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Synthesis and pharmacological properties of 3-(2-methyl-furan-3-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones

Research article

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Abstract: By the reaction of 2-methyl-furan-3-carboxylic acid hydrazide with isothiocyanates, 1-[(2-methyl-furan-3-yl)carbonyl]-4-substituted thiosemicarbazides **1** were obtained. Further cyclization with 2% NaOH led to the formation of 3-(2-methyl-furan-3-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones **2**. The pharmacological effects of 2 on the central nervous system in mice were investigated. Strong antinociceptive properties of the investigated derivatives were observed in a wide range of doses.

Keywords: *Δ^2-1,2,4-triazoline-5-thione • CNS activity • DFT*

1. Introduction

1,2,4-Triazole and its derivatives constitute an important class of organic compounds with diverse biological activities, such as anticonvulsant, antidepressant, anti-inflammatory, antitumor, analgesic, antiviral, antibacterial and fungicidal [1-15]. Among the pharmacological profiles of 1,2,4-triazoles, their antimicrobial, anticonvulsant and antidepressant properties are best documented. Although limited, there are also examples of the antibacterial [16], antinociceptive, anti-inflammatory, and antioxidant properties [17,18] of furan derivatives. Therefore, we have considered it pharmacologically promising to obtain novel compounds containing the furan moiety at the position 3 of 4-substituted-1,2,4-triazoline-5-thiones, **2**. In particular, we examined their behavioral effects on mice in order to determine if they can be transported into the brain, and to highlight their anticonvulsant, antidepressant or antinociceptive potentials. In this contribution, results of synthesis, structural studies, and biological activity of three such compounds are presented.

2. Material and Methods

2.1. Synthesis

Melting points were determined in Fisher-Johns blocks and are presented without corrections. IR spectra (ν, cm^{-1}) were recorded in KBr using a Specord IR-75 spectrophotometer. ^1H and ^{13}C NMR spectra (δ, ppm) were recorded on a Bruker Avance 300 in DMSO-d_6 with TMS as internal standard. The mass spectra were obtained on a Finnigan Trace DSQ spectrometer

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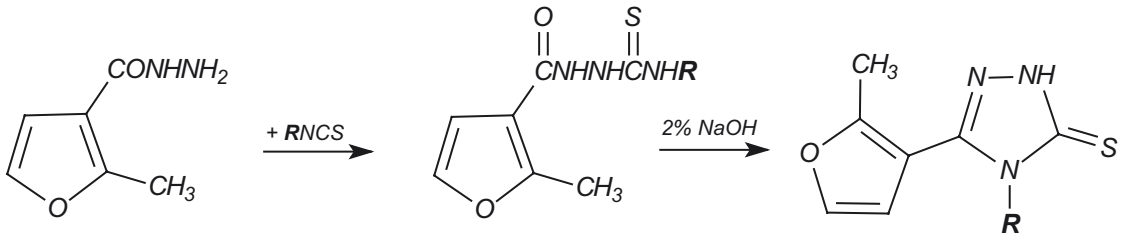


R = C_6H_5 (a), 2-$CH_3OC_6H_4$ (b), C_6H_{11} (c)

Scheme 1. Synthesis of the 1-[(2-methyl-furan-3-yl)carbonyl]-4-substituted thiosemicarbazides **1** and 3-(2-methyl-furan-3-yl)-4-substituted-Δ²-1,2,4-triazoline-5-thiones **2**.

operating at 70 eV. Chemicals were purchased from Merck Co. or Lancaster and used without further purification. The results of elemental analyses for C, H and N were within ±0.4% of the theoretical values. General synthetic route is outlined in Scheme 1.

Preparation of 1-[(2-methyl-furan-3-yl)carbonyl]-4-substituted thiosemicarbazides **1**

2-Methyl-furan-3-carboxylic acid hydrazide (0.01 mol) and appropriate isothiocyanate (0.01 mol) were heated in an oil bath at 80°C for 12 h. The formed product was washed first with diethyl ether, then with hot water. Subsequently it was dried and crystallized from ethanol.

1-[(2-methyl-furan-3-yl)carbonyl]-4-phenylthiosemicarbazide **1a**

Yield 95%, m.p. 183-185°C. IR (KBr): 3349 (NH), 3191, 1600 (Ar), 2964, 1450, 1355 (Aliph.), 1680 (C=O), 1527, 1355 (C=S), 1184 (C–O–C), 733 (1-subst. Ar) cm^{-1}. ^1H NMR (DMSO-d_6): 2.54 (s, 3H CH_3), 6.92-6.93 (d, 1H, ArH), 7.12-7.46 (m, 5H, ArH), 7.55-7.56 (d, 1H, ArH), 9.60, 9.76 10.05 (s, 3H, 3 NH) ppm. ^{13}C NMR (DMSO-d_6): 13.3 (CH_3), 109.5, 114.0, 124.9, 126.0, 128.0, 139.2, 140.6 (10C, ArC), 157 (C=S), 162.7 (C=O). MS m/z (%): [M^+] 275 (4), 140 (10), 109 (100), 93 (26), 77 (23.5), 65 (8), 51 (16.5), 43 (14). Anal. Calcd. $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.54; H, 5.08; N, 14.98.

4-(2-methoxyphenyl)-1-[(2-methyl-furan-3-yl)carbonyl]thiosemicarbazide **1b**

Yield 85%, m.p. 168-170°C. IR (KBr): 3257 (NH), 3149, 1603 (Ar), 2978, 1496, 1344 (Aliph.), 1681 (C=O), 1545, 1372 (C=S), 1187 (C–O–C), 728 (1,2-disubst. Ar) cm^{-1}. ^1H NMR (DMSO-d_6): 2.49 (s, 3H, CH_3), 4.72 (s, 3H, $\underline{CH_3}$OAr), 6.90 (d, 1H, ArH), 7.19-7.34 (m, 4H, ArH), 7.54-7.55 (d, 1H, ArH), 9.35, 9.45, 9.93 (3s, 3H, 3NH) ppm. ^{13}C NMR (DMSO-d_6): 13.3 (CH_3), 55.8 (OCH_3), 109.2, 113.7, 119.8, 120.6, 125.5, 125.8, 127.6, 127.8, 140.9 (10C, ArC), 151.7 (C=S), 162.7 (C=O). MS m/z (%): [M^+] 305 (5.5), 182 (6), 166 (7.5), 165 (40.5), 151 (9), 140 (14.5), 132 (9.5), 123 (30.5), 122 (21.5), 110 (7.5), 109 (100), 108 (21), 107 (4), 92 (4), 80 (10.5), 77 (6), 65 (6), 53 (11.5), 52 (12.5), 43 (22.5). Anal. Calcd. $C_{14}H_{15}N_3O_3S$: C, 55.07; H, 4.95; N, 13.76. Found: C, 55.21; H, 5.15; N, 13.96.

4-cyclohexyl-1-[(2-methyl-furan-3-yl)carbonyl]thiosemicarbazide **1c**

Yield 94%, m.p. 143-145°C. IR (KBr): 3366 (NH), 2932, 2855, 1496, 1361, 733 (Aliph.), 1680 (C=O), 1527, 1361 (C=S), 1185 (C–O–C). ^1H NMR (DMSO-d_6): 1.03-1.77 (m, 10H, 5×CH_2.), 2.51 (s, 3H, CH_3), 4.11 (s, 1H, CH), 6.89-6.90 (d, 1H, ArH), 7.54-7.55 (d, 1H, ArH), 7.64, 9.10, 9.78 (s, 3H, 3 NH) ppm. ^{13}C NMR (DMSO-d_6): 13.2 (CH_3), 24.9, 25.2, 31.8 (5C, Aliph.C), 52.9 (1C, Aliph.C), 109.4, 113.9, 140.6 (4C, ArC), 156.9 (C=S), 162.5 (C=O). MS m/z (%): [M^+] 281 (6.5), 157 (10), 140 (9), 126 (14), 109 (100), 98 (46), 83 (19), 81 (15.5), 67 (7.5), 56 (11), 55 (40.5), 53 (14.5), 43 (28), 41 (30), 39 (13). Anal. Calcd. $C_{13}H_{19}N_3O_2S$: C, 55.49; H, 6.81; N, 14,93. Found: C, 55.12; H, 6,51; N 15,09.

Preparation of 3-(2-methyl-furan-3-yl)-4-substituted-Δ²-1,2,4-triazoline-5-thiones **2**

The thiosemicarbazide derivative **1** (0.01 mol) was dissolved in 2% NaOH (10 mL) and refluxed for 2 h. The reaction mixture was cooled and acidified with 3M HCl, whereupon a solid separated out. The solid formed was filtered, dried and crystallized from ethanol.

4-phenyl-3-(2-methyl-furan-3-yl)-Δ²-1,2,4-triazoline-5-thione **2a**

Yield: 92%, m.p. 230-232°C. IR (KBr): 3106, 1563 (Ar), 3040, 1230 (C–O–C), 2936, 1457, 1380 (Aliph.), 1610 (C=N), 1499 (C–N), 696 (1-subst. Ar) cm^{-1}. ^1H NMR (DMSO-d_6): 2.38 (s, 3H, CH_3), 5.60-5.61 (d, 1H, ArH), 7.32-7.55 (m, 5H, ArH), 7.42-7.43 (d, 1H, ArH), 14.02 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): 12.9 (CH_3), 106.9, 109.4, 128.7, 129.3, 129.5, 134.3, 141.5, 153.5 (10C, ArC), 145.8 (C=N), 167.8 (C=S). MS m/z (%): [M^+] 257 (100), 256 (35), 240 (8.5), 228 (20), 184 (13), 182 (7.5), 169 (10.5), 150 (9), 149 (20), 128 (8), 121

(9.5), 115 (6), 107 (11), 106 (19), 104 (7.5), 91 (10), 85 (8), 78 (9), 77 (49.5), 69 (5.5), 65 (10.5), 52 (18.5), 51 (32), 50(8), 43 (20.5), 39 (10). Anal. Calcd. $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33. Found: C, 60.46; H, 4.14; N, 16.36.

4-(2-methoxyphenyl)-3-(2-methyl-furan-3-yl)-Δ²-1,2,4-triazoline-5-thione **2b**

Yield: 95%, m.p. 258-260°C. IR (KBr) 3433, 3080 (NH), 3047, 1566 (Ar), 2927, 2759, 1411, 1383 (Aliph.), 1626 (C=N), 1566 (C–N), 1228 (C–O–C), 747 (1,2-disubst. Ar) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 3.66 (s, 3H, $\underline{CH_3}OAr$), 5.64 (d, 1H, ArH), 7.07-7.37 (m, 3H, ArH), 7.42-7.43 (d, 1H, ArH), 7.45-7.55 (m, 1H, ArH), 13.96 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): 12.9 (CH_3), 55.8 (OCH_3), 106.9, 108.7, 112.8, 120.8, 122.7, 130.4, 131.5, 141.6, 153.3, 154.8 (10C, ArC), 146.2 (C=N), 168.1 (C=S). MS m/z (%): [M^+] 287 (53), 256 (24), 254 (100), 180 (5), 170 (11), 169 (5.5), 150 (10), 149 (53.5), 123 (9), 122 (17.5), 120 (28), 119 (9.5), 108 (22.5), 107 (31.5), 106 (36), 105 (30), 93 (11.5), 92 (19), 91 (20), 90 (10.5), 79 (24.5), 77 (46), 66 (12), 65 (27.5), 64 (27), 63 (25), 53 (19), 52 (54.5), 51 (59), 43 (48), 39 (29.5). Anal. Calcd. $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.66; H, 4.80; N, 14.33.

4-cyclohexyl-3-(2-methyl-furan-3-yl)-Δ²-1,2,4-triazoline-5-thione **2c**

Yield: 85%, m.p. 161-163°C. IR (KBr): 3031, 1258 (C–O–C), 2950, 2761, 1450, 1376, 746 (Aliph.), 1639 (C=N), 1498 (C–N). ^1H NMR (DMSO-d_6): 1.03-2.14 (m, 10H, 5×CH_2), 2.28 (s, 3H, CH_3), 4.28 (s, 1H, CH), 6.69 (d, 1H, ArH), 7.76 (d, 1H, ArH), 13.86 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6): 12.0 (CH_3), 24.6, 25.4, 29.2 (5C, Aliph.C), 56.5 (1C, Aliph.C), 107.2, 112.0, 142.1 (4C, ArC), 145.2 (C=N), 166.3 (C=S). MS m/z (%): [M^+] 263 (36), 182 (17), 181 (100), 152 (9.5), 108 (16), 106 (8.5), 81 (7), 79 (7.5), 67 (7.5), 55 (19.5), 53 (8), 43 (6.5), 41 (19), 39 (7.5). Anal. Calcd. $C_{13}H_{17}N_3OS$: C, 59.29; H, 6.51; N, 15.96. Found: C, 59.15; H, 6.25; N, 15.81.

2.2. Pharmacology

The experiments were carried out on male Albino Swiss mice (20-24 g) kept at room temperature of 18-20°C under natural day-night cycle with free access to food and water *ad libitum*. The permission for the animal tests and experiments has been given by the Ethical Board of the Medical University of Lublin. The investigated compounds were administered intraperitoneally (ip) as suspensions in 1% Tween 80 at the constant volume of 0.1 mL/10 g body weight of mice. The compounds were administered in doses equivalent to 0.1; 0.05; 0.025; 0.0125; 0.0062 or 0.00312 of LD_{50}. Control animals received the same volume of solvent. Each experimental group consisted of eight animals.

The screening of CNS activity in mice was performed in a series of tests described below. The rectal body temperature was measured with a thermometer (Ellab, Copenhagen) before the administration of compounds in the dose of 0.1 of their LD_{50} and 15, 30, 45, 60, 90 and 120 min afterwards. Mean values were obtained with uncertainties evaluated using the Student's t-test or the exact Fischer test.

Motor impairment was quantified with the "chimney test" [19]; 30 min after the administration of the investigated compounds mice had to climb up backwards in a plastic tube (3 cm inner diameter, 25 cm length). Mice unable to perform the task within 60 seconds were considered to display motor impairment. Motor impairment was quantified as the percentage of animals that failed to complete the test.

Anxiolityc activity was assessed by the "four plate" test in mice according to Aron *et al.* [20]; 30 min after the injection. The number of punished crossings was counted for 1 min.

Antidepressive properties were assessed by the "forced swimming" test according to Porsolt *et al.* [21]; 30 min after the administration of the tested compound mice were individually placed and forced to swim in a glass cylinder (27×16 cm) containing 15 mL of water (25°C). A mouse was considered immobile when it floated in the water, in an upright position, and made only small movements to keep its head above water. The total immobility time of mice was measured during the last 4 min of the 6-min test.

Thiopentanal-induced sleep. Thiopental (60 mg/kg ip) was given 30 min after the administration of compounds in doses varying from 0.025 to 0.1 of their LD_{50}. The sleeping time of mice (from disappearance to return of the righting reflex) was measured.

Pain reactivity was measured by the "writhing syndrome" test [22]. The test was performed by the ip injection of a 0.6% solution of acetic acid 30 min after the administration of compounds in doses varying from 0.0031 to 0.1 of their LD_{50}. The number of writhing episodes was counted for 30 min after the injection of acetic acid.

Pentetrazole-induced seizures. Pentetrazol (115 mg/kg sc) was administered 30 min after the injection of investigated compounds in the doses of 0.05 or 0.1 of their LD_{50}. The mice were placed singly in plexiglass cages (25×15×10 cm) and were observed for 30 min. The clonic and tonic seizures, as well as mortality, were recorded in this period.

L-5-hydrotryptophan-induced head-twitches. Head-twitches responses were measured according to Corn *et al.* [23]; L-5-hydrotryptophan, L-5HTP,

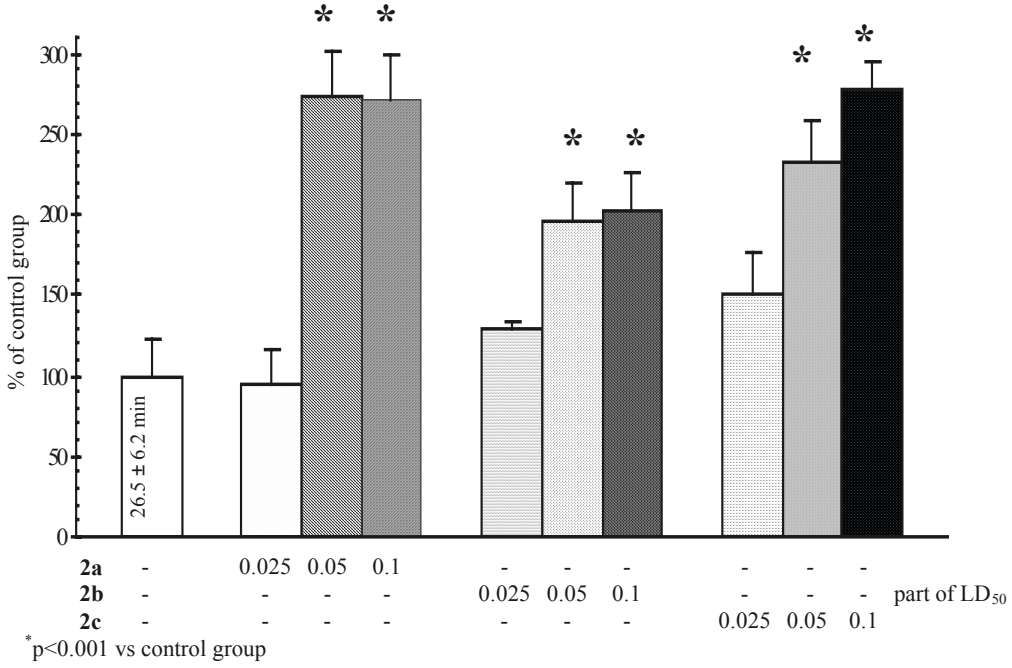


Figure 1. The effects of compounds **2** on the duration of thiopental-induced sleep in mice.

(190 mg/kg ip) was administered 30 min after the investigated compound. The number of head twitch episodes was observed during 60 min after the L-5HTP administration.

2.3. Computational methods

All calculations were carried out at the DFT level using the hybrid B3PW91 functional [24-26] and the 6-31G(d) basis set [27,28] as implemented in Gaussian [29]. Molecular geometries were fully optimized in the gas phase. Vibrational analysis has been carried out to confirm identity of the stationary points (3n-6 real vibrations). The default PCM implicit solvent model [30] with parameters corresponding to water was used. Partial atomic charges were obtained using CHELPG electrostatic fitting method [31]. Electrostatic mapping on the density surface was performed using GaussView program [32] with default settings. QSAR module of HyperChem [33] was used in calculations of logP values.

3. Results and discussion

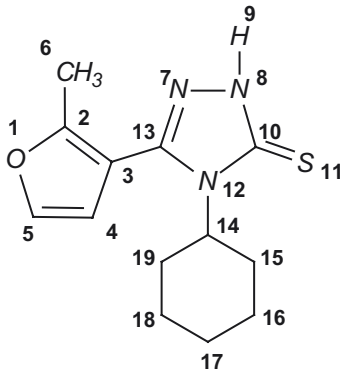
Three new 3-(2-methyl-furan-3-yl)-1,2,4-triazoles, **2**, with different substituents at the 4- position were synthesized. The synthesis showed an excellent averge yield of over 90% in the final step and about 83% in the overall procedure, making these compounds readily available. All synthesized compounds were characterized by IR and NMR spectra and by elemental analysis. Simultaneous presence of furan and triazole rings seemed pharmacologically promising. These expectations were confirmed by the series of performed biotests. Values of logP evaluated for **2** are 2.70, 2.45 and 2.16, respectively, indicating that these compounds should have good CNS accessibility.

Pharmacological results have shown the influence of **2** on the central nervous system (CNS) in mice.

Table 1. Antinociceptive activity of investigated compounds in mice.[a]

Compound	Treatment mg/kg i.p.	Part of LD_{50}	Inhibition (%)
Control	–	–	0
2a	2.5	0.00312	7.1
	5.0	0.0062	33.8[b]
	10.0	0.0125	22.8[b]
	20.0	0.025	39.5[b]
	40.0	0.05	41.8[b]
	80.0	0.1	85.2[b]
2b	10.0	0.0125	0
	20.0	0.025	44.6[b]
	40.0	0.05	50.0[b]
	80.0	0.1	58,6[b]
2c	6.25	0.0062	11.9
	12.5	0.0125	30.2[b]
	25.0	0.025	39.2[b]
	50.0	0.05	56.3[b]
	100.0	0.1	74.0[b]

[a] *% of inhibition obtained by comparison with control groups, mean writhing number in the control group 25.6 ± 1.8*
[b] *$p < 0.001$ vs. the control group*



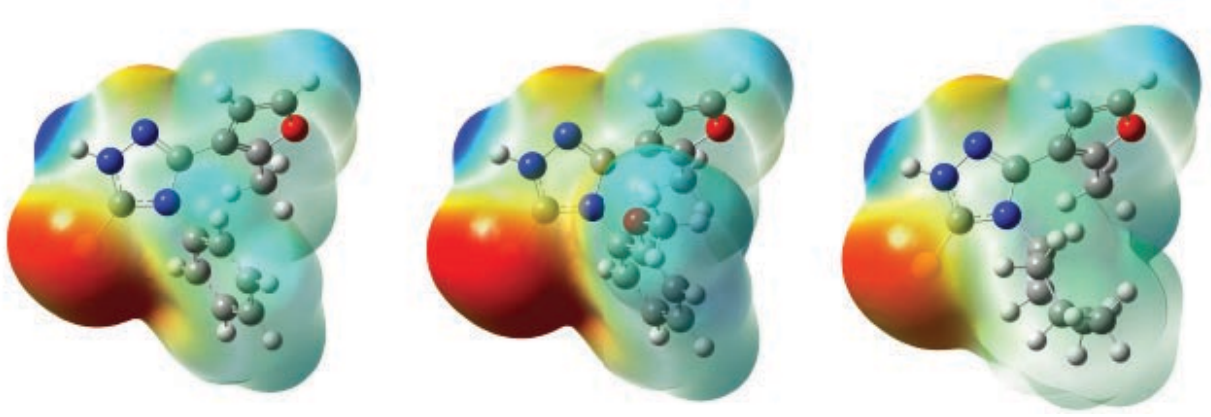
Scheme 2. General structure of **2** with a atom numbering.

None of the compounds was found to show neurotoxic activity because in the dose of 0.1 LD_{50} they did not affect the motor coordination of mice in the "chimney test". Compounds **2** in the doses of 0.05 and 0.1 of LD_{50} significantly prolonged the time of sleep induced by thiopental, Fig. 1. Of the three examined compounds, only **2b** in the dose of 0.1 of LD_{50} decreased (by about 25% vs. the control group) the tonic pentetrazole-induced seizures as well as mortality of mice. All the investigated compounds showed only weak antidepressive action; they were active only in the dose of 0.1 of LD_{50}. The results presented in Table 1 indicate antinociceptive effects of **2**. A significant decrease in the number of writhing episodes was observed in a wide range of doses. In the remaining tests all the new derivatives were inactive.

Different biological activity of closely related compounds is, not surprisingly, a result of high enzymes specificity. It does, however, pose significant problems in drug design; the rational methods are therefore still in the process of development and an old fashion "spray-and-pray" approach is not going to be given up really soon. None-the-less a SAR approach, from the phenomenological side, and computer modeling, from the theoretical one, allow us to rationalize observed bioactivities and provide background for rational synthesis of molecules with expected bioactivity. In particular, on the basis of isotope effects and computational modeling, Schramm and coworkers showed [34,35] that for enzymatic reactions the electrostatic interactions between the transition state and the active site fine-tune the enzyme reactivity. Similarly, electron density has been recently correlated [36] with the binding affinity of tetrazoles to the $P2X_7$ receptor that plays a role in CNS. Thus electrostatic properties might be indicative of a match between the receptor site and the particular molecule. Other parameters such as the presence of an aromatic ring with a coplanar proton accepting group, an auxiliary out-of-plane aromatic ring [37], and the molecular volume [38] have been found to correlate with binding of triazole compounds to various receptors. In the lieu of information on the target of interactions of the studied

Table 2. Selected geometric parameters (Å, °) of molecules **2** at B3PW91/6-31G(d).

	2a	2b	2c
bond distances			
01-C2	1.357	1.357	1.356
C2-C6	1.484	1.484	1.484
C2-C3	1.373	1.373	1.373
C3-C4	1.439	1.439	1.439
C4-C5	1.355	1.355	1.355
C5-O1	1.365	1.366	1.365
C3-C13	1.457	1.457	1.462
C13-N7	1.309	1.308	1.309
N7-N8	1.356	1.358	1.353
N8-H9	1.027	1.027	1.027
N8-C10	1.346	1.346	1.347
C10-S11	1.687	1.687	1.694
C10-N12	1.381	1.380	1.376
N12-C13	1.389	1.388	1.387
N12-C14	1.432		
valence angles			
O1-C2-C3	109.0	109.0	109.2
C2-C3-C4	106.7	106.7	106.6
C3-C4-C5	105.9	105.7	105.9
C4-C5-O1	110.2	110.2	110.2
C5-O1-C2	108.2	108.1	108.1
C13-N7-N8	104.5	104.4	104.1
N7-N8-C10	114.3	114.3	114.3
N8-C10-N12	102.9	102.9	103.3
C10-N12-C13	107.8	107.9	107.4
N12-C13-N7	110.5	110.5	110.9
dihedral angles			
C6-C2-C3-C13	1.2	1.2	0.3
C2-C3-C13-N7	125.0	125.0	116.4
C14-N12-C13-N7	174.2	171.9	174.4
C15-C14-N12-C13	118.9	113.0	121.3
ring flatness			
furan (F)	0.0 ± 0.5	0.0 ± 0.5	0.0
triazole (T)	0.0 ± 0.1	0.0 ± 0.4	0.002 ± 0.006
phenyl (P)	0.0 ± 0.4	0.0 ± 1.0	-
angles between rings			
T - P	65	74	-
T - F	52	55	64
F - P	63	67	-



2a 2b 2c

Figure 2. CHELPG electrostatic potential of compounds **2** mapped on the electron density surfaces.

compounds we have compared their electrostatic and geometrical properties in hope of gaining some more insight into their bioactivity.

Structures of molecules **2** were optimized at the DFT level in the gas phase and in water using continuum solvent model. No significant differences between geometries obtained in both phases were observed. Selected geometrical parameters are collected in Table 2. Atom numbering is provided in Scheme 2. Flatness of the rings was calculated as the average of the five (furan, triazole) or six (phenyl) dihedral angles, in which each bond of the rings defined the ledge of the angle. As can be seen, the geometries do not differ substantially. Also the volumes and surface areas of all three compounds are very similar excluding possibility that differentiation of the biological activity originates in the molecular shape.

Dipoles moments for **2** are 5.0, 5.9 and 4.9 D, respectively. These values show that electrostatic distribution in **2b** differs from that in the other two molecules. These differences are illustrated graphically in Fig. 2, in which electrostatic potential has been mapped onto the electron density surface. Color coding of this figure indicates electron rich space with red and electron deficient space with blue. Color intensity corresponds to the magnitude of partial charge in a given volume. Comparison of these three surfaces confirms higher polarity of **2b** and indicates that the major difference is in the vicinity of the sulfur atom. This might imply that the triazole moiety plays dominant role in the biological activity of these molecules.

4. Conclusion

Pharmacological activity of new 1,2,4-triazoles **2**, synthesized from thiosemicarbazide derivatives **1**, was studied. All three compounds showed weak antidepressive but strong antinociceptive properties in a wide range of doses. Furthermore, 2-methoxyphenyl derivative, **2b**, exhibits anticonvulsant activity. Enhanced bioactivity of this compound coincides with its largest polarization of the triazole ring. Low logP value makes it a promising candidate for further pharmacological testing.

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