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Reactions of thiiranes with NH-heterocycles: III*. The synthesis of N^2/N^4-mono- and N^2/N^4-dithietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones and their antidepressant activity

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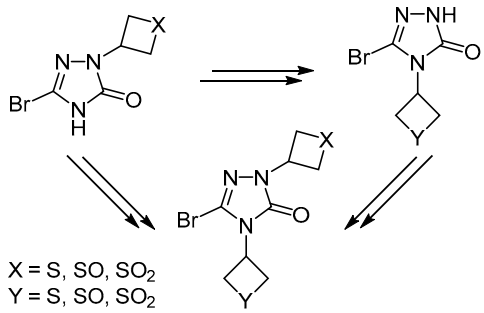


2-Thietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones were synthesized from 3,5-dibromo-1-(thietan-3-yl)-1,2,4-triazole by the reaction with sodium hydroxide solution followed by oxidation of the resulting 5-bromo-2-(thietan-3-yl)-1,2,4-triazol-3-one to 5-bromo-2-(1-oxothietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-one and 5-bromo-2-(1,1-dioxothietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-one. For the synthesis of isomeric 4-thiethane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones, the protective dioxothietanyl group of 5-bromo-2-(1,1-dioxothietan-3-yl)-4-(thietan-3-yl)-1,2,4-triazol-3-one was removed by a treatment with sodium ethoxide followed by oxidation. The reactions of 2/4-thiethane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones with 2-(chloromethyl)thiirane leading to the formation of regioisomeric 5-bromo-2,4-di(thietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-ones were studied. 5-Bromo-2,4-di(1-oxothietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-ones, 5-bromo-2,4-di(1,1-dioxothietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-ones, and 5-bromo-2/4-(1-oxothietan-3-yl)-2/4-(1,1-dioxothietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-ones were synthesized by oxidation reactions. A number of the synthesized compounds showed antidepressant activity.

Keywords: 2,4-dihydro-1,2,4-triazol-3-one, thietane, antidepressant activity, protective group.

Hybrid molecules containing two or three pharmacophore fragments often have a multimodal mechanism of action and exhibit fewer side effects.[2] A promising target for hybridization is 1,2,4-triazole, which presents one of the privileged structures of medicinal chemistry[3] and is capable of entering into noncovalent interactions to form hydrophobic, hydrogen, van der Waals, and dipole-dipole bonds with various biological targets.[3,4] According to the DrugBank Online web resource,[5] of the 31 substances containing the 1,2,4-triazole fragment registered to date, some such as trazodone (antidepressant), alprazolam (anxiolytic), rizatriptan (antimigraine agent), and loreclezole (anticonvulsant) exhibit psychotropic activity[6] (Fig. 1).

3-Substituted thietanes exhibit pronounced antidepressant activity[7–9] and are promising candidates for

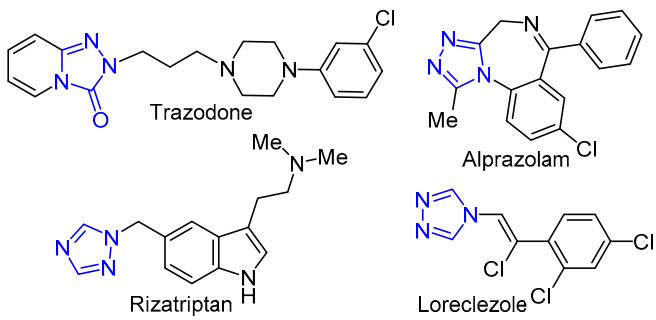


Figure 1. Medications – derivatives of 1,2,4-triazole.

* For Communication II, see [1].

hybridization with 1,2,4-triazoles. As we have shown in a number of studies,[10–13] the synthesis of 1,2,4-triazole- and thietane-based hybrid structures can lead to the creation of new antidepressants with low toxicity and high efficacy. 5-Bromo-2-(thietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-one and its 4-alkyl derivatives exhibit activity at the level of known antidepressants.[10,14] Therefore, *N*-thietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones, which combine 1,2,4-triazol-3-one and thietane fragments within their structure, are promising in the search for antidepressants.

To determine the effect of the position of the thietane ring (N-2/N-4), the degree of oxidation of sulfur (thietane, thietane 1-oxide, thietane 1,1-dioxide), and the number of rings (one or two) on the antidepressant properties, it is necessary to synthesize isomeric N^4-thietane-containing and N^2,N^4-dithietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones (Fig. 2).

No information regarding *N*,*N*-di(thietan-3-yl)aza-heterocycles can be found in the literature. Therefore, the aim of the work was the synthesis of regioisomeric N^2/N^4-mono- and N^2/N^4-dithietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones and the study of their antidepressant activity.

2-Thietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones **2a**,**b** were synthesized from thietane-containing 3,5-dibromo-1,2,4-triazoles **1a**,**b** by reactions with aqueous NaOH by convection heating[14] and microwave activation (Scheme 1). The formation of compounds **2a**,**b** was confirmed by a downfield shift of the signals of the C-3 carbon atoms by 21–25 ppm in the ^{13}C NMR spectra compared to the spectra of the starting compounds, while the IR spectra contained characteristic bands of the stretching vibrations of the C=O bond in the range of 1680–1670 cm^{-1}. The reaction of sulfone **1c** with NaOH proceeded with the elimination of the thietane dioxide ring, both by normal heating and microwave activation, to form 3,5-dibromo-1,2,4-triazole (**3**) and, presumably, 3-hydroxythietane 1,1-dioxide (**4**) (Scheme 1). For further modifications, compound **2c** was synthesized in 88% yield by

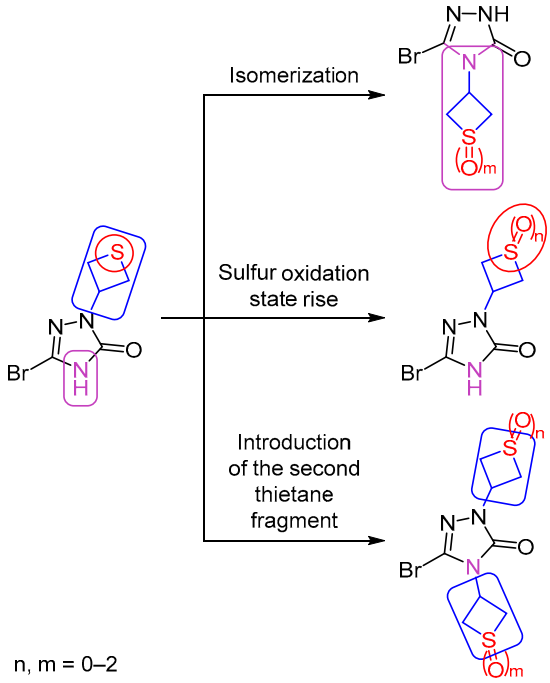
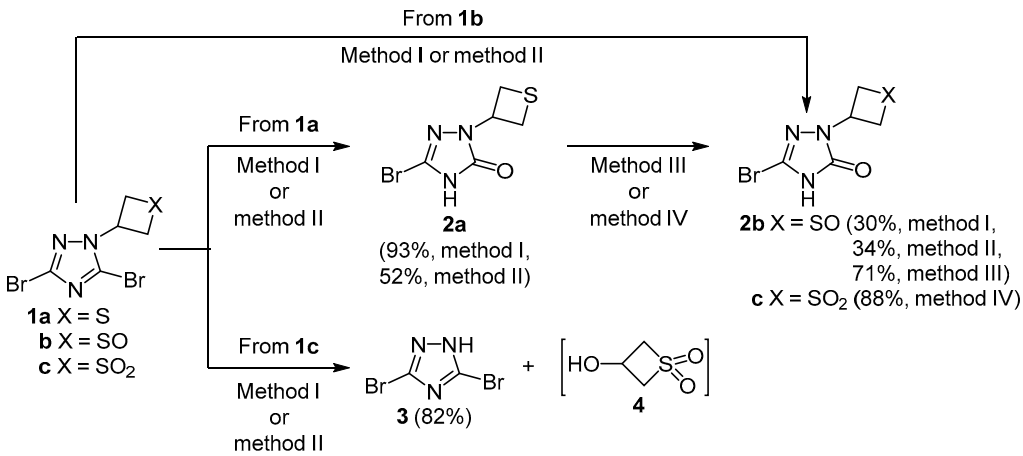


Figure 2. The routes of modification of 5-bromo-2-(thietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-one.

oxidation of triazolone **2a** with a 10-fold molar excess of H_2O_2 (Scheme 1).[14] Compounds **2b** were also obtained by oxidation of compound **2a** with a 2-fold molar excess of H_2O_2.[15] In the ^{1}H and ^{13}C NMR spectra of sulfoxide **2b**, a doubling of the signals of the thietane oxide ring was recorded, indicating the formation of two diastereomers. The *trans*-isomer is predominant, accounting for 97%.[16,17]

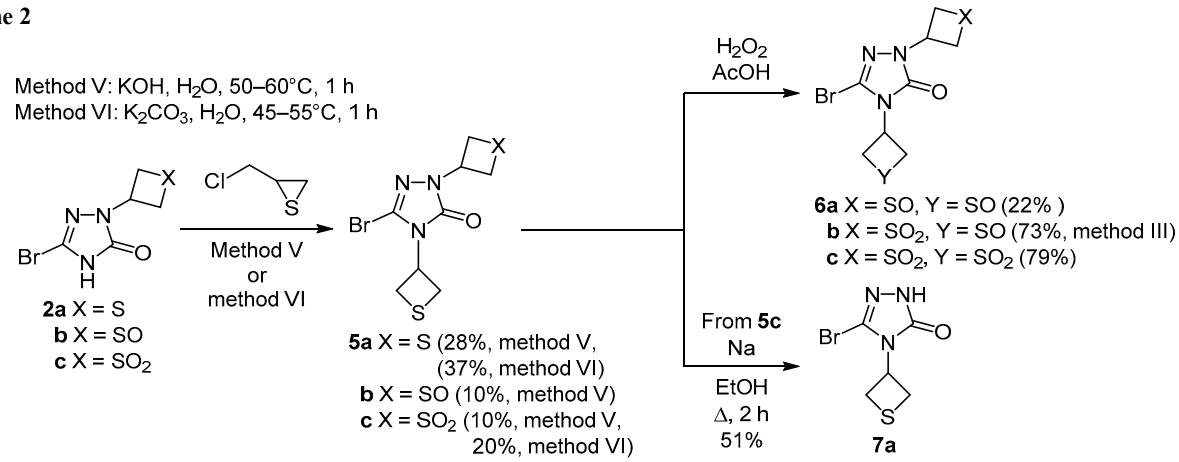
The presence of an unsubstituted N-4 position in triazolones **2a**–**c** made it possible to introduce the second thietane ring by reactions with 2-chloromethylthiirane in an aqueous medium in the presence of KOH. As a result of the thiirane-thietane rearrangement, 2,4-dithietanyltriazolones **5a**–**c** were obtained in 10–28% yields (Scheme 2). In order to increase the yield, the reaction conditions were

Scheme 1



Method I: NaOH, H_2O, Δ, 3–5 h
Method II: NaOH, H_2O, 115°C, 100 W, 40 min
Method III: H_2O_2 (2 equiv), AcOH, rt, 1 h
Method IV: H_2O_2 (10 equiv), AcOH, Δ, 1 h

Scheme 2



modified: K_2CO_3 was used as a base, the molar excess of 2-chloromethylthiirane was increased to 1.5-fold, which led to an increase in the yield of compounds **5a**,**c** to 37%. In the ^1H and ^{13}C NMR spectra of compounds **5a**–**c**, a double set of signals from the thietane ring was recorded. In the ^{13}C NMR spectra of compounds **5a**–**c**, the signals of the carbon atoms of the thietane ring in position N-4 were recorded at 32 ppm ($S(CH_2)_2$) and 50 ppm (NCH).

To unambiguously confirm the direction of alkylation of triazolones **2a**–**c** at the N-4 nitrogen atom, two-dimensional HMBC and NOESY spectra were recorded for compound **5a**. The ^1H–^{13}C HMBC spectrum of compound **5a** revealed a bond between the proton of the NCH group of the thietane ring at position N-4 and the signals of both carbon atoms C-3 and C-5 of the triazole ring, whereas the proton of the NCH group of the thietane ring at position N-2 interacted only with the C-3 carbon atom (Fig. 3*a*). The ^1H–^{15}N HMBC spectrum of compound **5a** revealed correlation between the protons of the $S(CH)_2$ group of the thietane ring and the N-4 nitrogen atom, the protons of the $S(CH)_2$ group of the other thietane ring and the N-2 nitrogen atom, and the protons of the NCH group and the N-1 nitrogen atom (Fig. 3*b*). The absence of cross peaks between the protons of two thietane rings in the NOESY spectrum of compound **5a** indirectly confirmed the alkylation of triazolone **2a** at the N-4 position.

Furthermore, the thietane rings in compound **5a** were oxidized to disulfoxide **6a** and the thietane ring in compound **5c** to sulfone-sulfoxide **6b** and disulfone **6c** (Scheme 2). In the case of sulfoxides **6a**,**b**, the *trans*-isomers were predominant according to the ^1H NMR spectra. Alkylation of *N*-unsubstituted 2,4-dihydro-1,2,4-triazol-3-ones occurred mainly at position N-2,[18] therefore the synthesis of N^4-thietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones could not be accomplished by alkylation of 5-bromo-2,4-dihydro-1,2,4-triazol-3-one with 2-chloromethylthiirane. To introduce a thietane ring into position N-4, it was first necessary to protect position N-2. We have previously shown that the thietane ring is a convenient protecting group,[19,20] which is easily removed by sodium ethoxide after oxidation to thietane dioxide. Therefore, compound **5c**, containing a thietane 1,1-dioxide ring in position N-2 and a thietane ring in position N-4, was used to synthesize N^4-thietanyl derivatives. Heating compound **5c** with NaOEt gave 5-bromo-4-(thietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-one (**7a**) in 51% yield (Scheme 2). Further oxidation of compound **7a** gave sulfoxide **7b** and sulfone **7c** (Scheme 3). Comparison of the ^1H and ^{13}C NMR spectra of regioisomeric compounds **2a**–**c** and **7a**–**c** showed that the N-4 isomers are characterized by a downfield shift in the signals of the protons of one of the $S(CH)_2$ groups by 0.2–0.5 ppm, while the signals of the carbon nuclei of the $S(CH_2)_2$ group shifted upfield by 1.3–2.6 ppm.

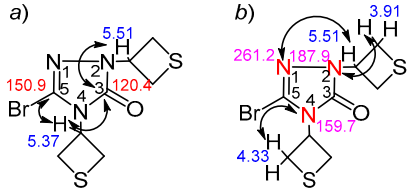


Figure 3. The major correlations in *a*) ^1H–^{13}C HMBC spectrum and *b*) ^1H–^{15}N HMBC spectrum of compound **5a** (δ, ppm).

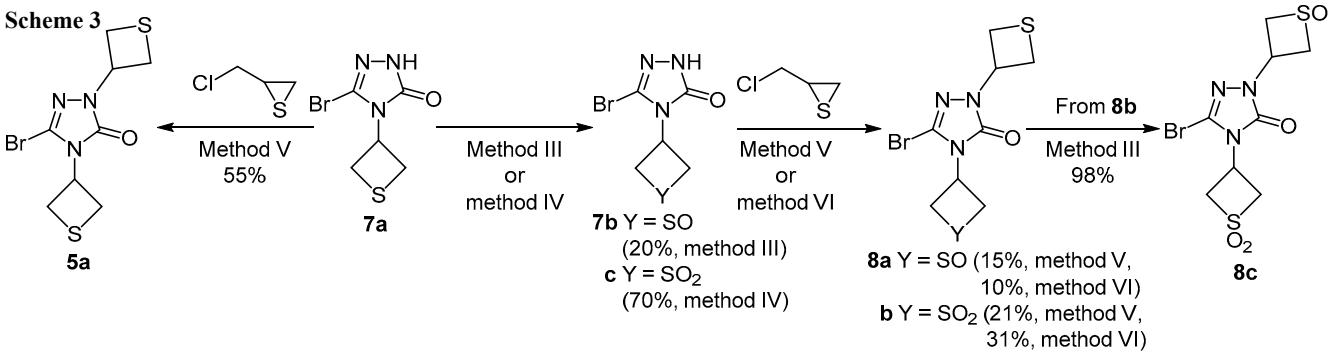
Subsequent alkylation of compounds **7a**–**c** with 2-chloromethylthiirane afforded 2,4-dithietanyltriazolones **5a**, **8a**,**b** in 10–55% yields (Scheme 3). A mixture of samples of compound **5a**, synthesized by alkylation of both triazolone **2a** and triazolone **7a**, did not yield a melting point depression, and their IR and NMR spectra coincided.

Sulfoxide-sulfone **8c** was synthesized in 98% yield by oxidation of the thietane ring of compound **8b** (Scheme 3); its ^1H NMR spectrum revealed a doubling of the signals of the thietane ring protons in the N-2 position. The ratio of *cis*- and *trans*-isomers, calculated from the integrated intensities of the proton signals of the (N-4)CH group, was 1:4.

Antidepressant activity was studied for a number of compounds. It was found that with a single administration of compounds **2a**–**c**, **5a**, **6a**, **7a**–**c**, only compounds **2a**, **6a**, **7a**–**c** in the group of experimental animals statistically significantly reduced the ID in the FST compared to the control group, which indicates an antidepressant effect (Table 1).

Analysis of the effect of the position of the thietane ring on the expression of the antidepressant effect showed that regioisomeric compounds **2a** and **7a**, differing in the position of the thietane ring, exhibited comparable antidepressant activity, significantly decreasing the FST ID by 40 and 27%, respectively (Fig. 4*a*, b). The introduction of a second thietane ring (compound **5a**) into compound **2a** led to the elimination of the antidepressant effect (Fig. 4*c*).

Scheme 3



Oxidation of sulfur in the thietane ring to sulfoxide and sulfone had a different effect on the antidepressant activity, which was also affected by the position of the thietane ring. In the case of N^4-thietanyl derivatives **2a–c**, oxidation resulted in a decrease (sulfoxide **2b**) or complete loss of the antidepressant effect (sulfone **2c**) (Fig. 4*a*), while in the case of N^2-derivatives **7a–c**, the intensity of the antidepressant effect did not change (Fig. 4*b*). The introduction of a second oxidized thietane ring into compound **7b** led to an increase in the severity of the antidepressant effect (FST ID 73% (compound **7b**) → 33% (compound **6a**)) (Fig. 4*c*). Compared with dithietane **5a**, the presence of two oxidized thietane rings in disulfoxide **6a** resulted in increased antidepressant activity (ID 91% (compound **5a**) → 33% (compound **6a**)) (Fig. 4*c*).

To conclude, a method for the synthesis of previously unknown regioisomeric N^2/N^4-mono- and N^2/N^4-dithietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones has been developed, among which compounds with antidepressant activity comparable to that of amitriptyline have been identified. The obtained data indicate the prospects for further in-depth study of these compounds in order to create agents for the treatment of depressive disorders.

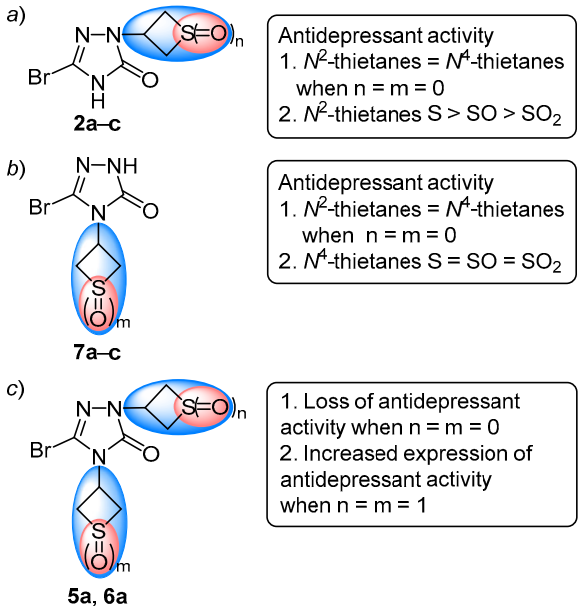


Figure 4. The effect of the modifications of 5-bromo-2-(thietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-one on antidepressant activity.

Table 1. The effect of compounds **2a–c**, **5a**, **6a**, **7a–c** on TST, FST indices after single intraperitoneal administration to male mice (% of control)*

Compound	FST** (IMD***)	FST** (ID*[4])	TST*[5] (IMD***)
Control	100 (72–128)	100 (85–119)	100 (70–137)
Amitryptiline	100.6 (93–113)	66.3*[6] (38–78)	81.8 (48–93)
2a	77*[6] (54–91)	60*[6] (43–65)	141 (66–171)
2b	61 (36–89)	94 (87–99)	90 (77–118)
2c	97 (81–105)	99 (75–116)	94 (73–129)
5a	83 (64–102)	91 (89–98)	116 (71–166)
7a	128 (93–137)	73*[6] (59–85)	109 (52–177)
Control	100 (82–113)	100 (92–105)	100 (62–110)
6a	122 (99–124)	33*[6] (23–53)	127 (103–151)
7b	108 (98–121)	73*[6] (49–78)	113 (92–128)
7c	105 (84–113)	53*[6] (43–72)	101 (87–138)

* The Table shows medians (interquartile ranges) expressed as a percentage relative to the control group value.
** FST – forced swimming test.
*** IMD – immobilization duration.
*[4] ID – ratio of the number of short periods of immobilization (<6 s) to the number of periods of active swimming.
*[5] TST – tail suspension test.
*[6] The differences are significant in comparison with the control ($p < 0.05$ for the Mann–Whitney U test).

Experimental

IR spectra were registered on a Infralum FT-02 Fourier transform spectrometer with samples in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on Bruker AM-300 (300 and 75 MHz, respectively; DMSO-d_6; compound **2b**) and Bruker Avance III (500 and 126 MHz, respectively) impulse spectrometers using a 5 mm PABBO Z-gradient probe at a constant sample temperature of 298K in DMSO-d_6 (compounds **2a**,**c**, **5a–c**, **6a–c**, **7a–c**, **8a–c**) and $CDCl_3$ (compound **5a**). The residual solvent signals (DMSO-d_6: 2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei; $CDCl_3$: 7.26 ppm for ^{1}H nuclei, 77.0 ppm for ^{13}C nuclei) were used as internal standard. Editing of ^{13}C NMR spectra was carried out on the basis of DEPT-90 and DEPT-135 experiments. Two-dimensional ^{1}H–^{13}C HMBC, NOESY, and ^{1}H–^{15}N HMBC spectra of compound **5a** were registered in standard modes of multipulse sequences of the device software. ^{15}N NMR spectra were recorded on a Bruker Avance III spectrometer with liquid ammonia as external standard. Elemental analysis was performed on a Hekatech Euro3000 CHNS-analyzer. Melting points were

determined on a Stuart SMP30 apparatus. The reaction progress and purity of the obtained compounds were monitored by TLC on Sorbfil TLC-P-UV plates, visualization in iodine vapor or under UV light, and by HPLC on an LC-20 Prominence chromatograph (Shimadzu, Japan). Chromato-mass spectra of the compounds were recorded on a gas-liquid chromatograph with an Agilent MSD 5977B quadrupole mass-selective detector, EI ionization (70 eV), the scanned mass range was from 40 to 500 *m*/*z*. Experimental data were recorded and processed using the Qualitative Analysis 10.0 software package. Microwave syntheses were performed in a CEM Discover SP monomode microwave system with an operating frequency of 2.45 GHz. The reactions were carried out in a 35-ml reaction vessel with a special lid. The reaction temperature was controlled by a built-in IR sensor on the outer surface of the reaction vessel.

All solvents and commercially available reagents were used as received. Compounds **1a–c** were prepared according to known methods.[21,22]

Synthesis of 2-thietane-containing 5-bromo-2,4-dihydro-1,2,4-triazol-3-ones 2a,b (General method). Method I. Triazole **1a**,**b** (3 mmol) was added to a solution of NaOH (220 mg, 6 mmol) in H_2O (25 ml), and the resulting mixture was heated under reflux for 5 h (compound **1a**) or 3 h (compound **1b**). The reaction mixture was cooled and filtered. The filtrate was acidified with dilute aqueous HCl to pH 3–4. The resulting precipitate was filtered off, washed with H_2O, and dried.

Method II. Compound **1a**,**b** (3 mmol) and a solution of NaOH (220 mg, 6 mmol) in H_2O (20 ml) were charged into a microwave reaction vessel. The vessel was sealed and placed in a microwave oven at 115°C and 100 W for 40 min in the dynamic control mode. The reaction mixture was cooled and filtered. The filtrate was acidified with dilute aqueous HCl to pH 3–4. The resulting precipitate was filtered off, washed with H_2O, and dried.

Synthesis of 5-bromo-2/4-(1-oxothietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-ones 2b, 6b, 7b, 8c (General method). Method III. Aqueous H_2O_2 (39.3%; 740 mg, 8 mmol) was added to a solution of compound **2a**, **5c**, **7a, 8b** (4 mmol) in glacial AcOH (15–50 ml), the resulting mixture was stirred at 18–20°C for 1 h. The progress of the reaction was monitored by HPLC (MeCN–H_2O, 1:1 was used as the mobile phase). The reaction mixture was cooled to 4–6°C, the resulting precipitate was filtered off, washed with H_2O, and dried.

Synthesis of 5-bromo-2/4-(1,1-dioxothietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-ones 2c, 7c (General method). Method IV. Aqueous H_2O_2 (39.3%; 3660 mg, 40 mmol) was added to a solution of compound **2a**, **7a** (4 mmol) in glacial AcOH (3.5–7 ml), and the resulting mixture was heated under reflux for 1 h. The reaction mixture was cooled to 4–6°C, the resulting precipitate was filtered off, washed with H_2O, and dried.

Synthesis of 5-bromo-2,4-di(thietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-ones 5a–c, 8a,b (General method). Method V. Triazolone **2a–c**, **7a–c** (13 mmol) was added to a solution of KOH (900 mg, 16 mmol) in H_2O (25 ml), and the resulting mixture was heated to 50°C. Then, 2-(chloromethyl)thiirane (1700 mg, 16 mmol) was added, and the resulting mixture was stirred at 55–60°C for 1 h. The reaction mixture was cooled to room temperature, the precipitate was filtered off, washed with 5% aqueous KOH followed by H_2O, and dried.

Method VI. Triazolone **2a**,**c**, **7a–c** (4.52 g, 20 mmol) was added to a solution of K_2CO_3 (2.76 g, 20 mmol) in H_2O (45 ml), and the resulting mixture was heated to 45°C. Then, 2-(chloromethyl)thiirane (1.63 g, 15 mmol) was added, and the resulting mixture was stirred at 45–48°C. After 30 min, K_2CO_3 (1.38 g, 10 mmol) and 2-(chloromethyl)thiirane (1630 mg, 15 mmol) were added, and stirring was continued at 50–55°C for 30 min. The reaction mixture was cooled to room temperature, the precipitate was filtered off, washed with 5% aqueous K_2CO_3 followed by H_2O, and dried.

5-Bromo-2-(thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (2a). Yield 650 mg (93%, method I), 470 mg (52%, method II), white crystals, mp 250–252°C (EtOH). IR spectrum, ν, cm^{-1}: 3131 (NH), 3070–2885 (CH), 1680 (C=O), 1530, 1166, (C–N, C=N). ^{1}H NMR spectrum, δ, ppm: 3.22–3.26 (2H, m, SCH_2); 3.71–3.74 (2H, m, SCH_2); 5.28–5.35 (1H, m, NCH). ^{13}C NMR spectrum, δ, ppm: 33.7 ($S(CH_2)_2$); 50.3 (NCH); 120.1 (C-5); 152.6 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 235 $[M(^{79}Br)]^+$ (16), 237 $[M(^{81}Br)]^+$ (16), 189 (100), 166 (29), 156 (23), 146 (15), 110 (14), 72 (31), 45 (19), 41 (14). Found, %: C 25.44; H 2.56; N 17.80; S 13.58. $C_5H_6BrN_3OS$. Calculated, %: C 25.46; H 2.58; N 17.76; S 13.56.

5-Bromo-2-(1-oxo-1λ^4-thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (2b). Yield 230 mg (30%, method I), 260 mg (34%, method II), 720 mg (71%, method III), white crystals, decomp. temp. 265°C (BuOH). IR spectrum, ν, cm^{-1}: 3119 (NH), 3031–2779 (CH), 1670 (C=O), 1530, 1194 (C–N, C=N), 1026 (S=O). ^{1}H NMR spectrum, δ, ppm: 3.45–3.58 (2H, m, SCH_2 *cis* and *trans*); 3.73–3.80 (2H, m, SCH_2 *trans*); 4.09–4.12 (2H, m, SCH_2 *cis*); 4.63–4.76 (1H, m, NCH *cis*); 5.37–5.52 (1H, m, NCH *trans*); 12.51 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 45.9 (NCH *trans*); 52.8 (NCH *cis*); 56.3 ($S(CH_2)_2$ *trans*); 58.7 ($S(CH_2)_2$ *cis*); 120.2 (C-5); 152.6 (C-3). Content of *trans*-isomer 97%. Found, %: C 23.82; H 2.40; N 16.67; S 12.72. $C_5H_6BrN_3O_2S$. Calculated, %: C 23.84; H 2.42; N 16.62; S 12.68.

3-(3-Bromo-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)-1λ^6-thietane-1,1-dione (2c). Yield 940 mg (88%, method IV), white crystals, decomp. temp. 260°C (EtOH). IR spectrum, ν, cm^{-1}: 3129 (NH), 3010–2857 (CH), 1696 (C=O), 1549, 1222 (C–N, C=N), 1325, 1132 (SO_2). ^{1}H NMR spectrum, δ, ppm: 4.46–4.51 (2H, m, SCH_2); 4.62–4.66 (2H, m, SCH_2); 4.95–5.01 (1H, m, NCH); 12.70 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 35.1 (NCH); 70.5 ($S(CH_2)_2$); 121.1 (C-5); 153.7 (C-3). Found, %: C 22.40; H 2.26; N 15.67; S 11.96. $C_5H_6BrN_3O_3S$. Calculated, %: C 22.38; H 2.28; N 15.69; S 11.98.

3,5-Dibromo-1,2,4-triazole (3) was obtained from compound **1c** using NaOH (300 mg, 7.5 mmol). Yield 560 mg (82%, method II), white crystals, mp 213–215°C (H_2O) (mp 210–212°C[19]). IR spectrum, ν, cm^{-1}: 3102 (NH), 2898, 2743 (CH), 1516, 1428, 1269, 1251, 1014 (C–N, C=N). Mass spectrum, *m*/*z* (I_{rel}, %): 229 $[M(^{81}Br)]^+$ (44), 227 $[M(^{79}Br,^{81}Br)]^+$ (100), 225 $[M(^{79}Br)]^+$ (33), 122 (35), 120 (39).

5-Bromo-2,4-di(thietan-3-yl)-2,4-dihydro-1,2,4-triazol-3-one (5a). Yield 1110 mg (28%, method V, from compound **2a**), 2250 mg (37%, method VI, from compound **2a**), 2210 mg (55%, method V, from compound **7a**), white crystals, mp 211–212°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 2998, 2943, 2852 (C–H), 1692 (C=O), 1514 (C=N), 1407, 1158 (C–N). ^{1}H NMR spectrum ($CDCl_3$) δ, ppm: 3.18–3.25 (4H, m, (N-2)CHSC$\underline{H}_2$, (N-4)CHSC$\underline{H}_2$); 3.89–3.93 (2H, m, (N-2)CHSC$\underline{H}_2$); 4.31–4.35 (2H, m, (N-4)CHSC$\underline{H}_2$); 5.33–5.40 (1H, m, (N-4)CH); 5.48–5.55 (1H, m, (N-2)CH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.20–3.27 (4H, m, (N-2)CHSC$\underline{H}_2$, (N-4)CHSC$\underline{H}_2$); 3.71–3.75 (2H, m, (N-2)CHSC$\underline{H}_2$); 4.13–4.17 (2H, m, (N-4) CHSC$\underline{H}_2$); 5.20–5.26 (1H, m, (N-4)CH); 5.33–5.40 (1H, m, (N-2)CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 32.5 ((N-4)CHS($\underline{C}H_2$)$_2$); 33.6 ((N-2)CHS($\underline{C}H_2$)$_2$); 50.3 ((N-4)CH); 50.6 ((N-2)CH); 120.4 (C-5); 150.9 (C-3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 32.4 ((N-4)CHS($\underline{C}H_2$)$_2$); 33.4 ((N-2)CHS($\underline{C}H_2$)$_2$); 50.4 ((N-4)CH); 50.6 ((N-2)CH); 122.2 (C-5), 150.9 (C-3). ^{15}N NMR spectrum, δ, ppm: 159.7 (N-4); 187.9 (N-2); 261.2 (N-1). Mass spectrum, *m*/*z* (I_{rel}, %): 307 [M(^{79}Br)]$^+$ (4), 309 [M(^{81}Br)]$^+$ (7), 263 (44), 238 (8), 182 (7), 73 (100), 45 (27). Found, %: C 31.16; H 3.27; N 13.64; S 20.80. $C_8H_{10}BrN_3OS_2$. Calculated, %: C 31.19; H 3.29; N 13.61; S 20.83.

5-Bromo-2-(1-oxo-1λ^4-thietan-3-yl)-4-(thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5b). Yield 390 mg (10%, method V), white crystals, mp 243–245°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3023, 2949 (C–H), 1696 (C=O), 1516 (C=N), 1155 (C–N), 1110 (SO). ^{1}H NMR spectrum, δ, ppm: 3.22–3.26 (2H, m, (N-4)CHSC$\underline{H}_2$); 3.55–3.59 (2H, m, (N-2)CHSC$\underline{H}_2$ *trans*); 3.75–3.78 (2H, m, (N-2)CHSC$\underline{H}_2$ *trans*); 4.15–4.19 (2H, m, (N-4)CHSC$\underline{H}_2$); 5.23–5.31 (1H, m, (N-4)CH); 5.45–5.50 (1H, m, (N-2)CH *trans*). ^{13}C NMR spectrum, δ, ppm: 31.8 ((N-4)CHS($\underline{C}H_2$)$_2$); 46.5 ((N-2)CH), 49.9 ((N-4)CH), 56.1 ((N-2)CHS($\underline{C}H_2$)$_2$); 122.0 (C-5); 150.9 (C-3). Found, %: C 31.20; H 3.24; N 13.61; S 20.74. $C_8H_{10}BrN_3O_2S_2$. Calculated, %: C 31.18; H 3.27; N 13.63; S 20.80.

5-Bromo-2-(1,1-dioxo-1λ^6-thietan-3-yl)-4-(thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (5c). Yield 520 mg (10%, method V), 1260 mg (20%, method VI), white crystals, mp 184–187°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3021, 2953 (C–H), 1717 (C=O), 1526 (C=N), 1304, 1137 (SO_2), 1225 (C–N). ^{1}H NMR spectrum, δ, ppm: 3.21–3.25 (2H, m, (N-4)CHSC$\underline{H}_2$); 4.14–4.17 (2H, m, (N-4)CHSC$\underline{H}_2$); 4.47–4.51 (2H, m, (N-2)CHSC$\underline{H}_2$); 4.64–4.69 (2H, m, (N-2)CHSC$\underline{H}_2$); 5.00–5.06 (1H, m, (N-2)CH); 5.22–5.30 (1H, m, (N-4)CH). ^{13}C NMR spectrum, δ, ppm: 31.9 ((N-4)CHS($\underline{C}H_2$)$_2$); 35.1 ((N-2)CH); 50.0 ((N-4)CH); 69.9 ((N-2)CHS($\underline{C}H_2$)$_2$); 122.2 (C-5); 152.0 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 339 [M(^{79}Br)]$^+$ (4), 341 [M(^{81}Br)]$^+$ (3), 268 (17), 215 (7), 72 (100), 45 (19). Found, %: C 28.29; H 2.96; N 12.35; S 18.85. $C_8H_{10}BrN_3O_3S_2$. Calculated, %: C 28.26; H 2.98; N 12.37; S 18.88.

5-Bromo-2,4-bis(1-oxo-1λ^4-thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (6a). Aqueous H_2O_2 (35.6%; 340 mg, 3.5 mmol) was added to a solution of compound **5a** (370 mg, 1.2 mmol) in glacial AcOH (21 ml), the resulting mixture was stirred at 20–23°C for 1.5 h. The reaction mixture was cooled to 4–6°C and neutralized with aqueous NH_3 to pH 7–8. The resulting precipitate was filtered off, washed with H_2O, and dried. Yield 90 mg (22%), white crystals, decomp. temp. 170°C (*i*-BuOH). IR spectrum, ν cm^{-1}: 3025, 2944 (C–H), 1694 (C=O), 1521 (C=N), 1186 (C–N), 1090, 1066 (S=O). ^{1}H NMR spectrum, δ, ppm: 3.41–3.50 (4H, m, (N-2)CHSC$\underline{H}_2$ *cis*, (N-4)CHSC$\underline{H}_2$ *trans*); 3.56–3.60 (2H, m, (N-2)CHSC$\underline{H}_2$ *trans*); 3.76–3.80 (2H, m, (N-2) CHSC$\underline{H}_2$ *trans*); 4.03–4.17 (8H, m, 2(N-4)CHS(C$\underline{H}$)$_2$ *cis*, (N-4)CHSC$\underline{H}_2$ *trans*, (N-2)CHSC$\underline{H}_2$ *cis*); 4.57–4.64 (1H, m, (N-2)CH *cis*); 4.75–4.82 (1H, m, (N-4)CH *cis*); 5.47–5.52 (1H, m, (N-2)CH *trans*); 5.53–5.59 (1H, m, (N-4)CH *trans*). ^{13}C NMR spectrum, δ, ppm: 46.4 ((N-2)CH); 47.7 ((N-4)CH); 53.5 ((N-4)CHS($\underline{C}H_2$)$_2$ *trans*); 56.0 ((N-2)CHS($\underline{C}H_2$)$_2$ *trans*); 56.4 ((N-4)CHS($\underline{C}H_2$)$_2$ *cis*); 58.5 ((N-2)CHS($\underline{C}H_2$)$_2$ *cis*); 122.9 (C-5); 150.5 (C-3). Found, %: C 28.24; H 2.96; N 12.35; S 18.85. $C_8H_{10}BrN_3O_3S_2$. Calculated, %: C 28.26; H 2.98; N 12.38; S 18.89.

5-Bromo-2-(1,1-dioxo-1λ^6-thietan-3-yl)-4-(1-oxo-1λ^4-thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (6b) was obtained by method III from compound **5c** with the following modification: after the reaction was complete, Na_2SO_3 (500 mg, 4 mmol) was added to the reaction mixture after which it was neutralized with aqueous NH_3 to pH 7–8. The reaction mixture was cooled to 4–6°C, the resulting precipitate was filtered off, washed with H_2O, and dried. Yield 1070 mg (73%), white crystalline powder, decomp. temp. 251°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3027, 2953 (C-H), 1682 (C=O), 1528 (C=N), 1323, 1137 (SO_2), 1195 (C-N), 1069 (S=O). ^{1}H NMR spectrum, δ, ppm: 3.46–3.51 (2H, m, (N-4)CHSC$\underline{H}_2$ *trans*); 4.03–4.09 (4H, m, (N-4)CHSC$\underline{H}_2$ *cis*, (N-4)CHSC$\underline{H}_2$ *trans*); 4.50–4.54 (4H, m, (N-2)CHSC$\underline{H}_2$, (N-4)CHSC$\underline{H}_2$ *cis*); 4.60–4.64 (1H, m, (N-4)CH *cis*); 4.67–4.72 (2H, m, (N-2)CHSC$\underline{H}_2$); 5.02–5.08 (1H, m, (N-2)CH); 5.53–5.59 (1H, m, (N-4)CH *trans*). ^{13}C NMR spectrum, δ, ppm: 35.0 ((N-2)CH); 47.7 ((N-4)CH *trans*); 53.5 ((N-4)CHS($\underline{C}H_2$)$_2$ *trans*); 56.4 ((N-4)CHS($\underline{C}H_2$)$_2$ *cis*); 69.8 ((N-2)CHS($\underline{C}H_2$)$_2$); 123.1 (C-5); 151.1 (C-3). Content of *trans*-isomer was 80%. Found, %: C 26.98; H 2.83; N 11.80; S 18.00. $C_8H_{10}BrN_3O_4S_2$. Calculated, %: C 26.95; H 2.87; N 11.79; S 18.03.

3,3'-(3-Bromo-5-oxo-1*H*-1,2,4-triazole-1,4(5*H*)-diyl)-di(1λ^6-thietane-1,1-dione) (6c). Aqueous H_2O_2 (39.3%; 1780 mg, 20 mmol) was added to a solution of compound **5c** (2 mmol) in glacial AcOH (4 ml), and the resulting mixture was heated under reflux for 1 h. The reaction mixture was cooled to 4–6°C, the resulting precipitate was filtered off, washed with H_2O, and dried. Yield 590 mg (79%), white crystals, mp 286–287°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3043–2949 (C–H), 1713 (C=O), 1530 (C=N), 1333, 1313, 1139, 1130 (SO_2), 1275 (C–N). ^{1}H NMR spectrum, δ, ppm: 4.48–4.54 (4H, m, (N-2)CHSC$\underline{H}_2$, (N-4)CHSC$\underline{H}_2$); 4.66–4.71 (2H, m, (N-2)CHSC$\underline{H}_2$); 4.92–4.94 (1H, m, (N-4)CH); 4.98–5.03 (3H, m, (N-4)CHS(C$\underline{H}$)$_2$, (N-2)CH). ^{13}C NMR spectrum, δ, ppm: 35.6 ((N-2)CH); 36.3 ((N-4)CH); 68.1 ((N-4)CHS($\underline{C}H_2$)$_2$); 70.4 ((N-2)CHS($\underline{C}H_2$)$_2$); 123.9 (C-5); 151.5 (C-3). Found, %: C 25.82; H 2.71; N 11.29; S 17.23. $C_8H_{10}BrN_3O_5S_2$. Calculated, %: C 25.85; H 2.75; N 11.32; S 17.25.

5-Bromo-4-(thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (7a). Metallic Na (110 mg, 4.8 mmol) was added to anhydrous EtOH (60 ml), and the mixture was heated until

gas evolution ceased. Then, compound **5c** (1500 mg, 4.4 mmol) was added, and the resulting mixture was heated under reflux for 2 h. The reaction mixture was evaporated to dryness under reduced pressure. PhH (20 ml) was added to the residue, and the mixture was extracted with H_2O (2×20 ml). The aqueous fraction was separated and acidified by aqueous HCl to pH 3. The formed precipitate was filtered off, washed with H_2O, and dried. Yield 530 mg (51%), white crystals, mp 190–192°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3127 (NH), 3019–2923 (C–H), 1702 (C=O), 1532 (C=N), 1145 (C–N). ^{1}H NMR spectrum, δ, ppm: 3.16–3.31 (2H, m, SCH_2); 4.16–4.19 (2H, m, SCH_2); 5.19–5.27 (1H, m, NCH); 12.16 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 32.3 ($S(CH_2)_2$); 49.9 (NCH); 121.9 (C-5); 153.9 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 235 $[M(^{79}Br)]^+$ (27), 237 $[M(^{81}Br)]^+$ (28), 207 (9), 166 (7), 72 (100), 45 (23). Found, %: C 25.44; H 2.56; N 17.84; S 13.58. $C_5H_6BrN_3OS$. Calculated, %: C 25.47; H 2.59; N 17.78; S 13.61.

5-Bromo-4-(1-oxo-1λ^4-thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (7b). Yield 200 mg (20%, method III), white crystals, decomp. temp. 253°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3084 (NH), 3012–2774 (C–H), 1694 (C=O), 1540 (C=N), 1209 (C–N), 1040 (SO). ^{1}H NMR spectrum, δ, ppm: 3.43–3.48 (2H, m, SCH_2 *trans*); 4.01–4.08 (6H, m, $2SCH_2$ *cis,* SCH_2 *trans*); 4.50–4.60 (1H, m, NCH *cis*); 5.51–5.57 (1H, m, NCH *trans*); 12.24 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 38.7 (NCH *cis*); 47.7 (NCH *trans*); 53.2 ($S(CH_2)_2$ *trans*); 57.0 ($S(CH_2)_2$ *cis*); 122.9 (C-5); 153.6 (C-3). Content of *trans*-isomer was 69%. Found, %: C 23.82; H 2.40; N 16.67; S 12.72. $C_5H_6BrN_3O_2S$. Calculated, %: C 23.85; H 2.43; N 16.70; S 12.69.

3-(3-Bromo-5-oxo-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)-1λ^6-thietane-1,1-dione (7c). Yield 750 mg (70%, method IV), white crystals, mp 247–249°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3125 (NH), 3045–2766 (C–H), 1701 (C=O), 1532 (C=N), 1327, 1135 (SO_2), 1213 (C–N). ^{1}H NMR spectrum, δ, ppm: 4.45–4.50 (2H, m, SCH_2); 4.86–4.91 (1H, m, NCH); 5.01–5.05 (2H, m, SCH_2); 12.30 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 35.9 (NCH); 67.9 ($S(CH_2)_2$); 123.3 (C-5); 153.5 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 267 $[M(^{79}Br)]^+$ (13), 269 $[M(^{81}Br)]^+$ (21), 207 (18), 191 (13), 163 (19), 124 (17), 64 (13), 55 (13), 44 (100), 41 (47). Found, %: C 22.40; H 2.26; N 15.67; S 11.96. $C_5H_6BrN_3O_3S$. Calculated, %: C 22.43; H 2.28; N 15.69; S 11.97.

5-Bromo-4-(1-oxo-1λ^4-thietan-3-yl)-2-(thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8a). Yield 620 mg (15%, method V, from compound **7b**), 670 mg (10%, method VI, from compound **7b**), white crystals, decomp. temp. 260°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3037–2947 (C–H), 1688 (C=O), 1521 (C=N), 1168 (C–N), 1075 (S=O). ^{1}H NMR spectrum, δ, ppm: 3.27–3.30 (2H, m, (N-2)CHSC$\underline{H}_2$); 3.45–3.49 (2H, m, (N-4)CHSC$\underline{H}_2$ *trans*); 3.73–3.79 (2H, m, (N-2)CHSC$\underline{H}_2$); 4.02–4.09 (6H, m, 2(N-4)CHSC$\underline{H}_2$ *cis*, (N-4)CHSC$\underline{H}_2$ *trans*); 4.56–4.61 (1H, m, (N-4)CH *cis*); 5.37–5.42 (1H, m, (N-2)CH); 5.52–5.57 (1H, m, (N-4)CH *trans*). ^{13}C NMR spectrum, δ, ppm: 33.0 ((N-2)CHS($\underline{C}H_2)_2$); 47.7 ((N-4)CH); 50.1 ((N-2)CH); 53.7 ((N-4)CHS($\underline{C}H_2)_2$ *trans*); 56.6 ((N-4)CHS($\underline{C}H_2)_2$ *cis*). Content of *trans*-isomer was 73%. Found, %: C 29.64; H 3.11; N 12.96; S 19.78. $C_8H_{10}BrN_3O_2S_2$. Calculated, %: C 29.66; H 3.15; N 12.99; S 19.80.

5-Bromo-4-(1,1-dioxo-1λ^6-thietan-3-yl)-2-(thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8b). Yield 910 mg (21%, method V, from compound **7c**), 2100 mg (31%, method VI, from compound **7c**), white crystals, decomp. temp. 270°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3021, 2953 (C–H), 1717 (C=O), 1526 (C=N), 1303, 1138 (SO_2), 1225 (C–N). ^{1}H NMR spectrum, δ, ppm: 3.26–3.30 (2H, m, (N-2)CHSC$\underline{H}_2$); 3.75–3.78 (2H, m, (N-2)CHSC$\underline{H}_2$); 4.48–4.53 (2H, m, (N-4)CHSC$\underline{H}_2$); 4.88–4.95 (1H, m, (N-4)CH); 5.00–5.04 (2H, m, (N-4)CHSC$\underline{H}_2$); 5.36–5.43 (1H, m, (N-2)CH). ^{13}C NMR spectrum, δ, ppm: 32.9 ((N-2)CHS($\underline{C}H_2)_2$); 35.8 ((N-4)CH); 50.2 ((N-2)CH); 67.6 ((N-4)CHS($\underline{C}H_2)_2$); 122.9 (C-5); 149.9 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 339 $[M(^{79}Br)]^+$ (12), 341 $[M(^{81}Br)]^+$ (13), 295 (100), 268 (35), 207 (22), 191 (23), 82 (10), 72 (85), 55 (15), 41 (30). Found, %: C 28.24; H 2.96; N 12.35; S 18.85. $C_8H_{10}BrN_3O_3S_2$. Calculated, %: C 28.26; H 2.98; N 12.38; S 18.87.

5-Bromo-4-(1,1-dioxo-1λ^6-thietan-3-yl)-2-(1-oxo-1λ^4-thietan-3-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one (8c) was obtained according to method III from compound **8b** with the following modification: after the reaction was complete, Na_2SO_3 (500 mg, 4 mmol) was added to the reaction mixture after which it was neutralized with aqueous NH_3 to pH 7–8. The reaction mixture was cooled to 4–6°C, the resulting precipitate was filtered off, washed with H_2O, and dried. Yield 700 mg (98%), white crystals, mp 241–243°C (*i*-BuOH). IR spectrum, ν, cm^{-1}: 3025, 2951 (C–H), 1680 (C=O), 1525 (C=N), 1135; 1325 (SO_2), 1198 (C–N), 1067 (S=O). ^{1}H NMR spectrum, δ, ppm: 3.41–3.43 (2H, m, (N-2)CHSC$\underline{H}_2$ *cis*); 3.54–3.58 (2H, m, (N-2)CHSC$\underline{H}_2$ *trans*); 3.74–3.77 (2H, m, (N-2)CHSC$\underline{H}_2$ *trans*); 4.08–4.12 (2H, m, (N-2)CHSC$\underline{H}_2$ *cis*); 4.48–4.53 (2H, m, (N-4)CHSC$\underline{H}_2$); 4.65–4.70 (1H, m, (N-4)CH); 4.73–4.80 (1H, m, (N-2)CH *cis*); 4.88–4.95 (1H, m, (N-2)CH *trans*); 4.98–5.06 (2H, m, (N-4)CHSC$\underline{H}_2$). ^{13}C NMR spectrum, δ, ppm: 35.6 ((N-4)CH); 36.3 ((N-2)CH *trans*); 47.1 ((N-2) CH, *cis*); 56.5 ((N-2)CHS($\underline{C}H_2)_2$ *cis*); 59.1 ((N-2)CHS($\underline{C}H_2)_2$ *trans*); 68.1 ((N-4)CHS($\underline{C}H_2)_2$); 123.9 (C-5); 151.5 (C-3). Content of *trans*-isomer was 80%. Found, %: C 26.98; H 2.83; N 11.80; S 18.00. $C_8H_{10}BrN_3O_4S_2$. Calculated, %: C 26.95; H 2.87; N 11.79; S 18.03.

The assay of the antidepressant activity of compounds 2a–c, 5a, 6a, 7a–c was done on non-inbred male mice (18–23 g), randomly divided into groups of 6 animals each. The animals were kept under standard vivarium conditions with natural light conditions and unlimited access to food and water (feed according to GOST R 50258–92). All experiments were conducted in accordance with the "Rules of good laboratory practice of the Eurasian Economic Union in the sphere of circulation of medicinal products" in compliance with the "International recommendations of the European Convention for the protection of vertebrate animals used for experimental or other scientific purposes (1998)".[23,24]

Two sets of experiments were performed, in each of which the activity of the compounds was compared with the control group (mice received the solvent intraperitoneally in equivolume amounts) and the active control amitriptyline 10 mg/kg (amitriptyline, solution for intravenous and intramuscular administration 10 mg/ml,

Moscow Endocrine Plant, Russia). The compounds were suspended *ex tempore* with 1–2 drops of Tween-80 and diluted with isotonic NaCl solution; administration was carried out in equimolar 10 mg/kg doses (at the rate of 0.2 ml per 20 g of body weight) intraperitoneally once 30 min before testing. Antidepressant activity was studied in the tail suspension test (TST)[25] and forced swimming test (FST).[26] In the FST, the duration of immobilization (IMD) and periods of active and passive swimming were assessed, on the basis of which the depressiveness index (ID) was calculated – the ratio of the number of short periods of immobilization (<6 s) to the number of periods of active swimming. In the TST, only DIM was considered.

The Statistica 13.3 program (TIBCO Software Inc.) was used for statistical data processing; the normality of the distribution was determined (it was different from normal in all cases), the median and interquartile ranges (25 and 75%) were calculated. The Kruskal–Wallis H-test was used for comparison of groups, and the Mann–Whitney U-test was used for pairwise intergroup comparison.[27]

Supplementary information file containing ^{1}H and ^{13}C NMR spectra for all synthesized compounds **2**, **5**–**8** **a**–**c**, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, ^{1}H–^{15}N HMBC, and NOESY spectra for compound **5a**, as well as mass spectra for compounds **2a**, **5a**,**c**, **7a**,**c**, **8b** is available at the journal website http://link.springer.com/journal/10593.

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References

1. Klen, E. E.; Makarova, N. N.; Khaliullin, F. A.; Shepilova, S. O.; Ishkinina, A. R.; Baikova, I. P. *Russ. J. Org. Chem.* **2022**, *58*, 1192.
2. Shaveta; Mishra, S.; Singh, P. *Eur. J. Med. Chem.* **2016**, *124*, 500.
3. Aggarwal, R.; Sumran, G. *Eur. J. Med. Chem.* **2020**, *205*, 112652.
4. Nasri, S.; Bayat, M.; Kochia, K. *Mol. Diversity* **2022**, *26*, 717.
5. Wishart, D. S.; Feunang, Y. D.; Guo, A. C.; Lo, E. J.; Marcu, A; Grant, J. R.; Sajed, T.; Johnson, D.; Li, C.; Sayeeda, Z.; Assempour, N.; Iynkkaran, I.; Liu, Y.; Maciejewski, A.; Gale, N.; Wilson, A.; Chin, L.; Cummings, R.; Le, D.; Pon, A.; Knox, C.; Wilson, M. *Nucleic Acids Res.* **2018**, *46*, 1074.
6. Chemical Structure Search, DrugBank Online. Accessed 22.04.2024. https://go.drugbank.com/structures/search/small_molecule_drugs/structure#results.
7. Khaliullin, F. A.; Nikitina, I. L.; Klen, E. É.; Gaisina, G. G.; Makarova, N. N. *Pharm. Chem. J.* **2020**, *53*, 1106.
8. Nikitina, I. L.; Gaisina, G. G. *Res. Results Pharmacol.* **2021**, *7*, 63.
9. Klen, E. E.; Nikitina, I. L.; Makarova, N. N.; Miftakhova, A. F.; Ivanova, O. A.; Khaliullin, F. A.; Alekhin, E. K. *Pharm. Chem. J.* **2017**, *50*, 642.
10. Khaliullin, F. A.; Nikitina, I. L.; Klen, E. E.; Miftakhova, A. F.; Makarova, N. N.; Gabidullin, R. A.; Gilmanova, A. G. *Pharm. Chem. J.* **2021**, *55*, *123*.
11. Klen, E. E.; Makarova, N. N.; Khaliullin, F. A.; Alekhin, E. K.; Nikitina, I. L.; Ivanova, O. A.; Gabidullin, R. A. *Bashkir. khim. zhurn.* **2008**, *15*, 112.
12. Klen, E. E.; Nikitina, I. L.; Ivanova, O. A.; Makarova, N. N.; Khaliullin, F. A. *Vopr. Biol. Med. Farm. Khimii* **2017**, *20*, 4.
13. Nikitina, I. L.; Gabidullin, R. A.; Klen, E. E.; Tyurina, L. A.; Alekhin, E. K.; Khaliullin, F. A. *Pharm. Chem. J.* **2012**, *46*, 213.
14. Klen, E. E.; Nikitina, I. L.; Gil'manova, A. G.; Miftakhova, A. F.; Ivanova, O. A.; Khaliullin, F. A.; Alekhin, E. K. RF patent No. 2459818 C1.
15. Gil'manova, A. G. *PhD (Pharm.) thesis*, Moscow, 2013. https://medical-diss.com/medicina/sintez-biologicheski-aktivnyh-tietansoderzhaschih-1-2-4-triazol-3-onov
16. Contreras, J.; Madariaga, S. *Bol. Soc. Chil. Quím.* **2000**, 45.
17. Dittmer, D. C.; Patwardhan, B. H.; Bartholomew, J. T. *Org. Magn. Reson*. **1982**, *18*, 82.
18. Voronkov, M. G.; Yarosh, N. O.; Zhilitskaya, L. V.; Shagun, L. G.; Dorofeev, I. A.; Larina, L. I. *Russ. J. Gen. Chem.* **2013**, *83*, 2340.
19. Khaliullin, F. A.; Klen, E. E. *Russ. J. Org. Chem*. **2009**, *45*, 135.
20. Khaliullin, F. A.; Klen, E. E.; Makarova, N. N. *Russ. J. Org. Chem*. **2018**, *54*, 1856.
21. Klen, E. E.; Khaliullin, F. A.; Iskhakova, G. F. *Russ. J. Org. Chem*. **2005**, *41*, 1847.
22. Klen, E. E.; Khaliullin, F. A; Makarova, N. N. *Russ. J. Org. Chem.* **2008**, *44*, 1708.
23. Decision of the EEU Council of November 3, 2016 No. 81 "On approval of the Rules of Good Laboratory Practice of the Eurasian Economic Union in the field of circulation of medicines (2020)".
24. European Convention for the protection of vertebrate animals used for experimental or other scientific purposes, ETS No. 123; Strasbourg, 1986.
25. Steru, L.; Chermat, R.; Thierry, B.; Simon, P. *Psychopharmacology* **1985**, *85*, 367.
26. Schetinin, E. V.; Baturin, V. A.; Arushanyan, E. B.; Ovanesov, K. B.; Popov, A. V. *Zhurnal vysshei nervnoi deyatel'nosti* **1989**, *39*, 958.
27. *Matematicheskaya statistika v eksperimental'noi i klinicheskoi farmakologii* (*Mathematical statistics in experimental and clinical pharmacology* [in Russian]); Khafiz'yanova, R. Kh.; Burykin, I. M.; Galeeva, G. N., Eds.; Kazan: Medicina, 2006, p. 374.