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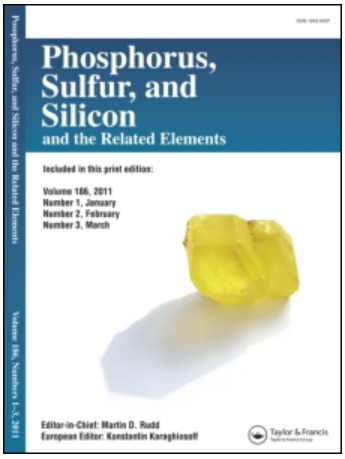

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Chemical and Pharmacological Properties of 3-(Thiophen-2-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones

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Three 3-(thiophen-2-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones were synthesized by intramolecular cyclization of 1-(thiophen-2-ylcarbonyl)-4-substituted thiosemicarbazides in alkaline medium. Their effects on the central nervous system (CNS) of mice in some behavioral tests were investigated. All investigated compounds displayed antinociceptive activity. The correlation between the structural features and bioactivity has been discussed.

Keywords Δ^2-1,2,4-Triazoline-5-thione; CHELPG; CNS-activity; DFT

INTRODUCTION

Organic compounds containing five-membered aromatic heterocyclic rings are widely distributed in nature and often play an important role in various biochemical processes. Thiophene and 1,2,4-triazole derivatives belong to aromatic heterocyclic group, which constitutes an important structural fragment in many pharmaceutical and chemical compounds. Thiophene and 1,2,4-triazole compounds have been found to show nematocidal, insecticidal, antifungal, antiviral, antibacterial, antitumor activity.[1]Apart from wide practical applications of these compounds,[2] they exhibit also interesting chemistry, including unresolved problem thiol-thione equilibrium.[3] We have recently examined a series of three 3-(2-methylfuran-3-yl)-1,2,4-triazoles with different

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substituents at the N4 atom.[4] Studies of antinociceptive and antidepressive activity indicated that the best effects were obtained with phenyl substituent while the weakest influence was observed for 2-methoxy-phenyl substituent at N4. In the literature, the influence of an aromatic ring conjugated with the triazole ring has been analyzed, and it has been postulated that the relative positions of these rings plays a role in the strength of biological activity—the strongest effect has been postulated for the rings being positioned perpendicularly. In an attempt to further explore this suggestion, herein, we present studies of a series of three compounds with the same substituents at N4 as reported earlier but with thiophen rather than 4-methylfuran as the second substituent.

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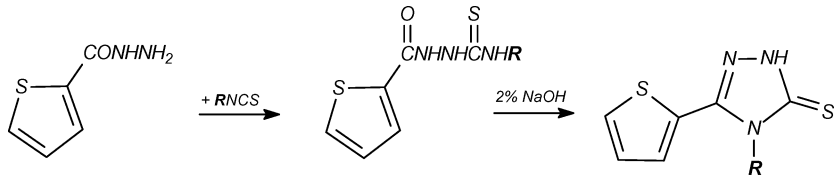
RESULTS AND DISCUSSION

Chemistry

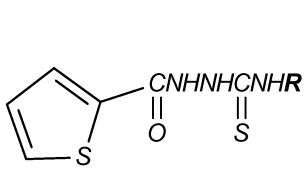
The synthesis of the title compounds **2a**–**2c** is illustrated in Scheme 1. The preparation of the intermediate thiosemicarbazides **1a**–**1c** was carried out with the reaction of thiophen-2-carboxylic acid hydrazide with isothiocyanates. The 1-(thiophen-2-ylcarbonyl)-4-substituted tiosemicarbazides **1a**–**1c**, when subjected to reaction with 2% NaOH, underwent intramolecular cyclization to furnish the corresponding 3-(thiophen-2-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones **2a**–**2c**. The structures of all compounds were confirmed by the results of elemental analysis as well as by IR and ^{1}H NMR. The characterization data and the spectral data of original compounds, **1a**–**1c**, **2b** and **2c**, are presented in Table I and Table II, respectively. Characterization data of noted compound **2a** were reported previously.[4]

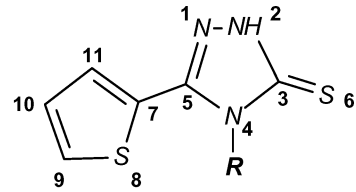


R = C_6H_5 (a), 2-$CH_3OC_6H_4$ (b), C_6H_{11} (c)

SCHEME 1 Synthesis of the 1-(thiophen-2-ylcarbonyl)-4-substituted thiosemicarbazides **1a**–**1c** and 3-(thiophen-2-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones **2a**–**2c.**

TABLE I Characterization Data of Compounds 1a–1c and 2b, 2c





1a-1c **2a-2c**

Compound no.	R	Yield %	M.p. °C	% Carbonyl Found	% Carbonyl Calcd.	% Hydrogen Found	% Hydrogen Calcd.	% Nitrogen Found	% Nitrogen Calcd.
1a	C_6H_5	91	198–200	52.02	51.96	4.25	4.00	14.89	15.15
1b	2-$OCH_3C_6H_4$	89	167–169	50.45	50.79	4.12	4.26	13.98	13.67
1c	C_6H_{11}	93	198–200	50.88	50.85	6.17	6.05	14.52	14.83
2b	2-$OCH_3C_6H_4$	87	253–255	53.87	53.96	3.64	3.83	14.78	14.52
2c	C_6H_{11}	89	162–164	54.36	54.31	5.89	5.70	15.78	15.83

TABLE II Spectral Data of Compounds 1a–1c and 2b, 2c

Compound no.	
1a	IR(KBr, ν in cm^{-1}): 3319 (–NH), 3101, 1498 (ArH), 1661 (–C=O), 1240 (–C=S), 756 (C–S–C); ^{1}H-NMR: δ 7.13–7.46 (m, 6H, thiophene 1H & 5ArH), 7.84–7.88 (m, 2H, thiophene H), 9.72, 9.88, 10.56 (3s, 3H, 3NH, D_2O exchangeable).
1b	IR(KBr, ν in cm^{-1}): 3550 (–NH), 3030, 1497 (ArH), 2835, 1466, 1436 (–OCH_3), 1670 (–C=O), 1243 (–C=S), 808 (C–S–C); ^{1}H-NMR: δ 3.75 (s, 3H, OCH_3), 6.93–7.90 (m, 7H, thiophene 3H & 4ArH), 9.26, 9.82, 10.64 (3s, 3H, 3NH, D_2O exchangeable).
1c	IR(KBr, ν in cm^{-1}): 3313 (–NH), 2933, 2855, 1447, 721 (Aliph.), 1642 (–C=O), 1549, 1255 (–C=S), 747 (C–S–C); ^{1}H-NMR: δ 1.03–1.77 (m, 10H, cyclohexane H), 4.13 (s, 1H, cyclohexane H), 7.17–7.20 ($t_{(J=4.3)}$, 1H, thiophene H), 7.83–7.85 (m, 2H, thiophene H), 7.70, 9.21, 10.27 (3s, 3H, 3NH, D_2O exchangeable).
2b	IR(KBr, ν in cm^{-1}): 3398 (–NH), 3071, 1600 (ArH), 2834, 1466 (–CH_3), 1577 (–C=N), 1259 (–C=S), 794 (C–S–C); ^{1}H-NMR: δ 3.67 (s, 3H, OCH_3), 6.83–6.85 ($dd_{(J=1.2,3.8)}$, 1H, thiophene H), 6.99–7.02 ($dd_{(J=3.8,5.1)}$, 1H, thiophene H), 7.13–7.18 (m, 1H, ArH),), 7.25–7.29 ($dd_{(J=1.0,8.4)}$, 1H, ArH), 7.40–7.43 ($dd_{(J=1.8,7.8)}$, 1H, ArH), 7.56–7.62 (m, 1H, ArH), 7.66–7.68 ($dd_{(J=1.2,5.1)}$, 1H, thiophene H), 14.06 (s, 1H, NH, D_2O exchangeable).
2c	IR(KBr, ν in cm^{-1}): 3313 (–NH), 2933, 2855, (Aliph.), 1577 (–C=N), 1270 (–C=S), 791 (C–S–C); ^{1}H-NMR: δ 1.08–1.80 (m, 10H, cyclohexane H), 4.14 (s, 1H, cyclohexane H), 7.17–7.22 ($t_{(J=4.3)}$, 1H, thiophene H),), 7.80-7.86 (m, 2H, thiophene H), 14.30 (s, 1H, NH, D_2O exchangeable).

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Pharmacological Part

Preliminary behavioral study showed that 3-(thiophen-2-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones **2a**–**2c** prolonged the thiopental sleeping time. In the test of pentetrazole seizures compounds **2a** and **2c** showed weak antiepileptic action; they were active only in the dose of 0.1 their LD_{50}. Compounds **2a**–**2c** displayed significantly antinociceptive effect in the "writhing syndrome" test. Compound **2b** produced strong antinociceptive properties in a wide range of doses. Of the three examined compounds, only **2b** produced weak antidepressive and antiserotoninergic activity in mice. In the remaining tests all compounds were inactive.

Computational

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Structures of molecules **2a**–**2c** 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 III. Atom numbering is provided in Table I. Flatness of the rings was calculated as the average of the five (thiophene, triazole) or six (phenyl, 2-methoxyphenyl) dihedral angles, in which each bond of the rings defined the ledge of the angle. Several parameters that are frequently used in QSAR studies on pharmacologically active compounds are collected in Table IV. As can be seen, the volumes and surface areas of all three compounds are similar, excluding the possibility that differentiation of the biological activity originates in the molecular shape. The major differences are geometries, in particular the angle between triazole and thiophene rings.

Dipoles moments for **2a**–**2c** are substantially higher than when 2-methylfuran instead of thiophene is connected with the triazole ring. However, they are in the same order, with the dipole moment of **2b** being the largest indicating that the electrostatic distribution in **2b** differs from that in the other two molecules. These differences are illustrated graphically in Figure 1, 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 supports our previous conclusion that the triazole moiety plays dominant role in the biological activity of these molecules. It is worth noticing that these differences are not apparent

TABLE III Selected Geometric Parameters (Å, °) of Molecules 2a–2c at B3PW91/6-31G(d)

	2a	**2b**	**2c**
Bond distances			
N1-N2	1.355	1.355	1.352
N2-C3	1.345	1.344	1.348
C3-N4	1.380	1.381	1.376
N4-C5	1.386	1.386	1.386
C5-N1	—	1.313	—
C5-C7	1.450	1.450	1.458
C7-S8	1.742	1.742	1.744
S8-C9	1.722	1.722	1.722
C9-C10	1.370	1.370	1.369
C10-C11	1.418	1.417	1.422
C11-C7	1.379	1.380	1.375
N4-C(**R**)	1.433	1.427	1.476
C3-S6	1.687	1.686	1.693
Valence angles			
N1-N2-C3	114.3	114.3	114.3
N2-C3-S6	128.1	128.1	125.7
C3-N4-C(**R**)	124.6	124.3	127.3
N4-C5-C7	127.1	127.3	126.5
C7-S8-C9	91.5	91.6	91.6
Dihedral angles			
N1-C5-C7-S8	155.9	174.6	120.5
Ring flatness			
Thiophene	0.0 ± 0.1	0.00 ± 0.03	0.0 ± 0.8
Triazole	0.0 ± 0.7	0.0 ± 0.4	0.0 ± 0.9
R	0.0 ± 0.4	0.0 ± 0.5	—
Angles between rings			
Triazole - **R**	82.3	87.6	—
Triazole - thiophene	24.0	5.4	59.5

TABLE IV Selected Properties of Molecules 2a–2c

	2a	**2b**	**2c**
Dipole moment [D]	8.0	8.5	7.9
logP	2.68	2.43	2.58
Volume [Å^3]	709	778	747
Surface area [Å^2]	435	468	450
Hydration energy [kJ/mol]	−60.0	−44.2	−35.7
Partial atomic charges			
S6	−0.45	−0.45	−0.44
S8	0.33	0.33	0.32
H(N2)	0.46	0.46	0.46

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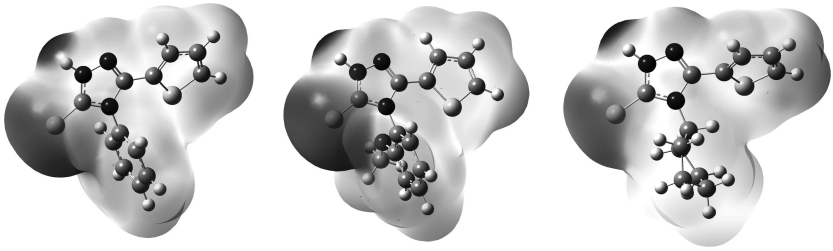

FIGURE 1 CHELPG electrostatic potential of compounds **2a**–**2c** (from left to right) mapped on the electron density surfaces.

from the Mulliken partial charge analysis (see last 3 entries in Table IV), indicating that the partial charges are frequently confusing and not very informative.

In conclusion, we have found that CNS effects of investigated derivatives **2a**–**2c** are weak and only their antinociceptive properties could be worth examining in more detail. Although at present the number of biologically active compounds that we have characterized is too small to launch full statistical analysis, our previous results[5] obtained for an analogous series of compounds seem to indicate that their bioactivity is correlated with the charge distribution of the triazole ring. On the other hand, we did not find a correlation with the conformation of the auxiliary aromatic ring(s).

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EXPERIMENTAL

Chemistry

Melting points were determined in a Fischer–Johns block and are uncorrected. IR spectra (ν, cm^{-1}) were recorded in KBr using a Specord IR-75 spectrophotometer. ^1H NMR spectra (δ, ppm) were recorded on a Bruker Avance 300 in DMSO-d_6 with TMS as internal standard.

1-(Thiophen-2-ylcarbonyl)-4-substituted Thiosemicarbazides 1a–1c

The thiophene-2-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 with diethyl ether, next with hot water, dried, and crystallized from ethanol.

3-(Thiophen-2-yl)-4-substituted-Δ^2-1,2,4-triazoline-5-thiones 2a–2c

The thiosemicarbazide derivative **1a**–**1c** (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.

Pharmacology

The study was carried on Albino Swiss male mice (23–25 g). Compounds **2a**–**2c** were administered intraperitoneally (ip) as a suspensions in a 1% solution of Tween 80. Control animals received the same volumes (0.1 cm^3/10 g to mice of the solvent). In all experiments compounds were used in doses starting from 0.1 LD_{50} and decreasing gradually until there were no further pharmacological activity. Each experimental group consisted of 10 animals. This work has been approved by the Ethics Committee of Medical University in Lublin.

The screening of CNS activity in mice was performed 30 min after the administration of the derivatives in the tests described below. The results obtained were presented as means and evaluated statistically using Student's *t*-test or the exact Fischer test.

Motor coordination was quantified with the "chimney test."[6] The rectal body temperature was measured by Ellab thermometer. Anxiolytic properties were assessed by the "four plate" test.[7] Antidepressive activity was measured by the "forced swimming" test.[8] The thiopental (60 mg/kg ip) sleeping time of mice (from disappearance to return of the righting reflex) was measured. Pain reactivity was measured in mice by the "writhing syndrome" test.[9] Antiepileptic activity was observed in the pentetrazole (90 mg/kg sc)-induced seizures. Antiserotoninergic effects were measured according to Corn et al.[10]

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Computational Methods

All calculations were carried out at the DFT level using the hybrid B3PW91 functional[11] and the 6-31G(d) basis set[12] as implemented in Gaussian.[13] 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[14] with parameters corresponding to water was used. Partial atomic charges were obtained using CHELPG electrostatic fitting method.[15] Electrostatic mapping on the density surface was performed using GaussView program[16] with default settings. QSAR module of HyperChem[17] was used in calculations of logP values.

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