ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2010, *55*(11-12), 831-841

Dedicated to the memory of
Professor Ioan Silaghi-Dumitrescu (1950 – 2009)

HETEROCYCLES 22. SYNTHESIS, CHARACTERIZATION AND EVALUATION OF ANTIMICROBIAL POTENTIAL OF SOME NEW SULFONYLHYDRAZINO-THIAZOLES

Valentin ZAHARIA,[a*] Manuela CURTICAPEAN,[b] Nicolae PALIBRODA,[c] Mircea VLASSA[d] and Anca SILVESTRU[d]

[a] Faculty of Pharmacy, "Iuliu Hatieganu" University of Medicine and Pharmacy, RO-400012, Cluj-Napoca, Roumania.
Fax: 0040 264 597257; Tel: 0040 264 594148; E-mail: vzaharia@umfcluj.ro
[b] University of Medicine and Pharmacy Targu-Mures, RO-540139, Targu Mures, Roumania.
Fax: 0040 265 210407; Tel: 0040 265 215551
[c] National Institute for Isotopic and Moleculat Technologies, RO-400293, Cluj-Napoca, Roumania.
Fax: 0040 264 420042; Tel: 0040 264 584037
[d] Faculty of Chemistry & Chemical Engineering, "Babes-Bolyai" University, RO-400028, Cluj-Napoca, Roumania.
Fax: 0040 264 590818; Tel: 0040 264 593833; E-mail: ancas@chem.ubbcluj.ro

Received March 29, 2010

Sulfonylhydrazinothiazoles **3a**-**e** were obtained by condensation reactions between the benzenesulfonylthiosemicarbazide **1** with the corresponding α-halogenocarbonyls **2**, while derivatives **5a**-**c** were obtained by bromination of sulfonylhydrazinothiazles **3a**-**c**. The acetyl derivatives **4** and **6** were obtained by acylation reactions with acetic anhydride. All compounds were structurally characterized by IR and NMR spectroscopy, as well as by mass spectrometry. For two derivatives (**3d** and **4d**) the molecular structures were determined by single-crystal X-ray diffraction. A moderate antimicrobial activity was found towards different bacteria (*Bacillus subtilis – I*, *Staphylococcus aureus – II*, *Citrobacter – III*, *Escherichia coli – IV*, *Klebsiella pneumoniae – V*, *Yersinia – VI)* and fungus (*Candida albicans – VII*). The best results were observed against *Candida albicans*.

INTRODUCTION

In previous papers we described the synthesis and evaluation of antimicrobial potential of some hydrazinothiazoles,[1,2] as well as the synthesis and characterization of some aroyl-hydrazinothiazoles which were used as intermediates in preparation of some thiazolo[2,3-c][1,2,4]triazoles.[3,4] B.S. Holla and coworkers reported the synthesis of some arylidene-hydrazinothiazoles and of 2-furanylidene-hydrazinothiazoles with antimicrobial and anti-inflammatory potential,[5] while K. Bhat and B. Holla have used acyl-thiosemicarbazides in preparation of some thiazolo[2,3-c][1,2,4]triazoles.[6] There was also reported data on MAOI activity of thiosemicarbazides and of hydrazinothioles,[7] on antithrombotic action of some aryl-sulfonylthiosemicarbazides,[8] as well as on MAOI[9] and antineoplazic action of sulfonylhydrazines.[10,11]

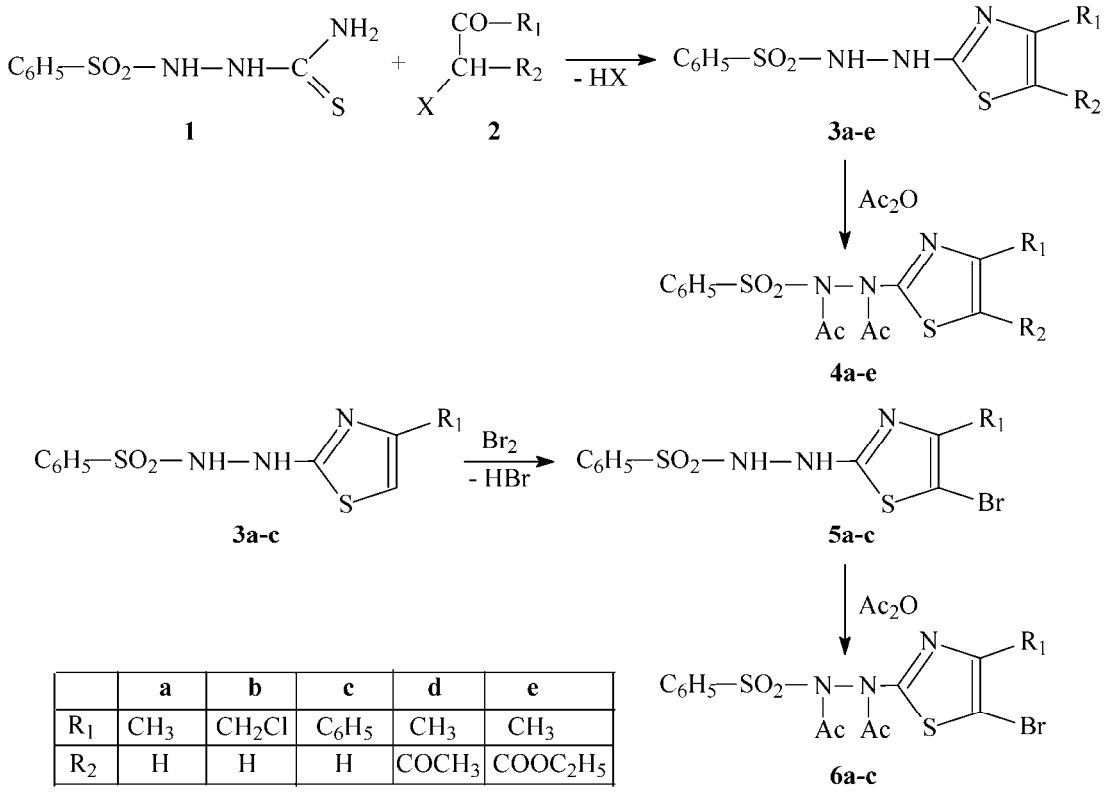
Taking into consideration the biological potential of the sulfonylhydrazine moiety as well as of hydrazinothiazoles, we describe here the preparation of some benzene-sulfonylhydrazinothiazoles, compounds which present both structural elements in the same molecule, as well as evaluation data of the antimicrobial activity of these compounds.

RESULTS

The benzenesulfonyl-hydrazinothiazoles **3a** – **3e** were prepared by condensation of

* Corresponding author: vzaharia@umfcluj.ro

benzenesulfonyl-thiosemicarbazide with a series of α-halogenocarbonyles, *i.e.* monochloroacetone (**3a**), 1,3-dichloroacetone (**3b**), α-bromoacetophenone (**3c**), 3-chloro-acetylacetone (**3d**) and ethyl α-bromoacetoacetate (**3e**), respectively. The reactions were performed at room temperature, in acetone as solvent, when the corresponding halohydrates were isolated. The free bases were obtained by neutralization of the aqueous suspensions of halohydrates with $NaHCO_3$. Compounds **5a – 5c** were obtained by bromination of the corresponding unsubstituted in position 5 thiazoles (**3a – 3c**), in acetic acid. By treating the compounds **3** and **5** with acetic anhydride, at room temperature in presence of pyridine or at higher temperature, the diacetyl derivatives **4** and **6** were obtained (Scheme 1).



	a	b	c	d	e
R_1	CH_3	CH_2Cl	C_6H_5	CH_3	CH_3
R_2	H	H	H	$COCH_3$	$COOC_2H_5$

Scheme 1

The new compounds were investigated by elemental analysis, IR and NMR (^1H and ^{13}C) spectroscopy, as well as by mass spectrometry, confirming their identity. Some analytical data of the title compounds are given in Table 1.

Table 1

Analytical data of benzene-sulfonylhydrazinothiazoles **3 - 6**

Compound	M.p. (°C)	Yield (%)	Colour	Molecular formula	Elemental analysis [%]
					C; H; N; S Calculated / Found
3a	187-189	68	beige	$C_{10}H_{11}N_3S_2O_2$	44.59; 4.12; 15.60; 23.81 44.54; 4.97; 15.29; 24.36
3b	163-165	60	beige	$C_{10}H_{11}N_3S_2O_2Cl$	39.54; 3.65; 13.83; 21.11 39.29; 3.00; 13.52; 21.84
3c	169-170	75	beige	$C_{15}H_{13}N_3S_2O_2$	54.36; 3.95; 12.68; 19.35 53.84; 3.83; 12.16; 19.21
3d	215	60	colorless	$C_{12}H_{13}N_3O_3S_2$	46.29; 4.21; 12.68; 19.35 45.88; 3.77; 12.83; 18.90
3e	195-196	55	beige	$C_{13}H_{15}N_3S_2O_4$	45.73; 4.43; 12.31; 18.78 45.13; 4.16; 12.04; 19.14

Table 1 (continued)

4a	152-153	75	colorless	$C_{14}H_{15}N_3S_2O_4$	47.58; 4.24; 11.89; 18.14 47.13; 4.20; 11.73; 18.48
4b	128-131	75	colorless	$C_{14}H_{14}N_3S_2O_4Cl$	43.35; 3.64; 10.83; 16.53 42.90; 3.45; 10.36; 16.08
4c	158-160	78	pink	$C_{19}H_{17}N_3S_2O_4$	54.92; 4.12; 10.11; 15.43 54.63; 4.51; 10.02; 15.61
4d	157-158	65	colorless	$C_{16}H_{17}N_3O_5S_2$	48.59; 4.33; 10.63; 16.21 48.06; 3.90; 11.03; 16.65
4e	156-158	65	colorless	$C_{17}H_{19}N_3S_2O_6$	47.99; 4.50; 9.88; 15.07 47.70; 4.21; 9.68; 15.33
5a	108-110	35	beige	$C_{10}H_{10}N_3S_2O_2Br$	34.49; 2.89; 12.07; 18.41 34.68; 2.42; 12.15; 17.98
5b	132	25	colorless	$C_{14}H_{13}N_3S_2O_4BrCl$	36.02; 2.81; 9.00; 13.74 36.17; 2.30; 9.43; 13.88
5c	153-155	25	pink	$C_{15}H_{12}N_3S_2O_2Br$	43.91; 2.95; 10.24; 15.63 43.08; 2.58; 9.80; 16.53
6a	192-194	40	colorless	$C_{14}H_{14}N_3S_2O_4Br$	38.89; 3.26; 9.72; 14.83 38.56; 3.04; 9.35; 14.97
6b	191-192	28	colorless	$C_{14}H_{13}N_3S_2O_4BrCl$	36.02; 2.81; 9.00; 13.74 35.76; 2.22; 8.53; 14.10
6c	161-163	30	pink	$C_{19}H_{16}N_3S_2O_4Br$	46.16; 3.26; 8.50; 12.97 46.46; 2.85; 7.54; 12.49

In order to investigate the structural differences determined by acylation and to evaluate the corelation between the molecular structure and the biological activity of the title compounds, we determined the single-crystal X-ray structures of derivatives **3d** and **4d**. Single-crystals suitable for X-ray diffraction studies were obtained from an acetone solution (**3d**) or a chloroform / n-hexane mixture (**4d**).

The newly synthesized compounds were screened for their anti-microbial activity against Gram-positive strains (*Bacillus subtilis – I*, *Staphylococcus aureus – II*, *Citrobacter – III)*, Gram-negative strains (*Escherichia coli – IV*, *Klebsiella pneumoniae – V*, *Yersinia – VI)* and fungus (*Candida albicans – VII*) either by the disk diffusion method or by the dillution method in liquid medium. G Penicillin (for Gram-positive strains), Cloramfenicol (for Gram-negative strains) and Nistatin (for *Candida albicans*) were used as reference anti-microbial substances. The results, given in minimum inhibitory concentration, are presented in Tables 2 and 3.

Table 2

Antimicrobial activity against Gram-positive strains

Compound	Disk method			Dilution method		
	MIC(u.i.) for strains:			M C(u.i.) for strains:		
	I	II	III	I	II	III
G Penicillin	0.5	2.0	1.5	6.25	12.5	6.25
1	1.5	-	2.0	100.0	>100.0	100.0
3a	1.8	1.8	2.0	100.0	100.0	100.0
3b	1.8	-	1.8	100.0	>100.0	100.0
3c	1.5	-	2.0	100.0	>100.0	100.0
3d	1.8	1.8	1.8	100.0	50.0	50.0
3e	2.0	-	1.5	100.0	>100.0	25.0
4a	1.5	2.0	1.8	100.0	100.0	100.0
4b	1.5	1.8	1.5	50.0	50.0	25.0
4c	1.8	-	1.8	100.0	>100.0	100.0
4d	1.5	1.8	1.5	50.0	50.0	25.0
4e	1.8	-	1.8	100.0	>100.0	50.0
5a	1.5	2.0	0.5	>100.0	>100.0	25.0
5c	1.8	2.0	1.0	>100.0	>100.0	25.0
6a	1.0	1.8	0.5	50.0	100.0	12.5
6c	1.5	1.8	0.5	50.0	100.0	25.0

Table 3

Antimicrobial activity against Gram-negative strains and *Candida albicans*

Compound	Disk method				Dilution method			
	MIC (μg) for strains				MIC (μg) for strains			
	IV	V	VI	VII	IV	V	VI	VII
Cloramfenicol	5.0	25.0	5.0	-	0.6	0.6	0.6	-
Nistatin	-	-	-	5.0	-	-	-	0.6
1	25.0	25.0	25.0	25.0	10.0	10.0	5.0	10.0
3a	20.0	25.0	20.0	20.0	10.0	10.0	2.5	5.0
3b	20.0	>25.0	20.0	25.0	10.0	>10.0	10.0	10.0
3c	20.0	25.0	>25.0	20.0	10.0	10.0	>10.0	5.0
3d	20.0	25.0	20.0	5.0	10.0	10.0	10.0	1.25
3e	20.0	>25.0	>25.0	10.0	>10.0	>10.0	>10.0	1.25
4a	20.0	25.0	20.0	20.0	10.0	10.0	2.5	5.0
4b	10.0	>25.0	>25.0	15.0	5.0	>10.0	>10.0	2.5
4c	15.0	25.0	10.0	10.0	5.0	10.0	5.0	1.25
4d	10.0	25.0	15.0	25.0	2.5	10.0	5.0	10.0
4e	15.0	25.0	20.0	10.0	10.0	10.0	5.0	1.25
5a	20.0	25.0	20.0	15.0	>10.0	>10.0	10.0	10.0
5c	20.0	25.0	15.0	15.0	>10.0	>10.0	10.0	10.0
6a	10.0	25.0	5.0	5.0	10.0	>10.0	5.0	1.25
6c	5.0	20.0	5.0	5.0	5.0	>10.0	5.0	2.5

DISCUSSION

Spectroscopic characterization

The IR spectra for compounds **3** and **5** present characteristic valence vibration bands for the NH groups of the hydrazine moiety, in the range 3452-3218 cm^{-1}, which are not present in the IR spectra of the acetyl derivatives **4** and **6**. In the IR spectra of these acetyl derivatives are present two vibration bands characteristic for the amide carbonyl group, in the range 1740-1638 cm^{-1}, which proof that both nitrogen atoms from the hydrazine moiety were acetylated.

The mass spectra (EI) of these derivatives contain in most cases the molecular peak, but with a low intensity. The main fragmentation takes place to both sides of the sulfonyl group, between the hydrazine moiety and the thiazole ring, as well as at the level of the thiazole ring. The same fragmentation mode is preserved in case of the acetyl derivatives, where in addition a successive elimination of acetyl moieties from the molecule takes place.

The ^{1}H and ^{13}C NMR data are in agreement with the identity and structure of the synthesized compounds and they shown the expected resonances. Only for the acetylated derivative **6b** an AB spin system was observed for the CH_2 protons in the ^{1}H NMR spectrum. For the other derivatives containing CH_2Cl groups the rotation seems to be very fast in solution at the NMR time scale at room temperature and the non-equivalence of the CH_2 protons could not be observed. The N*H* resonances were not observed in all spectra, probably due to exchange with DMSO when DMSO-d_6 was used as deuterated solvent.

*Crystal and molecular structure of 5-acetyl-4-methyl-2-(2-benzenesulfonylhydrazino)-thiazole (**3d**)*

The Ortep like diagram of **3d** with the atom numbering scheme is shown in Figure 1, while selected bond lengths and angles are given in Table 4.

Compound **3d** crystallizes in the tetragonal *P4(2)bc* space group. Comparing with other substituted thiazoles or benzothiazole derivatives,[12-18] the bond distances and angles in the thiazole and benzene ring, respectively, are of similar magnitude. The thiazole and the phenyl rings are almost planar and the dihedral angle between the two planes [19.39(15)°] is much smaller than the values found in 2-amino-5-(*p*-nitrophenylsulfonyl)-1,3-thiazole [68.85(5)°],[15] or 4-tert-butyl-5-(2,4,5-trimethoxybenzyl)-thiazol-2-amine [65.9(2)°].[18]

The C7-S2-C9 angle [88.17(17)°] in **3d** is of the same magnitude as in 2-amino-5-(*p*-nitrophenylsulfonyl)-1,3-thiazole [88.26(7)°][12] or 2-amino-4-(4-methoxyphenyl)-1,3-thiazole [88.4(3)°],[13] but smaller than that one found in 2-amino-4-phenylthiazole hydrobromide monohydrate [90.17°].[14] The S1 atom has a trigonal pyramidal geometry, with N1 in apices and the angles around the S1 in the range 104.7(2) - 120.4(3)° (the largest being the O1-S1-O2 angle). S1 is placed at a distance of 0.422 Å from the mean trigonal plane O1C1O2.

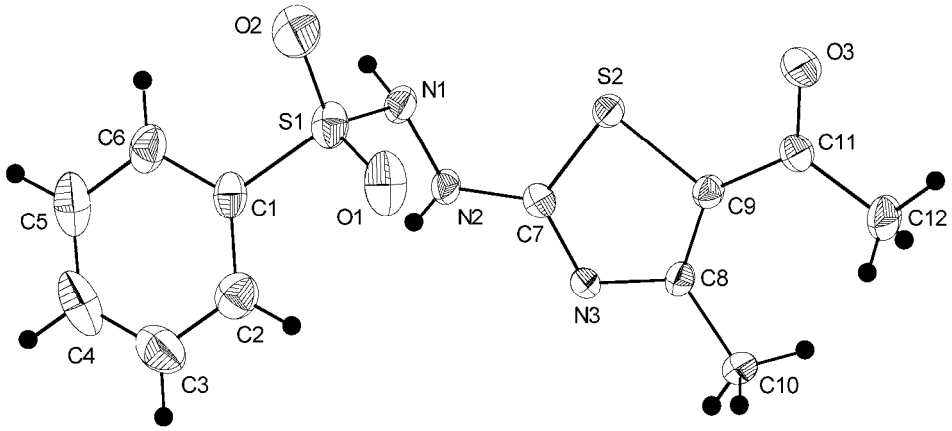


Fig. 1 – ORTEP plot diagrame of compound **3d**. The atoms are drawn with 30% probability ellipsoids.

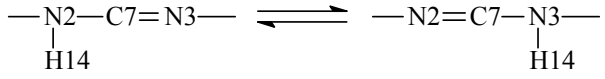
Table 4

Selected interatomic distances (Å) and angles (^{o}) in **3d** and **4d**

3d		**4d**	
C7-S2	1.710(3)	C11-S2	1.713(4)
N2-C7	1.333(5)	N2-C11	1.399(5)
N2-N1	1.382(5)	N2-N1	1.391(4)
N3-C7	1.316(4)	N3-C11	1.303(4)
N3-C8	1.355(4)	N3-C12	1.379(5)
C8-C9	1.368(5)	C12-C13	1.362(5)
N1-S1	1.651(4)	N1-S1	1.719(3)
O1-S1	1.427(4)	O1-S1	1.421(3)
O2-S1	1.423(4)	O2-S1	1.427(3)
N3···H14a	2.09(5)	O3c-H13	
O3-H13b	1.84(4)		
S1-N1-H13	109.9(24)	S1-N1-C7	121.6(2)
N2-N1-H13	116.9(28)	N2-N1-C7	120.1(3)
S1-N1-N2	114.4(3)	S1-N1-N2	117.0(2)
C7-N2-H14	124.8(34)	C11-N2-C9	122.8(3)
N1-N2-H14	117.4(34)	N1-N2-C9	119.7(3)
C7-N2-N1	117.6(3)	C11-N2-N1	117.1(3)
C7-N3-C8	111.3(3)	C11-N3-C12	110.1(3)
C7-S2-C9	88.17(17)	C(11)-S(2)-C(13)	88.08(18)
O1-S1-O2	120.4(3)	O(1)-S(1)-O(2)	120.71(18)
N1-S1-C1	107.82(19)	O(1)-S(1)-N(1)	106.48(16)
N1-S1-O1	106.4(2)	O(2)-S(1)-N(1)	102.45(15)
N1-S1-O2	104.7(2)	O(1)-S(1)-C(1)	108.67(17)
O1-S1-C1	107.9(2)	O(2)-S(1)-C(1)	109.53(18)
O2-S1-C1	108.9(2)	N(1)-S(1)-C(1)	108.26(16)

symmetry codes: -x, -y, z (a); 0.5 - x, 0.5 + y, z (b); 0.5 - x, -0.5 + y, z (c)

The N-C7 bond length and the sum of the bond angles Σ(N2) = 359.8° suggest a sp^2 character of the N2 atom and a tautomeric process, as described below,



while the N1 atom is basically pyramidal [sp^3 character, Σ(N1) = 341.2°].

The crystal structure is stabilized by intermolecular hydrogen bonding. The molecules of **3d** are connected in dimeric units (Figure 2) through week contacts between the N3 atom and the·H14a atom of a neighbouring molecule [2.09(5) Å] (cf. Σ_{vdW}(N, H) 2.74 Å[19]). The dimmers are further connected through O3···H13b [1.84(4) Å] interactions [cf. Σ_{vdW}(O, H) 2.60 Å], resulting in a layered network (Figure 3).

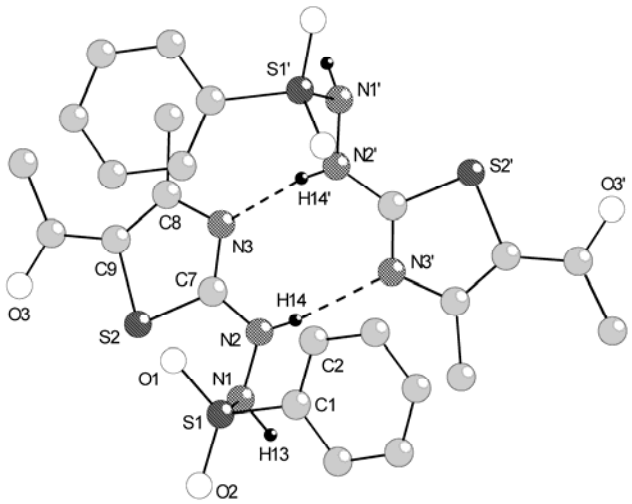


Fig. 2 – Dimeric association in the crystal of **3d**.

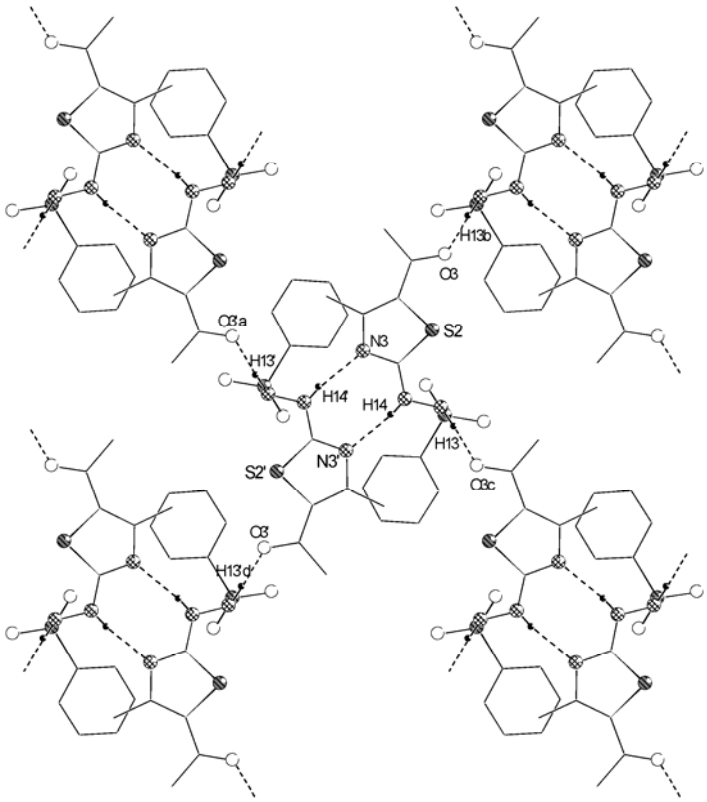


Fig. 3 – Supramolecular association in the crystal of **3d**.

*Crystal and molecular structure of 5-acetyl-4-methyl-2-(1,2-diacetyl-2-benzene-sulfonylhydrazino)-thiazole (**4d**)*

The Ortep like diagram of **4d** with the atom numbering scheme is shown in Figure 4 and selected bond lengths and angles are given in Table 4.

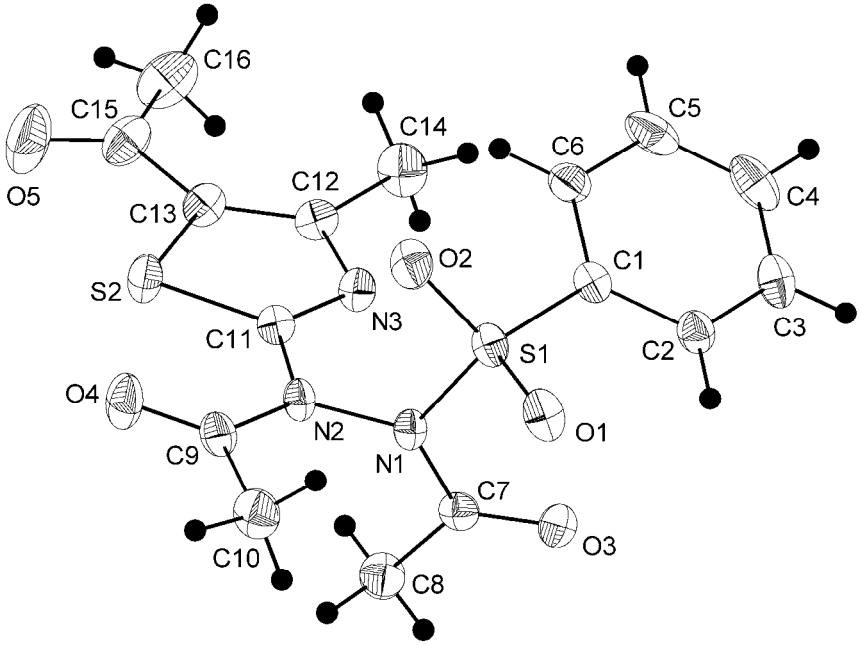


Fig. 4 – ORTEP plot diagrame of compound **4d**. The atoms are drawn with 30% probability ellipsoids.

By contrast with **3d**, the acylated compound **4d** has a monomeric structure and displays some structural differences, as followings:

- the two almost planar rings are tilted one to the other at an angle of 23.56(11)°, larger than the angle found in **3d** [19.39(15)°] or other substituted thiazoles.

- the acylated compound **4d** has a *cis* conformation [S1-N1-N2-C11 torsion angle 86.12(35)°] with respect to the relativ orientation of the phenyl and the thiazole rings towards the S1N1N2 plane (the distances of C1 and C11 to the S1N1N2 plane are 1.536 and 1.242 Å, respectively), while **3d** has a *trans* conformation [S1-N1-N2-C7 torsion angle -101.55(34)°] with the atoms C1 and C7 at a distance of 1.541 and -1.162 Å from the S1N1N2 plane.

- the S1 atom has again a trigonal pyramidal geometry with N1 in apices and the angles around the S1 in the range 102.45(15) - 120.71(18)°. S1 is placed at a distance of 0.407 Å from the mean trigonal plane O1C1O2.

- the sum of the bond angles around the N1 and N2 atoms, Σ(N1) = 358.7° and Σ(N2) = 359.6° , respectively, suggests a sp^2 character for both of them.

The N2-C bond distance in **4d** is much longer than in **3d** [1.399(5) Å vs. 1.333(5) Å in **3d**], thus suggesting that no tautomeric process is present in case of **4d**.

The other bond distances and angles differ not significantly from those found in **3d** or other related substituted thiazoles.[12-17]

The C11-S2-C13 [88.08(18)°] and C9-N2-C11 [110.1(3)°] angles in the thiazole ring are of similar magnitude as in **3d** or other related compounds.[12-17]

Microbiology

The investigated compounds have shown a moderate anti-microbial activity, lower than that of the reference substances. For all compounds the best results were noticed with respect to *Candida albicans*. Hydrochlorides of derivatives **3a**[20] and **3e**[21] were obtained and tested against *Mycobacterium tuberculosis* and others microorganisms before.

EXPERIMENTAL

Starting materials were of commercial quality (Aldrich). Melting points are uncorrected. Elemental analysis were performed on a VarioEL analyzer. IR spectra were recorded in the range 4000-400 cm^{-1} in KBr pellets on a FTIR spectrophotometer Nicolet 210. Mass spectra were recorded on a MAT 311 mass spectrometer with EI ion source, at an ionization energy of 70 eV, with direct inlet probe. ^1H and ^{13}C

NMR spectra were recorded either on a BRUKER DRX 400 instrument operating at 400.13 and 100.61 MHz, respectively, or on a BRUKER AVANCE 300 instrument operating at 300.11 and 75.4 MHz, respectively, with TMS as internal standard. The chemical shifts are reported in δ units (ppm) relative to the residual peak of the deuterated solvent (ref. $CHCl_3$: ^1H 7.26, ^{13}C 77.0 ppm; DMSO-d_6: ^1H 2.50, ^{13}C 39.43 ppm). The ^1H and ^{13}C chemical shifts were assigned based on 2D experiments using standard BRUKER XWIN-NMR pulse sequences.

*Preparation of benzene-sulfonyl-thiosemicarbazide (**1**)*

Thiosemicarbazide (1.82 g, 0.02 mol) was dissolved in a 5% aqueous NaOH solution (20 ml). To the resulted solution benzenesulfonylchloride (5.3 g, 0.03 mol) was added under stirring, and the reaction mixture was stirred for 1 hr more. After that the solution vas diluted twofold with water and neutralized with acetic acid. The resulted precipitate was separated by filtration and recrystallized from ethanol. Yield 65%; M..p. = 207-208 ^oC; IR (KBr, ν cm^{-1}): 3450, 3325, 3168, 3007, 2810 (νNH, νCH), 1287 (νC=S), 1347, 1176 (νSO_2); EI MS *m/z* (%): 231 (11) $[M]^+$, 172 (4) $[C_6H_8N_2SO_2]^+$, 142 (43) $[C_6H_6SO_2]^+$, 125 (16) $[C_6H_5SO]^+$, 94 (19), 77 (100) $[C_6H_5]^+$, 60 (63), 51 (54). ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.49 (s, br, 1H NH), 7.60 (m, 2H C_6H_5-*meta*), 7.72 (m, 1H C_6H_5-*para*), 7.81 (d, 2H C_6H_5-*ortho*, $^3J_{HH}$ = 7.6 Hz), 8.14 (s, br, 1H NH), 9.40 (s, 1H NH_2), 9.97 (s, br, 1H NH_2). ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ (ppm): 128.34 (C-*meta*), 129.60 (C-*ortho*), 133.79 (C-*para*), 138.26 (C-*ipso*), 183.04 (s, C=S).

*General procedure for the preparation of compounds **3a-3e**.*

Compound **1** (0.01 mol) was dissolved in a mixture of acetone (10 ml) and DMF (10 ml). To the resulted solution the corresponding chloroacetone **2** (0.01 mol) was added and the mixture was stirred for additional 2 hr and then was left without stirring for 24 hr. The resulted precipitate of the corresponding hydrochloride was filtered off, washed with water and diethyl ether and dried. Subsequently, the obtained suspention in water was neutralized with a $NaHCO_3$ saturated solution. The obtained solid product was separated by filtration and recrystalized from ethanol.

3a: IR (KBr, ν cm^{-1}): 3274 (νNH), 1342, 1165 (νSO_2); EI MS, *m/z* (%): 269 (12) $[M]^+$, 206 (6), 176 (4), 175 (4), 142 (29) $[C_6H_6SO_2]^+$, 128 (57) [hydrazynothiazole]$^+$, 99 (71) [methylthiazole + H]$^+$, 77 (100) $[C_6H_5]^+$, 51 (64), 45 (87). ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.07 (s, 3H CH_3), 6.34 (s, 1H thiazole H), 7.61 (m, 2H C_6H_5-*meta*), 7.70 (m, 1H C_6H_5-*para*), 7.83 (d, 2H C_6H_5-*ortho*, $^3J_{HH}$ = 7.5 Hz).

3b: IR (KBr, ν cm^{-1}): 3268 (νNH), 1342, 1164 (νSO_2); EI MS, *m/z* (%): 303 (4) $[M]^+$, 240 (5) [M - $C_2H_4Cl]^+$, 162 (32) [M - $C_6H_5SO_2]^+$, 142 (32) $[C_6H_5SO_2]^+$, 133 (36) [M - $C_6H_7N_2SO_2]^+$, 98 (41), 77 (100) $[C_6H_5]^+$, 51 (55), 45 (70). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 4.19 (s, 2H, CH_2), 6.45 (s, 1H C*H*), 7.45 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 7.6 Hz), 7.55 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.4 Hz), 7.90 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 40.96 (*C*H_2), 108.65 (*C*H), 127.22 (*C*-NH), 128.56 (C_6H_5–*ortho*), 129.28 (C_6H_5–*meta*), 134.04 (C_6H_5–*para*), 138.21 (C_6H_5–*ipso*), 173.5 (*C*-CH_2).

3c: IR (ν, cm^{-1}): 3206(νNH), 1365, 1168 (νSO_2); EI MS (*m/z*, %): 331 (3) $[M]^+$, 268 (2), 238 (2), 189 (29) [M - $C_6H_5SO_2]^+$, 161 (35) [thiazole + H]$^+$, 142 (24) $[C_6H_5SO_2]^+$, 134 (35), 102 (100) $[C_8H_6]^+$, 77 (70) $[C_6H_5]^+$, 51 (41%). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 6.72 (s, 1H thiazole H), 7.26 – 7.38 (m, 3H C_6H_5- *meta* + *para*), 7.42 (d, 2H C_6H_5-*ortho*, $^3J_{HH}$ = 7.5 Hz), 7.53 (m, 3H C_6H_5-*meta* + *para*), 7.87 (d, 2H C_6H_5-*ortho*, $^3J_{HH}$ = 7.5 Hz).

3d: IR (ν, cm^{-1}): 3442 (νNH), 1598 (νCO cetone), 1349, 1165 (νSO_2); EI MS (*m/z*, %): 311 (3) $[M]^+$, 170 (10) $[C_6H_6N_2SO_2]^+$, 141 (57) $[C_6H_5SO_2]^+$, 126 (28) $[C_6H_6SO]^+$, 94 (20), 77 (100) $[C_6H_5]^+$, 51 (46). ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.36 (s, 3H CH_3), 2.40 (s, 3H OCH_3), 7.64 (m, 2H C_6H_5-*meta*), 7.72 (m, 1H C_6H_5-*para*), 7.84 (d, 2H C_6H_5-*ortho*, $^3J_{HH}$ = 7.5 Hz).

3e: IR (ν, cm^{-1}): 3218 (νNH), 1710 (νCO esther), 1348, 1167 (νSO_2); EI MS (*m/z*, %): 341 (6) $[M]^+$, 296 (9) [M-$CO_2]^+$, 278 (8), 200 (26) [M - $C_6H_5SO_2]^+$, 171 (92) $[C_6H_7N_2SO_2]^+$, 142 (41) $[C_6H_6SO_2]^+$, 125 (28) $[C_6H_5SO]^+$, 113 (19), 85 (61) $[C_4H_5O_2]^+$, 77 (100) $[C_6H_5]^+$, 67 (75), 51 (45). ^1H NMR (DMSO-d_6, 300 MHz) : δ (ppm): 1.25 (t, 3H, CH_2-C*H*$_3$, $^3J_{HH}$ = 7.2 Hz), 2.38 (s, 3H, C*H*$_3$), 4.18 (q, 2H, C*H*$_2$-CH_3, $^3J_{HH}$ = 7.2 Hz), 7.64 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 7.3 Hz), 7.73 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.0 Hz), 7.84 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 7.5 Hz). ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ (ppm): 14.24 (*C*H_3), 60.17 (*C*H_2-CH_3), 127.72 (*C*H), 127.75 (C_6H_5–*meta*), 129.26 (C_6H_5–*ortho*), 133.48 (C_6H_5–*para*), 137.78 (C_6H_5–*ipso*), 137.86 (*C*-R_1), 161.77 (*C*O).

*General procedure for the preparation of compounds **4a-4e**, **6a** and **6c***

Method I. Compounds **3a-e**, **5a** or **5c** (0.2 g) were treated with acetic anhydride (0.5 ml) and boiled for 3 minutes. The resulted solution was poured into water and stirred until all acetic anhydride was consumed. The resulting precipitate was separated by filtration and recrystallized form ethanol.

Method II. Compounds **3a-e**, **5a** or **5c** (0.2 g) were dissolved in acetic anhydride (1.5 ml) and few drops of pyridine were added. The reaction mixture was kept at room temperature for 24 hr. The obtained precipitate was separated by filtration and dried.

4a: IR (ν, cm^{-1}): 1726, 1708 (νCO amide), 1366, 1168 (νSO_2); EI MS (*m/z*, %): 353 (4) $[M]^+$, 311 (14) [M - $CH_3CO]^+$, 212 (26), 170 (100) $[C_6H_6SO_2N_2]^+$, 128 (55), 100 (34), 77 (21) $[C_6H_5$, 51 (9). ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm): 1.96 (s, 3H, C*H*$_3$), 2.13 (s, br., 3H, COC*H*$_3$), 2.59 (s, 3H, SO_2NCOCH_3), 6.62 (s, 1H, C*H*), 7.47 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 8.0 Hz), 7.66 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.4 Hz), 7.90 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 16.78 (*C*H_3), 21.67 (SO_2NCOCH_3), 22.38 (CO*C*H_3), 111.55 (*C*H), 128.06 (C_6H_5–*meta*), 130.78 (C_6H_5–*ortho*), 134.51 (C_6H_5–*para*), 137.12 (C_6H_5–*ipso*), 146.93 (*C*OCH$_3$), 155.53 (*C*-R_1), 171.68 (*C*OCH$_3$).

4b: IR (ν, cm^{-1}): 1727, 1711 (νCO amide), 1365, 1168 (νSO_2); EI MS (*m/z*, %): 387 (9) $[M]^+$, 345 (22) [M - $CH_3CO]^+$, 303 (4) [M – 2 $CH_3CO]^+$, 246 (15) [M - $C_6H_5SO_2]^+$, 204 (100) [M - $C_6H_5SO_2$ - CH_3CO]$^+$, 162 (62), 134 (14) [thiazole + H]$^+$, 105 (6) $[C_6H_5S]^+$, 98 (13), 77 (23) $[C_6H_5]^+$, 51 (9). ^1H NMR ($CDCl_3$, 400 MHz): δ 2.12 (s br., 3H, COC*H*$_3$), 2.60 (s, 3H, SO_2NCOCH_3), 4.19 (s, 2H C*H*$_2$), 7.08 (s, 1H, C*H*), 7.51 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 7.6 Hz), 7.68 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.2 Hz), 7.96 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 21.58 (SO_2NCOCH_3), 22.29 (CO*C*H_3), 40.48 (*C*H_2), 115.57 (*C*H), 128.33 (C_6H_5–*meta*), 130.75 (C_6H_5–*ortho*), 134.72 (C_6H_5–*para*), 137.0 (C_6H_5–*ipso*), 146.48 (*C*OCH$_3$), 157.1 (*C*-R_1), 172.0 (*C*OCH$_3$).

4c: IR (ν, cm^{-1}): 1732, 1714 (νCO amide), 1378, 1172 (νSO_2); EI MS (*m/z*, %): 415 (13) $[M]^+$, 373 (4) [M - $CH_3CO]^+$, 274 (3) [M - $C_6H_3SO_2]^+$, 232 (60), 190 (22), 162 (21) [thiazole + 2H]$^+$, 134 (12), 102 (22) $[C_8H_6]^+$, 77 (19)

$[C_6H_5]^+$, 43 (100) $[CH_3CO]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.11 (s, 3H, COCH_3), 2.57 (s, 3H, SO_2NCOCH_3), 2.54 (s, 3H, COCH_3), 7.08 – 7.24 (m, 6H, $SO_2C_6H_5$–*meta* + C_6H_5–*meta+para* + C*H*), 7.34 (t, 1H, $SO_2C_6H_5$–*para*, $^3J_{HH}$ = 7.2 Hz), 7.80 (d, 2H, $SO_2C_6H_5$–*ortho*, $^3J_{HH}$ = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 21.55 (SO_2NCOCH_3), 22.40 (CO*C*H$_3$), 110.32 (*C*H), 125.68 ($SO_2C_6H_5$–*meta*), 128.34 (C_6H_5), 128.38 (C_6H_5), 130.53 ($SO_2C_6H_5$–*ortho*), 134.45 ($SO_2C_6H_5$–*ipso*), 136.87 ($SO_2C_6H_5$–*para*), 149.04 (*C*-R$_1$), 162.21 (*C*OCH$_3$), 171.94 (*C*OCH$_3$).

4d: IR (ν, cm^{-1}): 1741 (νCO cetone), 1715, 1638 (νCO amide), 1361, 1170 (νSO_2); EI MS (*m/z*, %): 353 (2) $[M]^+$, 254 (4) $[M - 2\ CH_3CO - CH_3]^+$, 212 (20) $[M - 3\ CH_3CO - CH_3]^+$, 170 (12), 142 (11) $[C_6H_6SO_2]^+$, 100 (4), 77 (12) $[C_6H_5]^+$, 43 (100) $[CH_3CO]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02 (s,3H, COCH_3), 2.09 (s, 3H, CH_3), 2.44 (s, 3H, SO_2NCOCH_3), 2.54 (s, 3H, COCH_3), 7.42 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 7.6 Hz), 7.61 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.2 Hz), 7.86 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 17.83 (*C*H$_3$), 21.55 (SO_2NCOCH_3), 22.40 (CO*C*H$_3$), 30.43 (CO*C*H$_3$), 128.26 (C_6H_5–*meta*), 130.71 (C_6H_5– *ortho*), 134.83 (C_6H_5–*para*), 136.87 (C_6H_5–*ipso*), 153.96 (*C*OCH$_3$), 172.07 (*C*OCH$_3$), 175.2 (*C*-R$_1$), 190.65 (*C*OCH$_3$).

4e: IR (ν, cm^{-1}): 1714 (νCO esther, amide), 1372, 1172 (νSO_2); EI MS (*m/z*, %): 425 (4) $[M]^+$, 383 (4) $[M - CH_3CO]^+$, 284 (13) $[M - CH_3CO - C_6H_5SO_2]^+$, 242 (67) $[M - 2\ CH_3CO - C_6H_5SO_2]^+$, 200 (30) $[M - 3\ CH_3CO - C_6H_5SO_2]^+$, 172 (16), 77 (28) $[C_6H_5]^+$, 43 (100) $[CH_3CO]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37 (t, 3H, CH_2-CH_3, $^3J_{HH}$ = 7.2 Hz), 2.09 (s, 3H, CH_3), 2.17 (s, 3H, COCH_3), 2.60 (s, 3H, SO_2NCOCH_3), 4.32 (q, 2H, CH_2-CH_3, $^3J_{HH}$ = 7.2 Hz), 7.49 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 7.6 Hz), 7.63 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.6 Hz), 7.92 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 14.34 (CH_2-*C*H$_3$), 16.87 (NCO*C*H$_3$), 21.56 (*C*H$_3$), 22.38 (SO_2NCOCH_3), 61.14 (*C*H$_2$-CH$_3$), 128.24 (C_6H_5–*meta*), 130.76 (C_6H_5–*ortho*), 134.79 (C_6H_5–*para*), 136.96 (C_6H_5–*ipso),* 155.27 (SO_2NCOCH_3), 162.31 (*C*OC_2H_5), 172.03 (NCO*C*H$_3$), [C_6H_5–*ipso*], 137.87 C_q, 169.82 (*C*-R$_1$).

6a: IR (ν, cm^{-1}): 1728, 1707 (νCO amide), 1360, 1173 (νSO_2), 542 (νCBr); EI MS (*m/z*, %): 433 (10) $[M]^+$, 391 (28) [M - CH_3CO, 292 (29) [M - $C_6H_5SO_2]^+$, 250 (63) [M - $C_6H_5SO_2$ - $CH_3CO]^+$, 208 (54) [M - $C_6H_5SO_2$ – 2 $CH_3CO]^+$, 178 (34) [thiazole + H]$^+$, 125 (12) $[C_6H_5SO]^+$, 77 (53) $[C_6H_5]^+$, 43 (100) $[CH_3CO]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.86 (s, 3H, CH_3), 2.1 (s, 3H, COCH_3), 2.56 (s, 3H, SO_2NCOCH_3), 7.41 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 7.6 Hz), 7.60 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.6 Hz), 7.86 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 15.13 (*C*H$_3$), 21.36 (SO_2NCOCH_3), 22.32 (CO*C*H$_3$), 102.27 (*C*Br), 128.15 (C_6H_5–*meta*), 130.77 (C_6H_5–*ortho*), 134.67 (C_6H_5–*para*), 137.02 (C_6H_5–*ipso*), 145.47 (*C*-R$_1$), 154.08 (*C*OCH$_3$), 171.90 (*C*OCH$_3$).

6b: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.11 (s, 3H, OCH_3); 2.56 (s, 3H, OCH_3), 4.42 (AB system, δ_A 4.52, δ_B 4.32, $^2J_{HH}$ 12 Hz), 7.66 (t, 2H, C_6H_5-*meta*, $^3J_{HH}$ 8.1 Hz); 7.83 (t, 1H, C_6H_5-*para*, $^3J_{HH}$ 7.5 Hz); 7.94 (d, 2H, C_6H_5-*ortho*, $^3J_{HH}$ 7.5 Hz). ^{13}C NMR (DMSO-d_6, 75.4 MHz) δ (ppm): 21.44 (SO_2NOCH_3), 22.21 (O*C*H$_3$), 107.02 (*C*H$_2$Cl), 125.33 (C_6H_5–*meta*), 130.74 (C_6H_5–*ortho*), 135.89 (C_6H_5–*para*), 136.72 (C_6H_5–*ipso*), 145.03 (*C*OCH$_3$),, 155.38 (*C*-R$_1$), 173.12 (*C*OCH$_3$).

6c: IR (ν, cm^{-1}): 1740, 1711(νCO amide), 1370, 1168 (νSO_2), 549 (νCBr); EI MS (*m/z*, %): 495 (10) $[M]^+$, 453 (5) [M - $CH_3CO]^+$, 410 (3) [M – 2 $CH_3CO]^+$, 312 (38) [M-$C_8H_5Br]^+$, 270 (16), 242 (10), 182 (6) $[C_8H_4Br]^+$, 77 (26) $[C_6H_5]^+$, 43 (100) $[CH_3CO]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 2.11 (s, 3H, COCH_3), 2.55s (3H, SO_2NCOCH_3), 7.1 – 7.24 (m, 5H C_6H_5–*meta+para* + $SO_2C_6H_5$–*meta*], 7.30 (t, 1H, $SO_2C_6H_5$–*para*, $^3J_{HH}$ = 7.2 Hz), 7.37 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 8.0 Hz), 7.81 (d, 2H, $SO_2C_6H_5$–*ortho*, $^3J_{HH}$ = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 21.34 (SO_2NCOCH_3), 22.34 (CO*C*H$_3$), 127.78 (C_6H_5-*ortho*), 127.99 (C_6H_5-*meta*), 128.31 ($SO_2C_6H_5$–*meta*), 128.38 (C_6H_5–*para*), 130.46 ($SO_2C_6H_5$–*ortho*), 132.38 (*C*Br) 134.49 ($SO_2C_6H_5$–*para*), 136.9 (*C*-R$_1$), 145.1 (C_6H_5 – *ipso*), 173.07 (*C*OCH$_3$), 176.65 (*C*OCH$_3$).

*General procedure for the preparation of compounds **5a-5c***

Compound **3a-c** (0.02 mol) was dissolved in acetic anhydride (5 ml). To the resulted solution was added dropwise a solution of bromine (0.11 ml) in acetic acid (2 ml). The resulted mixture was kept at room temperature for 24 hr and then was poured into a water-ice mixture. The obtained precipitate was filtered and recrystallized from ethanol.

5a: IR (ν, cm^{-1}): 3452(νNH), 1347, 1165 (νSO_2), 552 (νCBr); EI MS (*m/z*, %) 319 (1) $[M]^+$, 254, 204 (70) [M - $C_6H_5SO_2]^+$, 176 [thiazole + H]$^+$, 141 $[C_6H_7SO_2]^+$, 125, 119, 96, 77 (100), 72, 51.

^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.43 (s, 3H, CH_3), 7.54 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 7.6 Hz), 7.67 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.2 Hz), 7.90 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (ppm): 15.2 (*C*H$_3$), 125.98 (*C*Br), 129.49 (C_6H_5–*meta*), 130.65 (C_6H_5–*ortho*), 135.6 (C_6H_5–*para*), 137.12 (C_6H_5–*ipso*), 158.53 (C_q),

5b: IR (ν, cm^{-1}): 3231 (νNH), 1348, 1170 (νSO2), 726 (νCCl), 577 (νCBr); EI MS (*m/z*, %): 346 (1) $[M - Cl]^+$, 286 (5) $[M - Cl - Br]^+$, 250 (5) $[M\text{-}CH_2Cl - Br]^+$, 240 (5), 206 (18), 178 (22), 141 (50) $[C_6H_5SO_2]^+$, 125 (22) $[C_6H_5SO]^+$, 77 (100) $[C_6H_5]^+$, 51 (42). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 4.49 (s, 2H, CH_2), 7.64 (t, 2H, C_6H_5–*meta*, $^3J_{HH}$ = 7.6 Hz), 7.73 (t, 1H, C_6H_5–*para*, $^3J_{HH}$ = 7.5 Hz), 7.85 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 7.6 Hz), 9.97(s, 1H N*H*), 10.47 (s, br, 1H N*H*). ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ (ppm):: 27.36 (*C*H$_2$), 96.54 (*C*H), 128.20 (*C*-NH), 129.79 (C_6H_5–*ortho*), 134.01 (C_6H_5–*meta*), 136.14 (C_6H_5–*para*), 147.09 (C_6H_5–*ipso*), 172.94 (*C*-CH$_2$).

5c: IR (ν, cm^{-1}): 3428 (νNH), 1360, 1180 (νSO2), 576 (νCBr); EI MS (*m/z*, %): 381 (8) $[M]^+$, 316 (7), 268 (10) [hydrazynothiazole]$^+$, 240 (24) $[C_6H_9SO_2N_2]^+$, 182 (17) $[C_8H_6Br]^+$, 159 (100) [thiazole – Br], 141 (11) $[C_6H_5SO_2]^+$, 133 (42) $[C_8H_5S]^+$, 89 (37) $[C_7H_5]^+$, 77 (96) $[C_6H_5]^+$, 51 (48). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 7.39 (m, 3H C_6H_5–*meta+para*), 7.56 (t, 2H, $SO_2C_6H_5$–*meta*, $^3J_{HH}$ = 8.0 Hz), 7.69 (t, 1H, $SO_2C_6H_5$–*para*, $^3J_{HH}$ = 7.2 Hz), 7.83 (d, 2H, C_6H_5–*ortho*, $^3J_{HH}$ = 6.8 Hz), 7.93 (d, 2H, $SO_2C_6H_5$–*ortho*, $^3J_{HH}$ = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ (ppm):128.55 (C_6H_5-*meta*), 128.68 (C_6H_5-*ortho*), 129.54 ($SO_2C_6H_5$–*meta*), 130.35 (C_6H_5-*para*), 130.69 ($SO_2C_6H_5$–*ortho*), 135.39 ($SO_2C_6H_5$–*para*).

*Crystal structure determination of compounds **3d** and **4d***

X-ray quality crystals were obtained from acetone (**3d**) and a chloroform / n-hexane mixture (1/4 v/v) (**4d**), respectively.

Colourless, block crystals of **3d** and **4d** were mounted on cryoloops. Data collection and processing was carried out on a Bruker SMART APEX CCD X-ray machine using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Details of the crystal structure determination and refinement for compounds **3d** and **4d** are given in Table 5.

Table 5

Crystal data and structure refinement for *5-acetyl-4-methyl-2-(2-benzenesulfonyl-hydrazino)-thiazole* (**3d**) and *5-acetyl-4-methyl-2-(1,2-diacetyl-2-benzenesulfonyl-hydrazino)-thiazole* (**4d**)

	3d CCDC 663514	**4d** CCDC 663513
Empirical formula	$C_{12}H_{13}N_3O_3S_2$	$C_{16}H_{17}N_3O_5S_2$
Formula weight	311.37	395.45
Temperature, K	297(2)	297(2)
Wavelength, Å	0.71073	0.71073
Crystal system	tetragonal	triclinic
Space group	*P4(2)bc*	*P-1*
a (Å)	15.0900(13)	8.910(2)
b (Å)	15.0900(13)	10.420(3)
c (Å)	12.944(2)	10.808(3)
α (°)	90	74.703(4)
β (°)	90	70.927(4)
γ (°)	90	81.461(4)
Volume, $Å^3$	2947.5(6)	912.7(4)
Z	8	2
Density (calculated), g/cm^3	1.403	1.439
Absorption coefficient, mm^{-1}	0.371	0.324
F(000)	1296	412
Crystal size, mm	0.28 x 0.12 x 0.10	0.17 x 0.16 x 0.08
θ range for data collections (°)	1.91 to 26.37	2.03 to 26.37
Reflections collected	22203 / 3012 [R(int) = 0.0811]	9722 / 3701 [R(int) = 0.0452]
Independent reflections	3012 [R(int) = 0.0811]	3701 [R(int) = 0.0452]
Max. and min. transmissions	0.9639 and 0.9033	0.9745 and 0.9469
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3012 / 3 / 191	3701 / 0 / 239
Goodness-of-fit on F^2	1.213	1.208
Final *R* indicies [I>2sigma(I)]	R1 = 0.0607, wR2 = 0.1295	R1 = 0.0787, wR2 = 0.1559
R indicies (all data)	R1 = 0.0665, wR2 = 0.1321	R1 = 0.1020, wR2 = 0.1651
Largest diff. peak and hole, $eÅ^{-3}$	0.556 and -0.287	0.375 and -0.343

The structures were solved by direct methods[22] and refined using SHELX-97.[23] All of the non-hydrogen atoms were treated anisotropically. The hydrogen atoms attached to nitrogen in **3d** were located from the difference map. The other hydrogen atoms were included in idealized positions with isotropic thermal parameters set at 1.2 times of that of the carbon atom to which they were attached, except the methyl protons for which the isotropic thermal parameters were set at 1.5. The drawings were created with the Diamond program.[24]

Antimicrobial screening

Discs of qualitative filter paper measuring 10 mm in diameter were sterilized by dry heating (140°C) for one hour. The solutions of the investigated compounds were prepared at different concentrations, taking into account the molar equivalence. The pairs of discs were impregnated separately, either with solutions of reference substances or with diluted solutions of test compounds and dried at 37°C for 30 minutes. After impregnation with corresponding concentrated solutions the discs were placed in nutrient agar medium which was seeded separately with fresh bacteria or fungus. The incubation was carried out at 37°C for 24 hr. The results were evaluated by measuring the diameter of the inhibition zone.

Supplementary material

Crystallographic data for the structural analysis of compounds **3d** and **4d** have been deposited with the Cambridge Crystallographic Data Centre CCDC No.. 663514

and 663513. Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

*Acknowledgements.*This work was financially supported by the Roumanian Ministry of Education and Research, grant CEx no. 11-55/2006.

REFERENCES

1. D. Zaharia, V. Zaharia, D. Matinca, I. Simiti, *Clujul Medical*, **1966**, *LXIX*, 304-313.
2. D. Zaharia, V. Zaharia, D. Matinca, I. Simiti, *Farmacia*, **1999**, *XLVII*, 51-60.
3. V. Zaharia, L. Vlase, N. Palibroda, *Farmacia*, **2001**, *XLIX*, 54-61.
4. V. Zaharia, Ileana Chirtoc, *Farmacia*, **2001**, *XLIX (6)*, 24-31.
5. B. S. Holla, K. V. Maloni, B. S. Rao, B. K. Sarojini, N. S. Kumari, *Eur. J. Med. Chem.*, **2003**, *38*, 313-318.
6. K. Bhat, B. Holla, *Phosphorus, Sulfur and Silicon and the Related Elements*, **2004**, *179*, 1019-1026.
7. R. Pignatello, S. Mazzone, I. Castelli, P. Mazzone, G. Racite, G. Mazzone, *Pharmazie*, **1994**, *49*, 272-276.
8. L. M. Lima, C. B. Ornelli, C. A. M. Fraga, A. L. P. Miranda, E. J. Barreiro, *J. Braz. Chem. Soc*., **1999**, *10*, 421-428.
9. C. S. Rooney, E. J. Cragoe, C. C. Porter, J. M. Sprague, *J. Med. Pharm. Chem*., **1962**, *52*, 155-167.
10. R. A. Finch, Krishnamurthy Shyam, Philip G. Penketh and Alan C. Sartorelli, *Cancer Research*, **2001**, *61*, 3033-3038.
11. F. Giles, S. Verstovsek, D. Thomas, S. Gerson, J. Cortes, S. Fader, A. Ferrajoli, F. Ravandi, S. Kornblau, G. Garcia-Manero, E. Jabbour, S. O'Brien, V. Karsten, A. Cahill, K. Yee, M. Albitar, M. Sznol, H. Kantarjian, *Clinical Cancer Research*, **2005**, *11*, 7817-7824.
12. Z. Seferoglu, T. Hoekelek, E. Sahin, F. Nuralin, *Acta Cryst.*, **2006**, *E62*, o2634-o2636
13. T. Hoekelek, Z. Seferoglu, N. Ertan, *Acta Cryst.,* **2006**, *E62*, o1609–o1611.
14. G. R. Form, E. S. Raper, T. C. Downie, *Acta Cryst.*, **1974**, *B30*, 342–348.
15. A. Latrofa, M. Franco, A. Lopedota, A. Rosato, D. Carone, C.Vitali, *Il Farmaco*, **2005**, *60*, 291–297.
16. I.Caleta, M. Grdiša, D. Mrvoš-Sermek, M. Cetina, V. Tralic-Kulenovic, K. Pavelic, G. Karminski-Zamola, *Il Farmaco,* **2004**, *59*, 297–305.
17. O. Bozdag-Dundar, O. Ozgen, A. Mentese, N. Altanlar, O. Atlı, E. Kendi, and R. Ertan, *Bioorg. & Med. Chem*., **2007**, *15*, 6012–6017.
18. Juan-Juan Xu, Ai-Xi Hua, Gao Cao, *Acta Cryst.*, **2007**, *E63*, o533-o534.
19. J. Emsley, Die Elemente, Walter de Gruyter, Berlin, 1993.
20. M. Lora-Tamato, C. Sunkel, R. Madronero, *Bull Soc. Chim. Fr*., **1964**, *2*, 251-254.
21. M. Lora-Tamato, R. Madronero, G. Alonso, C. Sunkel, *Bull Soc. Chim. Fr*., **1964**, *2*, 255-258.
22. G.M. Sheldrick, *Acta Crystallogr*., **1990**, *A46*, 467.
23. G.M. Sheldrick, SHELXL-97, University of Göttingen, Germany, **1997**.
24. K. Brandenburg, DIAMOND, Release 3.1d, Crystal Impact GbR, Bonn, Germany, **2006**.