Synthesis and antiinflammatory activity of novel 2,5-disubstituted thiophene derivatives

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New series of 2,5-disubstituted thiophenes were synthesized. Thiosemicarbazones 1a-b were reacted with various reagents, such as diethyl-2-bromomalonate, ethyl-2-chloroacetoacetate, thioglycolic acid, 4-substituted phenacyl bromides, and acetic anhydride, to afford heterocyclic substituted thiophene derivatives 2a-b, 3a-b, 4a-b, 5a-b, 6a-b, and 7a-b, respectively. Moreover, cyclization of the key intermediate 1b with chloroacetic acid yielded thiazolidine 9, which on reaction with appropriate aromatic aldehydes afforded the corresponding arylidene derivatives 10a-f. Finally, reaction of N-arylidene cyanoacetohydrazide 11 with sulfur and phenylisothiocyanate yielded thiazoline derivative 12, which on treatment with triethylorthoformate and acetic anhydride afforded thiazolo[4,5-d]pyrimidinone derivative 13. Some of the newly synthesized compounds showed promising antiinflammatory activity.

Key Words: Thiophenes, thiazoles, thiadiazoles, synthesis, antiinflammatory

Introduction

It has been reported in the literature that heterocyclic compounds such as thiophenes exhibited potent antiinflammatory activity.1-6 Likewise, thiazole, 1,3,4-thiadiazole, and their derivatives were found to possess antiinflammatory activity.7-14 In addition, hydrazone moiety also exhibited antiinflammatory activity.15,16 Encouraged by the above observations, it was planned to synthesize new substituted thiophenes incorporating an extra heterocyclic ring, thiazole 2a-b, 3a-b, 4a-b, 5a-b, 6a-b, 9, 10a-f, 12, and 13, and thiadiazole 7a-b, as promising nonsteroidal antiinflammatory compounds.
Experimental

Unless otherwise noted, all materials were obtained from commercial suppliers (Aldrich and Merck) and used without further purification. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analytical data (in accordance with the calculated values) were calculated at the microanalytical unit of Cairo University and were within ±0.4% of theoretical values. The IR spectra were recorded on a Mattson 5000 FT-IR spectrometer using a KBr disk at Mansoura University. The \(^1\)H-NMR and \(^{13}\)C-NMR spectra were recorded on an FT-NMR JNM-LA spectrometer (300 MHz) in CDCl\(_3\) or DMSO-\(d_6\) as solvent, using TMS as an internal standard. Chemical shifts are expressed as ppm \(\delta\) units. All reactions were followed by TLC on silica gel-protected aluminum sheets (type 60 F\(_{254}\), Merck).

**Synthesis of 2-(thiosemicarbazidomethyl)-5-nitrothiophene 1a.** To a solution of 5-nitro-2-thiophene carboxaldehyde (1.57g, 0.01 mol) in absolute ethanol (60 mL) was added an equimolar amount of thiosemicarbazide (0.91 g, 0.01 mol). The reaction mixture was heated under reflux for 2 h and then cooled to room temperature. The solid product was collected by filtration, washed with ethanol, dried, and recrystallized from ethanol to give a yellow compound in 92% yield, mp 253-255 \(^\circ\)C (Lit.\(^{17}\) mp 255-258 \(^\circ\)C); IR (KBr, \(\nu, cm^{-1}\)) : 3380, 3280, 3140 (NH), 1620 (C=N); \(^1\)H-NMR (DMSO-\(d_6\)) : \(\delta\) 7.46 (d, \(J = 4.4\) Hz, 1H, thiophene), 7.82 (d, \(J = 4.4\) Hz, 1H, thiophene), 8.25 (s, 1H, CH=N), 9.91 (brs, 2H, NH\(_2\), D\(_2\)O-exchangeable), 10.30 (brs, 1H, NH, D\(_2\)O-exchangeable).

**Synthesis of 2-[(4-phenylthiosemicarbazido)methyl]-5-nitrothiophene 1b.** In Scheme 1: a reported procedure.\(^{18}\) In Scheme 2: to a solution of 5-nitrothiophene-2-carbaldehydehydrazone\(^{19}\) 8 (1.71 g, 0.01 mol) in diethylene oxide (15 mL), phenylisothiocyanate (1.3 mL, 0.01 mol) was added. The reaction mixture was heated under reflux for 1 h. The solvent was evaporated under reduced pressure, then the residue was triturated with cold ethanol, filtered, dried, and recrystallized from ethanol to give a yellow compound, yield 90%, mp 210-211 \(^\circ\)C (Lit.\(^{18}\) mp 209-210 \(^\circ\)C); IR (KBr, \(\nu, cm^{-1}\)) : 3390, 3350 (NH), 1625 (C=N); \(^1\)H-NMR (DMSO-\(d_6\)) : \(\delta\) 7.04 (t, \(J = 8.8\) Hz, 1H, ar-H), 7.21 (t, \(J = 8.8\) Hz, 2H, ar-H), 7.41 (d, \(J = 8.8\) Hz, 2H, ar-H), 7.53 (d, \(J = 4.8\) Hz, 1H, thiophene), 7.90 (d, \(J = 4.8\) Hz, 1H, thiophene), 8.35 (s, 1H, CH=N), 10.42 (brs, 1H NH, D\(_2\)O-exchangeable), 10.90 (brs, 1H, NH, D\(_2\)O-exchangeable).

**General method for the synthesis of compounds 2a-b.** A mixture of 2-(thiosemicarbazidomethyl)-5-nitrothiophene 1a or 2-[(4-phenylthiosemicarbazido)methyl]-5-nitrothiophene 1b (0.005 mol), diethyl-2-bromo-malonate (0.85 mL, 0.005 mol), and anhydrous sodium acetate (1.64 g, 0.02 mol) in absolute ethanol (80 mL) was refluxed for 6-8 h with continuous stirring. The solvent evaporated under reduced pressure, and then the obtained solid was triturated with cold water and cold diethylether, dried, and recrystallized from appropriate solvent.

**2-[(5-Ethoxycarbonyl-4-oxo-thiazolidin-2-ylidene)hydrazonomethyl]-5-nitrothiophene 2a.** Crystallized from ethanol/water, yield 82%, mp 200-202 \(^\circ\)C; IR (KBr, \(\nu, cm^{-1}\)) : 3125 (NH), 1740 (COOET), 1710 (C=O), 1640, 1600 (C=N); \(^1\)H-NMR (DMSO-\(d_6\)) : \(\delta\) 1.05 (t, \(J = 7\) Hz, 3H, CH\(_3\)), 4.21 (q, \(J = 7\) Hz, 2H, CH\(_2\)), 4.91 (s, 1H, CH-thiazolidine), 7.42 (d, \(J = 4.8\) Hz, 1H, thiophene), 7.85 (d, \(J = 4.8\) Hz, 1H, thiophene), 8.31 (s, 1H, CH=N), 10.41 (brs, 1H, NH, D\(_2\)O-exchangeable); \(^{13}\)C-NMR (DMSO-\(d_6\)) : \(\delta\) 14.4 (CH\(_3\)), 57.0 (CH\(_2\)), 68.3 (CH-thiazolidine), 128.7, 128.9, 150.7, & 152.7 (C-thiophene), 146.3 (CH=N), 160.0 (C=N), 162.7 (C=O), 165.6 (C=O ring); Anal. Calcd. (%) for: C\(_{11}\)H\(_{10}\)N\(_4\)O\(_5\)S\(_2\) : C, 38.59, H, 2.94, N, 132.
2-[[5-Ethoxycarbonyl-4-oxo-3-phenylthiazolidin-2-ylidene]hydrazonon methyl]-5-nitrothiophene 2b. Crystallized from chloroform/pet.ether, orange compound, yield 68%, mp 183-185 °C; IR (KBr, ν, cm\(^{-1}\)): 1740 (COOET), 1710 (C=O), 1640, 1605 (C=N); \(^1\)H-NMR (CDCl\(_3\)):\ δ 1.36 (t, \(J = 7\) Hz, \(3H, CH_3\)), 2.58 (s, 3H, \(CH_3\)), 4.43 (q, \(J = 7\) Hz, 2H, \(CH_2\)), 7.08 (t, \(J = 8.5\) Hz, 1H, ar-H), 7.22 (t, \(J = 8.5\) Hz, 2H, ar-H), 7.41 (d, \(J = 4.4\) Hz, 1H, thiophene), 7.91 (d, \(J = 4.4\) Hz, 1H, thiophene), 8.43 (s, 1H, CH=N); Anal. Calcd. (%) for: C\(_{12}\)H\(_{12}\)N\(_4\)O\(_5\)S\(_2\): C, 42.34, H, 3.55, N, 16.46, Found; C, 42.23, H, 3.35, N, 16.56.

General method for the synthesis of compounds 3a-b. A mixture of 2-(thiosemicarbazidomethyl)-5-nitrothiophene 1a or 2-[(4-phenylthiosemicarbazido)methyl]-5-nitrothiophene 1b (0.001 mol), ethyl-2-chloroacetacetate (0.21 mL, 0.0015 mol), and anhydrous sodium acetate (0.246 g, 0.003 mol) in absolute ethanol (30 mL), glacial acetic acid (0.5 mL) was added as a catalyst. The reaction mixture was heated under reflux for 22-24 h with continuous stirring, partially concentrated under reduced pressure, and then allowed to attain room temperature; crushed ice water was poured on it. The precipitated solid was collected by filtration, washed thoroughly with water, dried, and recrystallized from ethanol/water.

2-[(5-Ethoxycarbonyl-4-methyl-3H-thiazol-2-yl-ylidene)hydrazonon methyl]-5-nitrothiophene 3a. Red compound, yield 85%, mp 192-194 °C; IR (KBr, ν, cm\(^{-1}\)): 3147 (NH), 1725 (COOET), 1625, 1600 (C=N); \(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 1.36 (t, \(J = 7\) Hz, 3H, \(CH_3\)), 2.58 (s, 3H, \(CH_3\)), 4.43 (q, \(J = 7\) Hz, 2H, \(CH_2\)), 7.08 (t, \(J = 8.5\) Hz, 1H, ar-H), 7.22 (t, \(J = 8.5\) Hz, 2H, ar-H), 7.41 (d, \(J = 4.4\) Hz, 1H, thiophene), 7.91 (d, \(J = 4.4\) Hz, 1H, thiophene), 8.43 (s, 1H, CH=N), 11.01 (brs, 1H, NH, \(D_2\)O-exchangeable); Anal. Calcd. (%) for: C\(_{12}\)H\(_{12}\)N\(_4\)O\(_5\)S\(_2\): C, 42.34, H, 3.55, N, 16.46, Found; C, 42.23, H, 3.35, N, 16.56.

2-[(5-Ethoxycarbonyl-4-methyl-3H-3-phenylthiazol-2-yl-ylidene)hydrazonon methyl]-5-nitrothiophene 3b. Red compound, yield 74%, mp 176-178 °C; IR (KBr, ν, cm\(^{-1}\)): 1725 (COOET), 1625, 1600 (C=N); \(^1\)H-NMR (CDCl\(_3\)): \(\delta\) 1.38 (t, \(J = 7\) Hz, 3H, \(CH_3\)), 2.58 (s, 3H, \(CH_3\)), 4.43 (q, \(J = 7\) Hz, 2H, \(CH_2\)), 7.08 (t, \(J = 8.5\) Hz, 1H, ar-H), 7.22 (t, \(J = 8.5\) Hz, 2H, ar-H), 7.41 (d, \(J = 4.8\) Hz, 1H, thiophene), 7.91 (d, \(J = 4.4\) Hz, 1H, thiophene), 8.43 (s, 1H, CH=N); \(^13\)C-NMR (CDCl\(_3\)): \(\delta\) 14.1 (\(CH_3\)), 16.4 (\(CH_3\)), 60.5 (\(CH_2\)), 117.1 & 149.2 (C-thiazole), arC: [126.2 (C), 128.0 (2C), 128.5 (2C), & 130.8 (C)], 128.7, 128.9, 153.3, & 155.1 (C-thiophene), 146.4 (CH=N), 161.4 (C=N), 163.2 (C=O); Anal. Calcd. (%) for: C\(_{18}\)H\(_{16}\)N\(_4\)O\(_5\)S\(_2\): C, 51.90, H, 3.87, N, 13.45, Found; C, 52.17, H, 3.73, N, 13.21.

General method for the synthesis of compounds 4a-b. A mixture of 2-(thiosemicarbazidomethyl)-5-nitrothiophene 1a or 2-[(4-phenylthiosemicarbazido)methyl]-5-nitrothiophene 1b (0.001 mol) and thioglycolic acid (0.1 mL, 0.0015 mol) in anhydrous benzene (100 mL) was heated under reflux with exclusion of moisture for 10 h with continuous stirring. Benzene was partially concentrated under reduced pressure and then left to cool. The precipitated solid was collected by filtration, dried, and recrystallized from acetone/water.

2-(4-Oxo-3-thioureido-thiazolidin-2-yl)-5-nitrothiophene 4a. Yellow compound, yield 68%, mp 266-268 °C; IR (KBr, ν, cm\(^{-1}\)): 3300, 3150, 320 (NH), 1700 (CO), 1200 (CS); \(^1\)H-NMR (DMSO-\(d_6\)): \(\delta\) 3.37 (s, 2H, CH\(_2\)-thiazolidine), 7.16 (s, 1H, CH-thiazolidine), 7.56 (d, \(J = 4.8\) Hz, 1H, thiophene), 7.92 (d, \(J = 4.8\) Hz, 1H, thiophene), 8.42 (brs, 2H, NH\(_2\), D\(_2\)O-exchangeable), 10.67 (brs, 1H, NH, D\(_2\)O-exchangeable); Anal. Calcd. (%) for: C\(_8\)H\(_8\)N\(_4\)O\(_3\)S\(_3\): C, 31.56, H, 2.64, N, 18.40, Found; C, 31.72, H, 2.91, N, 18.53.

2-(4-Oxo-3-phenylthioureido-thiazolidin-2-yl)-5-nitrothiophene 4b. Yellow compound, yield 16.36, Found; C, 38.37, H, 3.15, N, 16.48.
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64%, mp 225-227 °C; IR (KBr, v, cm⁻¹): 3300, 3150 (NH), 1700 (CO), 1200 (CS); ¹H-NMR (CDCl₃): δ 3.35 (s, 2H, CH₂ thiazolidine), 7.03 (t, J = 8 Hz, 1H, ar-H), 7.16 (s, 1H, CH-thiazolidine), 7.29 (t, J = 8 Hz, 2H, ar-H), 7.40 (d, J = 8 Hz, 2H, ar-H), 7.57 (d, J = 4.6 Hz, 1H, thiophene), 7.97 (d, J = 4.6 Hz, 1H, thiophene), 9.67 (brs, 1H, NH, D₂O-exchangeable), 10.96 (brs, 1H, NH, D₂O-exchangeable); Anal. Calcd. (%) for: C₄₁H₂₅N₄O₃S₂: C, 44.19, H, 3.18, N, 14.72, Found; C, 44.26, H, 2.98, N, 14.91.

General method for the synthesis of compounds 5a-b and 6a-b. To the intermediate; 2-(thiosemicarbazidomethyl)-5-nitrothiophene 1a or 2-[(4-phenylthio-semicarbazido)methyl]-5-nitrothiophene 1b (0.005 mol) in absolute ethanol (100 mL) were added equimolar amounts of the appropriate phenacyl bromides (0.005 mol) and anhydrous sodium acetate (0.02 mol). The reaction mixture was heated under reflux for 4-6 h with continuous stirring, then partially concentrated under reduced pressure and left to cool. The reaction mixture was poured onto crushed ice with stirring. The separated product was collected by filtration, washed thoroughly with water, dried, and recrystallized from ethanol/water.

2-[(4-(4-Bromophenyl)-3H-thiazol-2-yl-ylidene]hydrazonomethyl]-5-nitrothiophene 5a. Red compound, yield 87%, mp 202-204 °C; IR (KBr, v, cm⁻¹): 3130 (NH), 1625, 1595 (C=N); ¹H-NMR (DMSO-d₆): δ 7.36 (d, J = 8 Hz, 2H, ar-H), 7.49 (d, J = 4.2 Hz, 1H, thiophene), 7.61 (s, 1H, thiazole), 7.74 (d, J = 8 Hz, 2H, ar-H), 7.93 (d, J = 4.2 Hz, 1H, thiophene), 8.42 (s, 1H, CH=N), 10.68 (brs, 1H, NH, D₂O-exchangeable);¹C-NMR (DMSO-d₆): δ 108.2 & 150.0 (C-thiazole), arC: [124.4 (C), 128.3 (2C), 130.3 (2C), 133.5 (C)], 128.8, 129.0, 154.8, & 155.6 (C-thiophene), 147.0 (CH=N), 162.3 (C=N); Anal. Calcd. (%) for: C₂₄H₁₉BrN₄O₂S₂: C, 41.08, H, 2.21, N, 13.69, Found; C, 41.23, H, 2.41, N, 13.57.

2-[(4-(4-Methoxyphenyl)-3H-3-phenylthiazol-2-yl-ylidene]hydrazonomethyl]-5-nitrothiophene 6a. Brown compound, yield 82%, mp 223-225 °C; IR (KBr, v, cm⁻¹): 3280 (NH), 1640, 1600 (C=N); ¹H-NMR (CDCl₃): δ 3.86 (s, 3H, OCH₃), 7.18 (d, J = 7.5 Hz, 2H, ar-H), 7.52 (d, J = 4 Hz, 1H, thiophene), 7.63 (d, J = 7.5 Hz, 2H, ar-H), 7.74 (s, 1H, thiazole), 7.96 (d, J = 4 Hz, 1H, thiophene), 8.32 (s, 1H, CH=N), 10.82 (brs, 1H, NH, D₂O-exchangeable); Anal. Calcd. (%) for: C₂₅H₁₇N₄O₃S₂: C, 49.98, H, 3.35, N, 15.54, Found; C, 50.25, H, 3.47, N, 15.71.

2-[(4-(4-Methoxyphenyl)-3H-3-phenylthiazol-2-yl-ylidene]hydrazonomethyl]-5- nitrothiophene 6b. Red compound, yield 70%, mp 140-142 °C; IR (KBr, v, cm⁻¹): 1630, 1605 (C=N); ¹H-NMR (CDCl₃): δ 3.95 (s, 3H, OCH₃), 7.06 (t, J = 8 Hz, 1H, ar-H), 7.12 (d, J = 7.5 Hz, 2H, ar-H), 7.24 (t, J = 8 Hz, 2H, ar-H), 7.40 (d, J = 8 Hz, 2H, ar-H), 7.54 (d, J = 4 Hz, 1H, thiophene), 7.67 (d, J = 7.5 Hz, 2H, ar-H), 7.78 (s, 1H, thiazole), 7.91 (d, J = 4 Hz, 1H, thiophene), 8.42 (s, 1H, CH=N),¹C-NMR (CDCl₃): δ 57.6 (CH₃), 107.4 & 150.0 (C-thiazole), arC: [123.6 (C), 124.8 (C), 126.3 (2C), 127.2 (2C), 129.8 (2C), 130.2 (2C), 130.8 (C), 143.5 (C)], 128.6, 128.7, 155.7, & 157.1 (C-thiophene), 147.4 (CH=N), 161.4 (C=N); Anal. Calcd. (%) for: C₂₆H₁₇N₄O₃S₂: C, 57.78, H, 3.69, N, 12.83, Found; C, 57.94, H, 3.85, N, 12.94.

General method for the synthesis of compounds 7a-b. A solution of 2-(thiosemicarbazidomethyl)-
5-nitrothiophene 1a or 2-[(4-phenylthiosemicarbazido)methyl]-5-nitrothiophene 1b (0.001 mol) in acetic anhydride (12 mL) was heated under reflux for 3-5 h with continuous stirring and then allowed to attain room temperature. The reaction mixture was slowly added to 400 mL of ice-cooled water and then stirred at room temperature for 1 h. The separated product was collected by filtration, washed thoroughly with water, dried, and recrystallized from appropriate solvent.

2-(3-Acetyl-5-acetylamino-2,3-dihydro-[1,3,4]-thiadiazol-2-yl)-5-nitrothiophene 7a. Crystallized from acetic acid, buff compound, yield 68%, mp >300 °C; IR (KBr, ν, cm⁻¹): 3145 (NH), 1660, 1650 (COCH₃); ¹H-NMR (DMSO-d₆): δ 2.03 (s, 3H, CH₃), 2.06 (s, 3H, CH₃), 6.53 (s, 1H, thiadiazole), 7.58 (d, J = 4.8 Hz, 1H, thiophene), 7.90 (d, J = 4.8 Hz, 1H, thiophene), 10.71 (brs, 1H, NH, D₂O-exchangeable); Anal. Calcd. (%) for: C₁₀H₁₀N₄O₄S₂: C, 38.20, H, 3.20, N, 17.82, Found; C, 38.42, H, 3.36, N, 17.96.

2-[3-Acetyl-5-(N-phenylacetylamino)-2,3-dihydro-[1,3,4]-thiadiazol-2-yl]-5-nitrothiophene 7b. Crystallized from chloroform/ethanol, buff compound, yield 53%, mp 230-232 °C; IR (KBr, ν, cm⁻¹): 1660, 1650 (COCH₃); ¹H-NMR (CDCl₃): δ 2.03 (s, 3H, CH₃), 2.08 (s, 3H, CH₃), 6.50 (s, 1H, thiadiazole), 7.08 (t, J = 8 Hz, 1H, ar-H), 7.16 (t, J = 8 Hz, 2H, ar-H), 7.22 (t, J = 8 Hz, 2H, ar-H), 7.38 (d, J = 4.8 Hz, 1H, thiophene), 7.69 (d, J = 4.8 Hz, 1H, thiophene); ¹³C-NMR (CDCl₃) δ 23.5 (CH₃), 25.1 (CH₃), 67.2 (CH-thiadiazole), arC: [128.1 (C), 128.3 (2C), 130.0 (2C), 138.6 (C)], 128.7, 128.9, 151.6, & 153.9 (C-thiophene), 149.2 (C=N of thiadiazole), 165.4 (C=O), 166.4 (C=O); Anal. Calcd. (%) for: C₁₆H₁₄N₄O₄S₂: C, 49.21, H, 3.61, N, 14.35, Found; C, 49.44, H, 3.34, N, 14.21.

Synthesis of 2-[(4-oxo-3-phenylthiazolidin-2-ylidene)hydrazonomethyl]-5-nitrothiophene 9. A mixture of 2-[(4-phenylthiosemicarbazido)methyl]-5-nitrothiophene 1b (3 g, 0.01 mol), chloroacetic acid (1 g, 0.01 mol), and anhydrous sodium acetate (0.82 g, 0.01 mol) in glacial acetic acid (20 mL) was heated under reflux for 8 h with continuous stirring. The reaction mixture was left to cool and poured into ice-cold water, and the separated solid was filtered off, washed thoroughly with water, dried, and recrystallized from ethanol/water to give a red compound, yield 70%, mp 168-170 °C; IR (KBr, ν, cm⁻¹): 1725 (CO), 1630, 1595 (C=N); ¹H-NMR (CDCl₃): δ 4.07 (s, 2H, CH₂), 7.04 (t, J = 8.8 Hz, 1H, ar-H), 7.22 (t, J = 8.8 Hz, 2H, ar-H), 7.38 (d, J = 4.8 Hz, 1H, thiophene); ¹³C-NMR (CDCl₃) δ 1725 (CO), 25.1 (CH₃), 67.2 (CH-thiadiazole), arC: [128.1 (C), 128.3 (2C), 130.0 (2C), 138.6 (C)], 128.7, 128.9, 151.6, & 153.9 (C-thiophene), 149.2 (C=N of thiadiazole), 165.4 (C=O), 166.4 (C=O); Anal. Calcd. (%) for: C₁₆H₁₄N₄O₄S₂: C, 49.21, H, 3.61, N, 14.35, Found; C, 49.44, H, 3.34, N, 14.21.

General method for the synthesis of compounds 10a-f. To a solution of compound 9 (0.346 g, 0.001 mol) and anhydrous sodium acetate (0.12 g, 0.0015 mol) in glacial acetic acid (10 mL) were added the appropriate aromatic aldehydes (0.001 mol). The mixture was heated under reflux for 6 h with continuous stirring. The reaction mixture was left to cool and poured onto crushed ice with stirring. The separated solid was filtered off, washed thoroughly with water, dried, and recrystallized from chloroform/pet.ether.

2-[(5-Benzylidene-4-oxo-3-phenylthiazolidin-2-ylidene)hydrazonomethyl]-5-nitrothiophene 10a. Orange compound, yield 70%, mp 180-182 °C; IR (KBr, ν, cm⁻¹): 1700 (CO), 1630, 1595 (C=N); ¹H-NMR (CDCl₃): δ 7.02 (t, J = 8.5 Hz, 1H, ar-H), 7.16 (t, J = 8 Hz, 1H, ar-H), 7.28 (t, J = 8.5 Hz, 2H, ar-H), 7.37 (t, J = 8 Hz, 2H, ar-H), 7.44 (d, J = 8.5 Hz, 2H, ar-H), 7.58 (d, J = 4.2 Hz, 1H, thiophene), 7.69 (d, J = 8 Hz, 2H, ar-H), 7.94 (d, J = 4.2 Hz, 1H, thiophene), 8.11 (s, 1H, olefinic CH=), 8.48 (s, 1H, CH=N); ¹³C-NMR (CDCl₃): δ arC: [126.3 (C), 127.1 (C), 128.0 (2C), 128.2 (2C), 128.4 (2C), 129.3 (2C), 132.4 (C), 135.2 (C), 128.7, 128.9, 154.2, & 155.3 (C-thiophene), 147.5 (CH=N), 157.0 (C=N), 158.8 &
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159.3 (C=CH), 167.1 (CO); Anal. Calcd. (%) for: C$_{21}$H$_{14}$N$_4$O$_3$S$_2$: C, 58.05, H, 3.24, N, 12.89, Found: C, 58.24, H, 3.37, N, 12.74.

2-{[5-(3-Bromobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]hydrazonomethyl}-5-nitrothiophene 10b. Brown compound, yield 65%, mp 190-192 °C; IR (KBr, v, cm$^{-1}$): 1700 (CO), 1640, 1600 (C=N), 1585 (C=C); $^1$H-NMR (CDCl$_3$): $\delta$ 7.04 (t, $J = 8$ Hz, 1H, ar-H), 7.19 (t, $J = 8$ Hz, 2H, ar-H), 7.27 (t, $J = 7.5$ Hz, 1H, ar-H), 7.36 (d, $J = 7.5$ Hz, 1H, ar-H), 7.47 (d, $J = 8$ Hz, 2H, ar-H), 7.59 (d, $J = 4.2$ Hz, 1H, thiophene), 7.70 (d, $J = 7.5$ Hz, 1H, ar-H), 7.80 (s, 1H, ar-H), 7.93 (d, $J = 4.2$ Hz, 1H, thiophene), 8.14 (s, 1H, olefinic CH=), 8.46 (s, 1H, CH=N); Anal. Calcd. (%) for: C$_{21}$H$_{13}$BrN$_4$O$_3$S$_2$: C, 49.12, H, 2.55, N, 10.91, Found; C, 49.34, H, 2.31, N, 11.13.

2-{[5-(3-Nitrobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]hydrazonomethyl}-5-nitrothiophene 10c. Brown compound, yield 60%, mp 186-188 °C; IR (KBr, v, cm$^{-1}$): 1710 (CO), 1630, 1595 (C=N), 1548 (C=C); $^1$H-NMR (CDCl$_3$): $\delta$ 7.06 (t, $J = 8$ Hz, 1H, ar-H), 7.15 (t, $J = 8$ Hz, 2H, ar-H), 7.31 (d, $J = 8$ Hz, 2H, ar-H), 7.46 (t, $J = 7.5$ Hz, 1H, ar-H), 7.59 (d, $J = 4$ Hz, 1H, thiophene), 7.68 (d, $J = 7.5$ Hz, 1H, ar-H), 7.78 (d, $J = 7.5$ Hz, 1H, ar-H), 7.84 (s, 1H, ar-H), 7.96 (d, $J = 4$ Hz, 1H, thiophene), 8.13 (s, 1H, olefinic CH=), 8.47 (s, 1H, CH=N); Anal. Calcd. (%) for: C$_{21}$H$_{13}$N$_5$O$_3$S$_2$: C, 52.60, H, 2.73, N, 14.60, Found; C, 52.42, H, 2.51, N, 14.72.

2-{[5-(4-Chlorobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]hydrazonomethyl}-5-nitrothiophene 10d. Orange compound, yield 68%, mp 200-202 °C; IR (KBr, v, cm$^{-1}$): 1700 (CO), 1635, 1600 (C=N), 1565 (C=C); $^1$H-NMR (CDCl$_3$): $\delta$ 7.03 (t, $J = 8.2$ Hz, 1H, ar-H), 7.18 (t, $J = 8.2$ Hz, 2H, ar-H), 7.29 (d, $J = 7.5$ Hz, 2H, ar-H), 7.40 (d, $J = 8.2$ Hz, 2H, ar-H), 7.53 (d, $J = 4.4$ Hz, 1H, thiophene), 7.70 (d, $J = 7.5$ Hz, 2H, ar-H), 7.91 (d, $J = 4.4$ Hz, 1H, thiophene), 8.04 (s, 1H, olefinic CH=), 8.44 (s, 1H, CH=N); $^{13}$C-NMR (CDCl$_3$): $\delta$ arC: [127.0 (C), 128.0 (C), 128.6 (2C), 129.1 (2C), 133.1 (2C), 134.4 (2C), 135.6 (C), 138.1 (C)], 128.8, 128.9, 154.2, & 155.4 (C-thiophene), 147.3 (CH=N), 157.2 (C=N), 158.1 & 159.1 (C=CH), 168.2 (CO); Anal. Calcd. (%) for: C$_{21}$H$_{13}$ClN$_4$O$_3$S$_2$: C, 53.78, H, 2.79, N, 11.94, Found; C, 53.96, H, 2.63, N, 12.17.

2-{[5-(4-Flourobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]hydrazonomethyl}-5-nitrothiophene 10e. Orange compound, yield 72%, mp 210-212 °C; IR (KBr, v, cm$^{-1}$): 1710 (CO), 1635, 1600 (C=N), 1582 (C=C); $^1$H-NMR (CDCl$_3$): $\delta$ 7.05 (t, $J = 8$ Hz, 1H, ar-H), 7.18 (t, $J = 8$ Hz, 2H, ar-H), 7.32 (d, $J = 7.5$ Hz, 2H, ar-H), 7.45 (d, $J = 8$ Hz, 2H, ar-H), 7.60 (d, $J = 4.2$ Hz, 1H, thiophene), 7.72 (d, $J = 7.5$ Hz, 2H, ar-H), 7.89 (d, $J = 4.2$ Hz, 1H, thiophene), 8.00 (s, 1H, olefinic CH=), 8.38 (s, 1H, CH=N); Anal. Calcd. (%) for: C$_{21}$H$_{13}$F$_3$N$_4$O$_3$S$_2$: C, 55.74, H, 2.89, N, 12.38, Found; C, 55.52, H, 2.65, N, 12.16.

2-{[5-(4-Methoxybenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]hydrazonomethyl}-5-nitrothiophene 10f. Orange compound, yield 78%, mp 156-158 °C; IR (KBr, v, cm$^{-1}$): 1710 (CO), 1640, 1605 (C=N), 1585 (C=C); $^1$H-NMR (CDCl$_3$): $\delta$ 3.92 (s, 3H, CH$_3$O), 7.04 (t, $J = 8.4$ Hz, 1H, ar-H), 7.16 (t, $J = 8.4$ Hz, 2H, ar-H), 7.28 (d, $J = 7.8$ Hz, 2H, ar-H), 7.40 (d, $J = 8.4$ Hz, 2H, ar-H), 7.58 (d, $J = 4.2$ Hz, 1H, thiophene), 7.73 (d, $J = 7.8$ Hz, 2H, ar-H), 7.90 (d, 1H, $J = 4.2$ Hz, thiophene), 8.12 (s, 1H, olefinic CH=), 8.40 (s, 1H, CH=N); Anal. Calcd. (%) for: C$_{22}$H$_{16}$N$_4$O$_4$S$_2$: C, 56.88, H, 3.47, N, 12.06, Found; C, 56.67, H, 3.35, N, 12.24.

Synthesis of N\-{[5-nitrothiophen-2-yl]methylene}-2-cyanoacetohydrazide 11. A mixture of 5-nitro-2-thiophenecarboxaldehyde (3.14 g, 0.02 mol) and cyanoacetic acid hydrazide (1.98 g, 0.02 mol) in
absolute ethanol (30 mL) was heated under reflux for 2 h. The precipitate formed after cooling was filtered off, dried, and recrystallized from ethanol to give a buff compound, yield 85%, mp 235-237 °C; IR (KBr, ν cm⁻¹): 3200 (NH), 2226 (CN), 1695 (CO), 1600 (C=N); ¹H-NMR (DMSO-d₆): δ 4.12 (s, 2H, CH₂CN), 7.61 (d, J = 4.8 Hz, 1H, thiophene), 7.93 (d, J = 4.8 Hz, 1H, thiophene), 8.43 (s, 1H, CH=N), 10.24 (brs, 1H, NH, D₂O-exchangeable); Anal. Calcd. (%) for: C₈H₆N₄O₃S: C, 40.33, H, 2.53, N, 23.52, Found; C, 40.12, H, 2.68, N, 23.34.

Synthesis of 4-amino-N\((\text{-}[\text{5-nitrothiophen-2-yl}]\text{methylene}\)-3-phenyl-2-thioxo-2,3-dihydrotiazole-5-carbohydrazide \(12\).

To a mixture of \(11\) (0.47 g, 0.002 mol), finely divided sulfur (0.065 g, 0.002 mol), and triethylamine (0.3 mL) in absolute ethanol (40 mL), phenyl isothiocyanate (0.2 mL, 0.002 mol) was added. The reaction mixture was heated at 60 °C for 4 h with continuous stirring. The reaction mixture was cooled to room temperature, then poured into ice water containing a few drops of hydrochloric acid. The formed solid product was collected by filtration, washed thoroughly with water, dried, and recrystallized from ethanol/water to give a red compound, yield 65%, mp 140-142 °C; IR (KBr, ν cm⁻¹): 3300, 3250 (NH₂), 3150 (NH), 1675 (CO), 1605 (C=N), 1235 (CS); ¹H-NMR (DMSO-d₆): δ 6.29 (brs, 2H, NH₂, D₂O-exchangeable), 7.11 (t, J = 8.5 Hz, 1H, ar-H), 7.27 (t, J = 8.5 Hz, 2H, ar-H), 7.43 (d, J = 8.5 Hz, 2H, ar-H), 7.63 (d, J = 4.4 Hz, 1H, thiophene), 7.92 (d, J = 4.4 Hz, 1H, thiophene), 8.36 (s, 1H, CH=N), 8.95 (brs, 1H, NH, D₂O-exchangeable); Anal. Calcd. (%) for: C₁₅H₁₁N₅O₃S₃: C, 44.42, H, 2.73, N, 17.27, Found; C, 44.53, H, 2.86, N, 17.02.

Synthesis of 6-\{(\text{-}[\text{5-nitrothiophen-2-yl}]\text{methylene}]\text{amino}\}-3-phenyl-2-thioxo-2,3-dihydrotiazolo-[4,5-d]-pyrimidin-7(6H)-one \(13\).

A solution of compound \(12\) (0.81 g, 0.002 mol) in a mixture of triethylorthoformate (2.5 mL) and acetic anhydride (2.5 mL) was heated under reflux for 3 h with continuous stirring. The reaction mixture was allowed to cool to room temperature and left overnight in a refrigerator. The crude product was collected by filtration, washed with cold diethylether, dried, and recrystallized from ethanol/water to give a brown compound, yield 61%, mp 140-142 °C; IR (KBr, ν, cm⁻¹): 1680 (CO), 1640 (C=N), 1600 (C=C), 1289 (C=S); ¹H-NMR (DMSO-d₆): δ 7.13 (t, J = 8 Hz, 1H, ar-H), 7.30 (t, J = 8 Hz, 2H, ar-H), 7.46 (d, J = 8 Hz, 2H, ar-H), 7.54 (d, J = 4.4 Hz, 1H, thiophene), 7.97 (d, J = 4.4 Hz, 1H, thiophene), 8.46 (s, 1H, pyrimidine); ¹³C-NMR (DMSO-d₆): δ 116.1, 140.4, 160.3, & 165.0 (C-pyrimidinone), arC: [128.4 (C), 129.1 (2C), 132.4 (2C), 134.0 (C)], 128.7, 128.8, 154.6, & 156.2 (C-thiophene), 147.2 (CH=N), 176.5 (CS); Anal. Calcd. (%) for: C₁₆H₉N₅O₃S₃: C, 46.25, H, 2.18, N, 16.85, Found; C, 46.01, H, 2.33, N, 16.98.

Antiinflammatory activity

The newly synthesized compounds were evaluated for their in vivo antiinflammatory activity using the carrageenan-induced hind paw edema method.⁰ Adult Sprague-Dawley rats, weighing 150-200 g, were used. The animals were allowed food and water ad libitum, except during the experiment. They were housed in a room at 23 ± 2 °C with a 12 h light/dark cycle. The animals were randomly allocated into groups of 6 animals each at the beginning of the experiment and were fasted for 24 h before the experiment with free access to water. All of the compounds and the reference drug were suspended in a 0.5% carboxymethyl cellulose (CMC) solution. The standard drug Celecoxib was administered orally at a dose of 20 mg/kg. The tested compounds
were administered orally at an equimolar oral dose relative to 20 mg/kg of Celecoxib. The control group received a 0.5% CMC solution. Into the subplantar region of the right hind paw of each rat, 0.1 mL of 1% carrageenan solution in saline was injected subcutaneously, 1 h after the administration of the test compounds and standard drug. The right hind paw volume was measured after 3 h of carrageenan treatment by means of a plethysmometer. The percent edema inhibition was calculated from the mean effect in the control and treated animals according to the following equation:

\[
\text{percent edema inhibition} = \left( \frac{v_c - v_t}{v_c} \right) \times 100,
\]

where \( v_t \) represents the mean increase in paw volume in rats treated with tested compounds and \( v_c \) represents the mean increase in paw volume in the control group of rats. The potency was calculated as regards the percentage of the change of the standard and tested compounds, as depicted in the Table.

**Results and discussion**

The synthetic procedures adopted to obtain the target compounds are outlined in **Schemes 1, 2, and 3**. The key intermediate; 2-(thiosemicarbazidomethyl)-5-nitrothiophene 1a, was prepared previously in the literature through the reaction of 5-nitrothiophene-2-carboxaldehyde diacetate with thiosemicarbazide.\(^ {17} \) But in the present report, intermediate 1a was obtained in high yield by a modified procedure through the condensation of 5-nitro-2-thiophene carboxaldehyde with thiosemicarbazide in absolute ethanol. In **Scheme 1**, the intermediate; 2-[(4-phenylthiosemicarbazido)methyl]-5-nitrothiophene 1b was prepared following a previously reported literature procedure.\(^ {18} \) The reaction of the key intermediates 1a-b with diethyl-2-bromomalonate in refluxing ethanol containing a catalytic amount of anhydrous sodium acetate afforded 2-[(5-ethoxycarbonyl-2-(4-oxo-3-substituted thiazolidin-2-ylidene)hydrazonomethyl]-5-nitrothiophene 2a-b. Their IR spectra showed bands due to COOEt and CO at 1740 and 1710 cm\(^{-1} \), respectively. The \(^1\)H-NMR spectra showed a signal at 4.89-4.91 ppm attributed to CH-thiazolidine. The thiosemicarbazone derivatives 1a-b were allowed to react with ethyl-2-chloroacetacetate in an absolute ethanol solution that contained anhydrous sodium acetate and glacial acetic acid to produce 2-[(5-ethoxycarbonyl-4-methyl-3\(^H\)-3-substituted thiazol-2-yl-ylidene)hydrazonomethyl]-5-nitrothiophene 3a-b in good yield. Their IR spectra showed a band at 1725 cm\(^{-1} \) due to COOEt. In addition, reaction of intermediates 1a-b with thioglycolic acid in anhydrous benzene afforded the corresponding thioureido-thiazolidinone derivatives 4a-b. Their IR spectra showed, beside the bands due to NH, a carbonyl absorption band at 1700 cm\(^{-1} \). Their \(^1\)H-NMR spectra showed signals characteristic for NH protons and 2 new singlets at 3.35-3.37 and 7.16 ppm attributed to the CH\(_2\) and CH of 4-oxothiazolidinyl, respectively. Furthermore, treatment of thiosemicarbazone derivatives 1a-b with 4-substituted phenacyl bromides in boiling ethanol in the presence of anhydrous sodium acetate yielded the corresponding thiazol-2-yl-ylidene derivatives 5a-b and 6a-b. Their \(^1\)H-NMR spectra showed a new singlet at 7.61-7.78 ppm attributed to CH thiazol-2-yl-ylidene. Moreover, 2-[3-acetyl-5-\(\text{N-substituted acetylamino}\)-2,3-dihydro-[1,3,4]thiadiazol-2-yl]-5-nitrothiophene 7a-b were prepared by refluxing the thiosemicarbazones 1a-b with acetic anhydride. Their IR spectra showed a new band at 1650, 1660 cm\(^{-1} \) attributed to an acetyl group. Their \(^1\)H-NMR spectra showed a new singlet at 6.50-6.53 ppm attributed to the CH of 1,3,4-thiadiazoline, in addition to signals due to methyl groups (2CH\(_3\)CO) at 2.03-2.08 ppm.
In conclusion, the reaction time and the corresponding yields of the reaction of 1a-b with reagents diethyl-2-bromomalonate, ethyl-2-chloroacetoacetate, and 4-substituted phenacyl bromides revealed that intermediate 1a was more reactive than intermediate 1b because the steric effect of the phenyl group on the NH reduced the ability of compound 1b to undergo nucleophilic cyclization, and the greater electron density of the NH₂ in compound 1a than in the NH in compound 1b increased the ability of compound 1a to undergo nucleophilic cyclization. Likewise, the reaction time and the reaction yields of thiosemicarbazones 1a-b with acetic anhydride.

Scheme 1. Synthesis of compounds 2a-b – 7a-b.
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revealed that compound 1a was more reactive than compound 1b. The NH$_2$ of intermediate 1a, with strong nucleophilicity and without steric effect, may facilitate further nucleophilic substitution with acetic anhydride to yield the desired diacetyl-substituted compound 7a (reaction time was 3 h). Meanwhile, the resonance effect between NH and the phenyl group of intermediate 1b and the steric effect of phenyl group on the NH may reduce nucleophilic substitution with acetic anhydride. Therefore, the initial monoacetyl-substituted product was gradually converted to the desired diacetyl-substituted thiadiazoline 7b by further heating (reaction time was 5 h) (Scheme 1).

In Scheme 2; the intermediate 2-[(4-phenylthiosemicarbazido)methyl]-5-nitrothiophene 1b was synthesized by a new method in an excellent yield in 2 consequential steps by condensing 5-nitro-2-thiophene carboxaldehyde with hydrazine hydrate to afford 5-nitrothiophene-2-carbaldehydehydrazone $^9$ 8, which was heated under reflux with phenyl isothiocyanate in diethylene oxide to afford the desired intermediate 1b. Refluxing of this intermediate 1b with chloroacetic acid in the presence of anhydrous sodium acetate in glacial acetic acid afforded 2-[(4-oxo-3-phenyl thiazolidin-2-ylidene)hydrazonomethyl]-5-nitrothiophene 9. Its IR spectra showed the disappearance of NH bands of substituted thiosemicarbazone moiety and the presence of a new band at 1725 cm$^{-1}$ attributed to a carbonyl group of thiazolidin-4-one. The $^1$H-NMR spectra lacked signals characteristic of NH protons and showed a new singlet at 4.07 ppm attributed to CH$_2$ thiazolidinone. The condensation of compound 9 with substituted benzaldehyde derivatives in the presence of freshly fused sodium acetate in boiling glacial acetic acid yielded the corresponding arylidene derivatives 10a-f.

![Scheme 2](image)

On the other hand, condensation of 5-nitro-2-thiophene carboxaldehyde with cyanoacetic acid hydrazide afforded the desired intermediate N-arylidene cyanoacetic acid hydrazide 11, which on treatment with sulfur and phenyl isothiocyanate in the presence of triethylamine as a basic catalyst afforded 4-amino-N-[(5-nitrothiophen-2-yl)methylene]-3-phenyl-2-thioxo-2,3-dihydrothiazole-5-carbohydrazide 12. Its IR spectra
showed absorption bands at 3300, 3250, and 3150 cm\(^{-1}\) attributed to NH, a band at 1675 cm\(^{-1}\) due to hydrazide C=O, and a band at 1235 cm\(^{-1}\) attributed to C=S. Finally, 6-{{[(5-nitrothiophen-2-yl)methylene]amino}-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-\textit{d}]pyrimidin-7(6\textit{H})}-one 13 was prepared by heating compound 12 with a mixture of triethylorthoformate and acetic anhydride (1:1). Its IR spectra showed a band at 1680 cm\(^{-1}\) attributed to the C=O of pyrimidone. The \(^1\text{H}-\text{NMR}\) showed a new signal at 9.16 ppm attributed to thiazolopyrimidine C-5-H (Scheme 3). All of the newly synthesized compounds were spectroscopically characterized.

![Scheme 3. Synthesis of target compound 13.](image)

The antiinflammatory activity of the newly synthesized compounds was evaluated by the carrageenan-induced paw edema method.\(^{20}\) The standard drug Celecoxib was administered orally at a dose of 20 mg/kg. The tested compounds were administered orally at an equimolar oral dose relative to 20 mg/kg of Celecoxib. The synthesized compounds showed antiinflammatory activity ranging from 12.41% to 62.79% (Table), whereas the standard drug Celecoxib showed 72.88% inhibition of edema after 3 h.

The structure of the antiinflammatory activity relationship among the synthesized compounds revealed that the activity was dependent on the basic molecular skeleton; thiazolines and thiazolidines incorporated to the thiophene ring through hydrazono moiety. Compounds 2\textit{a-b}, 3\textit{a-b}, 5\textit{a-b}, 6\textit{a-b}, 9, 10\textit{a-f}, and 12 showed activity from moderate to good, at 49.76%, 47.30%, 53.48%, 55.06%, 62.79%, 58.13%, 53.48%, 50.37%, 48.83%, 51.16%, 51.95%, 48.04%, 56.60%, 58.93%, 52.69%, and 47.30%, respectively. Also; thiazolo[4,5-\textit{d}]pyrimidinone attached to the thiophene ring through methylene amino moiety, 13, also showed good activity, 52.69%. Meanwhile, thiazolidines and thiadiazolidines attached directly to thiophene ring 4\textit{a-b} and 7\textit{a-b} showed minimum activity, at 12.41%, 14.74 %, 17.06%, and 16.27%, respectively.
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Table. The anti-inflammatory activity of the newly synthesized compounds.

<table>
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<tr>
<th>Compound</th>
<th>Edema volume ± S.E.</th>
<th>% Inhibition of inflammation&lt;sup&gt;a&lt;/sup&gt; after 3 h</th>
<th>Potency&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>2a</td>
<td>1.080 ± 0.030*</td>
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<tr>
<td>2b</td>
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<tr>
<td>4b</td>
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<td>13</td>
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<tr>
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</table>

<sup>a</sup>Percent edema inhibition was calculated as regards control group.

<sup>b</sup>Potency was calculated as regards the percentage inhibition of the Celecoxib-treated group.

In conclusion, the best antiinflammatory activity was exhibited by compound 5a of chemical skeleton; 2-\{[4-(4-bromophenyl)-3\textit{H}-thiazol-2-yl-ylidene]hydrazonomethyl\}-5-nitrothiophene and compound 10e of chemical skeleton; 2-\{[5-(4-flourobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]hydrazonomethyl\}-5-nitrothiophene, at 62.79% and 58.93%, respectively; comparable to the other synthesized compounds with respect to the standard Celecoxib.

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References


