HETEROCYCLES 28. SYNTHESIS AND CHARACTERIZATION OF SOME BIS AND POLYHETERERocyclic COMPOUNDS WITH ANTI-INFLAMMATORY POTENTIAL

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Abstract

The synthesis of some thiazolyl-mercaptotriazolic thioethers and their use in the obtaining of some potential anti-inflammatory polyheterocyclic compounds with thiazolo[3,2-b][1,2,4]triazole and pyrazole rings is presented. A structural analysis of the synthesized compounds was performed by IR, NMR and MS, confirming the structures of synthesized compounds. A ^{1}H NMR spectrometric analysis confirmed the presence of keto-enol and ring-chain tautomeric equilibrium for the synthesized thioethers.

Rezumat

Lucrarea prezintă sinteza unor tioeteri tiazolil-mercapto-triazolici şi utilizarea acestora în obţinerea unor derivaţi poliheterociclici tiazolo[3,2-b][1,2,4]triazolici şi pirazolici cu potenţial antiinflamator. S-a efectuat analiza structurală a compuşilor sintetizaţi prin spectroscopie IR, RMN şi spectrometrie de masă. În cazul tioeterilor sintetizaţi s-a confirmat prin spectroscopie ^{1}H RMN existenţa unor echilibre tautomere de tip ceto-enolic şi inel-catenă.

Keywords: thiazolyl-thiazolo[3,2-b][1,2,4]triazoles, 3-thiazolyl-5-pyrazolyl-1,2,4-triazoles, anti-inflammatory activity.

Introduction

Several medicinal chemistry and pharmacologic experimental research revealed the biological potential of thiazole, 1,2,4-triazole and pyrazole compounds. The 1,2,4-triazolic compounds present a wide variety of biological properties: antimicrobial [1-3], antiviral [4], anti-inflammatory [5,6], analgesic [7], antitumoral [8,9], insecticide [10] and anticonvulsant [11,12]. Thus, fluotrimazol, ribavirine and furazonal are used in therapy for their antimicrobial and antiviral properties, while estazolam, alprazolam and rizatriptane are used for their central nervous system (CNS) activity, all

being 1,2,4-triazole derivatives. The pyrazole ring is present in the structure of some biologically active compounds such as celecoxib and sildenafil or other compounds with antipsychotic [13], antimicrobial [14], anti-inflammatory properties [15].

In previous papers we presented the synthesis of some 1,2,4-triazole and thiazolo-triazole derivatives with antimicrobial and anti-inflammatory potential [16-22]. As a continuation of this research, we intended to synthesize and evaluate the anti-inflammatory potential of some polyheterocyclic compounds which include also 1,2,4-triazole and pyrazole rings, apart from the thiazole ring, well-known for its biologic potential.

Materials and Methods

Melting points were determined in open glass capillary methods with an Electrothermal melting point meter and were uncorrected. Elemental analysis (C, H, N, S) was performed on a VarioEL analyzer. The obtained results were within the admission limits: ±0.4%. Infrared spectra were recorded as KBr pellets with 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. ^{1}H NMR spectra were recorded on a BRUKER DRX 400 instrument operating at 400.13 MHz, with tetramethylsilane (TMS) as internal standard. The chemical shifts were reported in δ units (ppm) relative to the residual peak of the deuterated solvent ($CDCl_3$ and DMSO-d_6).

3-[5-(2-Phenyl-thiazol-4-yl)-1,2,4-triazol-3-yl-thio]-pentan-2,4-dione (2a)[18]

0.002 Moles of **1a** were suspended in 10 mL anhydrous acetone; 0.40 g sodium acetate and 0.002 moles of 3-chloro-acetylacetone were added. The mixture was stirred for two hours at room temperature, then poured into ice-water, filtered and re-crystallized from ethanol-water. M.p. 161-63^{o}C; $C_{16}H_{14}N_4O_2S_2$ (358.42); IR(cm^{-1}): 3411, 3101, 2974, 2826, 2712(νNH, νOH, νCH), 1733, 1714(νCO); EIMS(m/z): 358(M^+, 24%), 341, 316, 301, 274, 260, 149, 104, 83, 70, 43(100%); ^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm):
x: 2.44(s, 6H, CH_3CO); 4.01(s, 1H, CH-acetylacetone); 7.44(m, 3H, C_6H_5-*m*+*p*); 7.90(m, 2H, C_6H_5 *o*); 8.04(s, 1H, thiazole);
y: 2.35(s, 3H, $COCH_3$); 2.77(s, 3H, CH_3); 7.44(m, 3H, C_6H_5-*m*+*p*); 7.90(m, 2H, C_6H_5-*o*); 7.97(s, 1H, thiazole); 8.03(s, OH enol);
z: 2.36(s, 3H, CH_3); 2.42(s, 3H, $COCH_3$); 4.16(s, 1H, CH-acetylacetone); 7.44(m, 3H, C_6H_5-*m*+*p*); 7.90(m, 2H, C_6H_5-*o*); 8.01(s, 1H, thiazole).

3-[5-(4-Methyl-2-phenyl-thiazol-5-yl)-1,2,4-triazol-3-yl-thio]-pentan-2,4-dione (2b)[20]

The same method as for **2a**. M.p. 142-4°C; $C_{17}H_{16}N_4O_2S_2$ (372.45); IR (cm^{-1}): 3434, 3089, 2965, 2908, 2751(νNH, νOH, νCH), 1735(νCO); EIMS(m/z): 372(M^+, 58%), 330(100%), 287, 201, 185, 104, 97, 83, 70, 43; ^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm): 2.47(s, 6H, $COCH_3$); 2.81(s, 3H, CH_3); 7.45(m, 3H, C_6H_5-*m*+*p*); 7.96(m, 2H, C_6H_5-*o*).

3-[N-Acetyl-5-(2-Phenyl-thiazol-4-yl)-1,2,4-triazol-3-yl-thio]-pentan-2,4-dione (3a)

0.001 Moles of **2a** were treated with 2 mL acetic anhydride, 2 drops of pyridine were added and then the mixture was heated on a water bath until solvation and then left for 24 h at room temperature. The obtained substance was filtered and re-crystallized from ethanol. M.p. 183-5°C; $C_{18}H_{16}N_4O_3S_2$ (400.46); EIMS(m/z): 400(M, 20%), 358, 341, 315(100%), 301, 287, 273, 242, 187, 104, 83; ^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm): 2.38(s, 6H, $COCH_3$); 2.87(s, 3H, N-$COCH_3$); 7.48(m, 3H, C_6H_5-*m*+*p*); 8.04(s, 1H, thiazole); 8.06(m, 2H, C_6H_5-*o*).

3-[N-Acetyl-5-(4-Methyl-2-phenyl-thiazol-5-yl)-1,2,4-triazol-3-yl-thio]-pentan-2,4-dione (3b)

The same method as for **3a**. M.p. 157-9°C; $C_{19}H_{18}N_4O_3S_2$ (414.48); EIMS(m/z): 414(M^+, 47%), 372, 354, 329(100%), 301, 287, 201, 104, 71, 43; ^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm): 2.39(s, 6H, $COCH_3$); 2.78(s, 3H, N-$COCH_3$); 2.80(s, 3H, CH_3); 7.46(m, 3H, C_6H_5-*m*+*p*); 7.99(m, 2H, C_6H_5-*o*).

6 - Acetyl - 5 - methyl - 2 - (2-phenyl-thiazol-4-yl) - thiazolo [3,2-b] [1,2,4]-triazole (4a)

a. 0.002 Moles of **3a** were dissolved in sulphuric acid and maintained 3 h at room temperature, then poured into ice, the deposed substance filtered and re-crystallized from ethanol.

b. 0.002 Moles of **1a** were suspended in 5 mL ethanol, then 0.002 moles of 3-chloro-acetylacetone was added, the mixture was heated on a water bath for 4 h. After the solution was cooled, the deposed substance was filtered and re-crystallized from ethanol. M.p. 196-8°C; IR(cm^{-1}): 3092, 3029, 2970, 2852, 2713(νCH), 1650(νCO ketone); EIMS(m/z): 340(M^+, 100%), 325, 237, 222, 83, 71; ^{1}H-RMN 300 MHz (DMSO-d_6), δ(ppm): 2.66(s, 3H, $COCH_3$); 2.95(s, 3H, CH_3); 7.56(m, 3H, C_6H_5-*m*+*p*); 8.04(m, 2H, C_6H_5-*o*); 8.41(s, 1H, thiazole).

6-Acetyl-5-methyl-2-(4-methyl-2-phenyl-thiazol-5-yl)-thiazolo[3,2-b][1,2,4]-triazole (4b)

The same method as for **4a**. M.p. 229-30°C; $C_{17}H_{14}N_4OS_2$ (354.43); IR (cm^{-1}): 3090, 2980, 2921(νCH), 1659(νCO ketone); EIMS(m/z): 354(M^+, 100%), 251, 182, 104, 71, 43; ^{1}H-RMN 300 MHz($CDCl_3$), δ(ppm): 2.62(s, 3H, $COCH_3$); 2.93(s, 3H, CH_3); 2.97(s, 3H, CH_3); 7.47(m, 3H, C_6H_5-*m*+*p*); 8.00(m, 2H, C_6H_5-*o*).

3-(4-Methyl-2-phenyl-thiazol-5-yl)-5-(3,5-dimethyl-pyrazol-4-yl-thio)-1,2,4-triazole (5b)

0.001 Moles of **3b** were dissolved in 5 mL ethanol, treated with 0.05 mL hydrazine hydrate and then heated on a water bath for 2 h. The solution was cooled and the deposed substance was filtered and re-crystallized from DMFA-water. M.p. 250-52°C; $C_{17}H_{16}N_6S_2$ (368.47); IR(cm^{-1}): 3200, 3074, 2963, 2872, 2734(νNH, νCH), 1573(νC=N); EIMS(m/z): 368(M^+, 100%), 335, 274, 265, 171, 141, 104, 97, 95, 45, 42; ^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm): 2.22(s, large, 6H, $2CH_3$); 2.70(s, 3H, CH_3); 7.50(m, 3H, C_6H_5-*m*+*p*); 7.95(m, 2H, C_6H_5-*o*).

N-Acetyl-3-(4-Methyl-2-phenyl-thiazol-5-yl)-5-(1-acetyl-3,5-dimethyl-pyrazol-4-yl-thio)-1,2,4-triazole (6b)

0.001 Moles of **5b** were treated with 2 mL acetic anhydride, 2 drops of pyridine were added; the mixture was heated on a water bath until solution and then left for 24 h at room temperature. The deposed substance was filtered and washed with ethanol. Mp. 193-4°C; $C_{21}H_{20}N_6O_2S_2$ (452.54); IR(cm^{-1}): 2969, 2923(νCH), 1733(νCO amidic), 1557(νC=N); EIMS(m/z): 452(M^+, 90%), 410(100%), 368, 335, 274, 200, 171, 141, 104, 97, 70, 43; ^{1}H-RMN 300 MHz (DMSO-d_6), δ(ppm): 2.32(s, 3H, CH_3); 2.67(s, 3H, CH_3); 2.72(s, 3H, CH_3); 2.76(s, 3H, $COCH_3$); 2.79(s, 3H, $COCH_3$); 7.45(m, 3H, C_6H_5-*m*+*p*); 7.96(m, 2H, C_6H_5-*o*).

3-(4-Methyl-2-phenyl-thiazol-5-yl)-5-(3,5-dimethyl-1-phenyl-pyrazol-4-yl-thio)-1,2,4-triazole (7b)

0.001 Moles of **3b** were dissolved in 5 mL ethanol, then treated with 0.11g phenyl-hydrazine and heated on a water bath for 2 h. The solution was cooled and the deposed substance was filtered and re-crystallized from ethanol. M.p. 217°C; $C_{23}H_{20}N_6S_2$ (444.56); IR(cm^{-1}): 3069, 2963, 2921, 2873, 2733(νNH, νCH), 1596(νC=N); EIMS(m/z): 444(M^+, 92%), 411, 272, 244, 222, 171(100%), 118, 171, 104, 77;

3-(2-Phenyl-thiazol-5-yl)-5-[p-bromophenyl-3,5-dimethyl-pyrazol-4-yl-thio]-1,2,4-triazole (8a)

0.001 Moles of **3a** were dissolved in 5 mL ethanol and then treated with 0.25g p-bromo-phenylhydrazine dissolved in 5 mL ethanol and heated on a

water bath for 6 h. The solution was cooled and the deposed substance was filtered and re-crystallized from ethanol. M.p. 253-4°C;$C_{22}H_{17}N_6S_2Br$ (509.44); IR(cm^{-1}): 3207, 2916(νCH), 159(νC=N); $C_{22}H_{17}N_6S_2Br$ (509.44); EIMS(m/z): 510, 508(M^+, 100%), 430, 338, 299, 254,171, 91, 83, 39; ^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm): 2.35(s, 3H, CH_3); 2.88(s, 3H, CH_3); 7.04(d, 2H, C_6H_4Br, $^3J_{HH}$=8.20 Hz); 7.42(d, 2H, C_6H_4Br, $^3J_{HH}$=8.20 Hz); 7.48(m, 3H, C_6H_5-*m*+*p*); 8.07(s, 1H, thiazole); 8.12(m, 2H, C_6H_5-*o*).

N-Acetyl-3-(4-methyl-2-phenyl-thiazol-5-yl)-5-(3,5-dimethyl-1-phenyl-pyrazol-4-yl-thio)-1,2,4-triazole (9b)

The same method as for **6b**. M.p. 160-2°C; $C_{25}H_{22}N_6OS_2$ (486.60); IR(cm^{-1}): 3067, 2919(νCH), 1728(νCO amide), 1598(νC=N); EIMS(m/z): 486(M^+, 73%), 444, 411, 214, 200, 171(100%), 130, 118, 104, 77, 43; ^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm): 2.38(s, 3H, CH_3); 2.39(s, 3H, CH_3); 2.75(s, 3H, CH_3); 2.80(s, 3H, $COCH_3$); 7.43-7.55(m, 2H, C_6H_5-*o*, 6H, C_6H_5-*m*+*p*); 7.97(m, 2H, C_6H_5 *o* phenyl-thiazole).

N-Acetyl-3-(2-phenyl-thiazol-5-yl)-5-[p-bromophenyl-3,5-dimethyl-pyrazol-4-yl-thio -1,2,4-triazole (10a)

The same method as for **6b**. M.p. 202-4°C; $C_{24}H_{19}N_6OS_2Br$ (551.45); IR(cm^{-1}): 3120, 3067, 2926(νCH), 1727(νCO amide), 1573(νC=N); EIMS(m/z): 552, 550(M^+, 8.5%), 510, 430, 249, 196, 187, 170, 155, 129, 104, 76, 43(100%); ^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm): 2.37(s, 3H, CH_3); 2.41(s, 3H, CH_3); 2.89(s, 3H, N-$COCH_3$); 7.43(d, 2H, C_6H_4Br *o*, $^3J_{HH}$=8.7 Hz); 7.47(m, 3H, C_6H_5-*m*+*p*); 7.65(d, 2H, C_6H_4Br-*m*, $^3J_{HH}$=8.7 Hz); 7.95(s, 1H, thiazole); 8.05(m, 2H, C_6H_5-*o*).

6-Bromoacetyl-5-methyl-2-(2-phenyl-thiazol-4-yl)-thiazolo[3,2-b][1,2,4]triazole (11a)

0.34g (0.001 moles) of **4a** were dissolved in 10 mL tetrachloromethane; 0.05 mL bromine were added and then refluxed for 4h on a water bath. The solvent was evaporated and the obtained residue was re-crystallized from ethanol. M.p. 203-5°C; $C_{16}H_{11}N_4OS_2Br$ (419.31); IR(cm^{-1}): 3062, 2917, 2848(νCH), 1654(νCO cetone); EIMS(m/z): 420, 418 (M^+, 42%), 339(100%), 325, 297, 236, 162, 151, 126, 103, 83, 70, 43;^{1}H-RMN 300 MHz ($CDCl_3$), δ(ppm): 2.64(s, 3H, CH_3); 3.04(s, 3H, CH_3); 7.49(m, 3H, C_6H_5-*m*+*p*); 8.01(m, 2H, C_6H_5-*o*); 8.12(s, 1H, thiazole).

Methyl 5-methyl-2-(2-phenyl-thiazol-4-yl)-thiazolo[3,2-b][1,2,4]-triazol-6-yl cetoxime (12a)

0.34g (0.001 moles) of **4a** were dissolved in 10 mL ethanol. A solution obtained from 0.14g (0.002 moles) hydroxylamine hydrochloride and 0.164g (0.002 moles) sodium acetate was added. The mixture was refluxed for 3 h, then the solution was cooled and the deposed oxime was filtered and

re-crystallized from ethanol. M.p. 287-88°C; $C_{16}H_{13}N_5OS_2$ (355.42); IR(cm^{-1}): 3162(νOH), 3082, 2916(νCH), 1557(νC=N); EIMS(m/z): 355(M^+, 100%), 339, 313, 252, 187, 104, 83, 77, 57, 39;
^{1}H-RMN 300 MHz (DMSO-d_6), δ(ppm): 2.32(s, 3H, CH_3); 2.76(s, 3H, CH_3); 7.56(m, 3H, C_6H_5-*m*+*p*); 8.04(m, 2H, C_6H_5-*o*); 8.31(s, 1H, thiazole).

5-Methyl-2-(2-phenyl-thiazol-4-yl)-thiazolo[3,2-b][1,2,4]triazol-6-carboxylic acid (13a)

0.34g (0.001 moles) of **4a** were dissolved in 15 mL dioxane and then added to a cooled solution obtained from 10 g sodium hydroxide, 40 mL water and 2.5 mL bromine. The mixture was stirred for 12 h. The solution was acidulated with hydrochloric acid and then $NaHSO_3$ was added to remove the excess of bromide. The deposed carboxylic acid was filtered and re-crystallized from DMFA-water (DMFA – dimethyl formamide). M.p. 279-80°C; $C_{15}H_{10}N_4O_2S_2$ (342.38); IR(cm^{-1}): 3107, 3062, 2960, 2930, 2853(νOH carboxyl, νCH), 1701(νCO carboxyl); EIMS(m/z): 342(M^+, 85%), 298(100%), 274, 239, 195, 187, 162, 149, 112, 104, 83, 71, 44;

5-Methyl-2-(4-methyl-2-phenyl-thiazol-5-yl)-thiazolo[3,2-b][1,2,4]triazol-6-carboxylic acid (13b)

The same method as for **14a**. M.p. >283°C; $C_{16}H_{12}N_4O_2S_2$ (356.41); IR(cm^{-1}): 3057, 3013, 2855, 2557(νOH carboxyl, νCH), 1671(νCO carboxyl); EIMS(m/z): 356(M^+, 18%), 312(100%), 253, 209, 176, 164, 156, 140, 114, 104, 96, 77, 70, 44;

5-Methyl-2-(2-phenyl-thiazol-4-yl)-thiazolo[3,2-b][1,2,4]-triazol-6-yl-ethandial (14a)

0.34 g (0.001 moles) of **4a** were dissolved in 5 mL warm acetic acid. 0.30g selenium dioxide dissolved in 2 mL of water were added and then the solution was refluxed for 1 h. The warm solution was filtered, diluted with water and then the dicarbonyl compound was separated and re-crystallized from ethanol. M.p. 205°C; $C_{16}H_{10}N_4O_2S_2$ (354.39); IR(cm^{-1}): 2916, 2848(νCH), 1716, 1664(νCO aldehyde and ketone); EIMS(m/z): 354(M^+, 36%), 326(100%), 298, 237, 222, 186, 149, 111, 103, 83, 70, 43;

5-Methyl-2-(4-methyl-2-phenyl-thiazol-5-yl)-thiazolo[3,2-b][1,2,4]-triazol-6-yl-ethandial (14b)

The same method as for **15a**. M.p. 221-3°C; $C_{17}H_{12}N_4O_2S_2$ (368.42); EIMS(m/z): 368(M^+, 3%), 339, 251(100%), 182, 141, 104, 96, 83, 71;

2-[5-Methyl-2-(2-phenyl-thiazol-4-yl)-thiazolo[3,2-b][1,2,4]-triazol-6-yl]-quinoxaline (15a)

0.35g (0.001 moles) of **15a** were dissolved in 5 mL ethanol, then 0.11g (0.001 moles) o-phenylendiamine dissolved in 2 mL ethanol were added. The mixture was refluxed for 2 h and then the deposed substance was

filtered after cooling and re-crystallized from ethanol. M.p. 234-6°C; $C_{22}H_{14}N_6S_2$ (426.50); IR(cm^{-1}): 3066, 2916, 2848(νCH), 1664(νC=N); EIMS(m/z): 426(M^+, 100%), 323, 251, 213, 199, 168, 129, 102, 83, 77; ^{1}H-RMN 300 MHz (DMSO-d_6), δ(ppm): 3.11(s, 3H, CH_3); 7.57(m, 2H, quinoxaline); 7.93(m, 2H, quinoxaline); 8.06(m, 3H, C_6H_5-*m*+*p*); 8.17(m, 2H, C_6H_5-*o*); 8.42(s, 1H, thiazole); 9.48(s, 1H, quinoxaline-*3*).

Results and Discussion

For the synthesis of the compounds, we applied the condensation reaction of the thiazolyl-mercaptotriazoles obtained previously [18, 20] with 3-chloro-acetylacetone (Figure 1). According to the reaction conditions, different results were obtained. Thus, if the reaction was performed in acetone, at room temperature and in the presence of a base (sodium acetate, sodium carbonate), the **2a** and **2b** thioethers were obtained, which were transformed in the corresponding derivates **3a** and **3b** by reacting with acetic anhydride. If no base was present, apart from the **2a,b** thioethers, the cyclisation products with a triazolo[3,2-b][1,2,4]triazolic structure **4a,b** were obtained. The cyclisation products were directly obtained, with very good results, if the condensation reaction was performed in ethanol at reflux. These compounds may also be obtained by the action of the concentrated sulphuric acid on the **2a,b** and **3a,b** tioethers, or by heating at boiling temperature the **2a,b** tioethers in ethanolic solution, in the presence of hydrochloric acid.

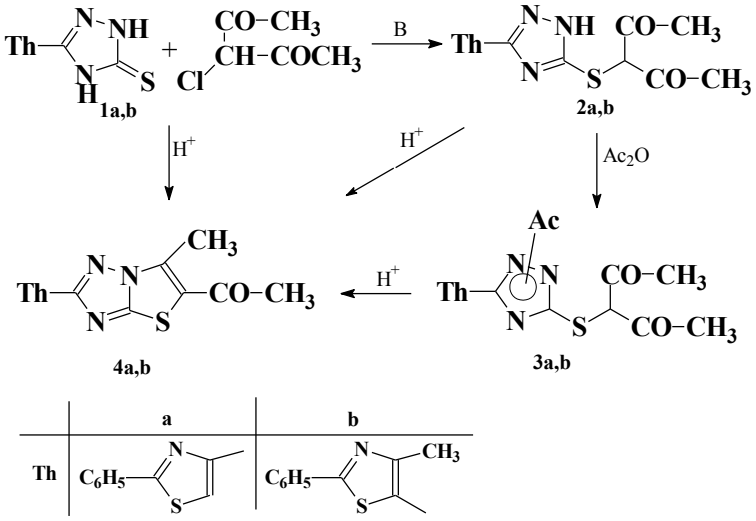

Figure 1

Synthesis and cyclisation of thiazolyl-mercaptotriazolic thioethers

Due to the acetyl-acetone fragment from **2a,b**, which renders them sensitive to binucleophils action, these compounds were transformed into the corresponding pyrazoles, **5b**, **7b** and **8a** by reacting with hydrazine, phenylhydrazine and p-bromo-phenylhydrazine (**Figure 2**). The obtained pyrazoles were transformed into the acetyl derivatives **6b**, **9b** and **10a** by reacting with acetic anhydride. By the acetylation of **5b**, the **6b** diacetylderivative was obtained due to the unsubstituted position 1 from the pyrazole ring.

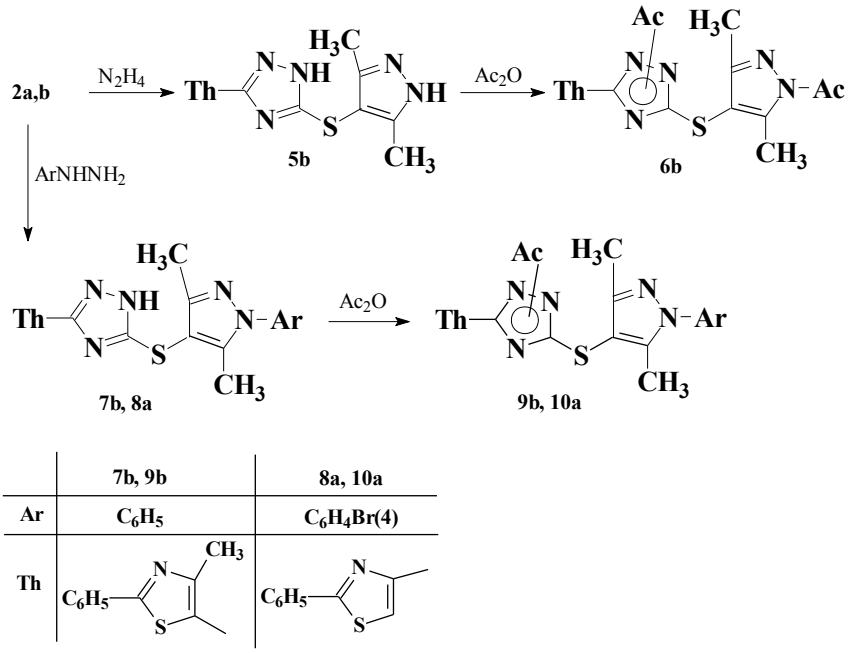

Figure 2
Synthesis of pyrazole derivatives

Subsequently, the chemical behaviour of the acetyl group from position 6 of the thiazolo[3,2-b][1,2,4]triazole system was studied. Thus, the ketone **4a** was subjected to a bromination reaction, obtaining the compound **11a** and transformed in the corresponding oxime **12a** by reacting with hydroxylamine (Figure 3). The compounds **2a,b** were subjected to a haloforme reaction, obtaining the carboxylic acids **13a,b**, which were also obtained by base hydrolysis of the corresponding ethyle esters. Considering the methylene-active character of the methyl from the acetyl group, we intended to obtain the ketoaldehyde **14a** by the reaction of the ketone **4a** with selenium dioxyde. Although an excess of oxidant was used (4 mol

SeO_2:1 mol ketone), the dicarbonylic compound was obtained with a low yield. This was characterized by the transformation into the corresponding 2,4-dinitro-phenylhydrazone, a corresponding quinoxaline, **15a**, being also obtained for the **14a** compound.

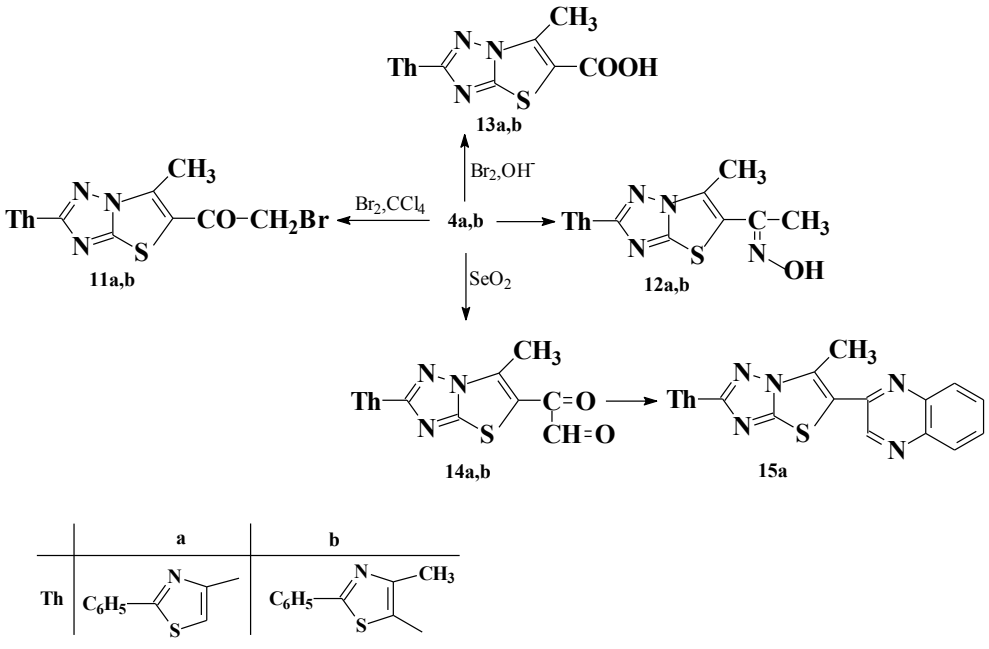

Figure 3
Chemical behaviour of thiazolo[3,2-b][1,2,4]triazoles **4a,b**

The IR, MS and NMR spectra confirmed the structures of the obtained compounds. A molecular peak was present in the mass spectra of all the synthesised compounds. Apart from the thioethers **2** and **3** and 14 dicarbonilic compounds, the molecular peak is relatively abundant or it is the base peak of the spectrum. The fragmentation peaks from the spectra are due to the fragmentations in the heterocyclic systems or in the functional groups from the molecule.

In the IR spectra of the tioethers **2a,b** several peaks can be associated with the vibrations of the NH, enolic OH/alcoholic OH and CO functional groups, which is an argument in favour of the existence of keto-enol and ring-chain tautomeric equilibrium (Figure 4). The IR spectra are simplified by cyclisation, because the peaks attributed to the OH and NH groups are missing and the peaks of νC=O vibrations were shifted toward lower wavelength values (1650, 1659 cm^{-1}). The νC=O peaks were also missing from the IR spectra of pyrazoles (apart from the acetylated

compounds **6, 9, 10**) which confirmed the fact that the reaction of thioethers **2** with the hydrazine derivatives has occurred. The vibrations bands of the functional groups from the thiazolo[3,2-b][1,2,4]triazoles **11, 12, 13 and 14**: carbonyl (aldehyde, ketone, carboxyl) and hydroxyl (oxime and carboxyl), were also present.

The ^{1}H NMR spectra of the compounds **2** confirmed the existence of some tautomers derived from acetylacetone rest, like in the case of some 1,2,4-triazole acetoacetate derivatives [23]. The ^{1}H NMR spectrum of the compound **2a** presented signals which were attributed to the protons from the tautomeric forms in equilibrium (Figure 4).

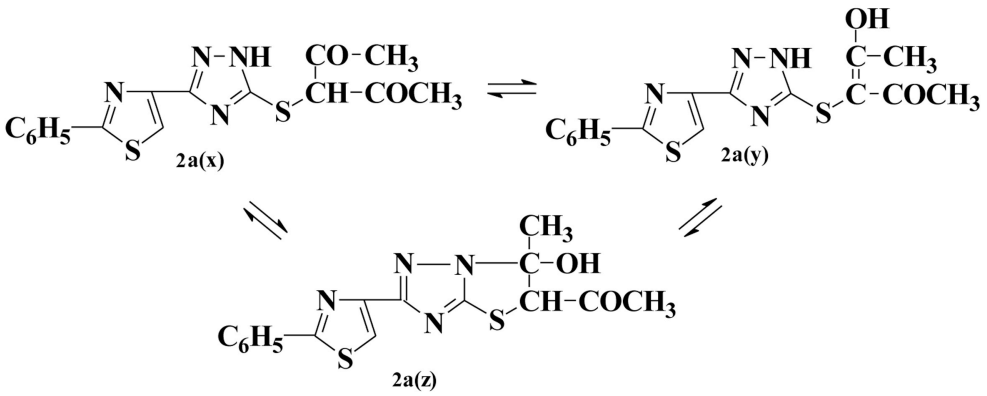

Figure 4
Tautomeric equilibriums of compounds **2a**

Thus, for the keto tautomer (***x***), the signal at 2.44 ppm was attributed to the six equivalent protons from the acetyl rest, at the proton from position 3 of the acetyl-acetone rest being attributed the signal at 4.01 ppm. For the enolic tautomer (***y***) the signals from 2.35 ppm (CO-CH_3), 2.77 ppm (CH_3) and 8.03 ppm (OH enolic) were attributed, while the signals at 2.36 ppm (CH_3) and 2.42 ppm (CO-CH_3) were assigned to the cyclic tautomer (***z***). The existence of keto-enolic tautomerism was confirmed, also, by the positive reaction with Fe(III) and Cu(II) (enol tautomer) and, also, with 2,4-dinitrophenylhydrazine (ketone tautomer).

Conclusions

A series of polyheterocyclic compounds with isolated and condensed rings, with biologic potential, were synthetised: thiazolyl-mercapto-1,2,4-triazolic thioethers (**2,3**), thiazolyl-thiazolo[3,2-b][1,2,4]triazoles (**4,11-15**) and thiazolyl-1,2,4-triazolyl-thio-pyrazoles (**5-10**).

The synthesized compounds were characterised by IR, ^{1}H NMR and MS analysis. For the thioethers **2a,b** the presence of keto-enolic and ring-chain tautomeric equilibriums, suggested by the chemical behaviour of these compounds, was confirmed by IR and ^{1}H NMR spectra.

The chemical behaviour of the functional groups from the position 6 of the thiazolo[3,2-b][1,2,4]triazole system was studied.

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