

SYNTHESIS OF SOME 2-(ACETOPHENON-HYDRAZIN)-THIAZOLES AND 2-(4-THIAZOLYL-METHYNYDRAZIN)-THIAZOLES AS POTENTIAL ANTIBACTERIAL AND ANTIFUNGAL AGENTS

OVIDIU ONIGA^{1*}, CRISTINA MOLDOVAN¹, SMARANDA ONIGA¹,
BRÎNDUȘA TIPERCIUC¹, ADRIAN PÂRNĂU², PHILIPPE VERITE³,
OVIDIU CRIȘAN¹, IOANA IONUȚ¹

¹*"Iuliu Hațieganu" University of Medicine and Pharmacy, Faculty of Pharmacy, 12 Ion Creangă Street, RO-400010 Cluj Napoca, Romania*

²*National Institute for Research and Development of Isotopic and Molecular Technologies, RO-400293 Cluj Napoca, Romania*

³*University of Medicine and Pharmacy Rouen, Faculty of Pharmacy, Department of Analytical Chemistry, 22 Boulevard Gambetta, F-76183 Rouen Cedex, France*

**corresponding author: onigao65@yahoo.com*

Abstract

A new series of 2-(acetophenon-hydrazin)-thiazoles **4a-x** and 2-(4-thiazolyl-methine-hydrazin)-thiazoles **5a-c** were synthesized starting from various thiosemicarbazones by the reaction with different $\alpha(\gamma)$ -halocarbonyl compounds. The newly synthesized compounds were characterized by IR, ¹H-NMR and mass spectral studies.

Rezumat

Au fost sintetizate noi serii de 2-(acetofenon-hidrazin)-tiazoli **4a-x** și de 2-(4-tiazolil-metinhidrazin)-tiazoli **5a-c** pornind de la diferite tiosemicarbazone prin reacția cu diferiți compuși $\alpha(\gamma)$ -halocarbonilici. Noii compuși sintetizați au fost caracterizați prin IR, ¹H-RMN și studii spectrale de masă.

Keywords: thiosemicarbazones, hydrazin-thiazoles, hydrazin-bisthiazoles, Hantzsch reaction

Introduction

The latest scientific literature is extremely rich in results obtained prospectating new antibacterial and antifungal chemotherapeutic agents, whose structural profiles are often different from those of the chemotherapeutics nowadays used in therapy [1,7,9]. The new agents have different structural models, among which are remarked the azolic heterocycles such as thiazole and its derivatives (thiazolin-ones, thiazolidin-diones) [2-4, 8]. Based on these data and on our previous experience regarding the research of thiazole and its derivatives [6, 10], we obtained new 2-hydrazon-thiazole compounds applying the Hantzsch condensation

between a variety of acetophenon-thiosemicarbazones and 4-formyl-thiazolyl-thiosemicarbazone and different $\alpha(\gamma)$ -halo-carbonyl compounds.

Materials and methods

Synthesis of 2-acetophenon-thiosemicarbazones 1a-c and 2-phenyl-4-formyl thiosemicarbazone 3

The thiosemicarbazones **1a-c** and **3** were synthesized by the reaction of 3 substituted acetophenones (4-Br, 2-OH, 2,4-di-OH) and by the reaction of 2-phenyl-4-formyl-thiazole **2** with thiosemicarbazide, in the presence of small quantities of concentrated sulphuric acid (Figure 1).

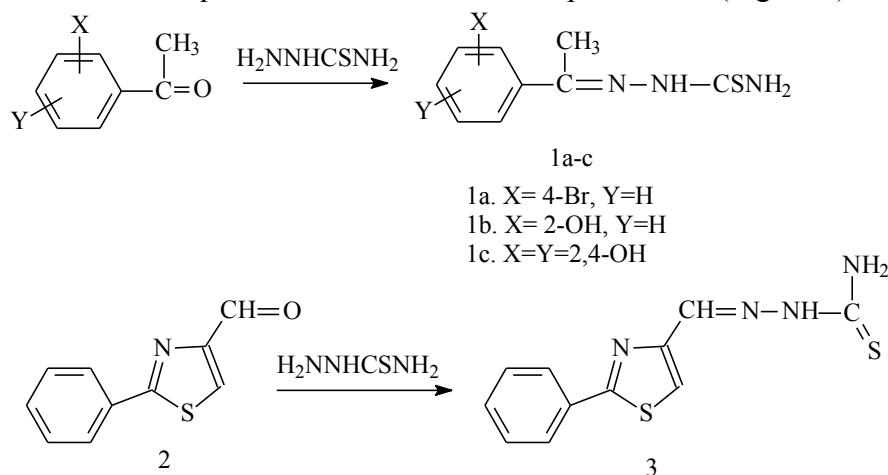
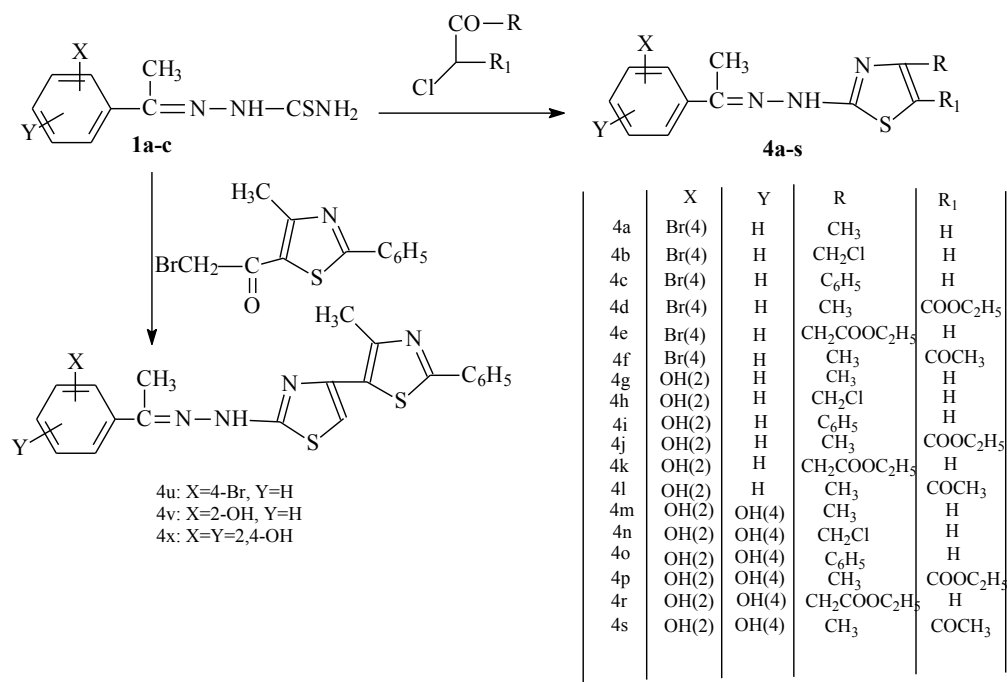


Figure 1

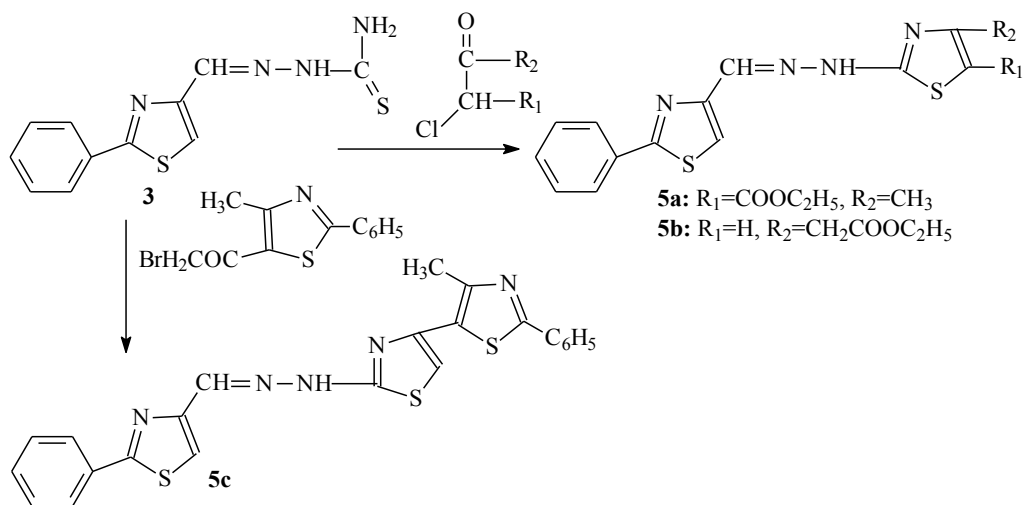
Synthesis of 2-acetophenon-thiosemicarbazones **1a-c** and 2-phenyl-4-formyl thiosemicarbazone **3**

Condensation of thiosemicarbazones with $\alpha(\gamma)$ -halo-carbonyl compounds

Three series of 2-acetophenon-hydrazin-thiazoles (**4a-f**, **4g-l**, **4m-s**), variously substituted in the 4 and 5 positions of the thiazole ring and at the phenyl nucleus, and also 2-acetophenon-hydrazin-4,5'-bisthiazoles (**4u-x**) were synthesized by the Hantzsch condensation of acetophenon-thiosemicarbazones **1a-c** with various α -halocarbonyl compounds (Figure 2). Starting from the thiosemicarbazone of the 2-phenyl-4-formyl-thiazole **3**, by the reaction with 2-chlor-ethyl acetoacetate, respectively with 4-chlor-ethyl acetoacetate, the 2-[(2'-phenyl-thiazole-4'-yl)-methinhydrazin]-thiazolic esters **5a-b** were obtained and by the reaction with 5-bromoacetyl-2-phenyl-4-methyl-thiazole it has been obtained 2-[(2''-phenyl-thiazole-4''-yl)-methinhydrazin]-2-phenyl-4-methyl-5,4'-bisthiazole **5c** (Figure 3). The synthesis of 5-bromoacetyl-2-phenyl-4-methyl-thiazole and 2-phenyl-4-formyl-thiazoles **2** were reported previously [5].

**Figure 2**

Synthesis of 2-acetophenon-hydrazin-4-R-5R₁-thiazoles **4a-s** and 2-acetophenon-hydrazin-2'-phenyl-4'-methyl-4,5'-bisthiazoles **4u-x**

**Figure 3**

Synthesis of 2-[(2'-phenyl-thiazole-4'-yl)-methinhydrazin-thiazolyl] esters **5a-b** and 2-[(2''-phenyl-thiazole-4''-yl)-methinhydrazin]-2-phenyl-4-methyl-5,4'-bisthiazole **5c**

Experimental protocol

The melting points were registered with an Electrothermal melting point meter and were uncorrected. FT-IR spectra were recorded on a Nicolet 210 FT-IR spectrometer using potassium bromide. The ^1H NMR spectra were recorded at room temperature on a Bruker Avance NMR spectrometer operating at 500 MHz. Chemical shift values were reported relative to tetramethylsilane (TMS) as internal standard. The samples were prepared by dissolving the compounds in dimethylsulfoxide (DMSO- d_6) (δH = 2.51 ppm) as solvent and the spectra were recorded using a single excitation pulse of 12 μs . GC-MS analyses were performed with an Agilent gas chromatograph 6890 equipped with an apolar Macherey Nagel PermaBond SE 52 capillary column. Elemental analysis was registered with a Vario El CHNS instrument. All compounds gave satisfactory quantitative elemental analysis results (CHNS). The purity of the synthesized compounds was verified by thin layer chromatography (TLC) and was carried out on precoated Silica Gel 60F254 sheets using heptan – ethyl-acetate 1:1 system and UV light for visualization.

2- acetophenon-thiosemicarbazones 1a-c (General procedure)

0.05 mol of substituted acetophenone (4-bromo, 2-hidroxy, 2,4-dihydroxy) dissolved in 50 mL alcohol was treated with 0.055 mol of thiosemicarbazide dissolved in 50 mL alcohol followed by the addition of 5 drops of concentrated sulphuric acid. The mixture was refluxed for 3 hours, cooled, after which the resulted precipitates were filtered and recrystallized from ethanol. **1a**: $\text{C}_9\text{H}_{10}\text{BrN}_3\text{S}$ (270.16), M.p.: 194-196 $^\circ\text{C}$ (ethanol), Yield 78%, **1b**: $\text{C}_9\text{H}_{11}\text{N}_3\text{OS}$ (209.26), M.p.: 197-198 $^\circ\text{C}$ (ethanol), Yield 76%, **1c**: $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2\text{S}$ (225.26), M.p.: 197-198 $^\circ\text{C}$ (ethanol), Yield 80%,.

2-phenyl-4-formyl-thiazole thiosemicarbazone 3

0.01 mol of **2** was dissolved in 15 mL ethanol and was treated with 0.01 mol of thiosemicarbazide. The mixture was refluxed 3 hours, after which it was cooled. The resulted compound was filtered and recrystallized from ethanol. $\text{C}_{11}\text{H}_{10}\text{N}_4\text{S}_2$ (262), M.p. 210-212 $^\circ\text{C}$, Yield 68%.

2-(acetophenon-hydrazin)-4-R-5-R'-thiazoles 4a-s and 2-(acetophenon-hydrazon)-4R-5R'-bisthiazoles 4u-x (General procedure)

0.005 mol of **1a-c** was dissolved in 20 mL absolute ethanol and 0.0055 mol α -(γ) halocarbonyl compound (chloropropanone, 1,3-dichloroacetone, α -chlor-acetophenone, 2-chlor-ethyl-acetoacetate, 4-chlor-ethyl-acetoacetate, 3-chlor-acetylacetone, 2-phenyl-4-methyl-5-bromacetyl-thiazole) was added. The mixtures were refluxed 2 hours, cooled, after which the resulted precipitates were filtered, washed with water in order to transform the halohydrates in bases. The resulted compounds were recrystallized from

ethanol. **4a**: $C_{12}H_{12}BrN_3S$ (310.21), M.p.: 148-149 $^{\circ}C$, Yield 68%, δ 7.62 (s, 1H, thiazole C5-H), 7.96 (s, 1H, NH), 2.2 (s, 3H, CH_3), 2.36 (s, 3H, CH_3 -4-thiazole), 7.63 (d, 2H, Ar-H), 7.82 (d, 2H, Ar-H), m/z = 310 (M^+), 294, 196, 182, 155, 128, 113, IR: $\nu(NH)$: 3294 cm^{-1} $\nu(C=N)$: 1590 cm^{-1} **4b**: $C_{12}H_{11}BrClN_3S$ (344.65), M.p.: 110 $^{\circ}C$, Yield 59%, δ 7.55 (s, 1H, thiazole C5-H), 7.92 (s, 1H, NH), 2.1 (s, 3H, CH_3), 2.86 (s, 2H, CH_2 -Cl), 7.53 (d, 2H, Ar-H), 7.71 (d, 2H, Ar-H) m/z = 345 (M^+), 330, 308, 196, 182, 155, IR: $\nu(NH)$: 3299 cm^{-1} $\nu(C=N)$: 1595 cm^{-1} **4c**: $C_{17}H_{14}BrN_3S$ (372.28), M.p.: 195-197 $^{\circ}C$, Yield 88%, δ (s, 1H, thiazole C5-H), 7.59 (s, 1H, NH), 2.36 (s, 3H, CH_3), 7.33-7.41 (m, 5H, C_6H_5 -4-thiazole), 7.55 (d, 2H, Ar-H), 7.72 (d, 2H, Ar-H), m/z = 372 (M^+), 358, 216, 196, 175, 155, IR: $\nu(NH)$: 3291 cm^{-1} $\nu(C=N)$: 1592 cm^{-1} **4d**: $C_{15}H_{16}BrN_3O_2S$ (382.27), M.p.: 176 $^{\circ}C$, Yield 67 %, δ 7.95 (s, 1H, NH), 2.12 (s, 3H, CH_3), 2.39 (s, 3H, CH_3 -4-thiazole), 1.24 (t, 3H, CH_2CH_3), 4.12 (q, 2H, CH_2CH_3), 7.66 (d, 2H, Ar-H) 7.86 (d, 2H, Ar-H), m/z = 382 (M^+), 368, 309, 226, 198, 184, IR: $\nu(NH)$: 3288 cm^{-1} $\nu(C=N)$: 1588 cm^{-1} **4e**: $C_{15}H_{16}BrN_3O_2S$ (382.27), M.p.: 190 $^{\circ}C$, Yield 48%, δ 7.87 (s, 1H, NH), 2.29 (s, 3H, CH_3), 3.51 (s, 2H, 4-thiazolyl- CH_2 -), 1.24 (t, 3H, CH_2CH_3), 4.21 (q, 2H, CH_2CH_3), 7.58 (d, 2H, Ar-H) 7.84 (d, 2H, Ar-H), 6.99 (s, 1H, thiazole C5-H), m/z =382 (M^+), 368, 336, 226, 198, 184, 182, 155, IR: $\nu(NH)$: 3292 cm^{-1} $\nu(C=N)$: 1597 cm^{-1} **4f**: $C_{14}H_{14}BrN_3OS$ (352), M.p.: 243-6 $^{\circ}C$, Yield 64 %, δ 7.85 (s, 1H, NH), 2.30 (s, 3H, CH_3), 2.49 (s, 3H, CH_3 -4-thiazole), 1.39 (s, 3H, $COCH_3$), 7.50 (d, 2H, Ar-H) 7.74 (d, 2H, Ar-H), m/z = 352 (M^+), 336, 310, 196, 182, 170, 155, IR: $\nu(NH)$: 3293 cm^{-1} $\nu(C=N)$: 1589 cm^{-1} **4g**: $C_{12}H_{13}N_3OS$ (247.31), Yield 66%, M.p.: 152 $^{\circ}C$, δ 7.60 (s, 1H, thiazole C5-H), 7.86 (s, 1H, NH), 2.46 (s, 3H, CH_3), 2.36 (s, 3H, CH_3 -4-thiazole), 12.95 (1H, s, OH), 7.63 (d, 1H, Ar-H), 7.86 (t, 1H, Ar-H), 7.74 (t, 1H, Ar-H), 7.30 (d, 1H, Ar-H), m/z = 247 (M^+), 232, 134, 120, IR: $\nu(NH)$: 3276 cm^{-1} $\nu(C=N)$: 1588 cm^{-1} **4h**: $C_{12}H_{12}ClN_3OS$ (281.75), M.p.: 116-118 $^{\circ}C$, Yield 74%, δ 7.66 (s, 1H, thiazole C5-H), 7.76 (s, 1H, NH), 2.28 (s, 3H, CH_3), 2.56 (s, 2H, CH_2 -Cl), 12.65 (1H, s, OH), 7.58 (d, 1H, Ar-H), 7.88 (t, 1H, Ar-H), 7.64 (t, 1H, Ar-H), 7.45 (d, 1H, Ar-H), m/z = 281(M^+), 232, 147, 134, 120, IR: $\nu(NH)$: 3288 cm^{-1} $\nu(C=N)$: 1595 cm^{-1} **4i**: $C_{17}H_{15}N_3OS$ (309.38), Yield 62%, δ (s, 1H, thiazole C5-H), 7.69 (s, 1H, NH), 2.49 (s, 3H, CH_3), 7.33-7.41 (m, 5H, C_6H_5 -4-thiazole), 12.95 (1H, s, OH), 7.66 (d, 1H, Ar-H), 7.68 (t, 1H, Ar-H), 7.74 (t, 1H, Ar-H), 7.33 (d, 1H, Ar-H), m/z = 309 (M^+), 189, 175, 134, 98, IR: $\nu(NH)$: 3283 cm^{-1} $\nu(C=N)$: 1593 cm^{-1} **4j**: $C_{15}H_{17}N_3O_3S$ (319.37), M.p.: 187-9 $^{\circ}C$, Yield 69%, δ 7.86 (s, 1H, NH), 2.36 (s, 3H, CH_3), 2.26 (s, 3H, CH_3 -4-thiazole), 1.38 (t, 3H, CH_2CH_3), 4.12 (q, 2H, CH_2CH_3), 12.65 (1H, s, OH), 7.81 (d, 1H, Ar-H), 7.88 (t, 1H, Ar-H), 7.54 (t, 1H, Ar-H), 7.34 (d, 1H, Ar-H), m/z = 319 (M^+),

302, 274, 229, 185, 134, IR: $\nu(\text{NH})$: 3282 cm^{-1} $\nu(\text{C}=\text{N})$: 1599 cm^{-1} **4k**: $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$ (319.37), M.p.: $126-9^{\circ}\text{C}$, Yield 68%, δ 7.77 (s, 1H, NH), 2.24 (s, 3H, CH_3), 3.61 (s, 2H, 4-methylene), 1.34 (t, 3H, CH_2CH_3), 4.21 (q, 2H, CH_2CH_3), 12.65 (1H, s, OH), 7.60 (d, 1H, Ar-H), 7.77 (t, 1H, Ar-H), 7.69 (t, 1H, Ar-H), 7.12 (d, 1H, Ar-H), 7.21 (s, 1H, thiazole C5-H), $m/z=319$ (M^+), 302, 228, 185, 134, IR: $\nu(\text{NH})$: 3289 cm^{-1} $\nu(\text{C}=\text{N})$: 1600 cm^{-1} **4l**: $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ (289.35), Yield 67%, M.p.: 200°C , δ 7.60 (s, 1H, NH), 2.20 (s, 3H, CH_3), 2.39 (s, 3H, CH_3 -4-thiazole), 1.39 (s, 3H, COCH_3), 12.55 (1H, s, OH), 7.45 (d, 1H, Ar-H), 7.78 (t, 1H, Ar-H), 7.72 (t, 1H, Ar-H), 7.22 (d, 1H, Ar-H), $m/z=289$ (M^+), 246, 155, 134, IR: $\nu(\text{NH})$: 3279 cm^{-1} $\nu(\text{C}=\text{N})$: 1590 cm^{-1} **4m**: $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$ (263.31), Yield 58%, M.p.: 210°C , δ 7.56 (s, 1H, thiazole C5-H), 7.86 (s, 1H, NH), 2.28 (s, 3H, CH_3), 2.46 (s, 3H, CH_3 -4-thiazole), 12.65 (1H, s, OH), 12.83 (1H, s, OH), 7.23 (s, 1H, Ar-H), 7.88 (d, 1H, Ar-H), 7.71 (d, 1H, Ar-H), $m/z=263$ (M^+), 248, 150, 113, IR: $\nu(\text{NH})$: 3296 cm^{-1} $\nu(\text{C}=\text{N})$: 1587 cm^{-1} **4n**: $\text{C}_{12}\text{H}_{12}\text{ClN}_3\text{O}_2\text{S}$ (297.75), Yield 56%, M.p.: $205-7^{\circ}\text{C}$, δ 7.56 (s, 1H, thiazole C5-H), 7.66 (s, 1H, NH), 2.14 (s, 3H, CH_3), 2.36 (s, 2H, $\text{CH}_2\text{-Cl}$), 12.35 (1H, s, OH), 12.13 (1H, s, OH), 7.29 (s, 1H, Ar-H), 7.59 (d, 1H, Ar-H), 7.64 (d, 1H, Ar-H), $m/z=298$ (M^+), 248, 150, 148, IR: $\nu(\text{NH})$: 3287 cm^{-1} $\nu(\text{C}=\text{N})$: 1595 cm^{-1} **4o**: $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ (325.38), Yield 61%, M.p.: $240-2^{\circ}\text{C}$, δ 7.46 (s, 1H, thiazole C5-H), 7.96 (s, 1H, NH), 2.32 (s, 3H, CH_3), 7.33-7.41 (m, 5H, C_6H_5 -4-thiazole), 12.75 (1H, s, OH), 12.89 (1H, s, OH), 7.22 (s, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 7.79 (d, 1H, Ar-H), $m/z=325$ (M^+), 308, 292, 216 175, 150, IR: $\nu(\text{NH})$: 3290 cm^{-1} $\nu(\text{C}=\text{N})$: 1592 cm^{-1} **4p**: $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ (335.37), Yield 70%, M.p.: 280°C , δ 7.28 (s, 3H, CH_3), 7.86 (s, 1H, NH), 2.46 (s, 3H, CH_3 -4-thiazole), 1.38 (t, 3H, CH_2CH_3), 4.22 (q, 2H, CH_2CH_3), 12.45 (1H, s, OH), 12.73 (1H, s, OH), 7.06 (s, 1H, Ar-H), 7.49 (d, 1H, Ar-H), 7.51 (d, 1H, Ar-H), $m/z=335$ (M^+), 318, 290, 150, 136, IR: $\nu(\text{NH})$: 3286 cm^{-1} $\nu(\text{C}=\text{N})$: 1591 cm^{-1} **4r**: $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ (335.37), M.p.: $127-8^{\circ}\text{C}$, Yield 56%, δ 7.46 (s, 1H, thiazole C5-H), 7.66 (s, 1H, NH), 2.19 (s, 2H, 4-thiazolyl- CH_2 -), 1.20 (t, 3H, CH_2CH_3), 4.12 (q, 2H, CH_2CH_3), 12.75 (1H, s, OH), 12.23 (1H, s, OH), 7.13 (s, 1H, Ar-H), 7.68 (d, 1H, Ar-H), 7.38 (d, 1H, Ar-H), $m/z=335$ (M^+), 318, 289, 272, 262, 244, 150, 136, IR: $\nu(\text{NH})$: 3294 cm^{-1} $\nu(\text{C}=\text{N})$: 1599 cm^{-1} **4s**: $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$ (305.35), M.p.: 316°C , Yield 67%, δ 7.56 (s, 1H, NH), 2.46 (s, 3H, CH_3 -4-thiazole), 2.67 (s, 3H, COCH_3), 12.75 (1H, s, OH), 12.62 (1H, s, OH), 7.23 (s, 1H, Ar-H), 7.81 (d, 1H, Ar-H), 7.76 (d, 1H, Ar-H), $m/z=305$ (M^+), 288, 272, 193, 150, 136, IR: $\nu(\text{NH})$: 3291 cm^{-1} $\nu(\text{C}=\text{N})$: 1591 cm^{-1} **4u**: $\text{C}_{21}\text{H}_{17}\text{BrN}_4\text{S}_2$ (469.41), M.p.: 180°C , Yield 58%, δ 7.34 (s, 1H, thiazole C5-H), 7.76 (s, 1H, NH), 2.43 (s, 3H, CH_3), 2.86 (s, 3H, CH_3 -4-thiazole), 7.53 (d, 2H, Ar-H), 7.8 (d, 2H, Ar-H), 7.33-7.42 (m,

5H, Ph), $m/z=469$ (M^+), 271, 198, 184, 169, 155, IR: ν (NH): 3290 cm^{-1} ν (C=N): 1589 cm^{-1} **4v**: $C_{21}H_{18}N_4OS_2$ (406.52), M.p.: $244-246^\circ\text{C}$, Yield 69%, δ 7.29 (s, 1H, thiazole C5-H), 7.76 (s, 1H, NH), 2.23 (s, 3H, CH_3), 2.44 (s, 3H, CH_3 -4-thiazole), 12.73 (1H, s, OH), 7.29 (d, 1H, Ar-H), 7.88 (t, 1H, Ar-H), 7.84 (t, 1H, Ar-H), 7.62 (d, 1H, Ar-H), 7.34-7.44 (m, 5H, Ph), $m/z=406$ (M^+), 389, 286, 273, 169, 134, 120, IR: ν (NH): 3297 cm^{-1} ν (C=N): 1591 cm^{-1} **4x**: $C_{21}H_{18}N_4O_2S_2$ (422.51), Yield 55%, M.p.: 190°C , 7.24 (s, 1H, thiazole C5-H), 7.84 (s, 1H, NH), 2.23 (s, 3H, CH_3), 2.42 (s, 3H, CH_3 -4-thiazole), 12.65 (1H, s, OH), 12.49 (1H, s, OH), 7.23 (s, 1H, Ar-H), 7.88 (d, 1H, Ar-H), 7.87 (d, 1H, Ar-H), 7.19-7.52 (m, 5H, Ph), $m/z=422$ (M^+), 404, 371, 268, 169, 150, IR: ν (NH): 3293 cm^{-1} ν (C=N): 1590 cm^{-1}

2-[(2'-phenyl-thiazole-4'-yl)-methinhydrazin-thiazolyl ethyl esters 5a-b and 2-[(2''-phenyl-thiazole-4''-yl-methinhydrazin)]-2-phenyl-4-methyl-5,4'-bisthiazole 5c

0.002 mol of **3** was suspended in 10 mL absolute ethanol and 0.0022 mol of ethyl-2-chlor-acetoacetate, ethyl-4-chlor-acetoacetate respectively 5-bromacetyl-2-phenyl-4-methyl-thiazole were added, after which the mixtures were refluxed 2 hours. After cooling, the thiazole halohydrates were precipitated with ethylic ether and filtered. The residues were washed on filter with water. The resulted compounds were recrystallized from ethanol **5a**: $C_{17}H_{16}N_4O_2S_2$ (372), M.p. $192-4^\circ\text{C}$, Yield 58%, δ 7.74 (s, 1H, NH) 7.46 (s, 1H, thiazole C5-H), 2.26 (s, 3H, CH_3 -4-thiazole), 12.20 (s, 1H, N=CH), 1.34 (t, 3H, CH_2CH_3), 4.12 (q, 2H, CH_2CH_3), 7.12-7.66 (m, 5H, Ph), $m/z=372$ (M^+), 322, 308, 187, IR: ν (NH): 3300 cm^{-1} ν (C=N): 1588 cm^{-1} **5b**: $C_{17}H_{16}N_4O_2S_2$ (372), M.p.= $140-2^\circ\text{C}$, Yield 58%, δ 7.67 (s, 1H, NH), 3.43 (s, 2H, thiazole-4-methylene), 12.40 (s, 1H, N=CH), 1.24 (t, 3H, CH_2CH_3), 4.12 (q, 2H, CH_2CH_3), 7.03-7.40 (m, 5H, Ph), 7.87 (s, 1H, thiazole C5-H), 7.53 (s, 1H, thiazole C5-H), $m/z=372$ (M^+), 314, 299, 187, IR: ν (NH): 3309 cm^{-1} , ν (C=N): 1590 cm^{-1} **5c**: $C_{23}H_{17}N_5S_3$ (459), M.p.= $163-5^\circ\text{C}$, Yield 56%, δ 7.97 (s, 1H, NH), 3.22 (s, 3H, CH_3), 12.20 (s, 2H, N=CH), 7.26-7.56 (m, 5H, Ph), 7.58-7.89 (m, 5H, Ph), 7.23 (s, 1H, thiazole C5-H), 7.25 (s, 1H, thiazole C5-H), $m/z=459$ (M^+), 242, 187, IR: ν (NH): 3305 cm^{-1} ν (C=N): 1593 cm^{-1} .

Results and discussion

Spectral data

The obtaining of thiazole was confirmed by recording the IR, ^1H -NMR and mass spectra of all the compounds.

IR spectra of **4a-x** showed absorbtion bands between $3280-3309\text{ cm}^{-1}$ due to NH and between $1588-1600\text{ cm}^{-1}$ (C=N).

The ^1H -NMR spectra of 4a-s showed a singlet corresponding to NH proton in the region δ 7.59-7.99 ppm. A singlet between δ 6.90-7.66 ppm was attributed to the C-5 proton of the thiazole ring in the compounds unsubstituted in 5. The aromatic protons of the aryl ring (4-Br-phenyl, 2-hydroxy-phenyl, 2,4-dihydroxy-phenyl) resonated in the region of 7.02-7.91 ppm. The N=CH proton resonated as a singlet at δ 12.20-12.40 ppm.

Mass spectra of the compounds showed molecular ion peaks with high abundances at m/z in agreement with their molecular formula. The most important fragmentation is the fragmentation of N-N bond with the formation of ion peaks ($m/z = M^+ - \text{N} = \text{C}(\text{CH}_3)\text{-Aryl}$).

In the case of bisthiazole compounds 4u-x and 5a-c, the IR spectra showed absorption bands between 3280-3310 cm^{-1} due to NH and between 1580-1600 cm^{-1} (C=N). The ^1H -NMR spectra showed a singlet corresponding to NH proton between δ 7.67-7.97 ppm, and a singlet between δ 7.24-7.35 attributed to the C-5 proton of the bisthiazole ring. Mass spectra of bisthiazole compounds showed molecular ion peaks at m/z in agreement with their molecular formula and the most important fragmentation took place at the N-N level of bond.

Acknowledgement

This work was supported by research grant PNII-ID1271 CNCIS

References

1. Ahmet Ozdemir, Gulhan Turan-Zitouni, Zafer Asim Kaplanikh, Gilbert Revial, Krymet Guven, Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolil)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives, *European Journal of Medicinal Chemistry*, 2007, 42, 3, 403-409
2. Alaaddin Cukorvali, Ibrahim Yilmaz, Seher Gur, Cavit Kazaz, Synthesis, antibacterial and antifungal activity of some new thiazolylhydrazone derivatives containing 3-substituted cyclobutane ring, *European Journal of Medicinal Chemistry*, 2006, 41, 201-207
3. B. Shivarama Holla, K.V. Malini, B. Sooryanarayana Rao, B.K. Sarojini, N. Suchetha Kumari, Synthesis of some new 2,4-disubstituted thiazoles as possible antibacterial and anti-inflammatory agents, *European Journal of Medicinal Chemistry*, 2003, 38, 313-318
4. Franco Chimenti, Bruna Bizzari, Elias Maccioni, Daniela Secci, Adriana Bolasco et al., Synthesis and *in vitro* activity of thiazolylhydrazone derivatives compared with the activity of clotrimazole against clinical isolates of *Candida spp.*, *Bioorganic and Medicinal Chemistry Letters*, 2007, 17, 4635-4640
5. Laura Preda, Oniga O, Brîndușa Tiperciuc, Philippe Verité, O. Crișan, Doina Ghiran, The synthesis of new 2'-Aryl-2-Phenyl-4R-5,4' dithiazole derivatives, *Farmacia*, 2003, LI, 2, 65-71
6. Oniga O, Veronica Brad, Smaranda Oniga, Brîndușa Tiperciuc, Obținerea unor noi 2

- metil(fenil)-5,4' ditiazoli, *Farmacia*, 2004, LII 2, 36-42
7. Oya Bozdog-Dundar, Ozen Ozgen, Arzu Mentese, et. all., Synthesis and antimicrobial activity of some new thiazolyl-thiazolidine-dione derivatives, *Bioorganic and Medicinal Chemistry*, 2007, 15, 6012-6017
 8. Paola Vicini, Athina Geronikaki, Kitka Anastasia, Matteo Inceri, Franca Zani, Synthesis and antimicrobial activity of novel 2-thiazolylimino-5-arylidene-4-thiazolidinones, *Bioorganic and Medicinal Chemistry*, 2006 14, 3859-3864
 9. Samir Bondock, Wesam Khalifa, Ahmed A., Fadda, Synthesis and antimicrobial evaluation of some new thiazole, thiazolidinone and thiazoline derivatives starting from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde, *European Journal of Medicinal Chemistry*, 2007, 42, 948-954
 10. Oniga Smaranda, Oniga O, Brîndușa Tiperciuc, Mariana Palage, Ana Mureșan, Doina Ghiran, Synthesis and antimicrobial activity of some new 5-dithiazolyl-2-R-1,3,4- Δ 4-oxadiazoline derivatives, *Farmacia*, 2000, XLVIII, 3, 65-73

Manuscript received: January 7th 2010