ORIGINAL ARTICLE

HETEROCYCLES 42. SYNTHESIS AND CHARACTERIZATION OF NEW THIAZOLO[3,2-B] [1,2,4]TRIAZOLE DERIVATIVES WITH ANTI-INFLAMMATORY POTENTIAL

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Abstract

Heterocyclic compounds containing the 1,2,4-triazole ring and the thiazolo[3,2-b][1,2,4]triazole fused ring system in their structure have been reported to exhibit antibacterial, antifungal, anticancer, anti-inflammatory and analgesic activities. Considering this fact, the aim of this study was the synthesis and characterization of novel thiazolo[3,2-b][1,2,4]triazole derivatives and their corresponding acyclic thioether intermediates, having different substituents which lead to anti-inflammatory activity. Thiazolo[3,2-b][1,2,4]triazole derivatives were obtained in a single step when the condensation between mercapto-triazoles and α-halogenocarbonyls was performed at reflux in acid catalysis, or *via* acyclic thioether intermediates, when the synthesis was performed at room temperature, in alkaline media. The synthesized compounds were purified and characterized by ^{1}H NMR, ^{13}C NMR, IR and MS. Their biological potential concerning anti-inflammatory and analgesic activities will be investigated in further studies.

Rezumat

Compușii heterociclici care conțin în structura lor sistemele 1,2,4-triazol și tiazolo[3,2-b][1,2,4]triazol prezintă proprietăți antibacteriene, antifungice, anticanceroase, antiinflamatoare și analgezice. Plecând de la acest aspect, obiectivul acestui studiu a fost sinteza și caracterizarea unor noi derivați tiazolo[3,2-b][1,2,4]triazolici și a intermediarilor tioeterici aciclici corespunzători, cu diverși substituenți care determină activitatea antiinflamatoare. Compușii tiazolo[3,2-b][1,2,4]triazolici s-au obținut direct, prin condensarea mercapto-triazolilor cu compuși α–halogenocarbonilici la cald, în cataliză acidă, sau prin intermediul tioeterilor aciclici, dacă reacția de condensare a avut loc la temperatura camerei, în mediu bazic. Compușii obținuți au fost purificați și caracterizați prin metode spectrale (^{1}H NMR, ^{13}C NMR, IR și MS) și vor fi evaluați din punct de vedere al potențialului antiinflamator și analgezic.

Keywords: 1,2,4-triazole, thiazolo[3,2-b][1,2,4]triazole, spectral analysis

Introduction

Triazoles are heterocyclic compounds presenting three nitrogen atoms as part of an aromatic five-membered ring. Triazole presents two isomers: 1,2,3-triazole and 1,2,4-triazole, the last one is found and used more often as a precursor in biologically active compounds [20, 22]. 1,2,4-Triazoles exist in two tautomeric forms: 4H-1,2,4-triazole and 1H-1,2,4-triazole which is more stable. Among substituted 1,2,4-triazole compounds, 3-mercapto-1,2,4-triazoles exist in two tautomeric forms: the thione form, when the mobile hydrogen is attached to the nitrogen, and the thiol form, when the mobile hydrogen is attached to the sulfur [16]. The 1,2,4-triazole ring represents a central core in the structure of many drugs, as well as other several drug candidates presenting anti-inflammatory [13], analgesic [1], antioxidant [21], antimicrobial [7], anticancer [3] and anticonvulsant [17] properties.

The thiazole ring is an important pharmacophore presenting antioxidant [8], anti-inflammatory [26], analgesic [19] and antimicrobial [14] properties.

Several reported studies revealed that the condensation of 1,2,4-triazole and 1,3-thiazole in a fused ring system could lead to the synthesis of new compounds possessing superior pharmacological activities, due to the thiazolo-triazole condensed ring system and to the reciprocal influence between the two hetero-

cyclic rings. Thiazolo-triazole compounds exist as two isomers, thiazolo[3,2-b][1,2,4]triazole and thiazolo-[2,3-c][1,2,4]triazole. Thiazolo[3,2-b][1,2,4]triazoles are presented in various molecules with biological activities like antimicrobial [5, 9], analgesic, anti-inflammatory [29], anticancer [11] and antioxidant [2] properties.

The importance of thiazolo[3,2-b][1,2,4]triazoles in bioactive molecules has stimulated interest in synthesizing new improved derivatives, characterized by the same biological activities and more reduced side effects. Based on these considerations and in continuation of the earlier work on the synthesis of thiazolo-triazole derivatives from our research laboratory [15, 23-26], the aim of the present work was the synthesis and characterization of new hetero-cyclic compounds through chemical and structural variations on molecules whose activity has been shown in several studies. The conducted research was oriented to the synthesis of new thiazolo[3,2-b] [1,2,4]triazole derivatives bearing various substituents that are found in the structure of several anti-inflammatory compounds, reported in literature. The anti-inflammatory and analgesic potential of the new synthesized thiazolo[3,2-b][1,2,4]triazole derivatives will be investigated in further studies.

Materials and Methods

All chemical reagents and solvents necessary for the synthesis were purchased from Sigma-Aldrich, TCI Chemicals or Merck.

Thin layer chromatography (TLC) was performed using Merck Kieselgel 60F254 sheets, and different eluents as mobile phase: a mixture of dichloromethane: acetone 25:1 v/v for thiazolo[3,2-b][1,2,4]triazoles and dichloromethane: acetone 9:1 v/v for their acyclic imino thioethers. The spots were visualized in the UV light at 254 nm. The compounds were recrystallized from ethanol or a mixture of ethanol: water. Preparative chromatographic purifications were performed especially for thiazolo-triazoles substituted with tri-fluoromethyl moiety, using Merck Kieselgel 60Å column chromatography and a mixture of dichloro-methane:acetone 2:1 v/v as eluent.

The mass spectra (MS) were recorded using an Agilent 1100 Ion trap mass spectrometer operating at 70 eV. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker Avance DPX-300 spectrometer operating at 600 MHz and 151 MHz, in DMSO-D_6 and $CDCl_3$ as solvents and TMS as internal standard. The spectral data are mentioned in the Results and Discussion section, using the following abbreviations for peak patterns: s-singlet, d-doublet, dd-double doublet, t-triplet, q-quartet, br s-broad signal.

The FT-IR analysis was performed on a Jasco FT/IR 470 Plus spectrometer by using the Spectra Manager software. The solid sample was introduced in the ATR (Attenuated Total Reflection) device's slot and the IR spectra were recorded between 4000 and 400 cm^{-1} wavelengths at 4 cm^{-1} resolution.

Melting points were determined using open glass capillaries on an Electrothermal IA 9000 digital apparatus and were uncorrected.

Chemical synthesis

The pathways of the synthesis leading to the thiazolo[3,2-b][1,2,4]triazole derivatives, as shown in Figure 1, are starting from the synthesis of 1,2,4-triazole. The 1,2,4-triazole derivatives were obtained by the cyclization of the acylthiosemicarbazides, previously synthesized by the condensation of the corresponding hydrazides with potassium thiocyanate in acid catalysis. The cyclisation of acylthiosemi-carbazides was performed in alkaline media (10% NaOH aqueous solution), at reflux. The sodium mercaptides formed as intermediates in the reaction media were transformed in the corresponding mercapto-triazoles **1-4** by treatment with concentrated acetic acid [15, 27].

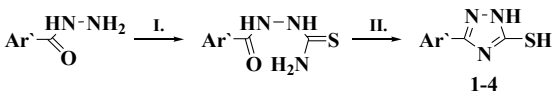
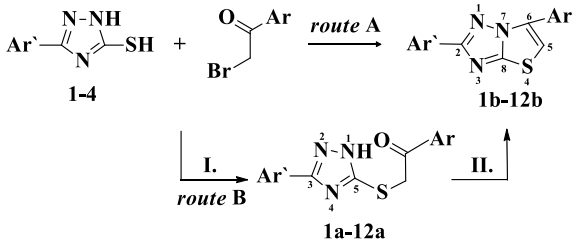


Figure 1.

The synthesis of 3-aryl-5-mercapto-1,2,4-triazole derivatives. Reaction conditions: **I.** HCl 36.5%, KSCN, reflux 3 h; **II. 1.** NaOH 10%, reflux 3 h, **2.** CH_3COOH conc. [15, 27]

The synthesis of the thiazolo[3,2-b][1,2,4]triazole derivatives is described in Figure 2 [15, 27-29]. The first route (**route A**) consists in the condensation of mercapto-triazoles **1-4** with different α-halogeno-ketones (phenacyl bromides, chloroacetone or ethyl 2-chloracetoacetate). The alternative pathway (**route B**) involves the formation and isolation of the imino thioether intermediates, which are cyclized in a further step, by treating with concentrated sulfuric acid, at room temperature [12, 24, 28].



Compounds	Ar`	Ar
1a, 1b	-C_6H_5	-C_6H_5
2a, 2b	-C_6H_5	(*p*)Br-C_6H_4-
3a, 3b	-C_6H_5	(*p*)CF_3-C_6H_4-
4a, 4b	-C_6H_5	(*p*)CH_3O-C_6H_4-
5a, 5b	(*p*)Cl-C_6H_4-	-C_6H_5
6a, 6b	(*p*)Cl-C_6H_4-	(*p*)Br-C_6H_4-
7a, 7b	(*p*)Cl-C_6H_4-	(*p*)CF_3-C_6H_4-
8a, 8b	(*p*)Cl-C_6H_4-	(*p*)CH_3O-C_6H_4-
9a, 9b	(*p*)CH_3O-C_6H_4-	-C_6H_5
10a, 10b	(*p*)CH_3O-C_6H_4-	(*p*)Br-C_6H_4-
11a, 11b	(*p*)CH_3O-C_6H_4-	(*p*)CF_3-C_6H_4-
12a, 12b	(*p*)CH_3O-C_6H_4-	(*p*)CH_3O-C_6H_4-

Figure 2.

The synthesis of the thiazolo[3,2-b][1,2,4]triazole derivatives and their imino thioether intermediates (**route A**: absolute ethanol, H_2SO_4 conc., reflux 2 - 30 h; **route B**: **I.** absolute ethanol, $NaHCO_3$, room temperature, 24 - 48 h; **II.** H_2SO_4 conc., 2 - 12 h)

*General procedure for the synthesis of 3-aryl-1,2,4-triazole thioethers **(1a-12a)***

To a stirred solution of 3-aryl-5-mercapto-1,2,4-triazole **1-4** (1 mmol) and sodium bicarbonate (1 mmol) in 10 mL absolute ethanol, the corresponding phenacyl bromide was added (1.2 mmol). The reaction mixture was stirred at room temperature for 24 to 48 hours, depending of the reaction progress, monitored by TLC. The formed precipitate was poured on ice, filtered and purified by recrystallization or by column chromatography.

*General procedure for the synthesis of thiazolo[3,2-b][1,2,4]triazole derivatives **(1b-12b)***

Procedure A. To a solution of 3-aryl-5-mercapto-1,2,4-triazole **1-4** (1 mmol) in 10 mL absolute ethanol, the corresponding phenacyl bromide was added (1.2 mmol). The reaction mixture was refluxed for 2 hours and after that, the solution was cooled. 0.5 mL of concentrated sulfuric acid was added to the mixture and it was refluxed for another 2 - 30 hours, depending of the reaction progress, monitored by TLC. The reaction mixture was cooled, poured on ice and neutralized with a solution of sodium hydroxide. The formed precipitate was filtered and purified by recrystallization or by column chromatography.

Procedure B. 0.1 g of 3-aryl-1,2,4-triazole thioether **1a-12a** previously obtained was poured into 0.5 mL of concentrated sulfuric acid for 1-12 hours, depending of the cyclization progress which was monitored by TLC. After the reaction was finished, the solution was poured onto ice and the formed precipitate was filtered. The obtained product was purified by re-crystallization or by column chromatography.

Results and Discussion

The new polyheterocyclic compounds were synthesized by adapting previously described methods [15, 24, 27], based on the alkylation of the thiol group with *α*-bromoketones. According to the reaction conditions (acidic or alkaline conditions), different results were obtained (Figure 2). The progress of each reaction was monitored by thin layer chromatography. The compounds **1b** [6, 18], **2b** [18], **5b** [6, 18], **6b** [18] **8b** [6] and **9b** [6] were synthesized before by different methods [6, 18]. The compounds **1b**, **5b**, **8b** and **9b** synthesized by our method were obtained in better yields compared to the method reported by Britsun [6] and the compounds **2b** and **6b** had almost the same yields compared to the method reported by Pundeer [18]. The structures of the synthesized compounds (**1a-12a**, **1b-12b**) were confirmed by spectral analysis (IR, ^{1}H NMR, ^{13}C NMR and MS). Since the compounds described by Britsun (**1b**, **5b**, **8b**, **9b**) [6] and Pundeer (**1b**, **2b**, **5b**, **6b**) [18] were not characterized by ^{13}C RMN and MS, we found it necessary to give the spectral data of these compounds synthesized in the present work.

*1-Phenyl-2-((3-phenyl-1H-1,2,4-triazol-5-yl)thio)-ethanone **(1a)***: Yield: 81%; white powder; m.p.: 112 - 113ºC; FT-IR (solid state, υ cm^{-1}): 3070, 2993, 2919, 2856, 2789 (C-H aromatic, N-H), 1685 (C=O); ^{1}H NMR (600 MHz, DMSO) δ 14.45 (br s, 1H, NH), 8.06 (d, *J* = 7.6 Hz, 2H, CH-2, CH-6), 7.89 (d, *J* = 6.7 Hz, 2H, CH-2', CH-6'), 7.70 - 7.67 (m, 1H, CH-4'), 7.60 - 7.38 (m, 5H, CH-3', CH-5', CH-3, CH-4, CH-5), 4.82 (s, 2H, S-CH_2); ^{13}C NMR (151 MHz, $CDCl_3$) δ 194.59 (C, C=O), 187.13 (C,

C-5 1,2,4-triazole), 184.90 (C, C-3 1,2,4-triazole), 135.41 (C, C-1), 134.11 (CH, C-4), 130.24 (CH, C-2`, C-6`), 128.97 (CH, C-3`, C-5`), 128.96 (CH, C-3, C-5), 128.82 (CH, C-2, C-6), 126.56 (CH, C-4`), 116.01 (C, C-1`), 39.95 (CH_2, S-CH_2); ESI^+-MS: *m/z* 296.6 $[M+H]^+$ (calcd. 296.3 for $C_{16}H_{13}N_3OS+H^+$).

*2,6-Diphenylthiazolo[3,2-b][1,2,4]triazole (**1b**)**: Yield: 87%; white powder; m.p.: 115 - 116ºC (135 - 139ºC [6, 18]); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.69 (C, C-8 thiazolo[3,2-b][1,2,4]triazole), 157.67 (C, C-2 thiazolo[3,2-b][1,2,4]triazole), 133.41 (C, C-6 thiazolo[3,2-b][1,2,4]triazole), 130.96 (C, C-1`), 130.01 (C, C-1), 129.99 (CH, C-3, C-5), 129.14 (CH, C-3`, C-5`), 128.83 (CH, C-4), 128.06 (CH, C-4`), 126.97 (CH, C-2, C-6), 126.83 (CH, C-2`, C-6`), 107.96 (C, C-5 thiazolo[3,2-b][1,2,4]triazole); ESI^+-MS: *m/z* 278.3 $[M+H]^+$ (calcd. 278.3 for $C_{16}H_{11}N_3S+H^+$).

*The IR and ^1H NMR spectra of **1b**, corresponds to the spectral data reported by Britsun [6] and Pundeer [18].

*1-(4-Bromophenyl)-2-((3-phenyl-1H-1,2,4-triazol-5-yl)thio)ethanone (**2a**)*: Yield: 72%; yellow powder; m.p.: 162 - 164ºC; FT-IR (solid state, υ cm^{-1}): 3060, 2917 (C-H aromatic, N-H), 1583 (C=O); ^1H NMR (600 MHz, DMSO) δ 14.45 (br s, 1H, NH), 7.99 (d, *J* = 8.5 Hz, 2H, CH-2, CH-6), 7.87 (d, *J* = 7.3 Hz, 2H, CH-2', CH-6'), 7.78 (d, *J* = 8.3 Hz, 2H, CH-3, CH-5), 7.50 (d, *J* = 7.0 Hz, 2H, CH-3', CH-5'), 7.42-7.36 (d, *J* = 7.1 Hz, 1H, CH-4'), 4.80 (s, 2H, S-CH_2); ^{13}C NMR (151 MHz, DMSO) δ 193.49 (C, C=O), 158.94 (C, C-5 1,2,4-triazole), 155.19 (C, C-3 1,2,4-triazole), 134.83 (C, C-1), 131.84 (CH, C-3, C-5), 130.40 (CH, C-2, C-6), 129.10 (CH, C-3`, C-5`), 128.63 (C, C-1`), 127.59 (C, C-4), 126.64 (CH, C-4`), 125.99 (CH, C-2`, C-6`), 38.64 (CH_2, S-CH_2); ESI^+-MS: m/z 374.7 ($[M+H]^+$, ^{79}Br); 376.1 ($[M+H]^+$, ^{81}Br) (calcd. for $C_{16}H_{12}BrN_3OS+H^+$: 374.2 ^{79}Br; 376.2 ^{81}Br).

*6-(4-Bromophenyl)-2-phenylthiazolo[3,2-b][1,2,4]-triazole (**2b**)**: Yield: 67%; yellow powder; m.p.: 171 - 172ºC (179 - 180ºC [18]); FT-IR (solid state, υ cm^{-1}): 3131, 3054 (C-H aromatic, N-H); ^{13}C NMR (151 MHz, DMSO) δ 165.90 (C, C-8 thiazolo[3,2-b][1,2,4]triazole), 157.80 (C, C-2 thiazolo[3,2-b] [1,2,4]triazole), 132.13 (CH, C-3, C-5), 130.80 (C, C-6 thiazolo[3,2-b][1,2,4]triazole), 130.66 (C, C-1'), 130.09 (CH, C-4'), 129.06 (CH, C-3', C-5'), 128.36 (CH, C-2, C-6), 127.01 (C, C-1), 126.43 (CH, C-2', C-6'), 123.08 (C, C-4), 111.57 (CH, C-5 thiazolo-[3,2-b][1,2,4]triazole); ESI^+-MS: *m/z* 356.7 ($[M+H]^+$, ^{79}Br), 358.1 ($[M+H]^+$, ^{81}Br) (calcd. for $C_{16}H_{10}BrN_3S$ + H^+: 356.2 ^{79}Br, 358.2 ^{81}Br).

*The ^1H RMN spectrum of **2b** corresponds to the spectral data reported by Pundeer [18].

*2-((3-Phenyl-1H-1,2,4-triazol-5-yl)thio)-1-(4-(tri-fluoromethyl)phenyl)ethanone (**3a**)*: Yield: 83%; yellow powder; m.p.: 104 - 105ºC; FT-IR (solid state, υ cm^{-1}): 3058, 3000, 2915, 2764 (C-H aromatic, N-H), 1688 (C=O); ^1H NMR (600 MHz, DMSO) δ 14.47 (br s, 1H, NH), 8.24 (d, *J* = 7.9 Hz, 2H, CH-2, CH-6), 7.94 (d, *J* = 8.1 Hz, 2H, CH-3, CH-5), 7.85 (d, *J* = 4.5 Hz, 2H, CH-2', CH-6'), 7.51-7.37 (m, 3H, CH-3', CH-4', CH-5'), 4.86 (s, 2H, S-CH_2); ^{13}C NMR (151 MHz, DMSO) δ 193.89 (C, C=O), 158.87 (C, C-5 1,2,4-triazole), 155.23 (C, C-3 1,2,4-triazole), 139.14 (C, C-1), 132.70 (q, *J* = 31.8 Hz, C, C-4), 130.44 (C, C-1'), 129.16 (d, *J* = 17.9 Hz, CH, C-2, C-6), 128.62 (CH, C-3', C-5'), 126.63 (CH, C-4'), 125.99 (CH, C-2', C-6'), 125.70 (d, *J* = 17.6 Hz, CH, C-3, C-5), 123.78 (q, *J* = 272.8 Hz, C, CF_3), 30.71 (CH_2, S-CH_2); ESI^+-MS: *m/z* 364.7 $[M+H]^+$ (calcd. 364.3 for $C_{17}H_{12}F_3N_3OS+H^+$).

*2-Phenyl-6-(4-(trifluoromethyl)phenyl)thiazolo[3,2-b][1,2,4]triazole (**3b**)**: Yield: 33%; yellow powder; m.p.: 126 - 128ºC (146 - 148ºC [10]).

*The IR, ^1H NMR, ^{13}C NMR and mass spectra of **3b**, corresponds to the spectral data reported by Le Meur [10].

*1-(4-Methoxyphenyl)-2-((3-phenyl-1H-1,2,4-triazol-5-yl)thio)ethanone (**4a**)*: Yield: 93%; white powder; m.p.: 150 - 152ºC; FT-IR (solid state, υ cm^{-1}): 3126, 3058, 3008, 2910 (C-H aromatic, N-H), 1678 (C=O); ^1H NMR (600 MHz, DMSO) δ 14.38 (br s, 1H, NH), 8.03 (d, *J* = 8.8 Hz, 2H, CH-2, CH-6), 7.90 (d, *J* = 6.9 Hz, 2H, CH-2', CH-6'), 7.55 - 7.41 (m, 3H, CH-3', CH-4', CH-5'), 7.08 (d, *J* = 8.7 Hz, 2H, CH-3, CH-5), 4.82 (s, 2H, S-CH_2), 3.86 (s, 3H, OCH_3); ^{13}C NMR (151 MHz, DMSO) δ 192.24 (C, C=O), 186.23 (C, C-5 1,2,4-triazole), 163.48 (C, C-4), 155.60 (C, C-3 1,2,4-triazole), 130.82 (CH, C-2, C-6), 129.01 (C, C-1'), 128.99 (C, C-1), 128.48 (CH, C-3', C-5'), 128.46 (CH, C-4'), 125.91 (CH, C-2', C-6'), 114.02 (CH, C-3, C-5), 55.64 (CH_3, OCH_3), 39.93 (CH_2, S-CH_2); ESI^+-MS: *m/z* 326.5 $[M+H]^+$ (calcd. 326.3 for $C_{17}H_{15}N_3O_2S+H^+$).

*6-(4-Methoxyphenyl)-2-phenylthiazolo[3,2-b][1,2,4]-triazole (**4b**)**: Yield: 77%; white powder; m.p.: 110 - 112ºC (134 - 136ºC [10]).

*The IR, ^1H NMR, ^{13}C NMR and mass spectra of **4b**, corresponds to the spectral data reported by Le Meur [10].

*2-((3-(4-Chlorophenyl)-1H-1,2,4-triazol-5-yl)thio)-1-phenylethanone (**5a**)*: Yield: 93%; yellow powder; m.p.: 180 - 182ºC; FT-IR (solid state, υ cm^{-1}): 3096, 2916 (C-H aromatic, N-H), 1685 (C=O); ^1H NMR (600 MHz, DMSO) δ 14.54 (br s, 1H, NH), 8.05 (d, *J* = 7.8 Hz, 2H, CH-2, CH-6), 7.89 (d, *J* = 8.4 Hz, 2H, CH-2', CH-6'), 7.74 – 7.44 (m, 5H, CH-3, CH-4, CH-5, CH-3', CH-5'), 4.82 (s, 2H, S-CH_2); ^{13}C NMR (151 MHz, DMSO) δ 193.99 (C, C=O), 160.46 (C, C-5 1,2,4-triazole), 159.21 (C, C-3 1,2,4-triazole), 154.18 (C, C-1), 151.76 (C, C-1'), 135.66 (CH, C-4), 135.00 (C, C-4'), 133.48 (CH, C-3', C-5'), 129.19 (CH, C-3, C-5), 128.75 (CH, C-2, C-6), 128.31 (CH, C-2', C-6'), 55.99 (CH_2, S-CH_2); ESI^+-MS: *m/z* 330.7 $[M+H]^+$ (calcd. 330.8 for $C_{16}H_{12}ClN_3OS+H^+$).

*2-(4-Chlorophenyl)-6-phenylthiazolo[3,2-b][1,2,4]-triazole (**5b**)**: Yield: 76%; yellow powder; m.p.: 143 - 145ºC (150 - 154ºC [6, 18]); ^{13}C NMR (151 MHz, DMSO) δ 164.69 (C, C-8 thiazolo[3,2-b] [1,2,4]triazole), 157.78 (C, C-2 thiazolo[3,2-b][1,2,4]-triazole), 134.49 (C, C-6 thiazolo[3,2-b][1,2,4]tri-azole), 131.62 (C, C-1`), 129.70 (C, C-4`), 129.66 (C, C-1), 129.03 (CH, C-3, C-5), 129.00 (CH, C-3`, C-5`), 128.00 (CH, C-2`, C-6`), 127.67 (CH, C-4), 126.35 (CH, C-2, C-6), 110.90 (C, C-5 thiazolo-[3,2-b][1,2,4]triazole); ESI$^+$-MS: *m/z* 312.3 [M+H]$^+$ (calcd. 312.7 for $C_{16}H_{10}ClN_3S+H^+$).

*The IR and ^{1}H NMR spectra of **5b**, corresponds to the spectral data reported by Britsun [6] and Pundeer [18].

*1-(4-Bromophenyl)-2-((3-(4-chlorophenyl)-1H-1,2,4-triazol-5-yl)thio)ethanone (**6a**)*: Yield: 80%; yellow powder; m.p.: 107 - 109ºC; FT-IR (solid state, υ cm^{-1}): 3086 (C-H aromatic), 1457 (C=O); ^{1}H NMR (600 MHz, DMSO) δ 14.52 (br s, 1H, NH), 7.97 (d, *J* = 8.5 Hz, 2H, CH-2, CH-6), 7.88 (d, *J* = 8.6 Hz, 2H, CH-2', CH-6'), 7.78 (d, *J* = 8.5 Hz, 2H, CH-3, CH-5), 7.54 (d, *J* = 8.6 Hz, 2H, CH-3', CH-5'), 4.87 (s, 2H, S-CH$_2$); ^{13}C NMR (151 MHz, DMSO) δ 193.22 (C, C=O), 160.83 (C, C-5 1,2,4-triazole), 152.81 (C, C-3 1,2,4-triazole), 134.69 (C, C-1), 131.93 (C, C-1'), 130.46 (C, C-4'), 129.11 (CH, C-3, C-5), 128.30 (CH, C-2, C-6), 128.08 (CH, C-3', C-5'), 127.79 (C, C-4), 127.66 (CH, C-2', C-6'), 40.06 (CH$_2$, S-CH$_2$); ESI$^+$-MS: *m/z* 408.4 ([M+H]$^+$, ^{79}Br), 410.1 ([M+H]$^+$, ^{81}Br) (calcd. for $C_{16}H_{11}BrClN_3OS+H^+$: 408.7 ^{79}Br, 410.7 ^{81}Br).

*6-(4-Bromophenyl)-2-(4-chlorophenyl)thiazolo[3,2-b][1,2,4]triazole (**6b**)**: Yield: 43%; yellow powder; m.p.: 170 - 172ºC (172 - 174ºC [18]); FT-IR (solid state, υ cm^{-1}): 3126 (C-H aromatic); ^{1}H NMR (600 MHz, DMSO) δ 8.25 (d, *J* = 8.6 Hz, 2H, CH-3, CH-5), 8.14 (d, *J* = 8.5 Hz, 2H, CH-2', CH-6'), 8.05 (s, 1H, CH-5 thiazolo[3,2-b][1,2,4]triazole), 7.81 (d, *J* = 8.6 Hz, 2H, CH-2, CH-6), 7.60 (d, *J* = 8.5 Hz, 2H, CH-3', CH-5'); ^{13}C NMR (151 MHz, DMSO) δ 164.71 (C, C-8 thiazolo[3,2-b][1,2,4]triazole), 157.79 (C, C-2 thiazolo[3,2-b][1,2,4]triazole), 134.55 (C, C-6 thiazolo[3,2-b][1,2,4]triazole), 131.98 (CH, C-3, C-5), 130.41 (C, C-1'), 129.05 (CH, C-3', C-5'), 128.20 (CH, C-2', C-6'), 127.99 (CH, C-2, C-6), 127.60 (C, C-4'), 126.82(C, C-1), 122.98(C, C-4), 111.75 (C, C-5 thiazolo[3,2-b][1,2,4]triazole); ESI$^+$-MS: *m/z* 390.1 ([M+H]$^+$, ^{79}Br), 392.1 ([M+H]$^+$, ^{81}Br) (calcd. for $C_{16}H_{11}BrClN_3OS+H^+$: 390.6 ^{79}Br, 392.6 ^{81}Br).

*The ^{1}H RMN spectrum of **6b** corresponds to the spectral data reported by Pundeer [18].

*2-((3-(4-Chlorophenyl)-1H-1,2,4-triazol-5-yl)thio)-1-(4(trifluoromethyl)phenyl)ethanone (**7a**)*: Yield: 76%; yellow powder; m.p.: 164 - 166ºC; FT-IR (solid state, υ cm^{-1}): 3079, 2919 (C-H aromatic, N-H), 1686 (C=O); ^{1}H NMR (600 MHz, DMSO) δ 14.54 (br s, 1H, NH), 8.24 (d, *J* = 8.2 Hz, 2H, CH-2, CH-6), 7.94 (d, *J* = 8.0 Hz, 2H, CH-3, CH-5), 7.86 (d, *J* = 8.6 Hz, 2H, CH-2', CH-6'), 7.63 - 7.44 (m, 2H, CH-3', CH-5'), 4.88 (s, 2H, S-CH$_2$); ^{13}C NMR (151 MHz, DMSO) δ 193.59 (C, C=O), 159.05 (C, C-5 1,2,4-triazole), 154.21 (C, C-3 1,2,4-triazole), 138.96 (C, C-1), 135.01 (C, C-1'), 133.54 - 132.14 (m, C, C-4), 131.27 (C, C-4'), 129.23 (CH, C-2, C-6), 129.11 (CH, C-3', C-5'), 127.59 (CH, C-2', C-6'), 125.79 (dd, *J* = 7.1, 3.4 Hz, CH, C-3, C-5), 123.77 (q, *J* = 272.7 Hz, C, CF$_3$), 30.70 (s, CH$_2$, S-CH$_2$); ESI$^+$-MS: *m/z* 398.4 [M+H]$^+$ (calcd. 398.8 for $C_{17}H_{11}ClF_3N_3OS+H^+$).

*2-(4-Chlorophenyl)-6-(4-(trifluoromethyl)phenyl)thiazolo[3,2-b][1,2,4]triazole (**7b**)*: Yield: 21%; white powder; m.p.: 160 - 162ºC; FT-IR (solid state, υ cm^{-1}): 3098 (C-H aromatic); ^{1}H NMR (600 MHz, DMSO) δ 8.49 (d, *J* = 8.1 Hz, 2H, CH-3, CH-5), 8.16 (s, 1H, CH-5 thiazolo[3,2-b][1,2,4]triazole), 8.12 (d, *J* = 8.4 Hz, 2H, CH-2', CH-6'), 7.95 (d, *J* = 8.2 Hz, 2H, CH-2, CH-6), 7.58 (d, *J* = 8.4 Hz, 2H, CH-3', CH-5'); ^{13}C NMR (151 MHz, DMSO) δ 164.78 (C, C-8 thiazolo[3,2-b][1,2,4]triazole), 157.86 (C, C-2 thiazolo-[3,2-b][1,2,4]triazole), 134.61 (C, C-6 thiazolo[3,2-b][1,2,4]triazole), 131.37 (C, C-1), 130.16 (C, C-1`), 129.54 (C, C-4`), 129.35 (C, C-4), 129.05 (CH, C-3`, C-5`), 128.01 (CH, C-2`, C-6`), 126.95 (CH, C-3, C-5), 126.02 - 125.79 (m, CH, C-2, C-6), 124.03 (q, C, CF$_3$), 113.63 (CH, C-5 thiazolo[3,2-b][1,2,4]-triazole); ESI$^+$-MS: *m/z* 380.2 [M+H]$^+$ (calcd. 380.7 for $C_{17}H_9F_3N_3S+H^+$).

*2-((3-(4-Chlorophenyl)-1H-1,2,4-triazol-5-yl)thio)-1-(4-methoxyphenyl)ethanone (**8a**)*: Yield: 85%; yellow powder; m.p.: 162 - 164ºC; FT-IR (solid state, υ cm^{-1}): 2920 (C-H aromatic), 1463 (C=O); ^{1}H NMR (600 MHz, DMSO) δ 14.52 (br s, 1H, NH), 8.03 (d, *J* = 8.8 Hz, 2H, CH-2, CH-6), 7.91 (d, *J* = 8.4 Hz, 2H, CH-2', CH-6'), 7.64 - 7.46 (m, 2H, CH-3', CH-5'), 7.08 (d, *J* = 8.3 Hz, 2H, CH-3, CH-5), 4.77 (s, 2H, S-CH$_2$), 3.85 (s, 3H, OCH$_3$); ^{13}C NMR (151 MHz, DMSO) δ 192.33 (C, C=O), 163.52 (C, C-5 1,2,4-triazole), 159.40 (C, C-4), 135.06 (C, C-3 1,2,4-triazole), 130.83 (C, C-1'), 129.26 (C, C-4'), 128.83 (CH, C-2, C-6), 127.76 (C, C-1), 127.48 (CH, C-3', C-5'), 125.64 (CH, C-2', C-6'), 114.04 (CH, C-3, C-5), 55.65 (CH$_3$, OCH$_3$), 39.93 (CH$_2$, S-CH$_2$); ESI$^+$-MS: *m/z* 360.9 [M+H]$^+$ (calcd. 360.8 for $C_{17}H_{14}ClN_3O_2S+H^+$).

*2-(4-Chlorophenyl)-6-(4-methoxyphenyl)thiazolo-[3,2-b][1,2,4]triazole (**8b**)**: Yield: 85%; white powder; m.p.: 130 - 132ºC (170 - 172ºC [6]); ^{13}C NMR (151 MHz, DMSO) δ 164.61 (C, C-8 thiazolo[3,2-b] [1,2,4]-triazole), 160.21 (C, C-4), 157.66 (C, C-2 thiazolo-[3,2-b][1,2,4]triazole), 134.43 (C, C-6 thiazolo[3,2-b] [1,2,4]triazole), 131.49 (C, C-1'), 129.71 (C, C-4'), 129.01 (CH, C-3', C-5'), 127.94 (CH, C-2', C-6'), 127.90 (CH, C-2,

C-6), 120.18 (C, C-1), 114.36 (CH, C-3, C-5), 108.53 (CH, C-5 thiazolo[3,2-b][1,2,4]-triazole), 55.35 (CH_3, OCH_3); ESI^+-MS: m/z 342.7 $[M+H]^+$ (calcd. 342.8 for $C_{17}H_{14}ClN_3O_2S+H^+$).

*The IR and ^1H NMR spectra of **8b**, corresponds to the spectral data reported by Britsun [6].

*2-((3-(4-Methoxyphenyl)-1H-1,2,4-triazol-5-yl)thio)-1-phenylethanone (**9a**)*: Yield: 85%; yellow powder; m.p.: 176 - 178ºC; FT-IR (solid state, υ cm^{-1}): 2913 (C-H aromatic), 1688 (C=O); ^1H NMR (600 MHz, DMSO) δ 14.24 (br s, 1H, NH), 8.05 (d, *J* = 7.5 Hz, 2H, CH-2, CH-6), 7.83 (d, *J* = 8.8 Hz, 2H, CH-2', CH-6'), 7.68 (t, *J* = 6.9 Hz, 1H, CH-4), 7.56 (d, *J* = 7.4 Hz, 2H, CH-3, CH-5), 7.06 (d, *J* = 7.6 Hz, 2H, CH-3', CH-5'), 4.81 (s, 2H, S-CH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (151 MHz, DMSO) δ 194.15 (C, C=O), 160.83 (C, C-5 1,2,4-triazole), 158.76 (C, C-4'), 155.17 (C, C-3 1,2,4-triazole), 135.80 (C, C-1), 133.51 (CH, C-3, C-5), 128.80 (CH, C-2, C-6), 128.39 (CH, C-2', C-6'), 127.65 (CH, C-4), 119.25 (C, C-1'), 114.51 (CH, C-3', C-5'), 55.37 (CH_3, OCH_3), 38.74 (CH_2, S-CH_2); ESI^+-MS: *m/z* 326.5 $[M+H]^+$ (calcd. 326.3 for $C_{17}H_{15}N_3O_2S+H^+$).

*2-(4-Methoxyphenyl)-6-phenylthiazolo[3,2-b][1,2,4]-triazole (**9b**)**: Yield: 96%; white powder; m.p.: 140 - 142ºC (140 - 141ºC [6]); ^{13}C NMR (151 MHz, DMSO) δ 165.78 (C, C-8 thiazolo[3,2-b][1,2,4] triazole), 160.58 (C, C-4`), 157.51 (C, C-2 thiazolo[3,2-b] [1,2,4]triazole), 131.61 (C, C-6 thiazolo-[3,2-b][1,2,4]-triazole), 129.62 (C, C-1), 128.99 (CH, C-3, C-5), 127.84 (CH, C-2`, C-6`), 127.81 (CH, C-4), 126.33 (CH, C-2, C-6), 123.34 (C, C-1`), 114.29 (CH, C-3`, C-5`), 110.09 (C, C-5 thiazolo[3,2-b] [1,2,4]triazole), 55.28 (CH_3, OCH_3); ESI^+-MS: *m/z* 308.2 $[M+H]^+$ (calcd. 308.3 for $C_{17}H_{13}N_3OS+H^+$).

*The IR and ^1H NMR spectra of **9b**, corresponds to the spectral data reported by Britsun [6].

*1-(4-Bromophenyl)-2-((3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl)thio)ethanone (**10a**)*: Yield: 95%; yellow powder; m.p.: 174 - 176ºC; FT-IR (solid state, υ cm^{-1}): 2836 (C-H aromatic), 1606 (C=O); ^1H NMR (600 MHz, DMSO) δ 7.98 (d, *J* = 8.5 Hz, 2H, CH-2, CH-6), 7.81 (d, *J* = 8.7 Hz, 2H, CH-2', CH-6'), 7.77 (d, *J* = 8.5 Hz, 2H, CH-3, CH-5), 7.03 (d, *J* = 8.8 Hz, 2H, CH-3', CH-5'), 4.81 (s, 2H, S-CH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (151 MHz, DMSO) δ 193.43 (C, C=O), 160.57 (C, C-5 1,2,4-triazole), 156.70 (C, C-4'), 142.59 (C, C-3 1,2,4-triazole), 134.78 (C, C-1), 131.86 (CH, C-3, C-5), 130.41 (CH, C-2, C-6), 127.65 (C, C-4), 127.51 (CH, C-2', C-6'), 120.34 (C, C-1'), 114.37 (CH, C-3', C-5'), 55.31 (CH_3, OCH_3), 38.90 (CH_2, S-CH_2); ESI^+-MS: *m/z* 404.2 ($[M+H]^+$, ^{79}Br), 406.4 ($[M+H]^+$, ^{81}Br) (calcd. for $C_{17}H_{14}BrN_3O_2S+H^+$: 404.2 ^{79}Br, 406.2 ^{81}Br).

*6-(4-Bromophenyl)-2-(4-methoxyphenyl)thiazolo-[3,2-b][1,2,4]triazole (**10b**)*: Yield: 89%; yellow powder; m.p.: 158 - 160ºC; FT-IR (solid state, υ cm^{-1}): 3124, 3003, 2934, 2832 (C-H aromatic, N-H); ^1H NMR (600 MHz, DMSO) δ 8.25 (d, *J* = 8.6 Hz, 2H, CH-3, CH-5), 8.06 (d, *J* = 8.8 Hz, 2H, CH-2', CH-6'), 7.98 (s, 1H, CH-5 thiazolo[3,2-b][1,2,4]-triazole), 7.80 (d, *J* = 8.6 Hz, 2H, CH-2, CH-6), 7.08 (d, *J* = 8.8 Hz, 2H, CH-3', CH-5'), 3.82 (s, 3H, OCH_3); ^{13}C NMR (151 MHz, DMSO) δ 165.81 (C, C-8 thiazolo[3,2-b][1,2,4]triazole), 160.62 (C, C-4`), 157.53 (C, C-2 thiazolo[3,2-b][1,2,4]triazole), 131.98 (CH, C-3, C-5), 130.51 (C, C-6 thiazolo[3,2-b] [1,2,4]triazole), 128.20 (CH, C-2, C-6), 127.85 (CH, C-2`, C-6`), 126.98 (C, C-1), 123.23 (C, C-1`), 122.89 (C, C-4), 114.30 (CH. C-3`, C-5`), 110.89 (CH, C-5 thiazolo[3,2-b][1,2,4]triazole), 55.29 (CH_3, OCH_3); ESI^+-MS: *m/z* 386.5 ($[M+H]^+$, ^{79}Br), 388.3 ($[M+H]^+$, ^{81}Br) (calcd. for $C_{17}H_{12}BrN_3OS+H^+$: 386.2 ^{79}Br, 388.2 ^{81}Br).

*2-((3-(4-Methoxyphenyl)-1H-1,2,4-triazol-5-yl)thio)-1-(4-(trifluoromethyl)phenyl)ethanone (**11a**)*: Yield: 51%; white powder; m.p.: 141 - 143ºC; FT-IR (solid state, υ cm^{-1}): 2915 (C-H aromatic), 1678 (C=O); ^1H NMR (600 MHz, DMSO) δ 14.24 (br s, 1H, NH), 8.05 (d, *J* = 7.5 Hz, 2H, CH-2, CH-6), 7.83 (d, *J* = 8.8 Hz, 2H, CH-2', CH-6'), 7.56 (d, *J* = 7.4 Hz, 2H, CH-3, CH-5), 7.06 (d, *J* = 7.6 Hz, 2H, CH-3', CH-5'), 4.81 (s, 2H, S-CH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (151 MHz, DMSO) δ 193.81 (C, C=O), 160.68 (C, C-4'), 158.52 (C, C-5 1,2,4-triazole), 155.48 (C, C-3 1,2,4-triazole), 139.10 (C, C-1), 132.75 (q, *J* = 31.8 Hz, C, C-4), 129.25 (CH, C-2, C-6), 127.56 (CH, C-2`, C-6`), 125.80 (q, *J* = 3.5 Hz, CH, C-3, C-5), 123.81 (q, *J* = 272.8 Hz, C, CF_3), 119.49 (CH, C-3', C-5'), 114.40 (C, C-1`), 55.34 (CH_3, OCH_3), 30.73(CH_2, S-CH_2); ESI^+-MS: *m/z* 394.4 $[M+H]^+$ (calcd. 394.3 for $C_{18}H_{14}F_3N_3O_2S+H^+$).

*2-(4-Methoxyphenyl)-6-(4-(trifluoromethyl)phenyl)-thiazolo[3,2-b][1,2,4]triazole (**11b**)*: Yield: 95%; yellow powder; m.p.: 112 - 114ºC; FT-IR (solid state, υ cm^{-1}): 2937 (C-H aromatic); ^1H NMR (600 MHz, DMSO) δ 8.50 (d, *J* = 8.2 Hz, 2H, CH-3, CH-5), 8.11 (s, 1H, CH-5 thiazolo[3,2-b][1,2,4]-triazole), 8.06 (dd, *J* = 8.2, 2.9 Hz, 2H, CH-2', CH-6'), 7.94 (d, *J* = 7.8 Hz, 2H, CH-2, CH-6), 7.07 (dd, *J* = 8.7, 3.1 Hz, 2H, CH-3', CH-5'), 3.82 (s, 3H, OCH_3); ^{13}C NMR (151 MHz, DMSO) δ 165.85 (C, C-8 thiazolo[3,2-b][1,2,4]triazole), 160.64 (C, C-4`), 157.57 (C, C-2 thiazolo[3,2-b][1,2,4]triazole), 131.50 (C, C-6 thiazolo[3,2-b][1,2,4]triazole), 130.12 (C, C-1), 129.35 (q, *J* = 32.0 Hz, C, C-4), 127.85 (CH, C-2, C-6), 126.91 (CH, C-2', C-6'), 125.89 (dd, *J* = 7.4, 3.6 Hz, CH, C-3, C-5), 124.03 (q, *J* = 272.2 Hz, CF3), 123.18 (C, C-1'), 114.28 (CH, C-3', C-5'), 112.82 (C, C-5 thiazolo[3,2-b][1,2,4]triazole), 55.27 (CH_3, OCH_3); ESI^+-MS: *m/z* 376.4 $[M+H]^+$ (calcd. 376.4 for $C_{18}H_{12}F_3N_3OS+H^+$).

*1-(4-Methoxyphenyl)-2-((3-(4-methoxyphenyl)-1H-1,2,4-triazol-5-yl)thio)ethanone (**12a**)*: Yield: 94%; yellow powder; m.p.: 94 - 96ºC; FT-IR (solid state, υ cm^{-1}): 2846 (C-H aromatic), 1596 (C=O); ^1H NMR

(600 MHz, DMSO) δ 8.03 (d, *J* = 8.8 Hz, 2H, CH-2, CH-6), 7.84 (d, *J* = 8.8 Hz, 2H, CH-2', CH-6'), 7.07 (d, *J* = 8.9 Hz, 2H, CH-3', CH-5'), 7.04 (d, *J* = 8.8 Hz, 2H, CH-3, CH-5), 4.79 (s, 2H, S-CH_2), 3.85 (s, 3H, C4-OCH_3), 3.80 (s, 3H, C4'-OCH_3); ^{13}C NMR (151 MHz, DMSO) δ 192.30 (C, C=O), 163.68 (C, C-5 1,2,4-triazole), 163.46 (C, C-4), 160.62 (C, C-4`), 131.24 (C, C-3 1,2,4-triazole), 130.81 (CH, C-2, C-6), 128.51 (C, C-1), 127.55 (CH, C-2`, C-6`), 114.40 (C, C-1`), 114.15 (CH, C-3, C-4), 114.02 (CH, C-3`, C-5`), 55.64 (CH_3, OCH_3), 55.33 (CH_3, OCH_3), 38.85 (CH_2, S-CH_2); ESI$^+$-MS: m/z 356.4 $[M+H]^+$ (calcd. 356.4 for $C_{18}H_{17}N_3O_3S+H^+$).

*2,6-Bis(4-methox-phenyl)thiazolo[3,2-b][1,2,4]triazole (**12b**)*: Yield: 90%; yellow powder; m.p.: 118 - 120ºC; FT-IR (solid state, υ cm^{-1}): 3123, 2935, 2838 (C-H aromatic); ^{1}H NMR (600 MHz, DMSO) δ 8.23 (d, *J* = 8.9 Hz, 2H, CH-2, CH-6), 8.07 (d, *J* = 8.8 Hz, 2H, CH-2', CH-6'), 7.74 (s, 1H, CH-5 thiazolo[3,2-b][1,2,4]triazole), 7.16 (d, *J* = 8.9 Hz, 2H, CH-3, CH-5), 7.08 (d, *J* = 8.8 Hz, 2H, CH-3', CH-5'), 3.85 (s, 3H, C4-OCH_3), 3.83 (s, 3H, C4`-$OCH_3$); $^{13}$C NMR (151 MHz, DMSO) δ 165.71 (C, C-8 thiazolo[3,2-b][1,2,4]triazole), 160.56 (C, C-4`), 160.19(C, C-4), 157.42 (C, C-2 thiazolo[3,2-b] [1,2,4]triazole), 131.49 (C, C-6 thiazolo[3,2-b][1,2,4]-triazole), 127.91 (CH, C-2, C-6), 127.81 (CH, C-2`, C-6`), 123.39 (C, C-1`), 120.35 (C, C-1), 114.40 (CH, C-3, C-5), 114.30 (CH, C-3`, C-5`), 107.79 (CH, C-5 thiazolo[3,2-b][1,2,4]triazole), 55.37 (CH_3, OCH_3), 55.29 (CH_3, OCH_3); ESI$^+$-MS: *m/z* 338.5 $[M+H]^+$ (calcd. 338.4 for $C_{18}H_{15}N_3O_2S+H^+$).

The IR spectra of the 3-aryl-1,2,4-triazole thioethers (**1a-12a**), showed the carbonyl stretching bands υC=O at 1688 - 1457 cm^{-1}, while in the IR spectra of the corresponding thiazolo[3,2-b][1,2,4]triazole derivatives (**1b-12b**), the carbonyl stretching band is missing. This fact confirms that the cyclization of the imino thioether intermediates **1a-12a** was successfully achieved. The absence of the absorption bands corresponding to υC=S and υSH [4] from **1a-12a**, confirmed that the alkylation occurred at sulphur atom and not at nitrogen.

In the ^{1}H NMR spectra of compounds **1a-12a**, a singlet at δ 14.24 - 14.54 ppm indicates the presence of the NH proton. The protons of the thiomethylene group S-CH_2- are appearing as a singlet at δ 4.77 - 4.88 ppm. In the ^{1}H NMR spectra of the thiazolo[3,2-b] [1,2,4]triazoles (**1b-12b**), the signals corresponding to the protons from NH and methylene group are not present, thus indicating that the cyclisation occurred well. Instead, a characteristic singlet in the aromatic area (δ 7.74 - 8.16 ppm) indicates the presence of the proton from the 5th position of the thiazolo[3,2-b][1,2,4]triazole ring.

The ^{13}C NMR spectra of the imino thioether intermediates **1a-12a** revealed the presence of the aliphatic signals corresponding to the carbon atoms of the thiomethylene group (S-CH_2-) at δ 38.64 - 40.06 ppm, as well as the characteristic carbonyl signals at δ 193.4 ppm. These signals are not present in the ^{13}C NMR spectra of the cyclization products **1b-12b,** thus confirming the cyclization step. In the case of trifluoromethyl derivatives **3a**, **7a**, **11a**, the signal corresponding to the carbon atom from the thiomethylene group appears at δ 30.71 - 30.73 ppm. In the ^{13}C NMR spectra of thiazolo[3,2-b][1,2,4]triazole derivatives (**1b-12b**), the aliphatic S-CH_2- and >C=O signals are replaced by two aromatic signals corresponding to the carbon atoms from the 5th and 6th positions of the thiazolo[3,2-b][1,2,4]-triazole ring system, this fact representing another proof that the cyclization of the intermediates **1a-12a** took place. In the ^{13}C NMR spectra of trifluoromethyl derivatives **3a**, **7a**, **11a** and their cyclized corresponding compounds **3b**, **7b** and **11b** it was observed the presence of a characteristic quartet for CF_3 group. The CF_3 carbon signal was split into a quartet of intensities 1:3:3:1 due to the effect of the three fluorine nuclei. The coupling constant *J* of the CF_3 quartet is approximately 272 Hz.

All signals of the carbon atoms of the aromatic rings are present in the aromatic region. The aliphatic signals corresponding to the carbon atoms from the methyl groups are also present.

The MS spectra confirmed the structures of the synthesized compounds **1a-12a**, **1b-12b** by revealing the presence of the molecular ion $[M+H]^+$ (in positive ionization mode), with different relative abundances. All the compounds containing bromine atoms it their structure showed characteristic peaks corresponding to the two isotopes (^{79}Br and ^{81}Br) and their intensity was in accordance with the relative distribution of the two isotopes.

Conclusions

In this study we reported the synthesis and characterization of new thiazolo[3,2-b][1,2,4]triazoles and their corresponding 3-aryl-1,2,4-triazole thioether intermediates, bearing adequate moieties which lead to anti-inflammatory and analgesic activities. The synthesis of thiazolo[3,2-b][1,2,4]triazole derivatives was performed in two different ways: directly, when the cyclization reaction of 5-mercapto-1,2,4-triazoles and 2-bromoacetophenone derivatives was performed at reflux, in acid media (concentrated H_2SO_4) and indirectly, through the cyclization of intermediate thioethers previously obtained at room temperature, in alkaline media (sodium bicarbonate).

The structures of the new compounds were confirmed by spectral analysis (IR, ^{1}H NMR, ^{13}C NMR and MS). The new synthesized molecules will be tested for their biological activity in further studies.

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