reference drug fluoxetine). Fluoxetine (10 mg/kg) was administered using an analogous scheme.

Statistical analysis used the specialized software R version 3.6.2 (R Foundation) [23]. Parameters of descriptive statistics [number of observations (*n*), median (*Me*), interquartile range (*IQR*)] and paired comparisons of groups were calculated using base and stats packages (Mann–Whitney criterion). Graphs were plotted using the ggplot2 package [24]. The critical significance level for statistical criteria was set at 0.05.

RESULTS AND DISCUSSION

Screening of the tested compounds revealed differently directed effects on the TDI and DI (Table 1). An analysis of the screening results led to the conclusion that lengthening the alkyl radical in the 4-position (from CH_3 to C_6H_{13}) in the series of tested thietane-containing 1,2,4-triazol-3-ones (**IIb-e**) and introducing a benzyl substituent (**IIf**) decreased the antidepressant activity (as compared to **I**) that nonetheless was typical to a certain extent of all molecules with an alkyl substituent (determined from the decrease of DI as compared to the control). Compound **I** was most active, decreased the TDI (by 20%, $p = 0.02$) and DI in the FST (by 17%, $p = 0.05$), and tended to decrease the TDI in the TST (by 29%, $p = 0.35$).

Horizontal locomotor activity of the animals did not change in the OF test of the compounds, meaning that they did not affect psychostimulatory/sedative effects that could influence the TDI.

The acute toxicity of the most active compound **I** was studied as the primary toxicological characteristic (determination of tolerated, toxic, and lethal doses). Compound **I** at doses up to 400 mg/kg did not cause any changes in the behavior, fur condition, mucous membranes, pupils, stools, and respiration of the mice during all 14 days of observation. Compound **I** at doses of 600 – 1000 mg/kg caused the death of some animals; at 1200 mg/kg and greater, total lethality. The LD_{50} of **I** was 834.48 mg/kg, which assigned **I** to hazard class IV (marginally toxic) according to the Sidorov classification [25].

Compound **I** decreased the TDI in an experiment studying the range of active doses starting at 2 mg/kg. The decrease was statistically significant in the TST at doses of 2, 4, 35, and 140 mg/kg (by 22 – 55%); in the FST, 2, 4, 8, and 70 mg/kg (by 35 – 55%). A statistically significant decrease of the biorhythm parameter (DI) was observed after administration of **I** at lower doses (0.2, 0.4, 2, and 4 mg/kg; by 22 – 41%). A clear tendency to decrease the DI as compared to the control group persisted at doses of 8 – 70 mg/kg (Table 2). The ED_{50} (13.68 mg/kg) and the therapeutic index (TI, 61) of **I** exceeded significantly that of fluoxetine (TI = 9) and were calculated using the obtained data.

A 14-day course of **I** at doses of 2 and 7.6 mg/kg decreased statistically significantly both the FST TDI (by 53 and 55%, respectively) and the DI (by 46 and 35%, respec-

TABLE 2. Effect on TST and FST Parameters of a Single Administration of **I** at Doses of 1/4000 – 1/6 of LD_{50}

Pattern	Parameter	Group								
		Control	0.2 mg/kg	0.4 mg/kg	2 mg/kg	4 mg/kg	8 mg/kg	35 mg/kg	70 mg/kg	140 mg/kg
TDI, s, TST	*n*	8	8	8	8	7	8	8	8	8
	Me (*IQR*)	142.5 (124.5, 204.2)	138.0 (56.2, 190.7)	156.0 (128.2, 180.0)	110.5 (78.5, 151.2)	111.0 (87.5, 116.0)	120.0 (97.7, 141.0)	67.5 (37.0, 108.5)	118.0 (98.2, 158.2)	111.0 (39.7, 139.7)
	p	-	0.29	0.79	0.06	0.01	0.11	0.05	0.11	0.05
TDI, s, FST	*n*	8	7	8	8	7	8	8	8	7
	Me (*IQR*)	104.5 (87.0, 121.5)	90.0 (57.5, 96.5)	102.0 (57.5, 117.5)	68.0 (41.7, 84.2)	48.0 (36.5, 91.0)	56.0 (44.2, 82.0)	76.5 (32.7, 123.0)	47.0 (42.0, 79.5)	90.0 (67.0, 148.0)
	p	-	0.281	0.574	0.028	0.037	0.007	0.382	0.016	0.908
DI, FST	*n*	8	7	8	8	7	8	8	8	7
	Me (*IQR*)	1.02 (0.87, 1.05)	0.79 (0.69, 0.87)	0.60 (0.49, 0.85)	0.68 (0.59, 0.73)	0.67 (0.63, 0.82)	0.86 (0.66, 0.95)	0.79 (0.66, 0.92)	0.56 (0.79, 0.94)	0.90 (0.79, 0.90)
	p	-	0.02	< 0.001	< 0.001	< 0.001	0.08	0.13	0.11	0.22

TABLE 3. Effect on FST and TST Parameters of **I** at Doses of 2 and 7.6 mg/kg and Fluoxetine at a Dose of 10 mg/kg After an Administration Course (14-day)

Pattern	Parameter	Group			
		Control	**I** 2 mg/kg	**I** 7.6 mg/kg	Fluoxetine, 10 mg/kg
TDI, s, TST	*n*	8	8	8	8
	Me (*IQR*)	99.0 (67.5, 145.2)	69.0 (48.2, 103.8)	54.5 (30.5, 108.0)	109.0 (95.2, 129.0)
	p	-	0.64	0.20	0.75
TDI, s, FST	*n*	8	8	8	8
	Me (*IQR*)	180.5 (118.5, 182.0)	85.5 (69.8, 95.0)	81.5 (67.8, 93.5)	88.0 (71.2, 149.0)
	p	-	< 0.001	< 0.001	0.06
DI, FST	*n*	8	8	8	8
	Me (*IQR*)	1.12 (1.09, 1.15)	0.60 (0.50, 0.69)	0.72 (0.55, 0.78)	0.41 (0.28, 0.76)
	p	-	< 0.001	< 0.001	< 0.001

TABLE 4. Prediction of Toxic Risks, Physicochemical Parameters, Drug Likeness, and Drug Score of **I** and **IIa-g** in Osiris DataWarrior and Osiris Property Explorer Programs

Compound	Toxic risks				clogP	nOH	nOHNH	MM, g/mol	Agreement with Lipinski's rule of five	TPSA, E^2	Drug-likeness	Drugscore
	mutage-nicity	oncoge-nicity	irritation	reproduc-tive								
I	(–)	(–)	(–)	(–)	0.34	4	1	236.09	yes	70.00	1.83	0.86
IIa	(–)	(–)	(–)	(–)	0.60	4	0	250.12	yes	61.21	0.54	0.79
IIb	(–)	(–)	(–)	(–)	1.00	4	0	264.14	yes	61.21	3.03	0.94
IIc	(–)	(–)	(–)	(–)	1.46	4	0	278.17	yes	61.21	3.46	0.94
IId	(–)	(–)	(–)	(–)	1.91	4	0	292.20	yes	61.21	1.40	0.85
IIe	(–)	(–)	(–)	(–)	2.82	4	0	320.25	yes	61.21	– 6.49	0.45
IIf	(–)	(–)	(–)	(–)	2.02	4	0	326.21	yes	61.21	3.43	0.91
IIg	(±)	(+)	(–)	(+)	1.36	4	0	343.04	yes	61.21	– 0.78	0.16

Note. (–), no risk, (±), medium risk, (+), high risk; clogP, lipophilicity coefficient; nOH, number of H acceptors; nOHNH, number of H donors; TPSA, topological polar surface area.

tively) as compared to the control (Table 3). Compound **I** in the TST also reduced the TDI by 38% at a dose of 2 mg/kg and by 45% at a dose of 7.6 mg/kg. However, the difference from the control group was statistically insignificant. The antidepressant effect of **I** was similar to that of fluoxetine, which reduced the TSI (by 51%, $p = 0.06$) and DI (by 62%, $p \le 0.001$) and did not affect the TST TDI (Table 3).

The compounds were studied *in silico* using Lipinski's rule of five [26, 27] in the Osiris Data Warrior [28] and Osiris Property Explorer programs [29] to predict toxic risks and physicochemical parameters and to evaluate the drug-likeness to known drugs and the drug score of the synthesized molecules. Table 4 presents the results.

The calculated toxic risks showed that negative effects on reproductive functions, mutagenicity, oncogenicity, and irritation were not predicted for the synthesized compounds (except for **IIg**).

The calculated physicochemical parameters of **I** and **IIa-g** were found to satisfy Lipinski's rule of five. The molecular masses of the synthesized compounds were less than 343.04 g/mol. The lipophilicity coefficient fell in the interval from 0.34 to 2.82. The number of H-acceptors was 4; H-donors, 0 (except for **I**). The topological polar surface area (61.21 – 70.0 $Å^2$) suggested that the synthesized compounds were able to penetrate well cellular membranes, including the blood–brain barrier.

The drug-likeness parameter of 6.49 – 3.46 confirmed that the structures of the tested compounds were novel. The drug score of ~0.9 for **I** and **IIb-d, f** was indicative of a high probability of designing a new pharmaceutical substance based on them.

Thus, compound **I** was found to have a more pronounced antidepressant effect than fluoxetine, was characterized by low toxicity (834.48 mg/kg, Sidorov class IV toxicity), and had a better TI and antidepressant effect than fluoxetine after an administration course. The calculated drug score and lack of predicted toxic risks allowed the conclusion to be drawn that the design of a new antidepressant pharmaceutical substance based on **I** was promising.

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