

# Design, Synthesis, Characterization and antibacterial activity of methyl -2-(mercaptomethyl)-3-(2-thienyl) acrylate

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## Abstract

In the present investigation, a series of novel methyl-2-(mercaptomethyl)-3-(2-thienyl) acrylate (**6-23**) have been synthesized. The newly synthesized compounds were characterized by IR, NMR (<sup>1</sup>H and <sup>13</sup>C) and mass. All the compounds were screened for their antimicrobial activities. Some of these compounds exhibited a wide range of activities, from completely inactive to the good active compounds.

**Key words:** Thienyl acrylate; Thiophene; Antimicrobial activity; Baylis-Hillman;

## Introduction

Nowadays, microorganisms resistant to multiple antimicrobial agents are serious problems worldwide in the fight against infectious diseases, increasing morbidity and mortality with an overall increase in health care costs<sup>1-5</sup>. For these reasons, there is an -overwhelming need to develop novel antimicrobial agents with difficult mechanism of action aimed at a better understanding of antimicrobial resistance. Nitrogen and sulfur heterocyclic system families are very interesting due to their versatile pharmacological activities, such as antitumour, diuretics, fungicides, bactericides, antihelmintic, antiallergic, anti-ulcer and local analgesic<sup>6-8</sup>, especially in the sense of design of new drugs.

Thiophene nucleus represents a very important field in drug discovery, which is present in many natural and synthetic products with a wide range of pharmacological activities<sup>9-17</sup>. The various changes in the structure of these compounds are worth studying in order to synthesize less toxic and more potent drugs. In continuation of our ongoing interest, we decided to combine the thienyl acrylate with various heterocyclic moieties<sup>18-25</sup> in hope that the resulting novel heterocycles would be biologically active.

By considering these heterocycles with potential antimicrobial effects, a new series of Thienyl acrylate compounds were synthesized via Baylis-Hillman reaction and their antimicrobial properties was evaluated. The Baylis-Hillman reaction<sup>26-32</sup> has attracted the attention of organic chemists for preparing synthetically useful multifunctional molecules, which have been successfully employed in various synthesis.

## Experimental section

All the chemicals and reagents were procured from Sigma Aldrich lab grade source. All the solvents used were from commercial sources and redistilled before use. All melting points were determined on a Buchi apparatus and are uncorrected. The Infra red spectra (in KBr pellets) were recorded on a JASCO spectrometer and frequencies are expressed in cm<sup>-1</sup>. Mass spectra (CG/MS) were recorded on a Agilent MSD VL mass spectrometer. <sup>1</sup>H NMR spectra were recorded on a Bruker Advance 400 spectrometer operating at 400.00 MHz and <sup>13</sup>C NMR spectra were recorded on a Bruker Advance 300 spectrometer operating at 300.00MHz. The chemical shifts are reported in ppm (δ) relative to tetra methyl silane. Proton and carbon spectra were typically obtained at room temperature. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using ethyl acetate: hexane or methylene dichloride: methanol as eluent and spots were developed in ultraviolet.

**General Synthetic procedure of methyl (2Z)-2-(bromomethyl)-3-(2-thienyl) acrylate, 4**

Thiophene-2-carboxaldehyde **1** (0.04 mole), methyl acrylate **2** (0.14 mole) 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.04 mole) were stirred at room temperature for 72 h and the reaction was monitored by TLC. Ethyl acetate was used to dilute the reaction mixture after the completion of the reaction and washed successively with 2N HCl, aqueous sodium bicarbonate solution and water. The organic layer was dried over anhydrous sodium sulphate and the solvent was evaporated to get crude hydroxy compound **3**. To the crude **3**, 47% HBr (0.285 mole) and Con.H<sub>2</sub>SO<sub>4</sub> (0.13 mole) were added and stirred in methylene chloride at 0-10°C for 3 h. The reaction mixture was extracted in methylene chloride and washed with sodium bicarbonate solution and water. It was then dried, solvent evaporated to get the residue, to obtain a yellow solid which was recrystallised from n-hexane (9 g) Yield 78 %; m.p. 52 °C. I.R (KBr pellets cm<sup>-1</sup>):  $\nu$  1710, 1602, 1415, 1214, 1201, 723; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  8.03 (s, 1H),  $\delta$  7.64 (d, J = 5 Hz, 1H),  $\delta$  7.47 (d, J = 3.6 Hz, 1H),  $\delta$  7.18 (dd, J = 3.96, 5.08 Hz, 1H),  $\delta$  4.59 (s, 2H),  $\delta$  3.87 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  166.02, 136.11, 135.78, 135.28, 133.96, 128.27, 123.57, 52.43, 27.91.

**General Synthetic procedure for methyl (2E)-2-[(pyridin-2-ylthio) methyl]-3-(2-thienyl) acrylate, 6**

Compound **4** (0.002 mole) was treated with 2-mercapto pyridine (0.002 mole) in the presence of Na<sub>2</sub>CO<sub>3</sub> in methanol for 1 h at room temperature. Water was added to the reaction mixture which precipitates out the solid was filtered and purified in methanol to get pure compound as yellow solid. Yield 56%; m.p. 80 °C. I.R (KBr pellets cm<sup>-1</sup>):  $\nu$  1706, 1608, 1411, 1265, 1201, 1120, 721 ppm; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  8.46 (d, J = 4.28 Hz, 1H),  $\delta$  7.97 (s, 1H),  $\delta$  7.90 (d, J = 4.96 Hz, 1H),  $\delta$  7.68-  $\delta$  7.62 (m, 2H),  $\delta$  7.35 (d, J = 8.32 Hz, 1H),  $\delta$  7.37 (m, 1H), 7.17 (dd, J = 5.0, 7.16 Hz, 1H),  $\delta$  7.22 (t, 1H),  $\delta$  4.43 (s, 2H),  $\delta$  3.75 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  166.81, 158.09, 149.35, 136.56, 134.52, 134.21, 132.42, 127.81, 122.42, 121.71, 119.87, 52.18, 27.74; MS: *m/z* 292.1 (M<sup>+</sup>).

**Methyl (2E)-2-[(pyrimidin-2-ylthio) methyl]-3-(2-thienyl) acrylate, 7:** Brown solid. Yield 58%; m.p. 98 °C. I.R (KBr pellets cm<sup>-1</sup>):  $\nu$  1710, 1610, 1380, 1263, 1199, 727 ppm; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  8.67 (d, J = 4.88 Hz, 2H),  $\delta$  8.0 (s, 1H),  $\delta$  7.91 (d, J = 5.04 Hz, 1H),  $\delta$  7.64 (d, J = 3.48 Hz, 1H),  $\delta$  7.28 (t, 1H),  $\delta$  7.23 (t, 1H),  $\delta$  4.44 (s, 2H),  $\delta$  3.74 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  170.72, 166.77, 157.76 (2C), 136.47, 134.82, 134.62, 132.59, 127.86, 121.64, 117.35, 52.24, 28.53; MS: *m/z* 293.1 (M<sup>+</sup>).

**Methyl(2E)-2-[(1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)methyl]-3-(2-thienyl) acrylate, 8:** Yellow solid. Yield 55%; m.p. 141 °C. I.R (KBr pellets cm<sup>-1</sup>):  $\nu$  1702, 1606, 1563, 1267, 1207, 858 ppm; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  14.14 (bs, 1H),  $\delta$  8.78 (s, 1H),  $\delta$  8.30 (s, 2H),  $\delta$  8.06 (s, 1H),  $\delta$  7.92 (d, J = 4.96 Hz, 1H),  $\delta$  7.68 (d, J = 3.56 Hz, 1H),  $\delta$  7.24 (t, 1H),  $\delta$  4.69 (s, 2H),  $\delta$  3.77 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  166.81, 163.82, 154.01, 152.19, 136.49, 135.22, 135.15, 132.95, 132.25, 128.09, 121.32, 110.83, 52.44, 26.86; MS: *m/z* 333.1 (M<sup>+</sup>).

**Methyl (2E)-2-[(1-methyl-1H-imidazol-2-yl)thio]methyl]-3-(2-thienyl) acrylate, 9:** Brown solid. Yield 68%; m.p. 134 °C. I.R (KBr pellets cm<sup>-1</sup>):  $\nu$  1708, 1627, 1397, 1271, 1209, 1151, 702 ppm; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  7.90 (d, J = 4.28 Hz, 2H),  $\delta$  7.57 (s, 1H),  $\delta$  7.25 (d, J = 1.0 Hz, 1H),  $\delta$  7.20 (s, 1H),  $\delta$  6.92 (d, J = 1.12 Hz, 1H),  $\delta$  4.13 (s, 2H),  $\delta$  3.67 (s, 3H),  $\delta$  3.61 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  166.59, 138.48, 136.51, 134.35, 135.55, 132.08, 128.84, 127.85, 123.78, 123.30, 52.16, 33.06, 32.15; MS: *m/z* 295.1 (M<sup>+</sup>).

**Methyl(2E)-2-[(1H-benzimidazol-2-ylthio)methyl]-3-(2-thienyl) acrylate, 10:** White solid. Yield 72%; m.p. 160 °C. I.R (KBr pellets cm<sup>-1</sup>):  $\nu$  1737, 1616, 1440, 1278, 1213, 736 ppm; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  7.99 (s, 1H),  $\delta$  7.87 (d, J = 5.0 Hz, 1H),  $\delta$  7.64 (d, J = 3.24 Hz, 1H),  $\delta$  7.41 (d, J = 3.84 Hz, 2H),  $\delta$  7.56 (t, 1H),  $\delta$  7.03 (d, J = 3.52 Hz, 2H),  $\delta$  4.53 (s, 2H),  $\delta$  3.77 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  167.0, 149.27, 136.29, 134.81, 134.71, 132.79, 127.98, 127.31, 126.05, 125.60, 122.17, 121.80, 121.33, 113.89, 52.52, 29.60; MS: *m/z* 331.1 (M<sup>+</sup>).

**Methyl(2E)-2-[(5-methoxy-1H-benzimidazol-2-yl)thio]methyl]-3-(2-thienyl) acrylate, 11:** White solid. Yield 75%; m.p. 165 °C. I.R (KBr pellets cm<sup>-1</sup>):  $\nu$  1705, 1614, 1273, 1206, 1154, 1027, 834, 710 ppm; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz):  $\delta$  7.99 (s, 1H),  $\delta$  7.90 (d, J = 4.88 Hz, 1H),  $\delta$  7.65 (d, J = 3.84 Hz, 1H),  $\delta$  7.35 (s, 1H),  $\delta$  7.23 (t, 1H),  $\delta$  6.97 (d, J = 13.6 Hz, 1H),  $\delta$  6.74 (t, 1H),  $\delta$  4.51 (s, 2H),  $\delta$  3.77 (s, 3H),  $\delta$  3.75 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  166.73, 155.42, 136.50, 135.54, 134.91, 134.75, 132.83, 128.04, 126.54, 125.35, 122.05, 110.55, 67.30, 55.45, 52.33, 29.98, 22.81; MS: *m/z* 361.1 (M<sup>+</sup>).

**Methyl(2E)-2-[(5-(difluoromethoxy)-1H-benzimidazol-2-yl)thio]methyl]-3-(2-thienyl) acrylate, 12:** Yellow solid. Yield 79%; m.p. 161 °C. I.R (KBr pellets cm<sup>-1</sup>):  $\nu$  1738, 1618, 1435, 1119, 1038, 708 ppm; <sup>1</sup>H

NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 12.79 (s, 1H), δ 8.02 (s, 1H), δ 7.93 (d, J = 4.96 Hz, 1H), δ 7.67 (d, J = 3.36 Hz, 1H), δ 7.23 - δ 7.18 (m, 4H), δ 6.99 (d, J = 7.72 Hz, 1H), δ 4.57 (s, 2H), δ 3.74 (s, 3H); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): δ 1669.25, 143.21, 136.94, 135.71, 133.85, 131.58, 127.94, 126.85, 125.82, 122.97, 118.75, 116.49, 115.45, 114.79, 101.36, 53.88, 30.61; MS: *m/z* 397.0 (M<sup>+</sup>).

**Methyl (2E)-2-[[5-nitro-1H-benzimidazol-2-yl]thio]methyl]-3-(2-thienyl) acrylate, 13:** Brown solid. Yield 70%; m.p. 176 °C. I.R (KBr pellets cm<sup>-1</sup>): ν 1691, 1610, 1405, 1280, 1209, 835, 703 ppm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 8.09 (d, J = 2.04 Hz, 1H), δ 7.93 (s, 1H), δ 7.88 (d, J = 4.84 Hz, 1H), δ 7.75 (dd, J = 2.04, 8.56 Hz, 1H), δ 7.67 (d, J = 3.36 Hz, 1H), δ 7.24 - δ 7.18 (m, 2H), δ 4.53 (s, 2H), δ 3.76 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 175.95, 153.90, 136.77, 133.97, 133.68, 132.19, 127.84, 127.48, 126.40, 125.95, 123.47, 113.55, 112.73, 109.80, 52.55, 28.93; MS: *m/z* 376.0 (M<sup>+</sup>).

**Methyl(2E)-2-[[5-methyl-1H-benzimidazol-2-yl]thio]methyl]-3-(2-thienyl) acrylate, 14:** Brown solid. Yield 78%; m.p. 140 °C. I.R (KBr pellets cm<sup>-1</sup>): ν 1737, 1616, 1436, 1274, 1205, 806, 705 ppm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 8.01 (s, 1H), δ 7.92 (d, J = 5.04 Hz, 1H), δ 7.67 (d, J = 3.64 Hz, 1H), δ 7.36 (d, J = 8.04 Hz, 1H), δ 7.26 - δ 7.21 (m, 2H), δ 6.99 (d, J = 8.2 Hz, 1H), δ 4.55 (s, 2H), δ 3.72 (s, 3H), δ 2.39 (s, 3H); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): δ 169.29, 144.58, 135.88, 133.33, 132.51, 131.83, 127.85, 126.28, 125.70, 124.23, 123.16, 118.12, 109.01, 108.57, 53.45, 23.29, 21.69; MS: *m/z* 345.1 (M<sup>+</sup>).

**Methyl(2E)-2-[[5-methyl-1,3,4-thiadiazol-2-yl]thio]methyl]-3-(2-thienyl) acrylate, 15:** White solid. Yield 77%; m.p. 142 °C. I.R (KBr pellets cm<sup>-1</sup>): ν 1702, 1627, 1398, 1270, 1209 ppm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 8.04 (s, 1H), δ 7.97 (d, J = 5.04 Hz, 1H), δ 7.66 (d, J = 3.48 Hz, 1H), δ 7.25 (dd, J = 3.92, 4.8 Hz, 1H), δ 4.53 (s, 2H), δ 3.76 (s, 3H), δ 2.70 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 166.45, 166.0, 152.86, 136.16, 135.13, 134.83, 132.84, 128.06, 121.58, 52.28, 51.02, 31.27; MS: *m/z* 313.0 (M<sup>+</sup>).

**Methyl (2E)-2-[(4,5-dihydro-1,3-thiazol-2-ylthio)methyl]-3-(2-thienyl) acrylate, 16:** Yellow solid. Yield 70%; m.p. 127 °C. I.R (KBr pellets cm<sup>-1</sup>): ν 1706, 1606, 1261, 1203, 1145, 962, 730 ppm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 7.98 (s, 1H), δ 8.06 (s, 1H), δ 7.96 (d, J = 4.96 Hz, 1H), δ 7.63 (d, J = 3.56 Hz, 1H), δ 7.25 (dd, J = 3.8, 5.08 Hz, 1H), δ 4.41 (s, 2H), δ 3.77 (s, 3H), δ 3.51 (s, 3H); <sup>13</sup>C NMR (300 MHz, CDCl<sub>3</sub>): δ 167.28, 165.14, 137.21, 135.30, 133.31, 131.12, 127.79 (2C), 122.18, 64.30, 52.43, 35.73, 30.62; MS: *m/z* 300.0 (M<sup>+</sup>).

**Methyl (2E)-2-[(1,3-benzothiazol-2-ylthio) methyl]-3-(2-thienyl) acrylate, 17:** White solid. Yield 72%; m.p. 103 °C. I.R (KBr pellets cm<sup>-1</sup>): ν 1704, 1608, 1423, 1263, 1205, 1155, 752 ppm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 8.06 (d, J = 4.44 Hz, 1H), δ 8.03 (s, 1H), δ 7.95 (d, J = 4.48 Hz, 1H), δ 7.86 (d, J = 8.12 Hz, 1H), δ 7.69 (d, J = 3.4 Hz, 1H), δ 7.49 - δ 7.46 (m, 1H), δ 7.39 - δ 7.35 (m, 1H), δ 7.25 (d, J = 3.88 Hz, 1H), δ 4.67 (s, 2H), δ 3.78 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 166.53, 165.48, 152.54, 136.31, 135.26, 134.79, 132.99, 127.98, 126.34, 124.54, 121.78, 121.17, 120.96, 52.33, 31.06; MS: *m/z* 348.0 (M<sup>+</sup>).

**Methyl(2E)-2-[[5-methoxy-1,3-benzothiazol-2-yl]thio]methyl]-3-(2-thienyl) acrylate, 18:** White solid. Yield 82%; m.p. 173 °C. I.R (KBr pellets cm<sup>-1</sup>): ν 1705, 1614, 1447, 1274, 1206, 1029, 835, 709 ppm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 8.0(s, 1H), δ 7.93 (d, J = 4.96 Hz, 1H), δ 7.67 (d, J = 3.28 Hz, 1H), δ 7.42 (s, 1H), δ 7.25 (t, 1H), δ 6.93 (d, J = 13.6 Hz, 1H), δ 6.78 (dd, J = 2.2, 8.76 Hz, 1H), δ 4.53 (s, 2H), δ 3.77 (s, 3H), δ 3.75 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 166.88, 163.24, 157.40, 139.25, 137.34, 136.33, 135.13, 133.28, 128.45, 127.95, 124.16, 121.06, 120.87, 52.17, 30.63, 23.96; MS: *m/z* 378.0 (M<sup>+</sup>).

**Methyl(2E)-2-[[4-phenyl-1,3-thiazol-2-yl]thio]methyl]-3-(2-thienyl) acrylate, 19:** White solid. Yield 83%; m.p. 173 °C. I.R (KBr pellets cm<sup>-1</sup>): ν 1708, 1608, 1265, 1203, 1033, 725 ppm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 8.08 (s, 1H), δ 8.02 (s, 1H), δ 7.94 - δ 7.88 (m, 3H), δ 7.67 (d, J = 3.44 Hz, 1H), δ 7.45 (t, 2H), δ 7.36 (t, 1H), δ 7.23 (dd, J = 3.76, 4.88 Hz, 1H), δ 4.56 (s, 2H), δ 3.74 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 166.58, 162.41, 154.43, 136.36, 134.99, 134.61, 133.47, 132.63, 128.69 (2C), 128.12, 127.96, 125.91 (2C), 121.90, 115.16, 52.25, 31.98; MS: *m/z* 374.0 (M<sup>+</sup>).

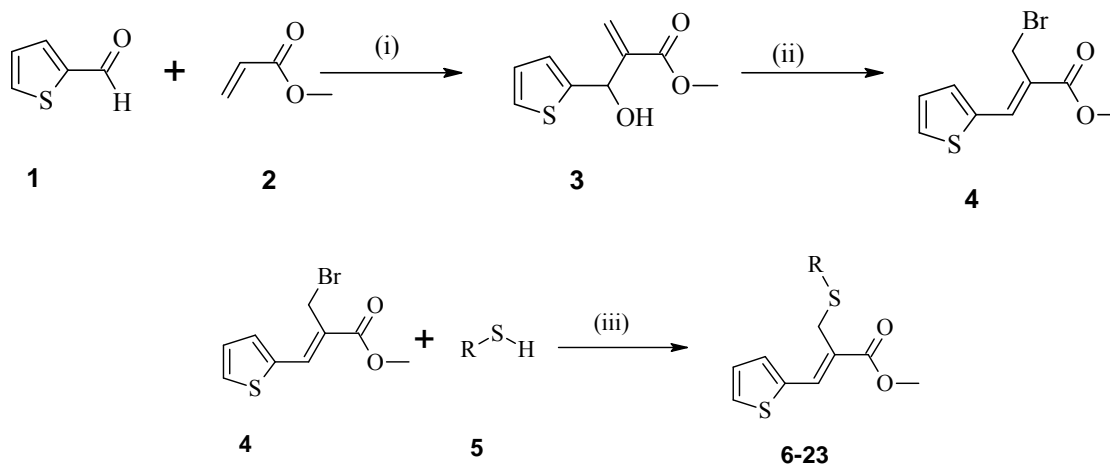
**Methyl (2E)-2-[[5-phenyl-1,3,4-oxadiazol-2-yl]thio] methyl]-3-(2-thienyl) acrylate, 20:** Yellow solid. Yield 75%; m.p. 186 °C. I.R (KBr pellets cm<sup>-1</sup>): ν 1712, 1612, 1467, 1272, 1209, 1193, 719, 700 ppm; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz): δ 8.06 (s, 1H), δ 87.99 (s, 1H), δ 7.95 - δ 7.90 (m, 2H), δ 7.69- δ 7.56 (m, 4H), δ 7.24 (dd, J = 3.76, 4.8 Hz, 1H), δ 4.60 (s, 2H), δ 3.73 (s, 3H); <sup>13</sup>C NMR (300 MHz, DMSO-*d*<sub>6</sub> + TFA-*d*): δ 166.67, 165.90, 162.77, 136.40, 135.58, 135.32, 132.98, 132.20, 129.51, 128.30, 126.57, 123.18, 121.67, 117.09, 113.27, 52.47, 30.86; MS: *m/z* 359.0 (M<sup>+</sup>).

**Methyl 2E)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]methyl]-3-(2-thienyl) acrylate, 21:** Pale yellow solid. Yield 74%; m.p. 149 °C. I.R (KBr pellets  $\text{cm}^{-1}$ ):  $\nu$  1704, 1619, 1432, 1280, 1214, 1168, 734  $\text{ppm}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  8.58 (s, 1H),  $\delta$  7.96 (s, 1H),  $\delta$  7.94 (d,  $J = 4.92$  Hz, 1H),  $\delta$  7.63 (d,  $J = 3.52$  Hz, 1H),  $\delta$  7.24 (t, 1H),  $\delta$  4.25 (s, 2H),  $\delta$  3.68 (s, 3H),  $\delta$  3.61 (s, 3H);  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  166.49, 147.77, 146.40, 136.33, 134.89, 134.33, 132.52, 127.98, 122.38, 52.22, 31.32, 30.90; MS:  $m/z$  297.1 ( $\text{M}^+$ ).

**Methyl (2E)-3-(2-thienyl)-2-[(1H-1,2,4-triazol-3-ylthio)methyl] acrylate, 22:** Brown solid. Yield 78%; m.p. 120 °C. I.R (KBr pellets  $\text{cm}^{-1}$ ):  $\nu$  1706, 1637, 1617, 1251, 1207, 705, 688  $\text{ppm}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  7.95 (s, 1H),  $\delta$  7.89 (d,  $J = 4.4$  Hz, 2H),  $\delta$  7.78 (bs, 1H),  $\delta$  7.63 (d,  $J = 3.24$  Hz, 1H),  $\delta$  7.21 (t, 1H),  $\delta$  4.27 (s, 2H),  $\delta$  3.74 (s, 3H);  $^{13}\text{C}$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  166.54, 146.37, 145.29, 138.01, 135.61, 131.85, 128.46, 119.99, 118.76, 52.77, 33.65; MS:  $m/z$  282.1 ( $\text{M}^+$ ).

**Methyl (2E)-2-[[1-methyl-1H-tetrazol-5-yl)thio]methyl]-3-(2-thienyl) acrylate, 23:** White solid. Yield 76%; m.p. 63 °C. I.R (KBr pellets  $\text{cm}^{-1}$ ):  $\nu$  1704, 1619, 1432, 1280, 1214, 1168, 734  $\text{ppm}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta$  8.04 (s, 1H),  $\delta$  7.98 (d,  $J = 5.0$  Hz, 1H),  $\delta$  7.68 (d,  $J = 3.52$  Hz, 1H),  $\delta$  7.26 (t, 1H),  $\delta$  4.47 (s, 2H),  $\delta$  3.97 (s, 3H),  $\delta$  3.72 (s, 3H);  $^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.04, 153.61, 136.74, 136.21, 134.16, 131.76, 128.03, 121.17, 52.59, 33.60, 31.64; MS:  $m/z$  297.1 ( $\text{M}^+$ ).

### Scheme 1



**Reagents and Condition:** (i) DABCO, room temperature, 80 h (ii) HBr, Con. $\text{H}_2\text{SO}_4$ , methylene chloride, 5-10 °C, 3 h (iii)  $\text{Na}_2\text{CO}_3$ , methanol, room temperature, 1 h

### Results and Discussion

Compound 3 Baylis-Hillman adduct was prepared using thiophene-2- carboxaldehyde 1 and methyl acrylate 2 as starting material without any solvent and DABCO as catalyst according the reported procedure<sup>33</sup>. The structure of this intermediate was confirmed by I.R and NMR spectral analysis. The sharp absorption at 1716  $\text{cm}^{-1}$ , 1631  $\text{cm}^{-1}$ , and 1438  $\text{cm}^{-1}$  in the I.R spectrum showed that compound 3 to be  $\alpha$ ,  $\beta$ -unsaturated ester. The broad absorption at 3448  $\text{cm}^{-1}$  in the I.R spectrum showed the presence of hydroxyl group. Three singlets at  $\delta$  5.7,  $\delta$  5.9 and  $\delta$  6.3 each integrating for one proton in the  $^1\text{H}$  NMR spectrum correspond to two vinylic protons and the single hydroxy methylene proton. The appearance of singlet at  $\delta$  5.7 is due to the presence of a hydroxy methylene group and the deshielding is due to its presence adjacent to vinylic group. Signals corresponding to thiophenyl protons appear around  $\delta$  6.9 and  $\delta$  7.7 and the 3-carbomethoxy protons as singlet at  $\delta$  3.7. The compound 3 is thus confirmed by the above spectral data.

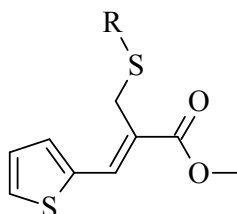
The hydroxy compound 3 was converted to thienyl bromo ester 4 by treatment with 47% HBr in the presence of Con. $\text{H}_2\text{SO}_4$  in MDC at rt according the reported procedure<sup>34</sup>. It was purified in hexane solvent to afford a low melting solid, which was the key intermediate in synthesizing the title compounds. The conversion of alcohol to bromide is evident from the appearance of absorption at 723  $\text{cm}^{-1}$  and disappearance of broad absorption around 3448  $\text{cm}^{-1}$  in the I.R spectrum. In  $^1\text{H}$  NMR spectrum, a singlet at  $\delta$  4.58 for two protons indicates the proton at the bromo methyl group and the vinylic protons appear much deshielded at  $\delta$  8.03. From the above data, the compound 4 is structurally confirmed.

The above synthesized bromo ester **4** was treated with various thiol substituted heterocyclic compounds in presence of  $\text{Na}_2\text{CO}_3$  and methanol to afford a series of esters (compounds **6** to **23**) at rt according the reported procedure<sup>35-36</sup>. Completion of the reaction was judged by TLC and the isolation of products involves simple workup. Crude product obtained was further purified by simple recrystallisation methods. Thio ether formation is evident from the absorption at  $1263\text{ cm}^{-1}$  and  $1153\text{ cm}^{-1}$  (compound **7**) and the thiomethylene protons appeared as singlet integrating for two protons at  $\delta$  4.44. The vinyl proton of the  $\alpha, \beta$ -unsaturated system were deshielded significantly and appeared as a singlet at  $\delta$  8.0. In the  $^{13}\text{C}$  NMR spectrum, a signal at  $\delta$  166.77 correspond to the carbonyl, with the thiomethylene and methoxy carbons appearing at  $\delta$  52.24 and  $\delta$  28.53 respectively. The mass spectrum of **7** showed a molecular ion peak at  $m/z$  293.1 ( $\text{M}^+$ ), which further confirms the structure.

Compounds **6-23** were prepared as per the **scheme 1** and their structures are presented in **Table 1**. The structures of all the compounds were confirmed by their spectral analysis, which are presented in the experimental section.

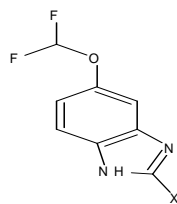
**Table 1**

Structural formulae of the synthesized compounds, **6-23**

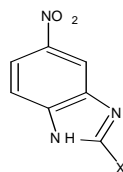


Compound no	R
<b>6</b>	
<b>7</b>	
<b>8</b>	
<b>9</b>	
<b>10</b>	
<b>11</b>	

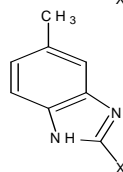
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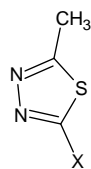
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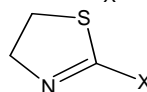
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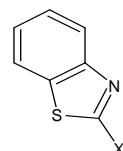
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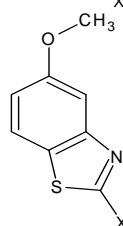
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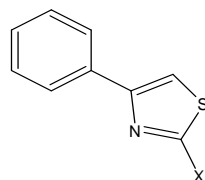
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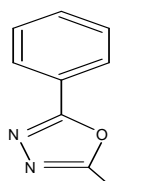
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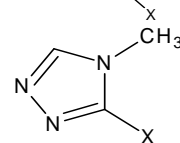
19

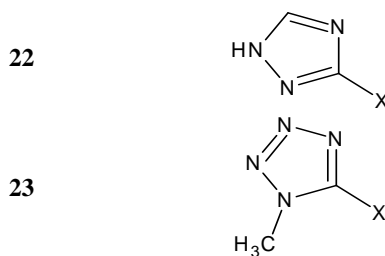


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21





### Antimicrobial activity

Antimicrobial activity of all the eighteen compounds synthesized was assayed by agar well diffusion method as recommended by CLSI<sup>37</sup> against four representative bacterial, and one fungal isolate namely *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *B. subtilis* ATCC 6633, and *Candida albicans* ATCC 90028. Bacterial cultures were grown to exponential phase and plated by pour-plate method into the 150 mm Petri dishes and allowed to settle. Wells were bored into the inoculated plate and the test compounds were dispensed in the wells at three concentrations such as 10 µg, 100 µg and 1000 µg per well respectively and allowed for complete diffusion. Three antibacterial agents (Cefepime, Amikacin & Linezolid) were used as internal assay standards and 100% DMSO was used as a control. The plates were incubated for 24 hours at 37°C. The zones of inhibition were measured using the digital Vernier's calipers.

The preliminary results of antimicrobial activities indicated that only eight compounds out of eighteen compounds exhibited a moderate to good activity against bacterial strains, while other compounds did not exert any antibacterial activity. All the eighteen compounds tested against fungi did not show any antifungal activity. The disc concentration and their zone of inhibition of the tested compounds were tabulated as per CLSI and is presented in **Table 2**

Compounds which showed significant activity in the preliminary screening were further tested for antibacterial activity by agar dilution method for MIC as per the CLSI against the clinical isolates of *S. aureus* ATCC 25923, *S. aureus* ATCC 43300, *B. subtilis* ATCC 6633, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *K. pneumoniae* ATCC 700603, *K. pneumoniae* ATCC 51503, *E. cloacae* 2160 P99+, *E. coli* J53 R6206, *E. coli* NCTC 13353 and *E. coli* ATCC BAA 200. All the nine compounds tested showed only Gram positive activity **Table 3**. From the activity data, it is observed that compound **22** was the most active derivative against *Bacillus subtilis* ATCC 6633 (MIC = 4 µg/mL), followed by MSSA *S. aureus* ATCC 25923 (MIC = 8 µg/mL) and MRSA *S. aureus* ATCC 43300 (MIC = 4 µg/mL) and the comparative activity of linezolid was 1, 4, and 2 µg/mL respectively. Among the Gram negative clinical isolates all the tested compounds showed an MIC of >1024 µg/mL.

**Table 2**

Antimicrobial activities of the newly synthesized compounds (Zone of inhibition in mm)

Compound	<i>S. aureus</i> ATCC 25923			<i>B. subtilis</i> ATCC 6633			<i>E. coli</i> ATCC 25922			<i>P. aeruginosa</i> ATCC 27853		
	1000 µg	100 µg	10 µg	1000 µg	100 µg	10 µg	1000 µg	100 µg	10 µg	1000 µg	100 µg	10 µg
<b>15</b>	18.96	12.32	nz	11.54	nz	nz	nz <sup>#</sup>	nz	nz	8.32	nz	nz
<b>16</b>	15.32	8.63	nz	13.85	nz	nz	10.52	nz	nz	7.62	nz	nz
<b>17</b>	14.53	11.78	nz	10.93	nz	nz	nz	nz	nz	nz	nz	nz
<b>18</b>	18.32	13.24	nz	13.64	8.54	nz	11.54	nz	nz	nz	nz	nz
<b>19</b>	21.32	16.75	8.32	16.54	9.85	nz	11.22	nz	nz	6.35	nz	nz
<b>21</b>	22.43	12.53	8.64	21.36	14.53	nz	13.52	nz	nz	9.54	nz	nz
<b>22</b>	23.52	18.65	15.35	25.60	20.66	18.45	14.35	8.6	nz	10.02	nz	nz
<b>23</b>	21.65	16.32	10.52	20.35	16.35	11.32	8.32	nz	nz	11.30	nz	nz
Linezolid		30.16			30.53			nz			nz	
Amikacin		25.42			35.13			25.23		26.37		
Cefepime		28.21			37.6			31.47		26.69		

# - no zone of inhibition

**Table 3**

Minimum inhibitory concentration (MIC, µg/mL) of selected compounds against Gram positive bacterial strains<sup>a</sup>

Compound	<i>S. aureus</i>	<i>S. aureus</i>	<i>B. subtilis</i>
	ATCC 25923 MIC µg/mL	ATCC 43300 MIC µg/mL	ATCC 6633 MIC µg/mL
<b>15</b>	64	512	256
<b>16</b>	256	128	64
<b>17</b>	512	512	512
<b>18</b>	256	128	64
<b>19</b>	128	512	256
<b>21</b>	64	32	16
<b>22</b>	8	16	4
<b>23</b>	32	32	16
Linezolid	4	2	1
Amikacin	2	128	0.5
Cefepime	2	32	2

<sup>a</sup> Disc diffusion method used to determine the MIC

### Conclusion

In conclusion, we have reported the synthesis of eighteen new thienyl acrylate compounds and evaluated their antibacterial activity. Among the compounds that exhibit antibacterial activity against Gram positive bacteria, compound **22** shows better antibacterial activity. We conclude that further improvement of the scaffold is underway to increase the efficacy and specificity by structural refinements and modulation.

### Acknowledgements

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