

## Tandem Knoevenagel–Michael reaction with oxidative cyclization in the synthesis of spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine] scaffold

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### 1. Experimental section

All melting points were measured with a Stuart SMP 30 melting point apparatus and are uncorrected.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with a Bruker AM-300 (300 and 75 MHz, respectively) at ambient temperature in  $\text{CDCl}_3$  solutions. Chemical shift values are given in  $\delta$  scale relative to  $\text{Me}_4\text{Si}$ . IR spectra were registered with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass-spectra ( $\text{EI} = 70 \text{ eV}$ ) were obtained directly with a Finningan MAT INCOS 50 spectrometer. Elemental analysis was performed on elemental analyzer multi EA® 5000.

### General procedures

#### Method A

Aldehyde **1a** (2 mmol), *N,N'*-dimethylbarbituric acid (2 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (2 mmol),  $\text{Et}_3\text{N}$  (2 mmol) and NBS (2.2 mmol) were stirred in EtOH (5 mL) for 30 min at ambient temperature. The reaction was completed (the color of the reaction mixture became pale), the formed solid was filtered, washed with an ice-cold ethanol/water solution (1:1, 3 mL), and dried to isolate pure spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine] **2a**.

#### Method B

Aldehydes **1a-j** (2 mmol), *N,N'*-dimethylbarbituric acid (2 mmol), 4-hydroxy-6-methyl-2*H*-pyran-2-one (2 mmol), and  $\text{Et}_3\text{N}$  (2 mmol) were stirred in EtOH (5 mL) for 30 min at ambient temperature. Then NBS (2.2 mmol) was added and stirring was continued for another 30 min. The reaction was completed (the color of the reaction mixture became pale), the formed solid was filtered, washed with an ice-cold ethanol/water solution (1:1, 3 mL), and dried to isolate pure spiro[furo[3,2-*c*]pyran-2,5'-pyrimidines] **2a-j**.

**1',3',6-Trimethyl-3-phenyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2a)**

Yield 0.67 g, (91%), mp 248-250 °C (decomp.) [Lit.<sup>S1</sup> mp 249-251 °C (decomp.)], <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.38 (s, 3H, CH<sub>3</sub>), 2.58 (s, 3H, CH<sub>3</sub>), 3.45 (s, 3H, CH<sub>3</sub>), 4.88 (s, 1H, CH), 6.28 (s, 1H, CH), 6.99-7.13 (m, 2H, Ar), 7.30-7.40 (m, 3H, Ar) ppm.

**3-(2-Methylphenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2b)**

Yield 0.70 g, (92%), mp: 282-283 °C (decomp.) [Lit.<sup>S1</sup> mp 249-251 °C (decomp.)]. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.25 (s, 3H, CH<sub>3</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 2.61 (s, 3H, CH<sub>3</sub>), 3.39 (s, 3H, CH<sub>3</sub>), 5.25 (s, 1H, CH), 6.28 (s, 1H, CH), 6.95-7.02 (m, 1H, Ar), 7.09-7.25 (m, 3H, Ar) ppm.

**3-(4-Methylphenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2c)**

Yield 0.69 g, (90%), mp 290-292 °C (decomp.), [Lit.<sup>S2</sup> mp 290-291 °C (decomp.)]. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.33 (s, 3H, CH<sub>3</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 2.60 (s, 3H, CH<sub>3</sub>), 3.43 (s, 3H, CH<sub>3</sub>), 4.85 (s, 1H, CH), 6.27 (s, 1H, CH), 6.93 (d, <sup>3</sup>*J* = 8.2 Hz, 2H, Ar), 7.14 (d, <sup>3</sup>*J* = 8.2 Hz, 2H, Ar) ppm.

**3-(3-Methoxyphenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2d)**

Yield 0.70 g (88%), mp: 184-185 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.38 (s, 3H, CH<sub>3</sub>), 2.64 (s, 3H, CH<sub>3</sub>), 3.44 (s, 3H, CH<sub>3</sub>), 3.76 (s, 3H, OCH<sub>3</sub>), 4.85 (s, 1H, CH), 6.28 (s, 1H, CH), 6.56 (s, 1H, Ar), 6.63 (d, <sup>3</sup>*J* = 8.2 Hz, 1H, Ar), 6.89 (d, <sup>3</sup>*J* = 8.2 Hz, 1H, Ar), 7.25 (t, <sup>3</sup>*J* = 8.2 Hz, 1H, Ar) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 20.7, 28.5, 29.5, 55.4, 58.9, 91.2, 95.5, 98.5, 113.9, 115.3, 118.3, 120.7, 130.0, 133.9, 149.9, 159.8, 160.0, 166.2, 167.8, 172.6 ppm. MS (*m/z* relative intensity %): 398 [*M*<sup>+</sup>] (7), 356 (19), 355 (99), 283 (3), 243 (6), 172 (14), 156 (2), 142 (7), 115 (8), 114 (10), 85 (15), 69 (15), 58 (17), 43 (100). IR (KBr) ν = 3449, 3087, 2968, 2353, 1951, 1736, 1692, 1594, 1253, 1126, 1034 cm<sup>-1</sup>. Anal. calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>7</sub>: C, 60.30; H, 4.55; N, 7.03 %. Found: C, 60.15; H, 4.52; N, 6.95 %.

**3-(2-Fluorophenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2e)**

Yield 0,67 g (86%), mp: 249-250 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.39 (s, 3H, CH<sub>3</sub>), 2.70 (s, 3H, CH<sub>3</sub>), 3.42 (s, 3H, CH<sub>3</sub>), 5.31 (s, 1H, CH), 6.27 (s, 1H, CH), 7.00-7.20 (m, 3H, Ar), 7.25-7.40 (m, 1H, Ar) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 20.7, 28.4, 29.4, 50.7, 89.8, 95.6, 97.3, 115.1 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.3 Hz), 119.7 (d, <sup>2</sup>*J*<sub>C-F</sub> = 14.3 Hz), 124.9 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.3 Hz), 130.4 (d, <sup>3</sup>*J*<sub>C-F</sub> = 4.9 Hz), 131.0 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.8 Hz), 149.8, 159.7, 160.8 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.4 Hz), 163.6, 166.0, 168.0, 172.9 ppm. MS (*m/z* relative intensity %): 386 [*M*<sup>+</sup>] (3), 344 (13), 343 (27), 217 (11), 160 (15), 125 (37), 85 (25), 58 (38), 43 (100). IR (KBr) ν = 3443, 3107, 2958, 2539, 1730, 1694, 1588, 1452, 1390, 1128, 1041 cm<sup>-1</sup>. Anal. calcd for C<sub>19</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>6</sub>: C, 59.07; H, 3.91; F, 4.92; N, 7.25 %. Found: C, 58.95; H, 3.87; F, 4.88; N, 7.19 %.

**3-(4-Fluorophenyl)-1',3',6-trimethyl-2'H,3H,4H-spiro[furo[3,2-c]pyran-2,5'-pyrimidine]-**

**2',4,4',6'(1'H,3'H)-tetraone (2f)**

Yield 0.66 g (85%), mp: 241-243 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.38 (s, 3H, CH<sub>3</sub>), 2.67 (s, 3H, CH<sub>3</sub>), 3.43 (s, 3H, CH<sub>3</sub>), 4.87 (s, 1H, CH), 6.28 (s, 1H, CH), 6.99-7.08 (m, 4H, Ar) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 20.7, 28.5, 29.5, 58.1, 90.9, 95.5, 98.5, 116.1 (d, <sup>2</sup>J<sub>C-F</sub> = 23.6 Hz) (2C), 128.3 (d, <sup>4</sup>J<sub>C-F</sub> = 3.2 Hz), 130.3 (d, <sup>3</sup>J<sub>C-F</sub> = 8.3 Hz) (2C), 149.8, 159.7, 163.2 (d, <sup>1</sup>J<sub>C-F</sub> = 246.3 Hz), 163.5, 166.0, 168.0, 172.5 ppm. MS (*m/z* relative intensity %): 386 [M<sup>+</sup>] (5), 344 (35), 343 (100), 286 (15), 217 (25), 189 (12), 160 (27), 125 (19), 85(21). IR (KBr) ν = 3435, 3115, 2956, 1723, 1697, 1587, 1450, 1376, 1122, 1041 cm<sup>-1</sup>. Anal. calcd for C<sub>19</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>6</sub>: C, 59.07; H, 3.91; F, 4.92; N, 7.25 %. Found: C, 59.01; H, 3.87; F, 4.86; N, 7.19 %.

**3-(2-Bromophenyl)-1',3',6-trimethyl-2'H,3H,4H-spiro[furo[3,2-c]pyran-2,5'-pyrimidine]-**

**2',4,4',6'(1'H,3'H)-tetraone (2g)**

Yield 0,74 g (83%), mp: 251-252 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.38 (s, 3H, CH<sub>3</sub>), 2.71 (s, 3H, CH<sub>3</sub>), 3.40 (s, 3H, CH<sub>3</sub>), 5.54 (s, 1H, CH), 6.26 (s, 1H, CH), 7.04 (d <sup>3</sup>J = 7.6 Hz, 1H, Ar), 7.15-7.28 (m, 2H, Ar), 7.53 (d, <sup>3</sup>J = 7.7 Hz, 1H, Ar) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 20.7, 28.4, 29.4, 56.7, 89.7, 95.4, 99.1, 124.6, 128.0, 130.8, 131.3, 132.3, 132.9, 149.8, 159.5, 163.7, 165.8, 167.9, 172.5 ppm. MS (*m/z* relative intensity %): 448 [M<sup>+</sup>] Br<sup>81</sup> (1), 446 [M<sup>+</sup>] Br<sup>79</sup> (1), 367 (22), 325 (7), 283 (34), 256 (15), 192 (3), 160 (5), 128 (16), 96 (18), 64 (100), 32 (69), 28 (14), 18 (49). IR (KBr) ν = 3434, 3095, 2956, 2536, 1738, 1679, 1588, 1453, 1377, 1264, 1188 cm<sup>-1</sup>. Anal. calcd for C<sub>19</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>6</sub>: C, 51.03; H, 3.38; Br, 17.87; N, 6.26 %. Found: C, 50.95; H, 3.33; Br, 17.81; N, 6.13 %.

**3-(4-Bromophenyl)-1',3',6-trimethyl-2'H,3H,4H-spiro[furo[3,2-c]pyran-2,5'-pyrimidine]-**

**2',4,4',6'(1'H,3'H)-tetraone (2h)**

Yield 0.76 g (85%), mp: 261-263 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.38 (s, 3H, CH<sub>3</sub>), 2.67 (s, 3H, CH<sub>3</sub>), 3.44 (s, 3H, CH<sub>3</sub>), 4.83 (s, 1H, CH), 6.28 (s, 1H, CH), 6.93 (d, <sup>3</sup>J = 8.5 Hz, 2H, Ar), 7.48 (d, <sup>3</sup>J = 8.5 Hz, 2H, Ar) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 20.7, 28.5, 29.5, 58.1, 90.7, 95.5, 98.2, 123.7, 130.1 (2C), 131.6, 132.1 (2C), 149.7, 159.6, 163.4, 165.9, 168.1, 172.6 ppm. MS (*m/z* relative intensity %): 448 [M<sup>+</sup>] Br<sup>81</sup> (5), 446 [M<sup>+</sup>] Br<sup>79</sup> (5), 406 (19), 405 (98), 404 (18), 403 (100), 325 (6), 324 (28), 323 (4), 277 (7), 267 (4), 222 (7), 220 (7), 182 (3), 126 (17), 85 (12), 43 (54). IR (KBr) ν = 3448, 3103, 2970, 2383, 1733, 1693, 1590, 1443, 1372, 1256, 1031 cm<sup>-1</sup>. Anal. calcd for C<sub>19</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>6</sub>: C, 51.03; H, 3.38; Br, 17.87; N, 6.26 %. Found: C, 50.93; H, 3.39; Br, 17.75; N, 6.20 %.

**3-(2-Chlorophenyl)-1',3',6-trimethyl-2'H,3H,4H-spiro[furo[3,2-c]pyran-2,5'-pyrimidine]-**

**2',4,4',6'(1'H,3'H)-tetraone (2i)**

Yield 0.66 g (84%), mp: 248-250 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 2.39 (s, 3H, CH<sub>3</sub>), 2.71 (s, 3H, CH<sub>3</sub>), 3.40 (s, 3H, CH<sub>3</sub>), 5.54 (s, 1H, CH), 6.27 (s, 1H, CH), 7.05-7.16 (m, 1H, Ar), 7.20-7.34 (m, 2H, Ar), 7.34-7.44 (m, 1H, Ar) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 20.7, 28.4, 29.3, 54.1, 89.6, 95.4, 98.6, 127.5, 129.5, 130.4, 130.5, 131.0, 133.9, 149.8, 159.5, 163.7, 165.9, 167.9, 172.6 ppm. MS (*m/z* relative intensity %): 404 [M<sup>+</sup>] Cl<sup>37</sup> (1), 402

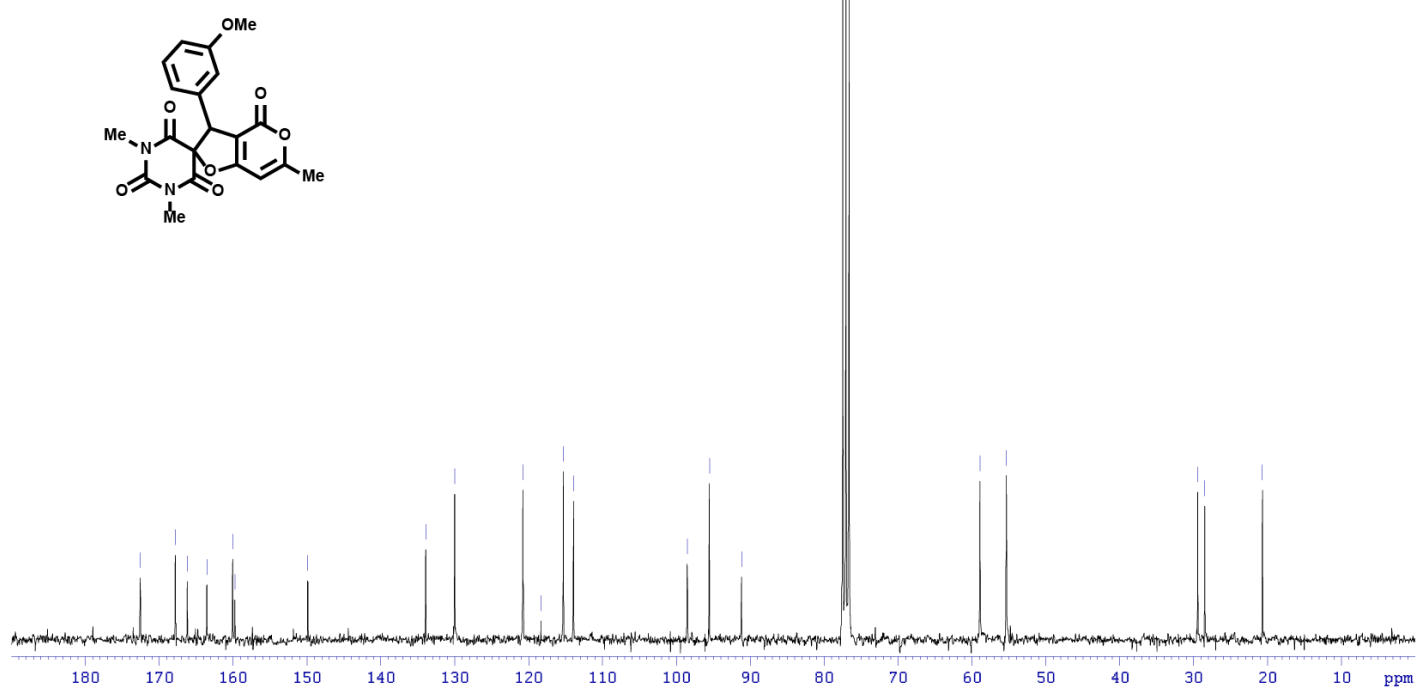
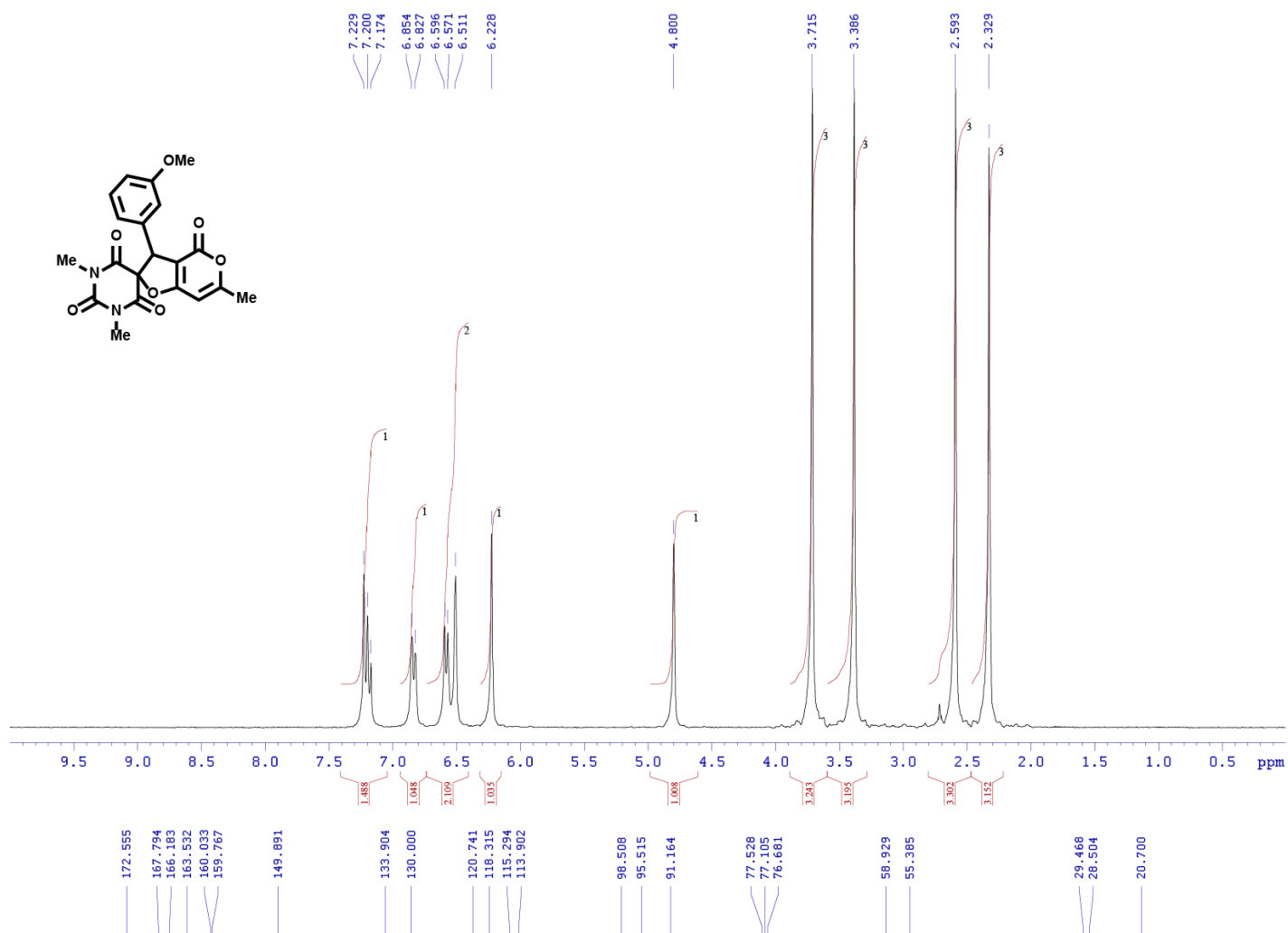
[M<sup>+</sup>] Cl<sup>35</sup> (3), 361 (1), 359 (3), 325 (18), 323 (6), 285 (2), 284 (17), 283 (100), 226 (4), 176 (6), 161 (4), 155 (1), 126 (5), 43 (29). IR (KBr)  $\nu$  = 3447, 3096, 2958, 2665, 2529, 1971, 1736, 1679, 1381, 1261, 1109, 1037 cm<sup>-1</sup>. Anal. calcd for C<sub>19</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>6</sub>: C, 56.66; H, 3.75; Cl, 8.80; N, 6.95 %. Found: C, 56.54; H, 3.71; Cl, 8.73; N, 6.87 %.

**3-(3-Chlorophenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2j)**

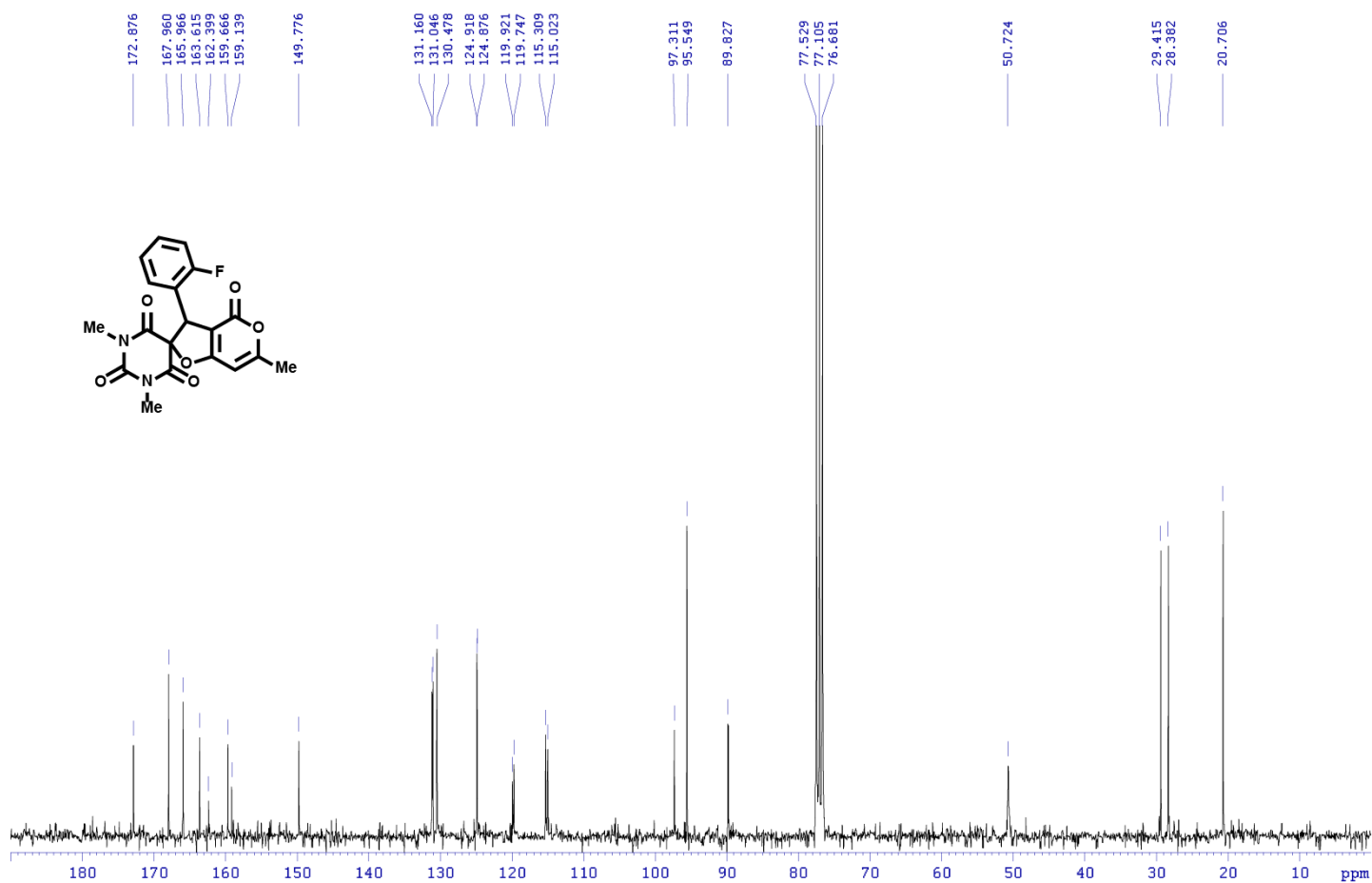
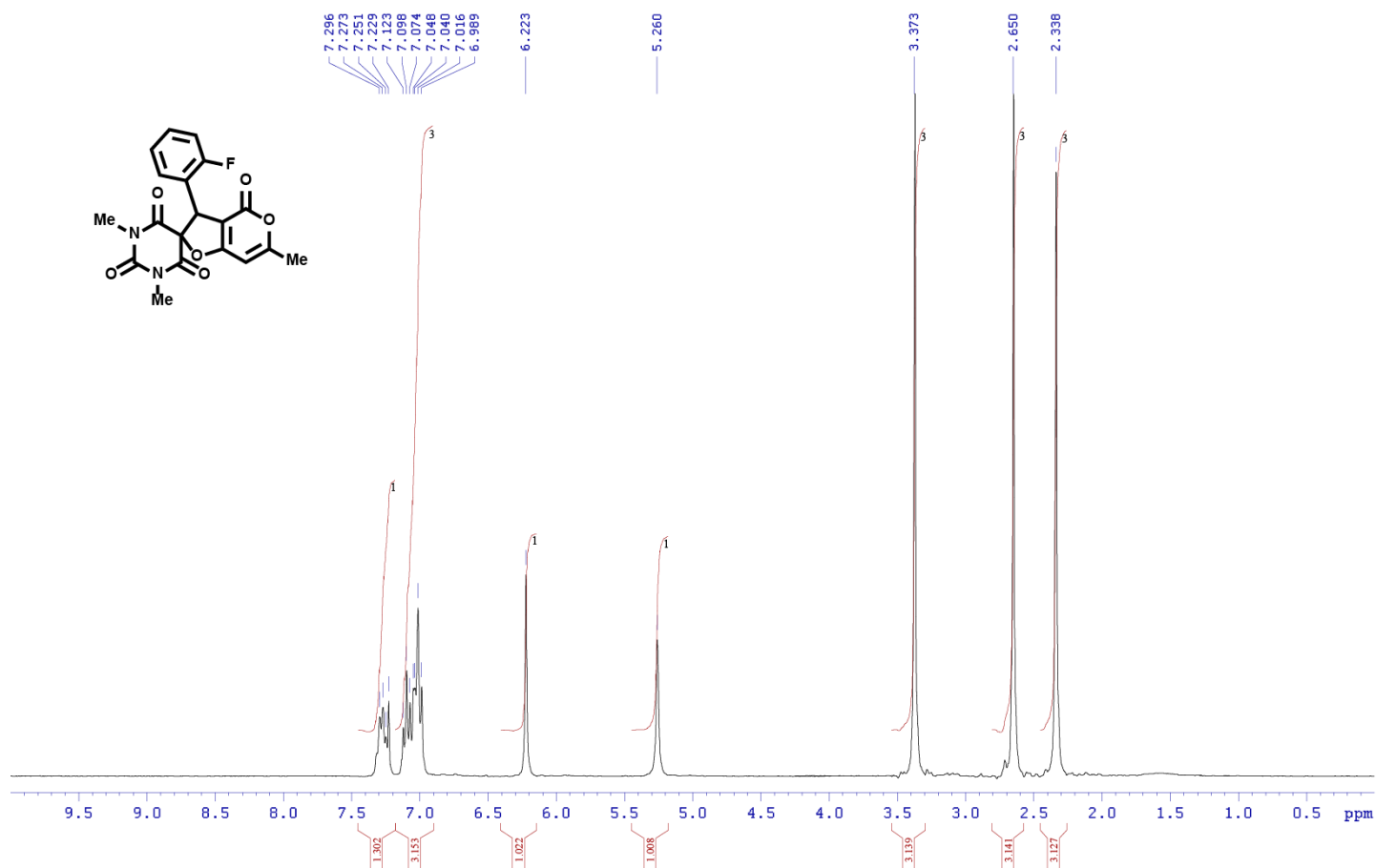
Yield 0,69 g (86%), mp: 244-245 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  2.39 (s, 3H, CH<sub>3</sub>), 2.68 (s, 3H, CH<sub>3</sub>), 3.44 (s, 3H, CH<sub>3</sub>), 4.83 (s, 1H, CH), 6.28 (s, 1H, CH), 6.95 (d, <sup>3</sup>*J* = 8.5 Hz, 1H, Ar), 7.04 (s, 1H, Ar), 7.18-7.32 (m, 2H, Ar), ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  20.7, 28.5, 29.5, 58.1, 90.8, 95.5, 98.2, 126.7, 128.6, 129.7, 130.2, 134.7, 135.1, 149.7, 159.6, 163.3, 165.9, 168.1, 172.7 ppm. MS (*m/z* relative intensity %): 404 [M<sup>+</sup>] Cl<sup>37</sup> (1), 402 [M<sup>+</sup>] Cl<sup>35</sup> (3), 361 Cl<sup>37</sup> (13), 359 Cl<sup>35</sup> (40), 325 (1), 323 (15), 287 (1), 233 (1), 176 (13), 163 (6), 126 (14), 85 (18), 69 (20), 58 (28), 43 (100). IR (KBr)  $\nu$  = 3397, 3109, 2957, 2667, 2534, 1925, 1689, 1448, 1379, 1264, 1035 cm<sup>-1</sup>. Anal. calcd for C<sub>19</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>6</sub>: C, 56.66; H, 3.75; Cl, 8.80; N, 6.96 %. Found: C, 56.57; H, 3.73; Cl, 8.71; N, 6.85 %.

## 2. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra for compounds

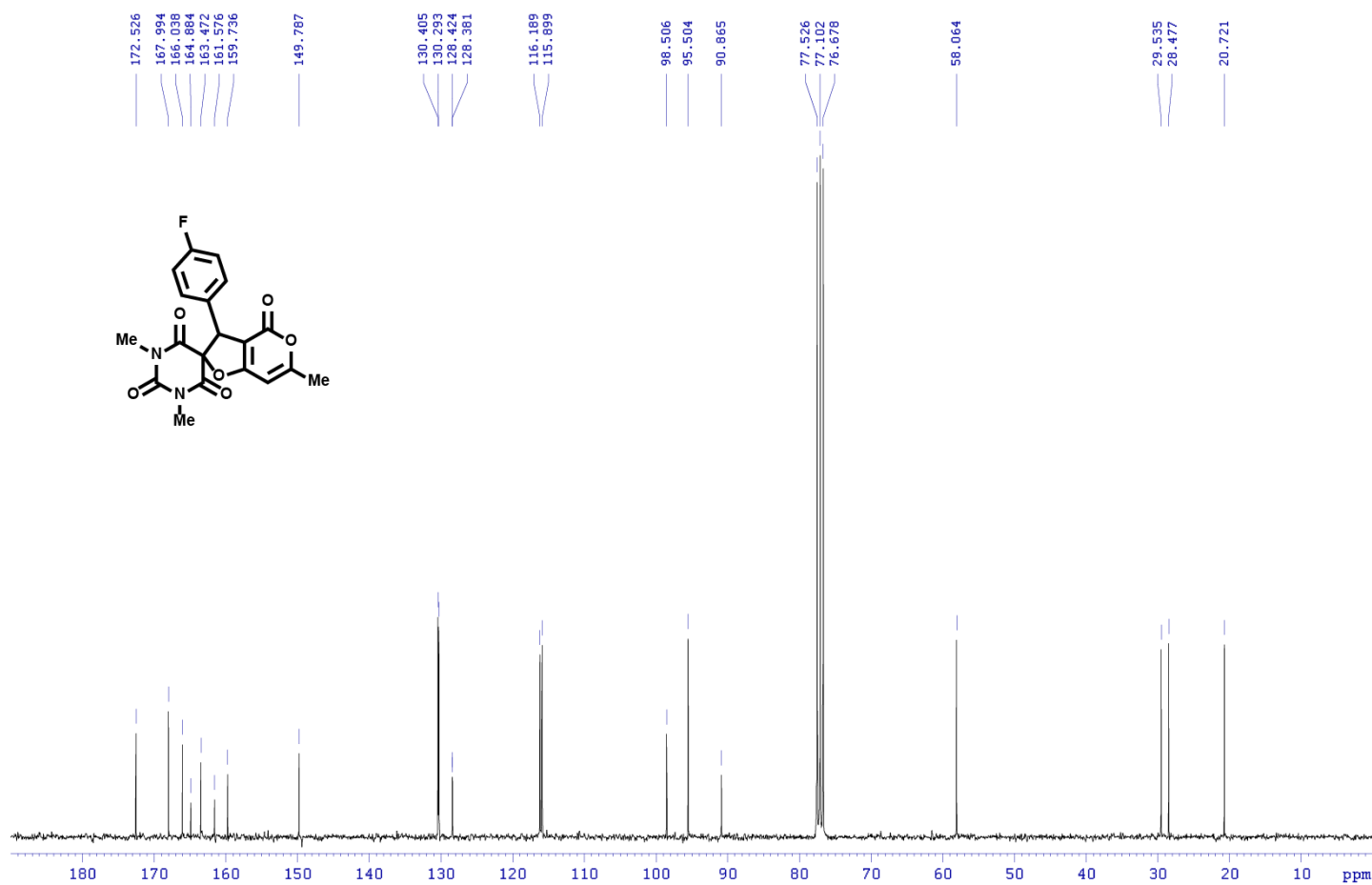
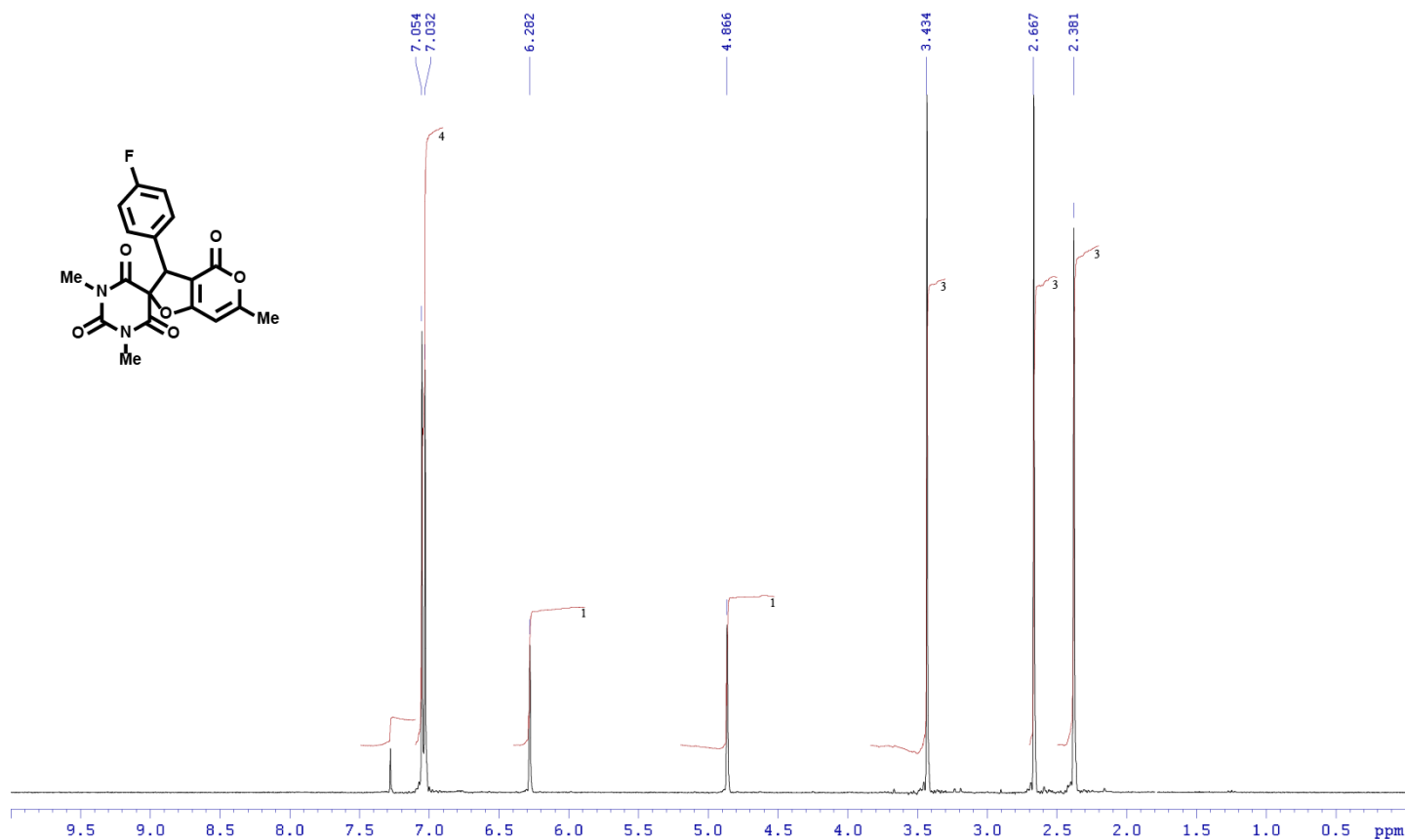
### 3-(3-Methoxyphenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2d)



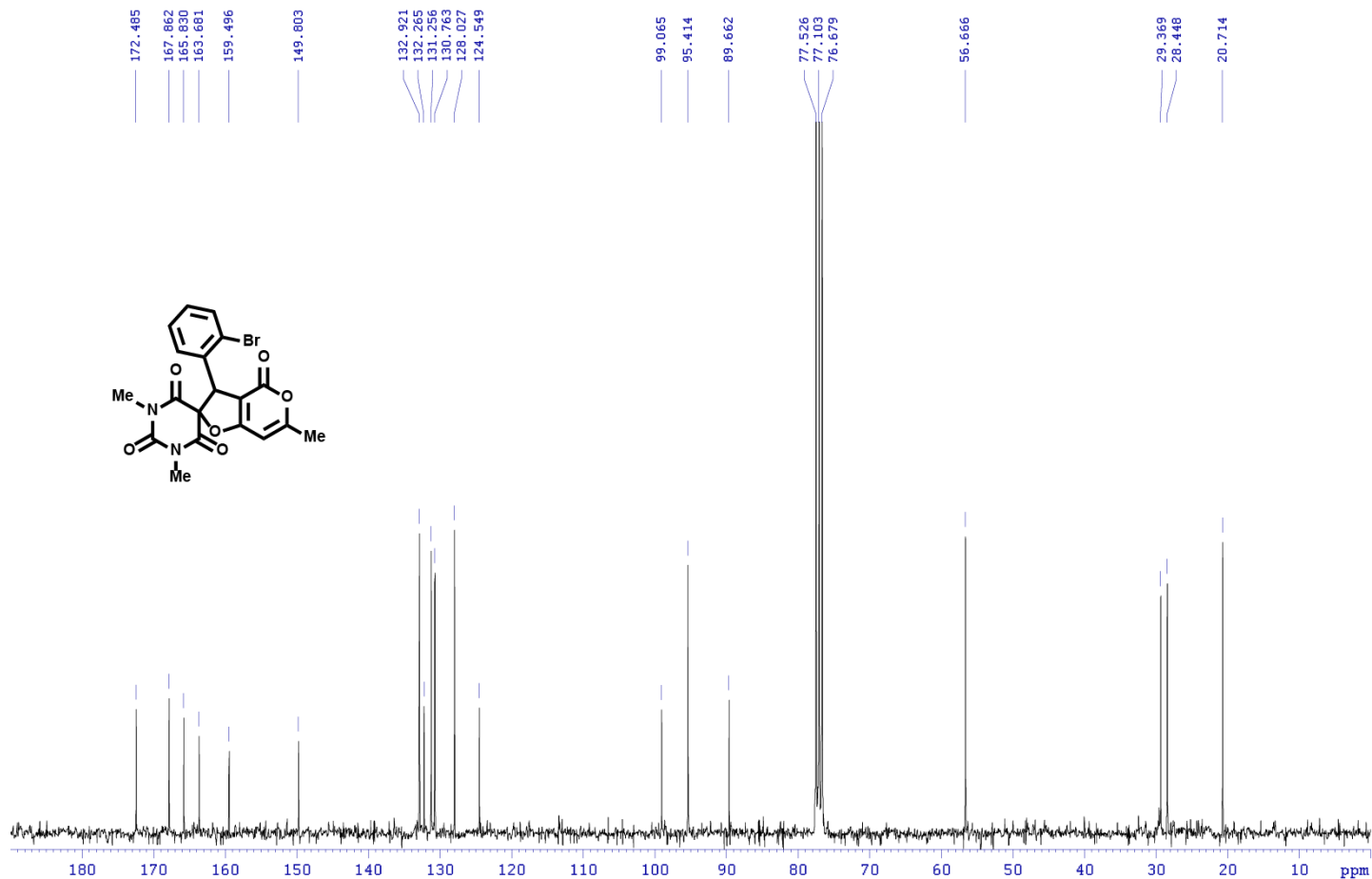
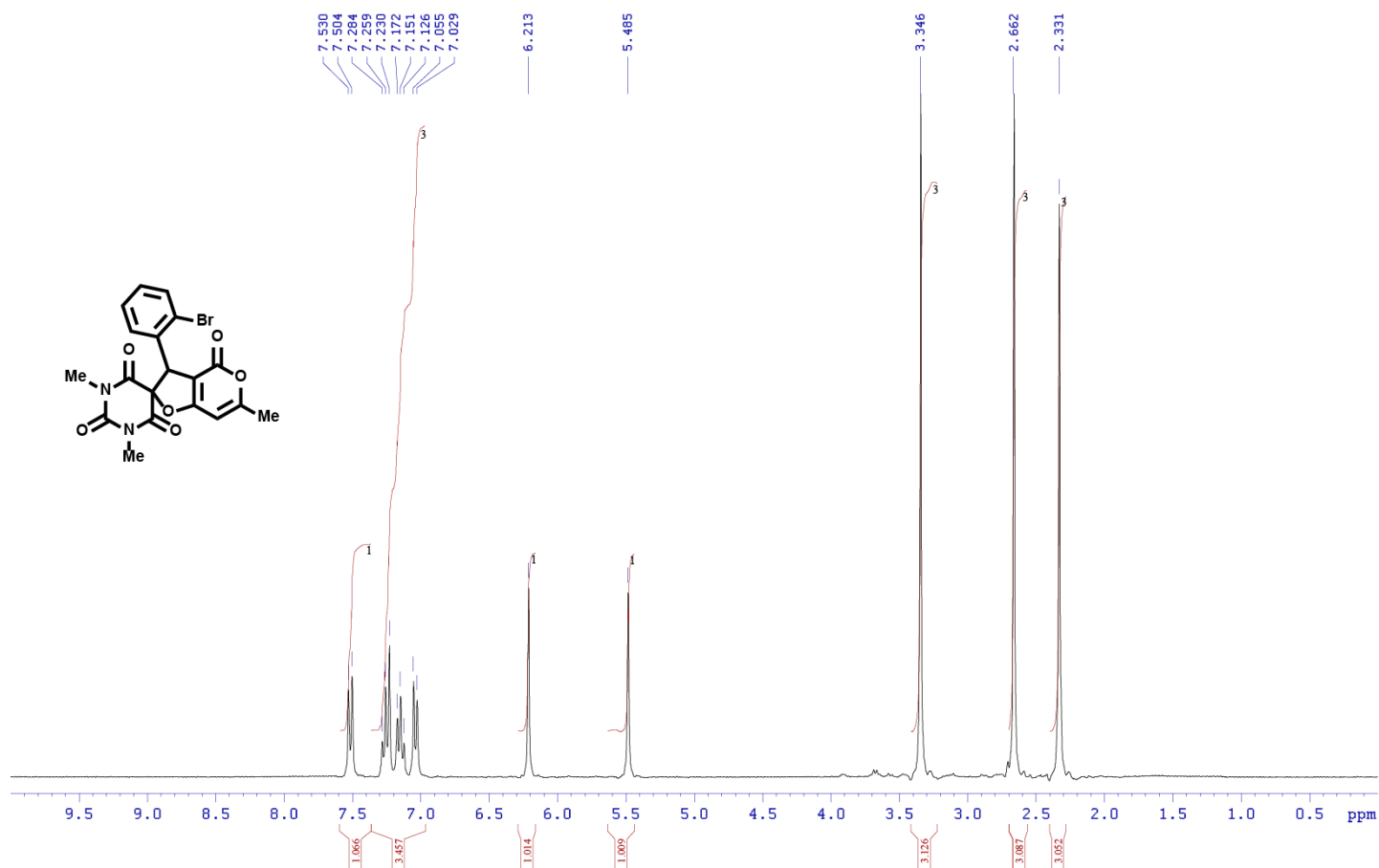
**3-(2-Fluorophenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2e)**



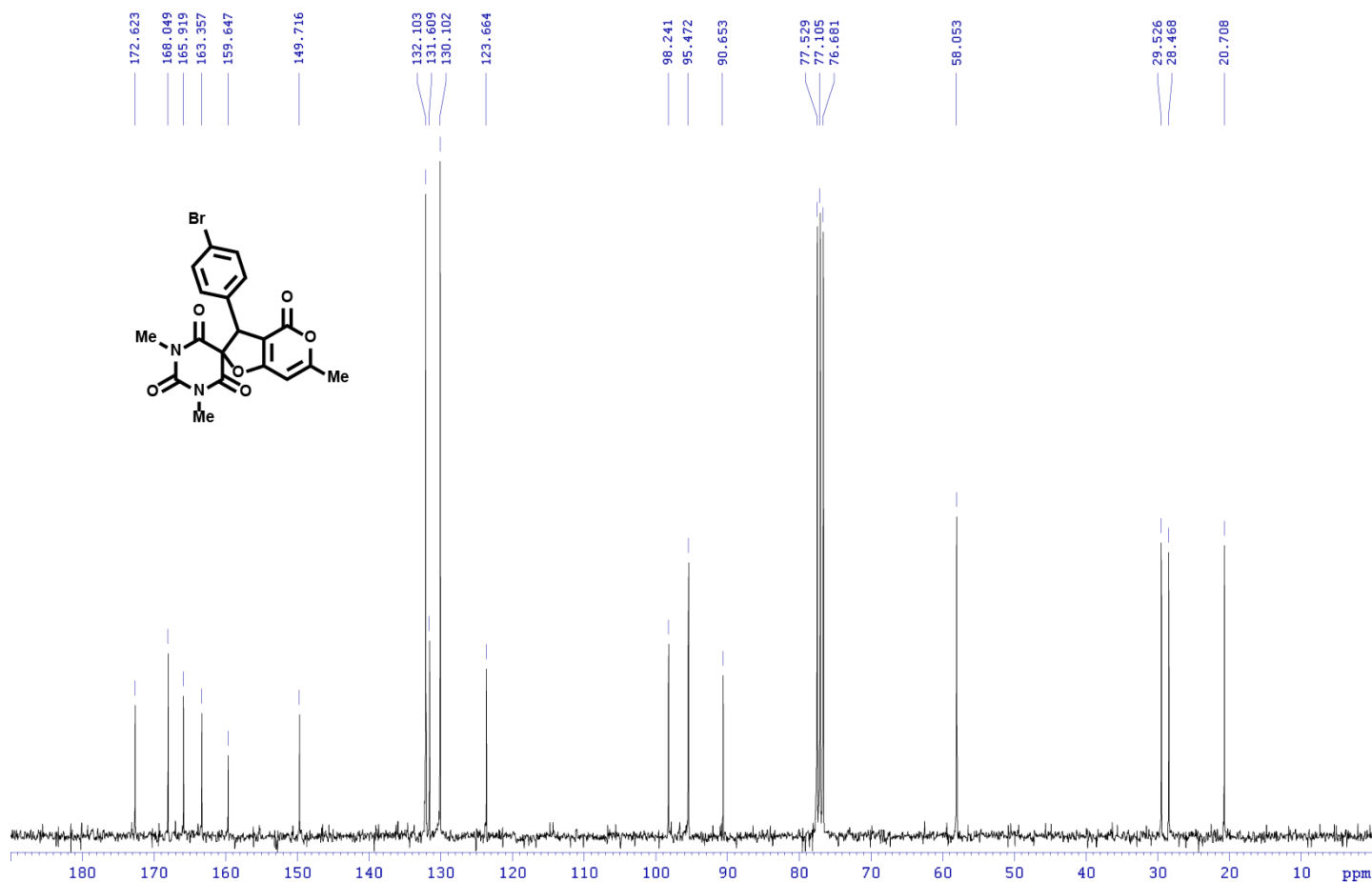
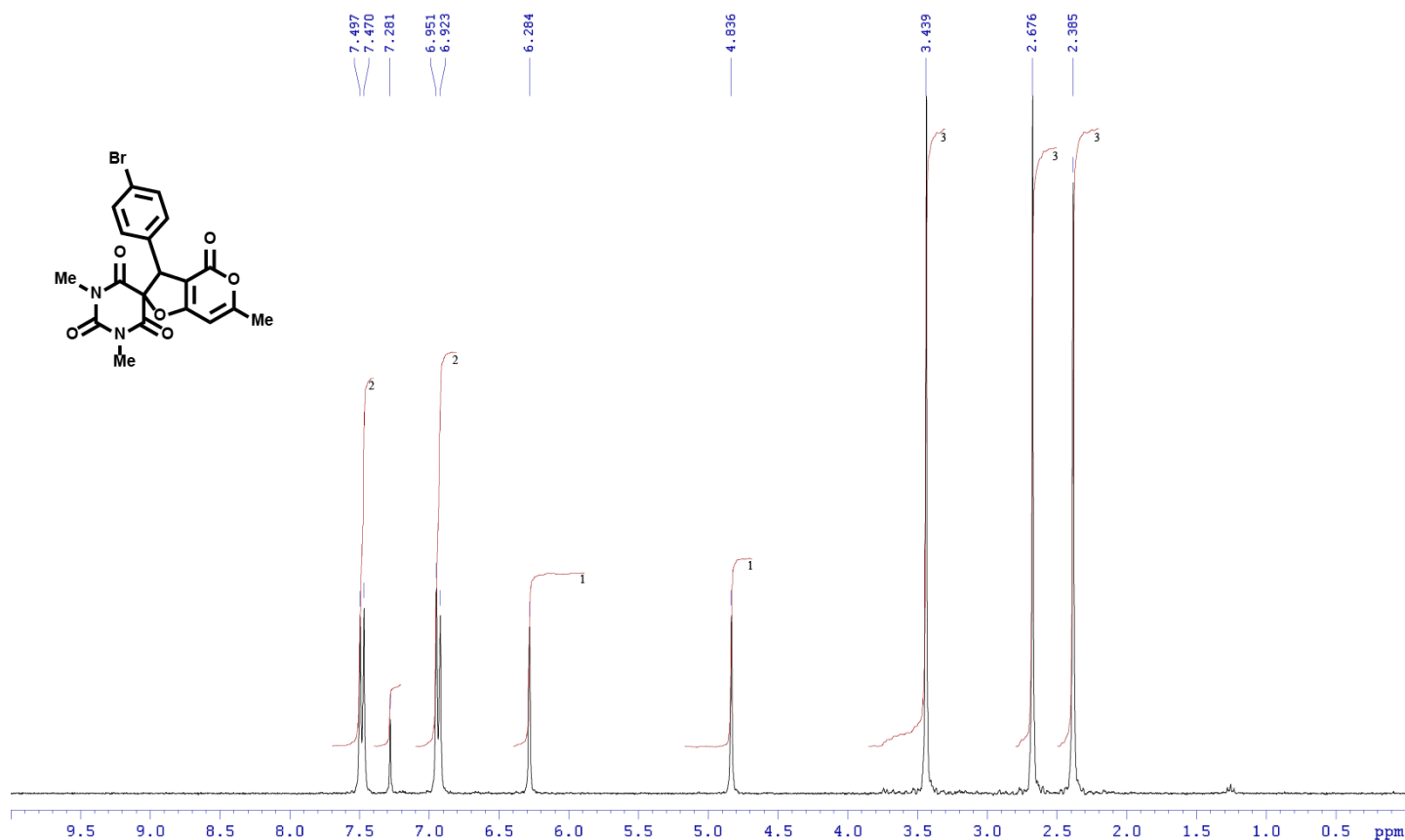
**3-(4-Fluorophenyl)-1',3',6-trimethyl-2'H,3H,4H-spiro[furo[3,2-c]pyran-2,5'-pyrimidine]-2',4,4',6'(1'H,3'H)-tetraone (2f)**



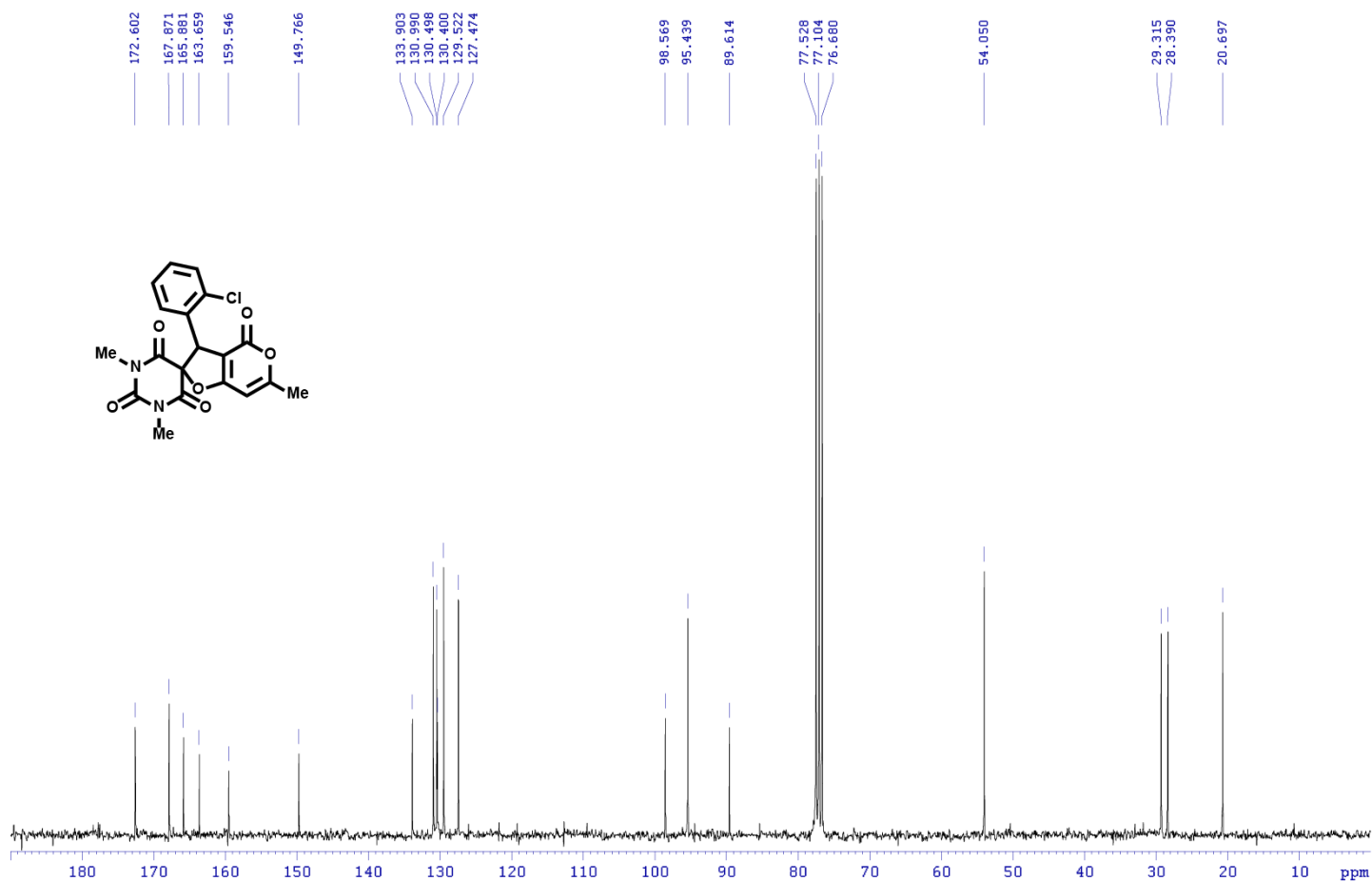
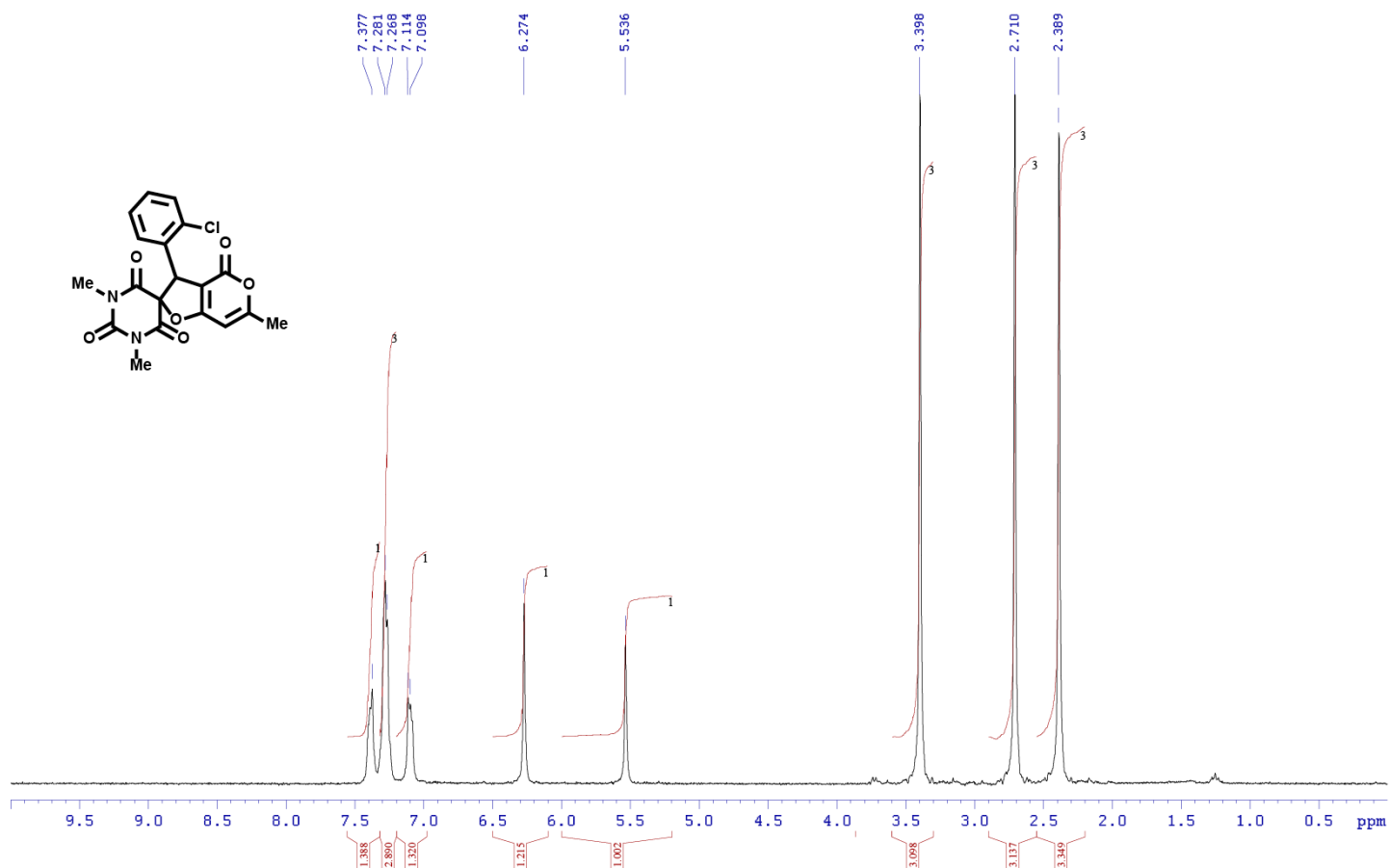
**3-(2-Bromophenyl)-1',3',6-trimethyl-2'H,3H,4H-spiro[furo[3,2-c]pyran-2,5'-pyrimidine]-2',4,4',6'(1'H,3'H)-tetraone (2g)**



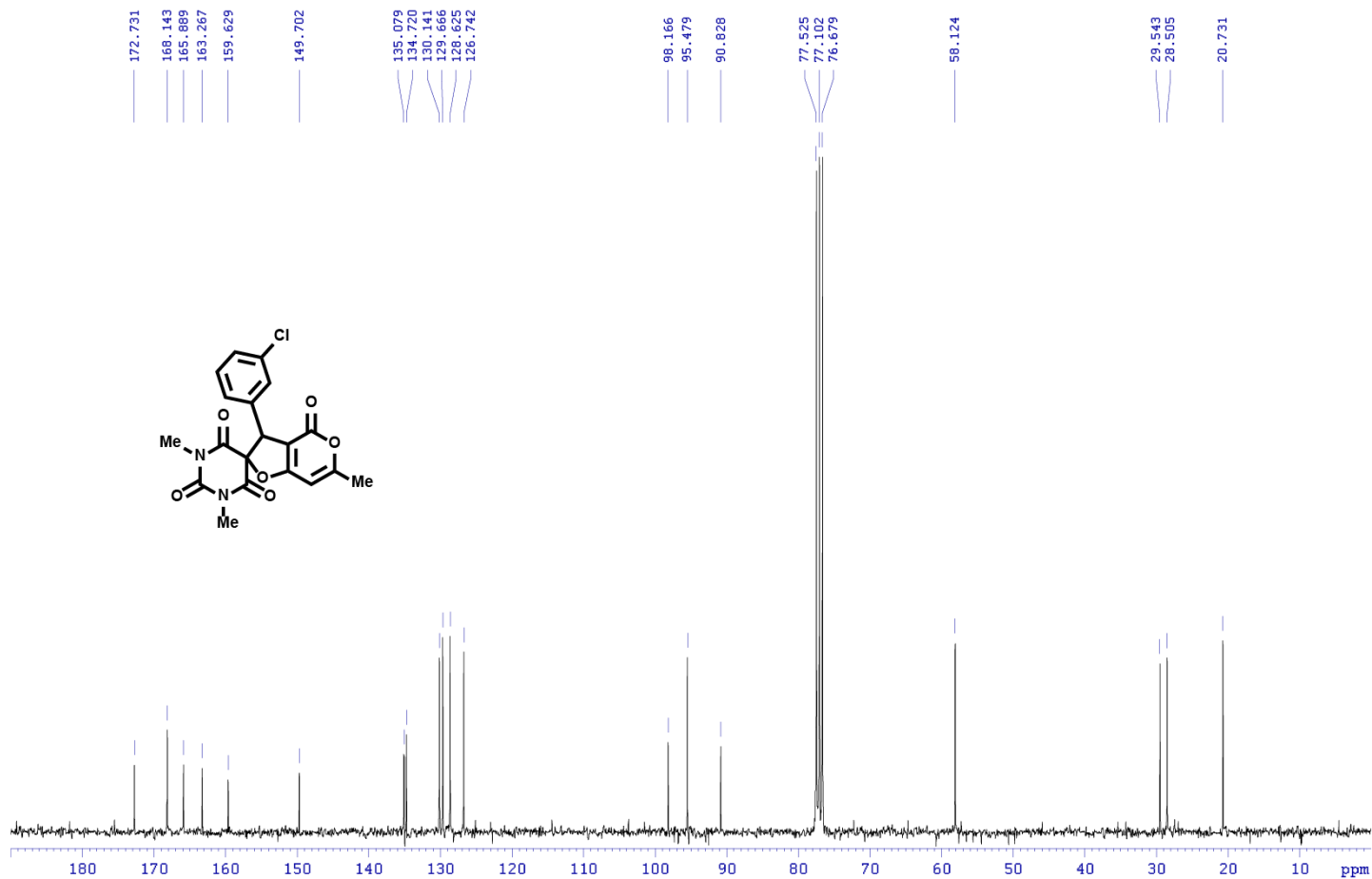
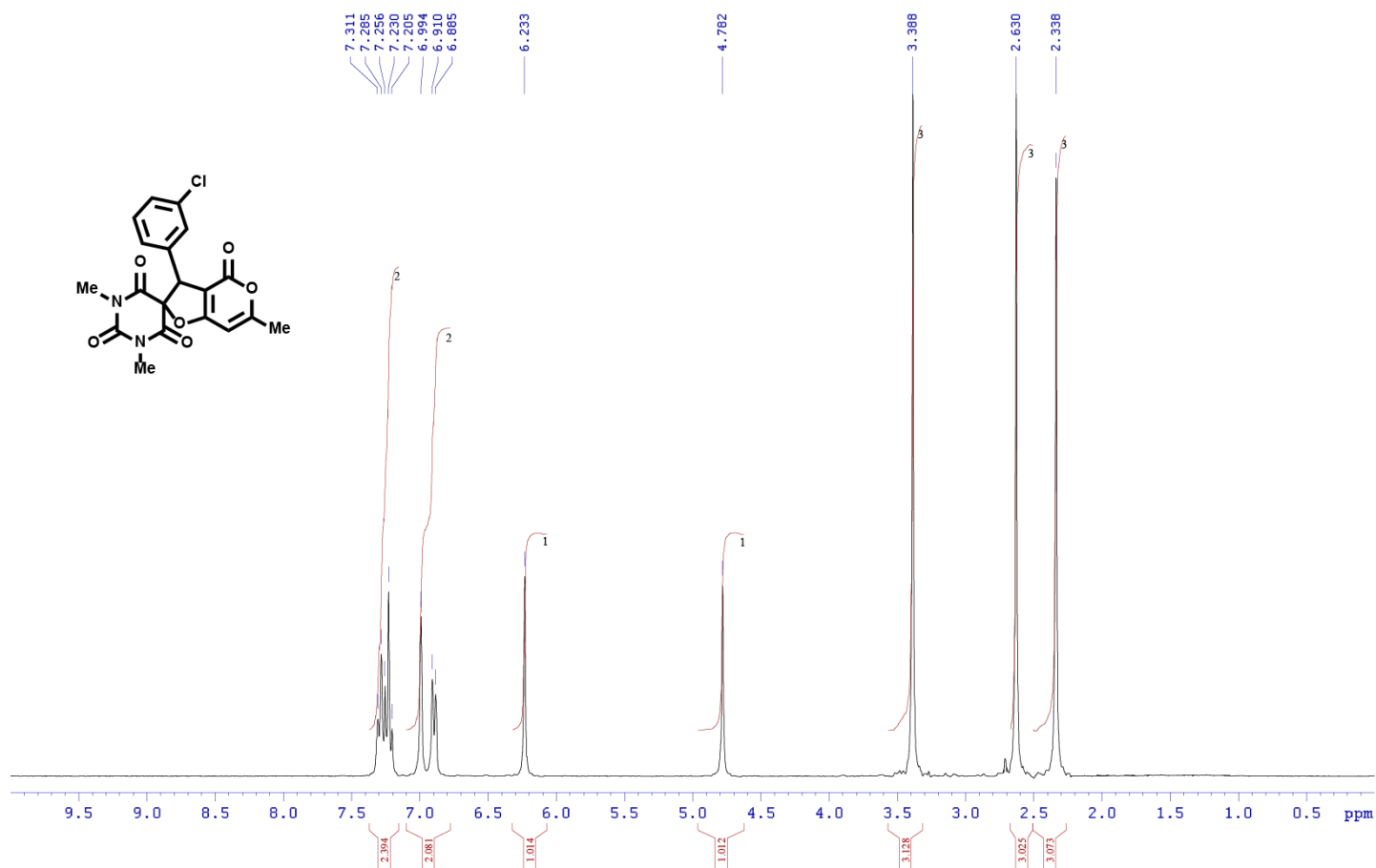
**3-(4-Bromophenyl)-1',3',6-trimethyl-2'H,3H,4H-spiro[furo[3,2-c]pyran-2,5'-pyrimidine]-2',4,4',6'(1'H,3'H)-tetraone (2h)**



**3-(2-Chlorophenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2i).**



**3-(3-Chlorophenyl)-1',3',6-trimethyl-2'*H*,3*H*,4*H*-spiro[furo[3,2-*c*]pyran-2,5'-pyrimidine]-2',4,4',6'(1'*H*,3'*H*)-tetraone (2j).**



#### **4. References**

- S1. Y. E. Ryzhkova, M. N. Elinson, A. N. Vereshchagin, K. A. Karpenko, F. V. Ryzhkov, I. E. Ushakov and M. P. Egorov, *Chemistry*, 2022, **4**, 615; <https://doi.org/10.3390/chemistry4020044>.
- S2. M. N. Elinson, A. N. Vereshchagin, Yu. E. Ryzhkova, K. A. Karpenko, V. M. Kalashnikova and M. P. Egorov, *Mendeleev Commun.*, 2023, **33**, 448; <https://doi.org/10.1016/j.mencom.2023.06.002>.