

Synthesis and Characterization of Some Novel 5,2 - and 4,2-bisthiazoles Derivatives

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19 new 5,2 and 4,2-bisthiazoles derivatives have been prepared by the Hantzsch reaction of the 4-methyl-2-phenyl-thiazole-5-carbothioamide (for the 5,2 - bisthiazoles) or the 2-phenyl-thiazole-4-carbothioamide (for the 4,2 bisthiazoles) with various α -halo-ketones. The synthesized compounds were characterized by ¹H NMR, mass spectrometry and quantitative elemental analysis.

Keywords: bisthiazoles, thiazolyl-carbothioamide, halo-ketones, Hantzsch reaction

The thiazolic ring is an important chemical moiety, especially in the field of medicinal chemistry. The thiazole is present in a series of bioactive natural products (ex. tiamine) and also in various synthetic drugs like: non-steroidal anti-inflammatories (meloxicam, fentiazac, fanetizole) [1-3], antibacterial agents (ceftriaxone, ceftazidime, cefixime, aztreonam etc.) [3,4], anti-HIV drugs (ex. ritonavir) [3,5] or anticancerous drugs (ixabepilene, dasatinib, bleomicine) [3].

Our research group has a long standing focus on obtaining new drug-like molecules, bearing the thiazole ring, with substantial biologic activity especially as anti-inflammatory and antimicrobial agents [6-17]. In recent years, the bisthiazole structure has been proven to be an interesting moiety in a variety of new molecules, with different biological activity such as anticancerous and anti-inflammatory activity [18-21].

The development of non-steroidal anti-inflammatory drugs (NSAIDs) is a current topic for medicinal chemistry research, due to the problems that this drugs present. An important number of molecules from this class have been withdrawn from market because of their potentially fatal side-effects. Also, most NSAIDs have a high risk of adverse reaction (especially gastro-intestinal bleeding) and a low safety profile [22-24].

In order to address these issues, we decided to obtain new bisthiazoles molecules with potential anti-inflammatory activity and a better safety profile.

Experimental part

Chemistry

Solvents and reagents used for synthesis and purification were purchased from Alfa Aesar (Karlsruhe, Germany). All chemicals were of analytical grade.

Thin layer chromatography was performed on Silica Gel sheets, with UV-light visualization. The melting points are uncorrected and were obtained by using an Electrothermal 9100 melting point apparatus. MS spectra were obtained by using a Varian Mat 111, 70 eV by directly introduction of the solid samples. The ¹H-NMR spectra were recorded on a Bruker Avance NMR spectrometer, operating at 500MHz, in DMSO-d₆ as solvent. Chemical shift values are reported

in ppm units, relative to TMS as internal standard. Microanalysis was performed by Vario El CHNS analyzer.

Synthesis of ethyl 4-methyl-2-phenyl-1,3-thiazole-5-carboxylate (1)

To a solution of thiobenzamide (13.7 g, 0.1 mol) in 40 mL ethanol an equimolar quantity of ethyl-2-chloro-acetoacetate (16.45 g, 0.1 mol) was added and it was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured over ice-cold water. The resulting mixture was neutralized with a 5% NaHCO₃ solution. The solid obtained was filtered, washed with water in order to yield the pure compound.

Synthesis of 4-methyl-2-phenyl-1,3-thiazole-5-carboxylic acid (2)

A solution of **1** (10 g, 0.04 mol) in 8 mL ethanol was refluxed with 10 mL of KOH 2N for 2 h. The solution was then cooled, neutralized with HCl 10% and filtered. The solid obtained was washed with water and recrystallized from ethanol.

Synthesis of 4-methyl-2-phenyl-1,3-thiazole-5-carboxamide (3)

In a two-necked round-bottomed flask a mixture of **2** (2 g, 0.0091 mol) and thionyl chloride (10 mL) were refluxed for 2 h. After completion of the reaction, excess thionyl chloride was distilled off under reduced pressure. To the cooled residue in acetone (5 mL) a solution of aqueous ammonia (10 mL) in acetone (10 mL) was added at 0-5°C. The reaction temperature was stirred at 10-15°C for 30 min, the resulting solid mass was filtered, washed with water and dried. The crude product was recrystallized from methanol.

Synthesis of 4-methyl-2-phenyl-1,3-thiazole-5-carbothioamide (4)

To a solution of **3** (2.98 g, 0.0136 mol) in tetrahydrofuran (40 mL) phosphorous pentasulfide (5.96 g, 0.026 mol) was slowly added at 50°C over a period of 2 h. The resulting mass was stirred at 50-55°C for 2 h and the reaction mass was poured into ice-cold water. The precipitated solid was

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5,2-Bisthiazoles	4,2-Bisthiazoles	R ₁	R ₂
			-CH ₃
5a	6'a		-CH ₃
5b	-		H
5c	6'c		H
5d	6'd		H
5e	6'e		H
5f	6'f		H
5g	6'g		H
5h	6'h		H
5i	-	-CH ₂ -Cl	H
5j	-	-CH ₃	-CO-CH ₃
5k	-	-CH ₃	-COOC ₂ H ₅
5l	-	-CH ₂ -COOC ₂ H ₅	H

Table 1
THE CHEMICAL STRUCTURES OF THE
SYNTHESIZED COMPOUNDS

filtered, washed with water and dried. The product was recrystallized from methanol.

General procedure for the synthesis of the 5,2-bisthiazoles (5a-h)

A mixture of 4-methyl-2-phenylthiazole-5-carbothioamide (**4**) (1 mM) and the corresponding α -bromoketone (1 mM) was dissolved in anhydrous acetone (5 mL) and stirred at room temperature for 24 h. The resulting solid was filtered and washed with a solution of Na₂CO₃ 5% until free of acid. The compounds were then recrystallised from methanol to yield the pure compounds.

General procedure for the synthesis of the 5,2-bisthiazoles (5i-l)

To a solution of 4-methyl-2-phenylthiazole-5-carbothioamide (**4**) (0.234g, 1 mM) in ethanol (5 mL) an equimolar quantity of the appropriate halocarboxyl was added (**5i**: 1,3 dichloroacetone; **5j**: 3-chloro-acetylacetone; **5k**: ethyl 2-chloro-acetoacetate; **5l**: ethyl 4-chloro-acetoacetate) and refluxed for 3 h. The obtained product was filtered, washed with water and recrystallized from ethanol.

The synthetic procedure of obtaining the 2-phenylthiazole-4-carbothioamide was already described in our previous work [6,7] and is illustrated in scheme 2.

General procedure for the synthesis of the 4,2-bisthiazoles (6'a-h)

A mixture of 2-phenylthiazole-4-carbothioamide (1 mM) [6] and the corresponding α -bromoketone (1 mM) was dissolved in anhydrous acetone (5 mL) and stirred at room temperature for 24h. The resulting solid was filtered and washed with a 5% Na₂CO₃ solution. The compounds were then recrystallised from methanol to yield the pure compound.

Results and discussions

A total of 19 new molecules were obtained and characterized. Their structures are presented in table 1.

The proposed structures of the newly synthesized molecules were in accordance with the data obtained from ¹H NMR, mass spectrometry and elemental analysis, given below.

Ethyl 4-methyl-2-phenyl-1,3-thiazole-5-carboxylate (**1**)

Pink-white powder. Yield 75%. m.p: 34°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ , 8.1 (m, 2H, Ph), 7.50 (m, 3H, Ph), 4.3 (m, 3H, -CH₂CH₃), 2.73 (s, 3H, CH₃), 1.3 (m, 3H, -CH₂CH₃). Anal. calcd. (%) for C₁₃H₁₃NO₂S (247.313): C, 63.13; H, 5.3; N, 5.66; S, 12.97. Found: C, 63.29; H, 5.25; N, 5.56; S, 13.05. MS (EI, 70eV): m/z 247 (M+).

4-Methyl-2-phenyl-1,3-thiazole-5-carboxylic acid (**2**)

White powder. Yield 73.3%. m.p: 213°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ , 12.5 (s, 1H, COOH), 8.02 (m, 2H, Ph), 7.55 (m, 3H, Ph), 2.73 (s, 3H, CH₃). Anal. calcd. (%) for C₁₁H₉NO₂S (219.26): C, 60.26; H, 4.14; N, 6.39 S, 14.62. Found: C, 60.45; H, 4.10; N, 6.37 S, 14.92. MS (EI, 70eV): m/z 219 (M+).

4-Methyl-2-phenyl-1,3-thiazole-5-carboxamide (**3**)

Off-white powder Yield 54%. m.p: 175°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ , 8.02 (m, 2H, Ph), 7.7 (s, 2H, C-NH₂), 7.55 (m, 3H, Ph), 2.74 (s, 3H, CH₃). Anal. calcd. (%) for C₁₁H₁₀N₂OS (218.275): C, 60.53; H, 4.62; N, 12.83 S, 14.69. Found: C, 60.59; H, 4.52; N, 12.90 S, 14.91. MS (EI, 70eV): m/z 218 (M+).

4-Methyl-2-phenyl-1,3-thiazole-5-carbothioamide (**4**)

Yellow powder. Yield 56%. m.p: 150°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ , 8,3 (s, 2H, C-NH₂), 8.02 (m, 2H, Ph), 7.55 (m, 3H, Ph), 2.75 (s, 3H, CH₃). Anal. calcd. (%) for C₁₁H₁₀N₂OS (234.341): C, 56.38; H, 4.3; N, 11.95 S, 27.37. Found: C, 56.25; H, 4.35; N, 11.82 S, 27.58. MS (EI, 70eV): m/z 234 (M+).

4-Methyl-5-(5-methyl-4-phenyl-1,3-thiazol-2-yl)-2-phenyl-1,3-thiazole (**5a**)

Light brown powder. Yield 85%. m.p. 245°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ , 7.40-8.06 (m, 10H, Ph), 2.75 (s, 3H, CH₃), 2.69 (s, 3H, CH₃). Anal. calcd. (%) for C₂₀H₁₆N₂S₂ (348.48): C, 68.93; H, 4.63; N, 8.04; S, 18.40. Found: C, 68.73; H, 4.60; N, 8.14; S, 18.53. MS (EI, 70eV): m/z 348 (M+).

4-Methyl-2-phenyl-5-(4-phenyl-1,3-thiazol-2-yl)-1,3-thiazole (5b)

Yellow powder. Yield 82%. m.p. 220-223°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.2 (s, 1H, thiazole-H), 7.39-8.04 (m, 10H, Ph), 2.76 (s, 3H, CH₃). Anal. calcd. (%) for C₁₉H₁₄N₂S₂ (334.46): C, 68.23; H, 4.22; N, 8.38; S, 19.17. Found: C, 68.13; H, 4.22; N, 8.43; S, 19.22. MS (EI, 70eV): m/z 334 (M+).

4-Methyl-5-[4-(4-nitrophenyl)-1,3-thiazol-2-yl]-2-phenyl-1,3-thiazole (5c)

Yellow powder. Yield 75%. m.p. 250°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.55 (s, 1H, thiazole C5-H), 8.33 (dd, 2H, Ph-NO₂), 8.25 (dd, 2H, Ph-NO₂), 8.03 (m, 2H, Ph), 7.55 (m, 3H, Ph), 2.74 (s, 3H, thiazol-CH₃). Anal. calcd. (%) for C₁₉H₁₃N₃O₂S₂ (379.45): C, 60.14; H, 3.45; N, 11.07; S, 16.90. Found: C, 60.10; H, 3.44; N, 11.03; S, 16.99. MS (EI, 70eV): m/z 379 (M+).

5-[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]-4-methyl-2-phenyl-1,3-thiazole (5d)

Pale yellow powder. Yield 80%. m.p. 150°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.6 (s, 1H, thiazole C5-H), 8.03 (dd, 2H, Ph-OCH₃), 7.99 (m, 2H, Ph), 7.53 (m, 3H, Ph), 7.06 (dd, 2H, Ph-OCH₃), 3.75 (s, 3H, -OCH₃), 2.74 (s, 3H, CH₃). Anal. calcd. (%) for C₂₀H₁₆N₂OS₂ (364.48): C, 65.91; H, 4.42; N, 7.69; S, 17.59. Found: C, 66.02; H, 4.43; N, 7.67; S, 17.65. MS (EI, 70eV): m/z 364 (M+).

4-[2-(4-Methyl-2-phenyl-1,3-thiazol-5-yl)-1,3-thiazol-4-yl]benzotrile (5e)

Yellow powder. Yield 85%. m.p. 198°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.58 (s, 1H, thiazole C5-H), 8.40 (dd, 2H, Ph-CN), 8.03 (m, 2H, Ph), 7.75 (dd, 2H, Ph-CN), 7.55 (m, 3H, Ph), 2.75 (s, 3H, thiazol-CH₃). Anal. calcd. (%) for C₂₀H₁₃N₃S₂ (359.47): C, 66.82; H, 3.65; N, 11.69; S, 17.84. Found: C, 66.90; H, 3.60; N, 11.60; S, 17.9. MS (EI, 70eV): m/z 359 (M+).

4-Methyl-5-[4-(naphthalen-1-yl)-1,3-thiazol-2-yl]-2-phenyl-1,3-thiazole (5f)

Yellow powder. Yield 75% m.p. 193-197°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.58 (d, 1H, Naph), 8.43 (s, 1H, thiazole-C5-H), 8.16 (dd, 2H, Ph), 8.05-8.02 (m, 2H, Naph), 7.95 (m, 3H, Ph), 7.56-7.53 (m, 4H, Naph), 2.78 (s, 3H, CH₃). Anal. calcd. (%) for C₂₃H₁₆N₂S₂ (384.51): C, 71.84; H, 4.19; N, 7.29; S, 16.68. Found: C, 71.73; H, 4.20; N, 7.32; S, 16.75. MS (EI, 70eV): m/z 384 (M+).

2-Hydroxy-5-[2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-1,3-thiazol-4-yl]benzamide (5g)

Pale orange powder. Yield 85%. m.p. 265°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 11.8 (s, 1H, Ar-OH), 8.59 (s, 1H, thiazole C5-H), 8.5 (d, 1H, Ph-R), 8.1 (s, 2H, C-NH₂), 8.07 (s, 1H, Ph-R), 8.01 (m, 2H, Ph), 7.53 (m, 3H, Ph), 7.02 (d, 1H, Ph-R), 2.75 (s, 3H, CH₃). Anal. calcd. (%) for C₂₀H₁₅N₃O₂S₂ (393.48): C, 61.05; H, 3.84; N, 10.68; S, 16.30. Found: C, 61.01; H, 3.82; N, 10.65; S, 16.39. MS (EI, 70eV): m/z 393 (M+).

5-[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-4-methyl-2-phenyl-1,3-thiazole (5h)

Yellow powder. Yield 75% . m.p. 215-217°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.50 (s, 1H, thiazole C5-H), 8.05 (m, 2H, Ph), 7.65 (dd, 2H, Ph-Cl), 7.55 (dd, 2H, Ph-Cl), 7.50 (m, 3H, Ph), 2.74 (s, 3H, thiazol-CH₃). Anal. calcd. (%) for C₁₉H₁₃ClN₂S₂ (368.9): C, 61.86; H, 3.55; N, 7.59; S, 17.38.

Found: C, 61.82; H, 3.53; N, 7.62; S, 17.48. MS (EI, 70eV): m/z 368 (M+).

5-[4-(Chloromethyl)-1,3-thiazol-2-yl]-4-methyl-2-phenyl-1,3-thiazole (5i)

Light brown powder. Yield 75%. m.p. 127-130°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.1 (s, 1H, thiazole C5-H), 8.00 (m, 2H, Ph), 7.53 (m, 3H, Ph), 4.89 (s, 2H, CH₂), 2.71 (s, 3H, CH₃). Anal. calcd. (%) for C₁₄H₁₁ClN₂S₂ (306.83): C, 54.80; H, 3.61; N, 9.13; S, 20.90. Found: C, 54.82; H, 3.59; N, 9.11; S, 20.95. MS (EI, 70eV): m/z 306 (M+).

1-[4-ethyl-2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-1,3-thiazol-5-yl]ethan-1-one (5j)

Green powder. Yield 90% m.p. 187°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 7.54-8.01 (m, 5H, Ph), 2.73 (s, 3H, thiazole-CH₃), 2.70 (s, 3H, thiazole-CH₃), 2.59 (s, 3H, COCH₃). Anal. calcd. (%) for C₁₆H₁₄N₂OS₂ (314.43): C, 61.12; H, 4.49; N, 8.91; S, 20.40. Found: C, 61.10; H, 4.47; N, 8.95; S, 20.54. MS (EI, 70eV): m/z 314 (M+).

Ethyl 4-methyl-2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-1,3-thiazole-5-carboxylate (5k)

Green powder. Yield 80%. m.p. 145-150°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 7.54-8.01 (m, 5H, Ph), 4.29-4.34 (dd, 2H, -CH₂), 2.72 (s, 3H, thiazole-CH₃), 2.68 (s, 3H, thiazole-CH₃), 1.32 (m, 3H, CH₂-CH₃). Anal. calcd. (%) for C₁₇H₁₆N₂OS₂ (344.45): C, 59.28; H, 4.68; N, 8.13; S, 18.62. Found: C, 59.24; H, 4.69; N, 8.11; S, 18.72. MS (EI, 70eV): m/z 344 (M+).

Ethyl 2-[2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-1,3-thiazol-4-yl]acetate (5l)

Yellow powder. Yield 75%. m.p. 96°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.06 (s, 1H, thiazole C5-H), 7.992 (m, 2H, Ph), 7.52 (m, 3H, Ph), 4.11-4.13 (m, 2H, CH₂-CH₃), 3.89 (s, 2H, thiazole-CH₂), 2.7 (s, 3H, thiazole-CH₃), 1.53 (m, 3H, -CH₂CH₃). Anal. calcd. (%) for C₁₇H₁₆N₂OS₂ (344.45): C, 59.28; H, 4.68; N, 8.13; S, 18.62. Found: C, 59.22; H, 4.62; N, 8.19; S, 18.69. MS (EI, 70eV): m/z 344 (M+).

5-Methyl-4-phenyl-2-(2-phenyl-1,3-thiazol-4-yl)-1,3-thiazole (6'a)

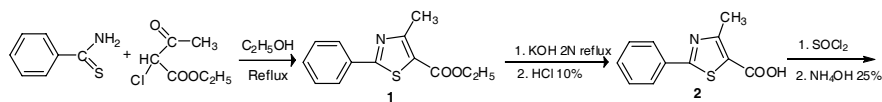
Yellow powder. Yield 85% m.p. 217°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.3 (s, 1H, thiazole-H), 7.42-8.1 (m, 10H, Ph), 2.75 (s, 3H, CH₃). Anal. calcd. (%) for C₁₉H₁₄N₂S₂ (334.46): C, 68.23; H, 4.22; N, 8.38; S, 19.17. Found: C, 68.13; H, 4.23; N, 8.42; S, 19.22. MS (EI, 70eV): m/z 334 (M+).

4-[4-(4Nitrophenyl)-1,3-thiazol-2-yl]-2-phenyl-1,3-thiazole (6'c)

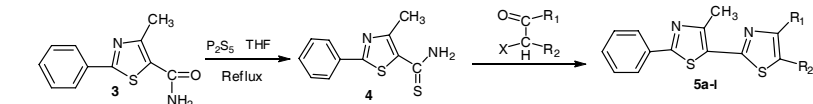
Yellow powder. Yield 75%. m.p. 230°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.55 (s, 1H, thiazole C5-H), 8.4 (s, 1H, thiazole C5-H), 8.33 (dd, 2H, Ph-NO₂), 8.25 (dd, 2H, Ph-NO₂), 8.01 (m, 2H, Ph), 7.54 (m, 3H, Ph). Anal. calcd. (%) for C₁₈H₁₁N₃O₂S₂ (365.43): C, 59.16; H, 3.03; N, 11.50; S, 17.55. Found: C, 59.12; H, 3.06; N, 11.52; S, 17.60. MS (EI, 70eV): m/z 365 (M+).

4-[4-(4-Methoxyphenyl)-1,3-thiazol-2-yl]-2-phenyl-1,3-thiazole (6'd)

Off-white powder. Yield 90%. m.p. 195°C. ¹H NMR (DMSO-d₆, 500 MHz, ppm): δ 8.4 (s, 1H, thiazole C5-H), 8.1 (s, 1H, thiazole C5-H), 8.04 (m, 2H, Ph), 8.00 (dd, 2H, Ph-OCH₃), 7.57 (m, 3H, Ph), 7.05 (dd, 2H, Ph-OCH₃), 3.82 (s, 3H, -OCH₃). Anal. calcd. (%) for C₁₉H₁₄N₂OS₂ (350.46):



Scheme 1. The procedure for the synthesis of the 5,2-bisthiazoles



Scheme 2. The procedure for the synthesis of the 4,2-bisthiazoles

C, 65.12; H, 4.03; N, 7.99; S, 18.30. Found: C, 65.15; H, 4.01; N, 7.95; S, 18.39. MS (EI, 70eV): m/z 350 (M+).

4-[2-(2-Phenyl-1,3-thiazol-4-yl)-1,3-thiazol-4-yl]benzamide (6'e)

Off-white powder. Yield 85%. m.p.240°C. ^1H NMR (DMSO- d_6 , 500 MHz, ppm): δ 8.58 (s, 1H, thiazole C5-H), 8.15 (s, 1H, thiazole C5-H), 8.45 (dd, 2H, Ph-CN), 8.02 (m, 2H, Ph), 7.77 (dd, 2H, Ph-CN), 7.56 (dd, 3H, Ph). Anal. calcd. (%) for $\text{C}_{19}\text{H}_{11}\text{N}_3\text{S}_2$ (345.44): C, 66.06; H, 3.21; N, 12.16; S, 18.56. Found: C, 66.01; H, 3.22; N, 12.14; S, 18.62. MS (EI, 70eV): m/z 345 (M+).

4-[4-(Naphthalen-1-yl)-1,3-thiazol-2-yl]-2-phenyl-1,3-thiazole (6'f)

Pale yellow powder. Yield 70% m.p.215-216°C. ^1H NMR (DMSO- d_6 , 500 MHz, ppm): δ 8.6 (s, 1H, thiazole-C5-H), 8.55 (d, 1H, Naph), 8.43 (s, 1H, thiazole-C5-H), 8.10 (dd, 2H, Ph), 8.06-8.03 (m, 2H, Naph), 7.65 (m, 3H, Ph), 7.56-7.53 (m, 4H, Naph). Anal. calcd. (%) for $\text{C}_{22}\text{H}_{14}\text{N}_2\text{S}_2$ (370.49): C, 71.32; H, 3.81; N, 7.56; S, 17.31. Found: C, 71.30; H, 3.80; N, 7.57; S, 17.33. MS (EI, 70eV): m/z 370 (M+).

2-Hydroxy-5-[2-(2-phenyl-1,3-thiazol-4-yl)-1,3-thiazol-4-yl]benzamide (6'g)

Pale yellow powder. Yield 75% m.p.250°C. ^1H NMR (DMSO- d_6 , 500 MHz, ppm): δ 11.8(s, 1H, OH) 8.59 (s, 1H, thiazole C5-H), 8.54(d, 1H, Ph-R), 8.4 (s, 1H, thiazole C5-H), 8.11 (m, 1H, Ph-R) 8.05 (s, 2H, -NH₂), 8.03 (m, 2H, Ph), 7.57 (m, 3H, Ph), 7.01 (d, 1H, Ph-R). Anal. calcd. (%) for $\text{C}_{19}\text{H}_{13}\text{N}_3\text{O}_2\text{S}_2$ (379.45): C, 60.14; H, 3.45; N, 11.07; S, 16.90. Found: C, 60.17; H, 3.42; N, 11.14; S, 16.98. MS (EI, 70eV): m/z 379 (M+).

4-[4-(4-Chlorophenyl)-1,3-thiazol-2-yl]-2-phenyl-1,3-thiazole (6'h)

Off-white powder. Yield 85%. m.p.180°C. ^1H NMR (DMSO- d_6 , 500 MHz, ppm): δ 8.55 (s, 1H, thiazole C5-H), 8.2 (s, 1H, thiazole C5-H) 8.0 (m, 2H, Ph), 7.60 (dd, 2H, Ph-Cl), 7.55 (dd, 2H, Ph-Cl) 7.50 (m, 3H, Ph). Anal. calcd. (%) for $\text{C}_{18}\text{H}_{11}\text{ClN}_2\text{S}_2$ (354.88): C, 60.92; H, 3.12; N, 7.89; S, 18.07. Found: C, 60.86; H, 3.10; N, 7.85; S, 18.17. MS (EI, 70eV): m/z 354 (M+).

The first step of the synthesis of the 4,2-bisthiazole derivatives was the Hantzsch condensation of thiobenzamide with ethyl-2-chloro-aceto-acetate

(scheme 1). The resulting ester (**1**) was then hydrolyzed in a basic catalysis, in order to obtain the corresponding acid (**2**). The transformation of the carboxylic group into an amidic group was a two phase process. The acyl chloride derivative first obtained was treated with concentrated ammonium hydroxide in order to form the amide (**3**). By using phosphorous pentasulfide the amide was converted into the corresponding thioamide (4). For both synthesis routes, the final phase involved a Hantzsch condensation between thiazolyl-thioamides and α -halo-ketones (scheme 1, 2).

The 5,2 bisthiazoles were obtained by the Hantzsch condensation of the 4-methyl-2-phenylthiazole-5-carbothioamide with α -chloro-ketones (reflux) or α -bromo-ketones (room temperature). In order to obtain the 4,2 bisthiazoles, the Hantzsch condensation of the 2-phenylthiazole-4-carbothioamide with various α -bromo-ketones (room temperature) was used. The condensations took place directly, without the formation of the intermediate hydroxy-thiazolines. No secondary reaction products were obtained, all condensations having yields above 70%. The overall yields of the two synthesis routes were good, proving these particular routes to be reliable and sustainable methods for obtaining the final products.

The structures of the compounds were confirmed by the ^1H NMR analysis. Assignments of the signals are based on the chemical shift and intensity pattern. The ^1H NMR spectra of compounds **6'c-6'h** show two singlet signal between 8.2-8.6 ppm corresponding to the 5-CH position in both thiazoles rings. Compounds **6'a** and **5b-i** show only one singlet corresponding to the 5-CH position of the thiazole.

The bisthiazole moiety, substituted with one or two aromatic rings, was chosen in order to facilitate the interaction with the four hydrophobic regions present in the COX 2 active site. Hopefully, this will lead to selective COX 2 inhibition, as the COX 1 active site has a smaller hydrophobic area.

Conclusions

This article describes the synthesis and characterization of 19 new molecules bearing the 2,4 or 2,5 bisthiazoles moiety. All synthesized structures were confirmed by ^1H NMR, mass spectrometry and elemental analysis. Further efforts will be taken in order to characterize the inhibitory effects of these molecules on cyclooxygenase (COX) 1 and 2 and on inducible nitric oxide synthase (iNOS). To that extent, docking studies will be performed and

corroborated with data from the biological assessment of the anti-inflammatory activity, obtained in an acute inflammation model on rats.

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