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### Synthesis of Mono- and Bis-chlorosulfonylarylpynes and Related Sulfonates and Sulfonamides

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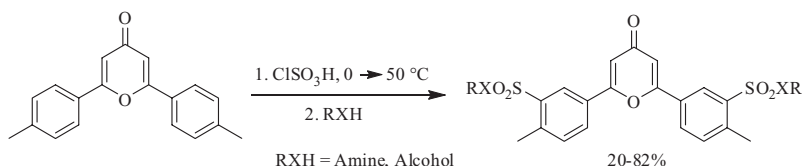
## SYNTHESIS OF MONO- AND BIS-CHLOROSULFONYLARYLPYRONES AND RELATED SULFONATES AND SULFONAMIDES

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### GRAPHICAL ABSTRACT



**Abstract** New 2,6-bis[(3-chlorosulfonyl-4-methyl)phenyl]-4H-pyran-4-one and 2-[(3-chlorosulfonyl-4-methyl)phenyl]-6-methyl-4H-pyran-4-one were synthesized by means of a reaction of chlorosulfonic acid with corresponding pyrones at 0→50°C and were treated with various alcohols and primary and secondary alkyl and aryl amines to give the corresponding sulfonates **4a–e** in 20–49% and sulfonamides **3a–l** in 55–82% yields.

**Keywords** Chlorosulfonyl derivatives; 4-pyrone derivatives; sulfonamide; sulfonate

## INTRODUCTION

The importance of the sulfonamide unit in medicinal chemistry can not be overstated.<sup>1</sup> This functional group constitutes the largest class of antimicrobial agents and has been shown to be a transition state mimetic of peptide hydrolysis, and in particular, the critical motif for potent irreversible inhibitors of cysteine proteases.<sup>2</sup> Starting in the 1950s, potent carbonic anhydrase inhibitors (CAIs) belonging to the heterocyclic sulfonamide class were developed that led to the benzothiadiazine and high ceiling diuretics, as well as to the systematic antiglaucoma drugs.<sup>3</sup> The discovery of these drugs highly benefited the chemistry of sulfonamides, as thousands of derivatives belonging to the heterocyclic, aromatic, and bis-sulfonamide classes have been synthesized and investigated for their biological activity.<sup>3b</sup> To date, the generation of sulfonamides has almost exclusively relied on

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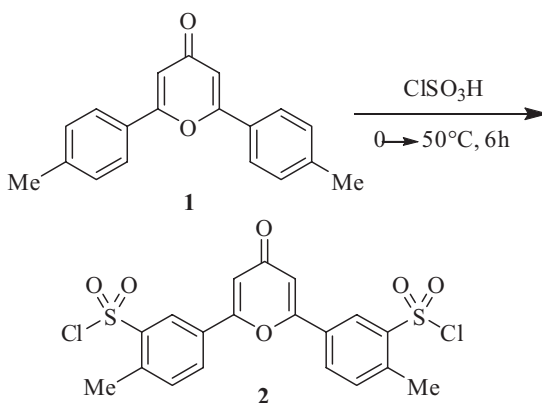
the synthesis of sulfonyl chlorides which then undergo reactions with amines.<sup>4</sup> In addition, various sulfonates inhibit interesting pharmacological properties.<sup>5</sup> The reaction of sulfonyl chlorides with alcohols in the presence of a base provides a well-established access for alkyl sulfonates.<sup>4d,6</sup> Other methods include the reaction of sulfonic acids with orthoformates<sup>7</sup> and other electrophiles such as epoxides<sup>8</sup> or aziridines.<sup>9</sup>

4-Pyrone and the corresponding derivatives have been the subject of much research due to their importance in various applications and their widespread biological significance.<sup>10</sup> In addition, 4-pyrone derivatives constitute a useful class of heterocyclic compounds that are widely distributed in nature.<sup>11</sup> Several synthetic routes to 4-pyrone derivatives have been reported in the literature.<sup>12</sup>

As part of our research on the synthesis and reactions of 4-pyrone derivatives,<sup>13</sup> in this article we report the synthesis of mono- and bis-chlorosulfonyl, sulfonamide, and sulfonate derivatives of 4*H*-pyran-4-ones **1** and **6**.

## RESULTS AND DISCUSSION

2,6-Bis(4-methylphenyl)-4*H*-pyran-4-one **1** was synthesized through cyclization of the related 1,3,5-triketone under acidic conditions, which represents an important method for the synthesis of a variety of 4-pyrone structures.<sup>14</sup> The reaction of pyrone **1** with chlorosulfonic acid resulted in the formation of sulfonyl chloride **2** (Scheme 1).

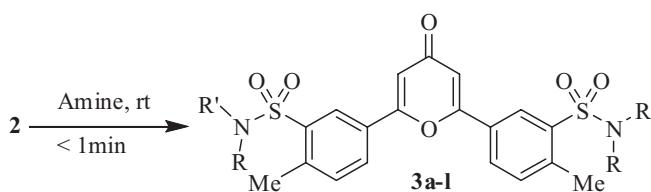


**Scheme 1** Synthesis of bis-chlorosulfonyl derivative **2**.

In dry media, 2,6-bis[(3-chlorosulfonyl-4-methyl)phenyl]-4*H*-pyran-4-one **2** was unstable, so its spectroscopic investigation was impossible. Therefore in wet form it was treated with various nucleophiles such as amines and alcohols to give the corresponding sulfonamide and sulfonate derivatives, respectively.

As shown in Scheme 2, the bis-sulfonamides **3a–l** were synthesized by the reaction of bis-sulfonylchloride **2** with excess amounts of various primary and secondary aliphatic and aromatic amines under solvent-free conditions at room temperature in 55–82% yields. The results are summarized in Table 1.

The reaction of bis-sulfonylchloride **2** with alcohols was investigated using excess amounts of alcohols under reflux conditions to give the corresponding sulfonates **4a–e** in 20–49% yields (Scheme 3).

Scheme 2 Synthesis of bis-sulfonamides **3a-l**.

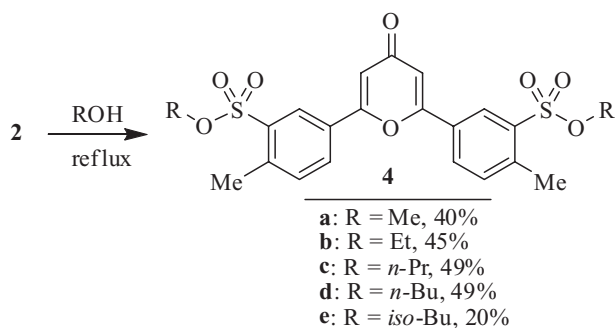
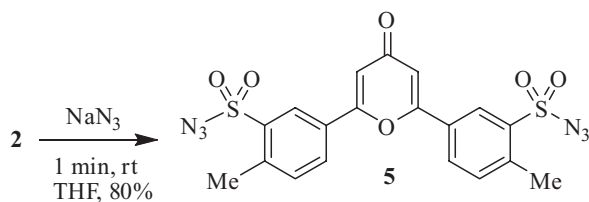
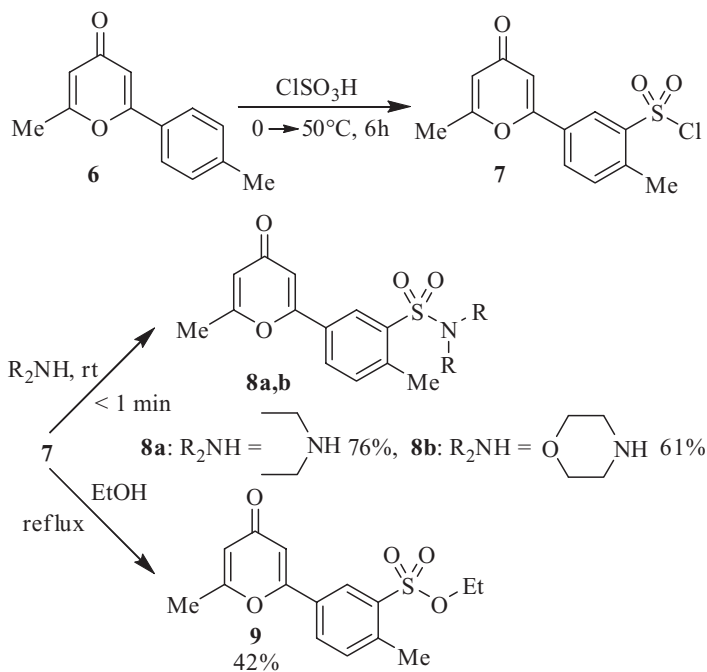
As shown in Scheme 4, the reaction of bis-chlorosulfonyl **2** with sodium azide was carried out in THF at room temperature, and 2,6-bis[3-(azidosulfonyl)-4-methylphenyl]-4*H*-pyran-4-one **5** was obtained in 80% yield.

In continuation of our investigation, the mono-sulfonamides **8a,b** were synthesized via the reaction of mono-sulfonyl chloride **7** with excess amounts of diethyl amine and morpholine under solvent-free conditions at room temperature in 76% and 61% yields, respectively. Treatment of **7** with an excess amount of ethanol under reflux conditions

Table 1 Yields of bis-sulfonamides **3a-l**

Entry	Amine	Product	Yield(%) <sup>a</sup>
1		<b>3a</b>	60
2		<b>3b</b>	65
3		<b>3c</b>	59
4		<b>3d</b>	73
5		<b>3e</b>	75
6		<b>3f</b>	60
7		<b>3g</b>	59
8		<b>3h</b>	68
9		<b>3i</b>	82
10		<b>3j</b>	71
11		<b>3k</b>	72
12		<b>3l</b>	55

<sup>a</sup>Isolated yields.

Scheme 3 Synthesis of bis-sulfonates **4a–e**.Scheme 4 Synthesis of bis-sulfonyl azide **5**.Scheme 5 Synthesis of mono-sulfonamides **8a,b** and sulfonate **9**.

produced the mono-sulfonate **9** in 42% yield (Scheme 5). Mono-sulfonyl chloride **7** was synthesized by the reaction of **6** with chlorosulfonic acid under the same conditions as described for compound **2** (Scheme 5).

## CONCLUSION

We have synthesized new *N*-alkyl and -arylsulfonamide and alkyl sulfonate derivatives of 2,6-bis-(4-methylphenyl)-4*H*-pyran-4-one **1** and 2-methyl-6-(4-methylphenyl)-4*H*-pyran-4-one **6** by chlorosulfonylation using chlorosulfonic acid followed by reaction with amines and alcohols under solvent-free conditions. The reaction of chlorosulfonyl derivatives with amines was carried out at ambient temperature, but the reactions with alcohols needed to be heated. Because of the higher nucleophilicity of amines compared with alcohols, the yield of sulfonamides was higher than that of the sulfonates.

## EXPERIMENTAL

All chemicals were purchased and used without any further purification. Melting points were determined on an Electrothermal MEL-TEMP apparatus (model 1202D) and are uncorrected. FT-IR spectra were obtained with a Bruker Tensor 27 spectrometer. NMR spectra were recorded at 400 or 500 MHz for protons and at 100 or 125 MHz for carbon nuclei in CDCl<sub>3</sub> and DMSO-*d*<sub>6</sub>. Elemental analyses were done by a Vario EL III, Elementar.

### General Procedure for the Synthesis of Chlorosulfonylpyrones **2** and **7**

To 0.2 g (0.72 mmol) of 2,6-bis-(4-methylphenyl)-4*H*-pyran-4-one (**1**) or 0.2 g (1 mmol) of 2-methyl-6-(4-methylphenyl)-4*H*-pyran-4-one (**6**), distilled chlorosulfonic acid (0.48 mL, 7.2 mmol, or 0.66 mL, 10 mmol) was added dropwise at 0°C, respectively. The mixture was stirred at 0°C for 15 min. Then the reaction mixture was heated at 50°C for 6 h. After the completion of the reaction, the mixture was cooled to room temperature and poured into crushed ice (15 g). The resulting white solids were separated by filtration and washed with cold water (20 mL).

### General Procedure for the Synthesis of Sulfonamides **3a–l** and **8a,b**

To the wet solid obtained from the reaction of 0.2 g (0.72 mmol) of **1** or 0.2 g (1 mmol) of **6** with chlorosulfonic acid (0.48 mL, 7.2 mmol, or 0.66 mL, 10 mmol, respectively), amine (3 mmol) was added at room temperature, and the reaction mixture rapidly solidified. The excess amount of amine was removed under vacuum, and resulting solid was washed with water (20 mL) and dried in air.

#### 2,6-Bis[3-(*N*-ethylaminosulfonyl)-4-methylphenyl]-4*H*-pyran-4-one (**3a**).

Recrystallized from MeOH:CHCl<sub>3</sub> (2:1), white crystals. Yield: 60%. Mp: 106–108°C. FT-IR (KBr):  $\nu$  3304 (NH), 3148, 2979, 2930, 2874, 1643 (C=O), 1587, 1417, 1322 (SO<sub>2</sub>), 1154 (SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.31 (d, *J* = 1.2 Hz, 2H, CH<sub>Ar</sub>), 8.14 (dd, *J* = 1.2 Hz, *J* = 7.8 Hz, 2H, CH<sub>Ar</sub>), 7.79 (s, br, 2H, NH), 7.62 (d, *J* = 8.1 Hz, 2H, CH<sub>Ar</sub>), 7.02 (s, 2H, CH<sub>Pyrone</sub>), 2.87–2.92 (m, 4H, CH<sub>2Ethyl</sub>), 2.66 (s, 6H, CH<sub>3</sub>), 0.99 (t, *J* = 7.2 Hz, 6H, CH<sub>3Ethyl</sub>) ppm; <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  179.4 (C=O), 162.1, 141.0, 140.8, 134.4, 130.3, 129.9, 126.3, 112.3, 38.3, 20.7, 15.9 ppm. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C 56.31; H 5.34; N 5.71. Found: C 56.20; H 5.45; N 5.43.

**2,6-Bis[3-(N-butylaminosulfonyl)-4-methylphenyl]-4H-pyran-4-one (3b).**

Purified by plc on silica gel using a mixture of acetone:hexane (3:7), colorless crystals. Yield: 65%. Mp: 98–100°C. FT-IR (KBr):  $\nu$  3288 (NH), 3176, 2866, 1648 (C=O), 1319 (SO<sub>2</sub>), 1151 (SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.51 (d,  $J$  = 1.3 Hz, 2H, CH<sub>Ar</sub>), 7.87 (dd,  $J$  = 1.3 Hz,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.49 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.88 (s, 2H, CH<sub>Pyrone</sub>), 5.07 (t,  $J$  = 5.9 Hz, 2H, NH), 3.01–3.07 (m, 4H, CH<sub>2</sub>), 2.74 (s, 6H, CH<sub>3</sub>), 1.47–1.54 (m, 4H, CH<sub>2</sub>), 1.28–1.34 (m, 4H, CH<sub>2</sub>), 0.85 (t,  $J$  = 7.3 Hz, 6H, CH<sub>3</sub><sub>Butyl</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.8 (C=O), 160.5, 140.0, 139.0, 132.6, 128.2, 128.1, 125.2, 110.5, 42.0, 30.9, 19.4, 18.6, 12.5 ppm. Anal. Calcd for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C 59.32; H 6.27; N 5.12; Found: C 59.21; H 6.35; N 4.98.

**2,6-Bis[3-(N-2-ethanolaminosulfonyl)-4-methylphenyl]-4H-pyran-4-one (3c).** Recrystallized from EtOH:CHCl<sub>3</sub> (2:1), white crystals. Yield: 59%. Mp: 204–206°C. FT-IR (KBr):  $\nu$  3379 (OH), 3254 (NH), 3165, 2942, 2866, 1651 (C=O), 1594, 1410, 1320 (SO<sub>2</sub>), 1152 (SO<sub>2</sub>), 1076, 956 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.35 (s, 2H, CH<sub>Ar</sub>), 8.15 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.86 (s, br, 2H, NH), 7.63 (d,  $J$  = 8.1 Hz, 2H, CH<sub>Ar</sub>), 7.04 (s, 2H, CH<sub>Pyrone</sub>), 4.69 (t,  $J$  = 5.4 Hz, 2H, OH), 3.37–3.42 (m, 4H, CH<sub>2</sub>), 2.93–2.94 (m, 4H, CH<sub>2</sub>), 2.66 (s, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>):  $\delta$  179.5 (C=O), 162.1, 141.1, 141.0, 134.4, 130.2, 129.9, 126.2, 112.3, 60.8, 45.8, 20.7 ppm. Anal. Calcd for C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>S<sub>2</sub>: C 52.86; H 5.01; N 5.36. Found: C 52.73; H 4.90; N 5.31.

**2,6-Bis[3-(N-2-(S)-propanolaminosulfonyl)-4-methylphenyl]-4H-pyran-4-one (3d).** Recrystallized from MeOH:CHCl<sub>3</sub> (2:1), white crystals. Yield: 73%. Mp: 155–157°C. FT-IR (KBr):  $\nu$  3308 (NH), 3158 (OH), 2974, 2917, 1640 (C=O), 1570, 1421, 1318 (SO<sub>2</sub>), 1151 (SO<sub>2</sub>), 1079, 945 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.34 (d,  $J$  = 1.5 Hz, 2H, CH<sub>Ar</sub>), 8.15 (dd,  $J$  = 1.5 Hz,  $J$  = 7.9 Hz, 2H, CH<sub>Ar</sub>), 7.82 (s, br, 2H, NH), 7.62 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.04 (s, 2H, CH<sub>Pyrone</sub>), 4.68 (d,  $J$  = 4.7 Hz, 2H, OH), 3.58–3.63 (m, 2H, CH), 2.79 (d,  $J$  = 5.6 Hz, 4H, CH<sub>2</sub>), 2.66 (s, 6H, CH<sub>3</sub>), 0.99 (d,  $J$  = 6.2 Hz, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>):  $\delta$  179.5 (C=O), 162.2, 141.1, 140.9, 134.3, 130.2, 129.9, 126.2, 112.3, 66.1, 50.8, 21.6, 20.7 ppm. Anal. Calcd for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>8</sub>S<sub>2</sub>: C 54.53; H 5.49; N 5.09. Found: C 54.20; H 5.45; N 4.91.

**2,6-Bis[3-(N,N-di-ethylaminosulfonyl)-4-methylphenyl]-4H-pyran-4-one (3e).** Purified by plc on silica gel using acetone:hexane (3:7), white crystals. Yield: 75%. Mp: 138–140°C. FT-IR (KBr): 3073, 2880, 1658 (C=O), 1319 (SO<sub>2</sub>), 1148 (SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.36 (s, 2H, CH<sub>Ar</sub>), 7.87 (d,  $J$  = 7.7 Hz, 2H, CH<sub>Ar</sub>), 7.47 (d,  $J$  = 7.7 Hz, 2H, CH<sub>Ar</sub>), 6.83 (s, 2H, CH<sub>Pyrone</sub>), 3.35 (q,  $J$  = 7.0 Hz, 8H, CH<sub>2</sub>), 2.67 (s, 6H, CH<sub>3</sub>), 1.15 (t,  $J$  = 7.0 Hz, 12H, CH<sub>3</sub><sub>Ethyl</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.4 (C=O), 160.9, 140.3, 139.0, 132.6, 128.3, 128.2, 125.7, 111.1, 39.9, 19.3, 12.7 ppm. Anal. calcd for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C 59.32; H 6.27; N 5.12; Found: C 58.95; H 6.30; N 5.20.

**2,6-Bis[3-(N,N-di-propylaminosulfonyl)-4-methylphenyl]-4H-pyran-4-one (3f).** Purified by plc on silica gel using a mixture of acetone:hexane (1:2), pale yellow solid. Yield: 60%. Mp: 118–120°C. FT-IR (KBr):  $\nu$  3069, 2967, 2934, 2876, 1652 (C=O), 1613, 1461, 1402, 1372, 1325 (SO<sub>2</sub>), 1146 (SO<sub>2</sub>), 993 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.37 (s, 2H, CH<sub>Ar</sub>), 7.91 (d,  $J$  = 7.8 Hz, 2H, CH<sub>Ar</sub>), 7.50 (d,  $J$  = 7.9 Hz, 2H, CH<sub>Ar</sub>), 6.86 (s, 2H, CH<sub>Pyrone</sub>), 3.26 (t,  $J$  = 7.4 Hz, 8H, CH<sub>2</sub>), 2.71 (s, 6H, CH<sub>3</sub>), 1.56–1.63 (m, 8H, CH<sub>2</sub>), 0.86 (t,  $J$  = 7.3 Hz, 12H, CH<sub>3</sub><sub>Propyl</sub>) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  179.9 (C=O), 162.4, 141.8, 140.5, 134.1, 129.7, 129.6, 127.0, 112.3, 49.1, 21.8, 20.9, 11.5 ppm. Anal. Calcd for C<sub>31</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C 61.77; H 7.02; N 4.65. Found: C 61.63; H 7.15; N 4.53.

**2,6-Bis[3-(N,N-di-2-ethanolaminosulfonyl)-4-methylphenyl]-4H-pyran-4-one (3g).** Recrystallized from MeOH:CHCl<sub>3</sub> (2:1), white crystals. Yield: 59%. Mp:

200–202°C. FT-IR (KBr):  $\nu$  3365 (OH), 3038, 2964, 2929, 2882, 1646 (C=O), 1614, 1406, 1331 (SO<sub>2</sub>), 1156 (SO<sub>2</sub>), 993 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.34 (d,  $J$  = 1.3 Hz, 2H, CH<sub>Ar</sub>), 8.16 (dd,  $J$  = 1.3 Hz,  $J$  = 7.7 Hz, 2H, CH<sub>Ar</sub>), 7.64 (d,  $J$  = 7.7 Hz, 2H, CH<sub>Ar</sub>), 7.07 (s, 2H, CH<sub>Pyrone</sub>), 4.90 (s, 4H, OH), 3.52 (t,  $J$  = 6.0 Hz, 8H, CH<sub>2</sub>), 3.38 (t,  $J$  = 5.7 Hz, 8H, CH<sub>2</sub>), 2.63 (s, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>):  $\delta$  178.7 (C=O), 161.3, 140.5, 139.8, 133.7, 129.7, 129.2, 125.2, 111.6, 59.4, 49.9, 20.0 ppm. Anal. calcd for C<sub>27</sub>H<sub>34</sub>N<sub>2</sub>O<sub>10</sub>S<sub>2</sub>: C 53.10; H 5.61; N 4.59. Found: C 52.88; H 5.50; N 4.54.

**2,6-Bis[4-methyl-3-(pyrrolidin-1-ylsulfonyl)phenyl]-4H-pyran-4-one (3h).**

Recrystallized from EtOH (96%), white crystals. Yield: 68%. Mp: 207–209°C. FT-IR (KBr):  $\nu$  3084, 2970, 1645 (C=O), 1366 (SO<sub>2</sub>), 1154 (SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.37 (d,  $J$  = 1.6 Hz, 2H, CH<sub>Ar</sub>), 7.87 (dd,  $J$  = 1.6 Hz,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.49 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.82 (s, 2H, CH<sub>Pyrone</sub>), 3.34 (t,  $J$  = 6.6 Hz, 8H, CH<sub>2</sub>), 2.71 (s, 6H, CH<sub>3</sub>), 1.92 (m, 8H, CH<sub>2</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.4 (C=O), 160.9, 140.5, 137.7, 132.7, 128.4, 128.3, 125.8, 110.9, 46.4, 24.6, 19.7 ppm. Anal. calcd for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C 59.76; H 5.57; N 5.16. Found: C 59.70; H 5.38; N 5.20.

**2,6-Bis[4-methyl-3-(piperidin-1-ylsulfonyl)phenyl]-4H-pyran-4-one (3i).**

Recrystallized from MeOH:CHCl<sub>3</sub> (2:1), white crystals. Yield: 82%. Mp: 200–202°C. FT-IR (KBr):  $\nu$  2946, 2855, 2807, 2737, 1650 (C=O), 1606, 1401, 1372 (SO<sub>2</sub>), 1165 (SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.39 (d,  $J$  = 1.0 Hz, 2H, CH<sub>Ar</sub>), 7.91 (dd,  $J$  = 1.3 Hz,  $J$  = 7.9 Hz, 2H, CH<sub>Ar</sub>), 7.52 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.86 (s, 2H, CH<sub>Pyrone</sub>), 3.23 (t,  $J$  = 5.2 Hz, 8H, CH<sub>2</sub>), 2.73 (s, 6H, CH<sub>3</sub>), 1.65–1.67 (m, 8H, CH<sub>2</sub>), 1.56–1.59 (m, 4H, CH<sub>2</sub>) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  179.5 (C=O), 162.3, 142.0, 138.4, 134.2, 129.9, 129.8, 127.9, 112.4, 46.6, 25.8, 24.1, 21.2 ppm. Anal. Calcd for C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C 61.03; H 6.00; N 4.91. Found: C 60.90; H 5.97; N 4.88.

**2,6-Bis[4-methyl-3-(morpholin-4-ylsulfonyl)phenyl]-4H-pyran-4-one (3j).**

Recrystallized from EtOH (96%), white crystals. Yield: 71%. Mp: 250–252°C. FT-IR (KBr):  $\nu$  3080, 2856, 1647 (C=O), 1333 (SO<sub>2</sub>), 1158 (SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.38 (d,  $J$  = 2.2 Hz, 2H, CH<sub>Ar</sub>), 7.89 (dd,  $J$  = 2.2 Hz,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.52 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.84 (s, 2H, CH<sub>Pyrone</sub>), 3.75 (t,  $J$  = 4.0 Hz, 8H, CH<sub>2</sub>), 3.22 (t,  $J$  = 4.0 Hz, 8H, CH<sub>2</sub>), 2.72 (s, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.3 (C=O), 160.5, 140.7, 135.6, 133.0, 128.7, 128.5, 126.6, 111.1, 65.3, 44.4, 20.0 ppm. Anal. calcd for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>8</sub>S<sub>2</sub>: C 56.43; H 5.26; N 4.87. Found: C 56.58; H 5.15; N 5.10.

**2,6-Bis[4-methyl-3-(phenylaminosulfonyl)phenyl]-4H-pyran-4-one (3k).**

White crystals. Yield: 72%. Decomp. 274°C. FT-IR (KBr):  $\nu$  3283 (NH), 3114, 3072, 2883, 2846, 1648 (C=O), 1596, 1340 (SO<sub>2</sub>), 1150 (SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  10.57 (s, 2H, NH), 8.37 (s, 2H, CH<sub>Ar</sub>), 8.05 (d,  $J$  = 7.9 Hz, 2H, CH<sub>Ar</sub>), 7.58 (d,  $J$  = 8.1 Hz, 2H, CH<sub>Ar</sub>), 7.14–7.22 (m, 8H, CH<sub>Ph</sub>), 9.95–6.98 [m, 2H (CH<sub>Ph</sub>), 2H (CH<sub>Pyrone</sub>)], 2.67 (s, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>):  $\delta$  178.5 (C=O), 160.9, 140.4, 138.6, 137.3, 133.6, 130.1, 129.3, 129.0, 126.4, 123.8, 119.1, 111.6, 19.7 ppm. Anal. calcd for C<sub>31</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C 63.46; H 4.47; N 4.77. Found: C 63.11; H 4.22; N 4.69.

**2,6-Bis[4-methyl-3-(3-methyl-1H-pyrazol-1-ylsulfonyl)phenyl]-4H-pyran-4-one (3l).** Recrystallized from MeOH:CHCl<sub>3</sub> (2:1), white crystals. Yield: 55%. Decomp. 192°C. FT-IR (KBr):  $\nu$  3068, 2967, 1663 (C=O), 1608, 1461, 1402, 1373 (SO<sub>2</sub>), 1134 (SO<sub>2</sub>), 771 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.48 (d,  $J$  = 1.3 Hz, 2H, CH<sub>Ar</sub>), 8.11 (d,  $J$  = 2.6 Hz, 2H, CH<sub>Pyrazole</sub>), 7.90 (dd,  $J$  = 1.4 Hz,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.45 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.78 (s, 2H, CH<sub>Pyrone</sub>), 6.21 (d,  $J$  = 2.6 Hz, 2H, CH<sub>Pyrazole</sub>), 2.64 (s, 6H, CH<sub>3</sub>), 2.19 (s, 6H, CH<sub>3</sub>Pyrazole) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>/DMSO-d<sub>6</sub>):  $\delta$  179.5 (C=O), 161.5, 155.9, 142.8, 137.5, 134.4, 133.0, 131.4, 130.3, 127.9, 112.6, 110.0, 20.9,



14.3 ppm. Anal. calcd for  $C_{27}H_{24}N_4O_6S_2$ : C 57.43; H 4.28; N 9.92. Found: C 57.09; H 4.12; N 9.61.

### General Procedure for the Synthesis of Sulfonates 4a–e, 9

To the wet solid obtained from the reaction of 0.2 g (0.72 mmol) of **1** or 0.2 g (1 mmol) of **6** with chlorosulfonic acid (0.48 mL, 7.2 mmol or 0.66 mL, 10 mmol), respectively, and as mentioned above alcohol (10 mL) was added, and refluxed until the mixture would be clear, then the solution was kept in a freezer for 24 h. The resulting solid was separated by filtration and washed with cold alcohol and dried in air.

**2,6-Bis[3-(methoxysulfonyl)-4-methylphenyl]-4H-pyran-4-one (4a).** Purified by plc on silica gel using ethyl acetate/petroleum ether 60–80°C (3:7), white crystals. Yield: 40%. Mp: 191–193°C. FT-IR (KBr):  $\nu$  3053, 2857, 1653 (C=O), 1355 (SO<sub>2</sub>), 1179 (SO<sub>2</sub>), 988, 785 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.47 (d,  $J$  = 1.6 Hz, 2H, CH<sub>Ar</sub>), 7.96 (dd,  $J$  = 1.6 Hz,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.57 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.88 (s, 2H, CH<sub>Pyrone</sub>), 3.84 (s, 6H, OCH<sub>3</sub>), 2.74 (s, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.2 (C=O), 160.4, 141.2, 134.3, 132.8, 129.5, 128.6, 126.5, 111.3, 55.5, 19.3 ppm. Anal. calcd for  $C_{21}H_{20}O_8S_2$ : C 54.30; H 4.34. Found: C 54.13; H 4.31.

**2,6-Bis[3-(ethoxysulfonyl)-4-methylphenyl]-4H-pyran-4-one (4b).** Purified by plc on silica gel using acetone:ethyl acetate:petroleum ether 60–80°C (3:3:7), white crystals. Yield: 45%. Mp: 178–180°C. FT-IR (KBr):  $\nu$  3052, 2933, 1652 (C=O), 1354 (SO<sub>2</sub>), 1179 (SO<sub>2</sub>), 909 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.46 (d,  $J$  = 1.6 Hz, 2H, CH<sub>Ar</sub>), 7.94 (dd,  $J$  = 1.6 Hz,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.56 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.86 (s, 2H, CH<sub>Pyrone</sub>), 4.20 (q,  $J$  = 8.0 Hz, 4H, CH<sub>2</sub>ethyl), 2.75 (s, 6H, CH<sub>3</sub>), 1.36 (t,  $J$  = 8.0 Hz, 6H, CH<sub>3</sub>ethyl) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.2 (C=O), 160.4, 140.9, 135.2, 132.6, 129.3, 128.5, 126.2, 111.1, 66.4, 19.3, 13.7 ppm. Anal. calcd for  $C_{23}H_{24}O_8S_2$ : C 56.08; H 4.91. Found: C 55.97; H 5.11.

**2,6-Bis[3-(propoxysulfonyl)-4-methylphenyl]-4H-pyran-4-one (4c).** Purified by plc on silica gel using acetone:ethyl acetate:petroleum ether 60–80°C (1:2:3), white crystals. Yield: 49%. Mp: 170–172°C. FT-IR (KBr):  $\nu$  3051, 2883, 1652 (C=O), 1354 (SO<sub>2</sub>), 1179 (SO<sub>2</sub>), 961, 836 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.46 (s, 2H, CH<sub>Ar</sub>), 7.95 (d,  $J$  = 7.2 Hz, 2H, CH<sub>Ar</sub>), 7.56 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.85 (s, 2H, CH<sub>Pyrone</sub>), 4.07 (t,  $J$  = 6.5 Hz, 4H, CH<sub>2</sub>), 2.74 (s, 6H, CH<sub>3</sub>), 1.68–1.77 (m, 4H, CH<sub>2</sub>), 0.94 (t,  $J$  = 7.3 Hz, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.2 (C=O), 160.4, 140.9, 135.1, 132.6, 129.3, 128.5, 126.2, 111.1, 71.8, 21.3, 19.3, 9.0 ppm. Anal. calcd for  $C_{25}H_{28}O_8S_2$ : C 57.68; H 5.42. Found: C 57.44; H 5.40.

**2,6-Bis[3-(butoxysulfonyl)-4-methylphenyl]-4H-pyran-4-one (4d).** Purified by plc on silica gel using a mixture of acetone:ethyl acetate:petroleum ether 60–80°C (3:3:7), white crystals. Yield: 49%. Mp: 165–167°C. FT-IR (KBr):  $\nu$  3053, 2872, 1652 (C=O), 1354 (SO<sub>2</sub>), 1179 (SO<sub>2</sub>), 946, 807 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.45 (d,  $J$  = 2.0 Hz, 2H, CH<sub>Ar</sub>), 7.95 (dd,  $J$  = 2.0 Hz,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.56 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 6.86 (s, 2H, CH<sub>Pyrone</sub>), 4.02 (t,  $J$  = 6.4 Hz, 4H, CH<sub>2</sub>), 2.74 (s, 6H, CH<sub>3</sub>), 1.65–1.70 (m, 4H, CH<sub>2</sub>), 1.35–1.41 (m, 4H, CH<sub>2</sub>), 0.88 (t,  $J$  = 7.3 Hz, 6H, CH<sub>3</sub>butyl) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.2 (C=O), 160.4, 140.9, 135.1, 132.6, 129.3, 128.5, 126.2, 111.1, 70.0, 29.8, 19.3, 17.6, 12.3 ppm. Anal. calcd for  $C_{27}H_{32}O_8S_2$ : C 59.10; H 5.88. Found: C 59.22; H 5.85.

**2,6-Bis[3-(isobutoxysulfonyl)-4-methylphenyl]-4H-pyran-4-one (4e).** Purified by plc on silica gel using a mixture of acetone:hexane (3:7), white crystals. Yield:

20%. Mp: 180–182°C. FT-IR (KBr):  $\nu$  3054, 2965, 2878, 1653 (C=O), 1609, 1406, 1355 (SO<sub>2</sub>), 1181 (SO<sub>2</sub>), 975 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.50 (d,  $J$  = 1.2 Hz, 2H, CH<sub>Ar</sub>), 7.99 (dd,  $J$  = 1.2 Hz,  $J$  = 7.8 Hz, 2H, CH<sub>Ar</sub>), 7.59 (d,  $J$  = 7.8 Hz, 2H, CH<sub>Ar</sub>), 6.89 (s, 2H, CH<sub>Pyrone</sub>), 3.91 (d,  $J$  = 6.4 Hz, 4H, CH<sub>2</sub>), 2.78 (s, 6H, CH<sub>3</sub>), 2.01–2.06 (m, 2H, CH), 0.98 (d,  $J$  = 6.7 Hz, 12H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  179.6 (C=O), 161.8, 142.3, 136.5, 134.3, 130.7, 129.9, 127.7, 112.6, 77.2, 28.5, 20.8, 19.1 ppm. Anal. calcd for C<sub>27</sub>H<sub>32</sub>O<sub>8</sub>S<sub>2</sub>: C 59.10; H 5.88 Found: C 59.02; H 5.77.

### Procedure for the Synthesis of Sulfonazide 5

To the wet solid obtained from the reaction of 0.5 g (1.8 mmol) of **1** with chlorosulfonic acid (1.2 mL, 18 mmol) as mentioned above, NaN<sub>3</sub> (0.2 g, 3.07 mmol) in THF was added at room temperature, and the reaction mixture rapidly solidified. The solid was separated by filtration, washed with cold water, and dried in air.

**2,6-Bis[3-(azidosulfonyl)-4-methylphenyl]-4H-pyran-4-one (5).** White crystals. Yield: 80%. Decomp. 160°C. FT-IR (KBr):  $\nu$  3051, 2982, 2137 (N<sub>3</sub>), 1652 (C=O), 1605, 1360 (SO<sub>2</sub>), 1170 (SO<sub>2</sub>) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  8.50 (d,  $J$  = 1.7 Hz, 2H, CH<sub>Ar</sub>), 8.36 (dd,  $J$  = 1.8 Hz,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.81 (d,  $J$  = 8.0 Hz, 2H, CH<sub>Ar</sub>), 7.18 (s, 2H, CH<sub>Pyrone</sub>), 2.69 (s, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>):  $\delta$  179.0 (C=O), 161.0, 142.0, 138.4, 134.2, 131.2, 130.0, 126.6, 112.5, 20.6 ppm. Anal. calcd for C<sub>19</sub>H<sub>14</sub>N<sub>6</sub>O<sub>6</sub>S<sub>2</sub>: C 46.91; H 2.90; N 17.28. Found: C 46.74; H 2.71; N 16.99.

**2-[3-(N,N-Di-ethylaminosulfonyl)-4-methylphenyl]-6-methyl-4H-pyran-4-one (8a).** White crystals. Yield: 76%. Mp: 134–136°C. FT-IR (KBr):  $\nu$  3054, 2976, 2933, 1661 (C=O), 1613, 1405, 1308 (SO<sub>2</sub>), 1143 (SO<sub>2</sub>), 925 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.25 (d,  $J$  = 1.4 Hz, 1H, CH<sub>Ar</sub>), 7.76 (dd,  $J$  = 1.8 Hz,  $J$  = 8.0 Hz, 1H, CH<sub>Ar</sub>), 7.39 (d,  $J$  = 8.0 Hz, 1H, CH<sub>Ar</sub>), 6.68 (d,  $J$  = 2.0 Hz, 1H, CH<sub>Pyrone</sub>), 6.16 (s, 1H, CH<sub>Pyrone</sub>), 3.31 (q,  $J$  = 7.0 Hz, 4H, CH<sub>2</sub>), 2.62 (s, 3H, CH<sub>3</sub>), 2.36 (s, 3H, CH<sub>3</sub>), 1.12 (t,  $J$  = 7.0 Hz, 6H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.7 (C=O), 164.4, 160.8, 139.9, 138.7, 132.4, 128.3, 128.0, 125.4, 113.4, 110.0, 39.7, 19.2, 18.8, 12.5 ppm. Anal. Calcd for C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>S: C 60.87; H 6.31; N 4.18. Found: C 60.66; H 6.30; N 4.37.

**2-Methyl-6-[4-methyl-3-(morpholinosulfonyl)phenyl]-4H-pyran-4-one (8b).** Recrystallized from EtOH (96%), yellow crystals. Yield: 61%. Mp: 186–188°C. FT-IR (KBr):  $\nu$  3021, 2976, 2891, 2856, 1660 (C=O), 1614, 1399, 1336 (SO<sub>2</sub>), 1163 (SO<sub>2</sub>), 932 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.25 (d,  $J$  = 2.0 Hz, 1H, CH<sub>Ar</sub>), 7.80 (dd,  $J$  = 1.6 Hz,  $J$  = 8.0 Hz, 1H, CH<sub>Ar</sub>), 7.44 (d,  $J$  = 8.0 Hz, 1H, CH<sub>Ar</sub>), 6.69 (d,  $J$  = 2.0 Hz, 1H, CH<sub>Pyrone</sub>), 6.17 (d,  $J$  = 1.2 Hz, 1H, CH<sub>Pyrone</sub>), 3.70 (t,  $J$  = 4.0 Hz, 4H, CH<sub>2</sub>), 3.16 (t,  $J$  = 4.0 Hz, 4H, CH<sub>2</sub>), 2.67 (s, 3H, CH<sub>3</sub>), 2.37 (s, 3H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  178.6 (C=O), 164.5, 160.5, 140.2, 135.3, 132.7, 128.6, 128.6, 126.3, 113.5, 110.2, 65.1, 44.2, 19.7, 18.8 ppm. Anal. Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub>S: C 58.44; H 5.48; N 4.01. Found: C 58.18; H 5.55; N 4.11.

**2-[3-(Ethoxysulfonyl)-4-methylphenyl]-6-methyl-4H-pyran-4-one (9).** Purified by plc on silica gel using hexane:acetone (2:1), pink crystals. Yield: 42%. Mp: 129–131°C. FT-IR (KBr):  $\nu$  3096, 2963, 2925, 2856, 1668 (C=O), 1618, 1402, 1375 (SO<sub>2</sub>), 1176 (SO<sub>2</sub>), 916 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.37 (d,  $J$  = 4.0 Hz, 1H, CH<sub>Ar</sub>), 7.85 (dd,  $J$  = 4.0 Hz,  $J$  = 8.0 Hz, 1H, CH<sub>Ar</sub>), 7.48 (d,  $J$  = 8.0 Hz, 1H, CH<sub>Ar</sub>), 6.73 (d,  $J$  = 2.1 Hz, 1H, CH<sub>Pyrone</sub>), 6.20 (d,  $J$  = 1.2 Hz, 1H, CH<sub>Pyrone</sub>), 4.15 (q,  $J$  = 8.0 Hz, 2H, CH<sub>2</sub>), 2.71 (s, 3H, CH<sub>3</sub>), 2.40 (s, 3H, CH<sub>3</sub>), 1.34 (t,  $J$  = 8.0 Hz, 3H, CH<sub>3</sub>) ppm; <sup>13</sup>C NMR

(100 MHz,  $\text{CDCl}_3$ ):  $\delta$  178.7 (C=O), 164.6, 160.4, 140.5, 134.9, 132.4, 129.2, 128.7, 125.9, 113.6, 110.3, 66.2, 19.3, 18.9, 13.7 ppm. Anal. calcd for  $\text{C}_{15}\text{H}_{16}\text{O}_5\text{S}$ : C 58.43; H 5.23; Found: C 58.39; H 5.33.

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