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Green multicomponent efficient approach to (aryl)di(hetaryl)methanes bearing barbituric and hydroxypyridone moieties

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Table of contents

1. Experimental section

All melting points were measured with a Stuart SMP 30 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM-300 (300 and 75 MHz, respectively) at ambient temperature in $CDCl_3$ solutions. Chemical shift values are given in δ scale relative to Me_4Si. IR spectra were registered with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass-spectra (EI = 70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer. Elemental analysis was performed on elemental analyzer multi EA® 5000.

General procedure

Aldehyde **1** (1 mmol), *N*,*N*′-dimethylbarbituric acid (1 mmol), 4-hydroxy-6-methylpyridin-2(1*H*)-one (1 mmol), and TsOH (0.1 mmol) were stirred in EtOH (4 ml) for 4 h at reflux. When the reaction was completed and cooled, the formed solid was filtered, washed with an ice-cold ethanol/water solution (1:1, 3 ml), and dried to isolate pure 5-[(aryl)(1,2-dihydropyridin-3-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **2**.

6-Hydroxy-5-((4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(phenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2a)

Yield 0.34 g (91%), mp: 212-213 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.19 (s, 6H, 2 N-CH_3), 6.26 (s, 2H, 2 CH), 7.02 (d, ^{3}J = 7.3 Hz, 2H, 2 CH Ar), 7.12 (t, ^{3}J = 7.3 Hz, 1H, CH Ar), 7.22 (t, ^{3}J = 7.3 Hz, 2H, 2 CH Ar), 11.49 (br s, 1H, OH), 12.38 (br s, 1H, NH), 16.25-17.55 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.2, 28.0, 28.3, 32.7 (br), 89.8 (br), 102.3 (br), 109.9, 125.3, 126.4 (2C), 127.9 (2C), 141.1, 145.5, 151.1, 161.8 (br), 163.8, 164.6, 167.8 ppm. MS (*m/z* relative intensity %): 369 [M^+] (100), 292 (3), 254 (11), 243 (12), 226 (14), 214 (55), 138 (17), 125 (19), 58 (7). IR (KBr) ν = 3090, 3062, 2950, 1685, 1621, 1450, 1379, 1312, 1256, 777 cm^{-1}. Anal. calcd for $C_{19}H_{19}N_3O_5$: C, 61.78; H, 5.18; N, 11.38 %. Found: C, 61.55; H, 5.11; N, 11.21 %.

6-Hydroxy-5-((4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(*m*-tolyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2b)

Yield 0.32 g (82%), mp: 176-177 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.19 (s, 6H, 2 N-CH_3), 6.15-6.29 (m, 2H, 2 CH), 6.77-6.87 (m, 2H, 2 CH Ar), 6.93 (d, ^{3}J = 7.4 Hz, 1H, CH Ar), 7.10 (t, ^{3}J = 7.4 Hz, 1H, CH Ar), 11.47 (br s, 1H, OH), 12.37 (br s, 1H, NH), 16.52-17.49 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.2, 21.2, 28.0, 28.3, 32.5 (br), 89.0 (br), 102.4 (br), 109.9 (br), 123.7, 126.0, 127.0, 127.8, 136.7, 141.1, 145.4, 151.1, 161.8 (br), 163.7, 164.6, 167.7 ppm. MS (*m/z* relative intensity %): 383 [M^+] (34), 258 (82), 257 (100), 243 (81), 228 (12), 200 (28), 186 (15), 156 (45), 115 (52). IR (KBr) ν = 3046, 2950, 1699, 1638, 1460, 1380, 1295, 1194, 1041, 824, 771 cm^{-1}. Anal. calcd for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52; N, 10.96 %. Found: C, 62.53; H, 5.46; N, 10.85 %.

5-((4-Ethylphenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2c)

Yield 0.30 g (75%), mp: 192-193 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16 (t, ^{3}J = 7.5 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.47-2.63 (m, 2H, CH_2), 3.18 (s, 6H, 2 N-CH_3), 6.16-6.30 (m, 2H, 2 CH), 6.91 (d, ^{3}J = 7.6 Hz, 2H, 2 CH Ar), 7.05 (d, ^{3}J = 7.6 Hz, 2H, 2 CH Ar), 11.48 (br s, 1H, OH), 12.38 (br s, 1H, NH), 16.60-17.51 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.6, 18.1, 27.6, 28.0, 28.3, 32.3 (br), 89.2 (br), 102.3, 110.0, 126.4 (2C), 127.3 (2C), 138.2 (br), 140.5, 145.2, 151.1, 161.8 (br), 163.8, 164.6, 167.7 ppm. MS (*m/z* relative intensity %): 397 [M^+] (10), 272 (67), 271 (100), 243 (75), 214 (15), 212 (17), 186 (12), 156 (35), 115 (29). IR (KBr) ν = 3436, 2964, 1693, 1634, 1460, 1380, 1300, 1228, 924 cm^{-1}. Anal. calcd for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.57 %. Found: C, 63.34; H, 5.77; N, 10.43 %.

6-Hydroxy-5-((4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(3-methoxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2d)

Yield 0.29 g (73%), mp: 162-163 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.18 (s, 6H, 2 N-CH_3), 3.67 (s, 3H, OCH_3), 6.16-6.32 (m, 2H, 2 CH), 6.53 (s, 1H, CH Ar), 6.59 (d, ^{3}J = 7.6 Hz, 1H, CH Ar), 6.72 (d, ^{3}J = 7.6 Hz, 1H, CH Ar), 7.14 (t, ^{3}J = 7.6 Hz, 1H, CH Ar), 11.50 (br s, 1H, OH), 12.39 (br s, 1H, NH), 16.55-

17.59 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.2, 28.0, 28.3, 32.6 (br), 54.8, 88.9 (br), 102.3 (br), 109.7 (br), 113.2, 119.0, 128.9, 129.1, 142.9, 145.5, 151.1, 159.1, 161.8 (br), 163.7, 164.6, 167.7 ppm. MS (*m/z* relative intensity %): 399 (10), 275 (15), 274 (100), 273 (98), 243 (20), 216 (21), 156 (25), 102 (11), 56 (22). IR (KBr) ν = 3472, 2934, 1668, 1625, 1560, 1451, 1305, 1257, 878 cm^{-1}. Anal. calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52 %. Found: C, 60.05; H, 5.21; N, 10.38 %.

5-((2,3-Dimethoxyphenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2e)

Yield 0.34 g (78%), mp: 166-167 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 3.14 (s, 3H, N-CH_3), 3.16 (s, 3H, N-CH_3), 3.49 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.15 (s, 1H, CH), 6.21 (brs, 1H, CH pyr), 6.53 (s, 1H, CH Ar), 6.77 (d, ^3J = 7.1 Hz, 1H, CH Ar), 6.77-96.95 (m, 2H, 2 CH Ar), 11.30 (br s, 1H, OH), 12.15 (br s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.1, 27.8 , 28.3, 30.1 (br), 55.5, 59.3, 73.0 (br), 101.8, 109.7, 110.6, 121.3, 122.5, 135.5, 144.9, 146.4, 151.3, 152.2, 162.8 (br), 163.7 (br), 164.6, 167.0 ppm. MS (*m/z* relative intensity %): 429 [M$^+$] (2), 369 (5), 304 (6), 274 (15), 273 (100), 242 (9), 216 (19), 156 (15), 58 (2). IR (KBr) ν = 3465, 2939, 1631, 1472, 1269, 1215, 1072, 823, 767 cm^{-1}. Anal. calcd for $C_{21}H_{23}N_3O_7$: C, 58.74; H, 5.40; N, 9.79 %. Found: C, 58.63; H, 5.32; N, 9.65 %.

5-((2,5-Dimethoxyphenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2f)

Yield 0.38 g (89%), mp: 178-179 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.11 (s, 3H, CH_3), 3.12 (s, 6H, 2 N-CH_3), 3.57 (s. 3H, OMe), 3.63 (s, 3H, OMe), 5.92 (br s, 1H, CH pyr), 6.04 (s, 1H, CH), 6.62-6.72 (m, 2H, 2 CH Ar), 6.72-6.81 (s, 1H, CH Ar), 7.19 (t, ^3J = 7.6 Hz, 1H, CH Ar), 7.34 (d, ^3J = 7.6 Hz, 1H, CH Ar), 11.06 (br s, 1H, OH), 11.92 (br s, 1H, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.1, 27.8, 28.2, 31.5 (br), 55.0, 56.1, 78.6 (br), 101.0 (br), 108.5 (br), 109.9, 111.4, 116.7, 117.1, 119.7, 131.2, 144.7, 151.2, 151.5, 152.6, 164.5, 166.5 ppm. MS (*m/z* relative intensity %): 429 [M$^+$] (3), 304 (27), 274 (22), 273 (100), 242 (19), 216 (38), 175 (11), 156 (26), 119 (8). IR (KBr) ν = 2957, 1697, 1631, 1562, 1462, 1311, 1222, 1045, 772, cm^{-1}. Anal. calcd for $C_{21}H_{23}N_3O_7$: C, 58.74; H, 5.40; N, 9.79 %. Found: C, 58.55; H, 5.35; N, 9.59 %.

5-((4-Chlorophenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2g)

Yield 0.35 g (87%), mp: 185-186 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.18 (s, 6H, 2 N-CH_3), 6.26 (s, 2H, 2 CH), 7.03 (d, ^3J = 8.2 Hz, 2H, 2 CH Ar), 7.27 (d, ^3J = 8.2 Hz, 2H, 2 CH Ar), 11.60 (br s, 1H, OH), 12.43 (s, 1H, NH), 16.13-17.61 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.2, 28.0 (br), 28.3 (br), 32.3 (br), 88.8 (br), 102.4, 109.4, 127.8 (2C), 128.4 (2C), 129.9, 140.3, 145.7, 151.1, 161.9 (br), 163.6, 164.5, 167.8 ppm. MS (*m/z* relative intensity %): 405 [M(^{37}Cl)]$^+$ (3), 403 [M(^{35}Cl)]$^+$ (10), 280 (21), 279 (40), 278 (66), 277 (66), 220 (13), 164 (9), 156 (22). IR (KBr) ν = 3066, 2954, 1699, 1624, 1489, 1454, 1380, 1090, 836 cm^{-1}. Anal. calcd for $C_{19}H_{18}ClN_3O_5$: C, 56.51; H, 4.49; Cl, 8.78; N, 10.41 %. Found: C, 56.38; H, 4.43; Cl, 8.62; N, 10.28 %

5-((3-Bromophenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2h)

Yield 0.42 g (94%), mp: 182-184 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 3.18 (s, 6H, 2 N-CH_3), 6.25 (s, 2H, 2 CH), 7.03 (d, ^{3}J = 7.6 Hz, 1H, CH Ar), 7.12 (s, 1H, CH Ar), 7.19 (t, ^{3}J = 7.6 Hz, 1H, CH Ar), 7.34 (d, ^{3}J = 7.6 Hz, 1H, CH Ar), 11.62 (br s, 1H, OH), 12.44 (s, 1H, NH), 16.15-17.46 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.2, 28.0 (br), 28.3 (br), 32.6 (br), 88.2 (br), 102.4, 109.1, 121.5, 125.8, 128.3, 129.1, 130.1, 144.4, 145.9, 151.1, 162.0, 163.6, 164.5, 167.8 ppm. MS (*m/z* relative intensity %): 449 [M(^{81}Br)]$^{+}$ (13), 447 [M(^{79}Br)]$^{+}$ (13), 369 (11), 324 (82), 323 (100), 322 (84), 321 (86), 266 (12), 264 (12), 243 (21), 156 (24). IR (KBr) ν = 3409, 1693, 1622, 1463, 1382, 1299, 1208, 956, 784 cm^{-1}. Anal. calcd for $C_{19}H_{18}BrN_3O_5$ C, 50.91; H, 4.05; Br, 17.83; N, 9.37 %. Found: C, 50.78; H, 4.01; Br, 17.67; N, 9.23 %.

5-((2,3-Dichlorophenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2i)

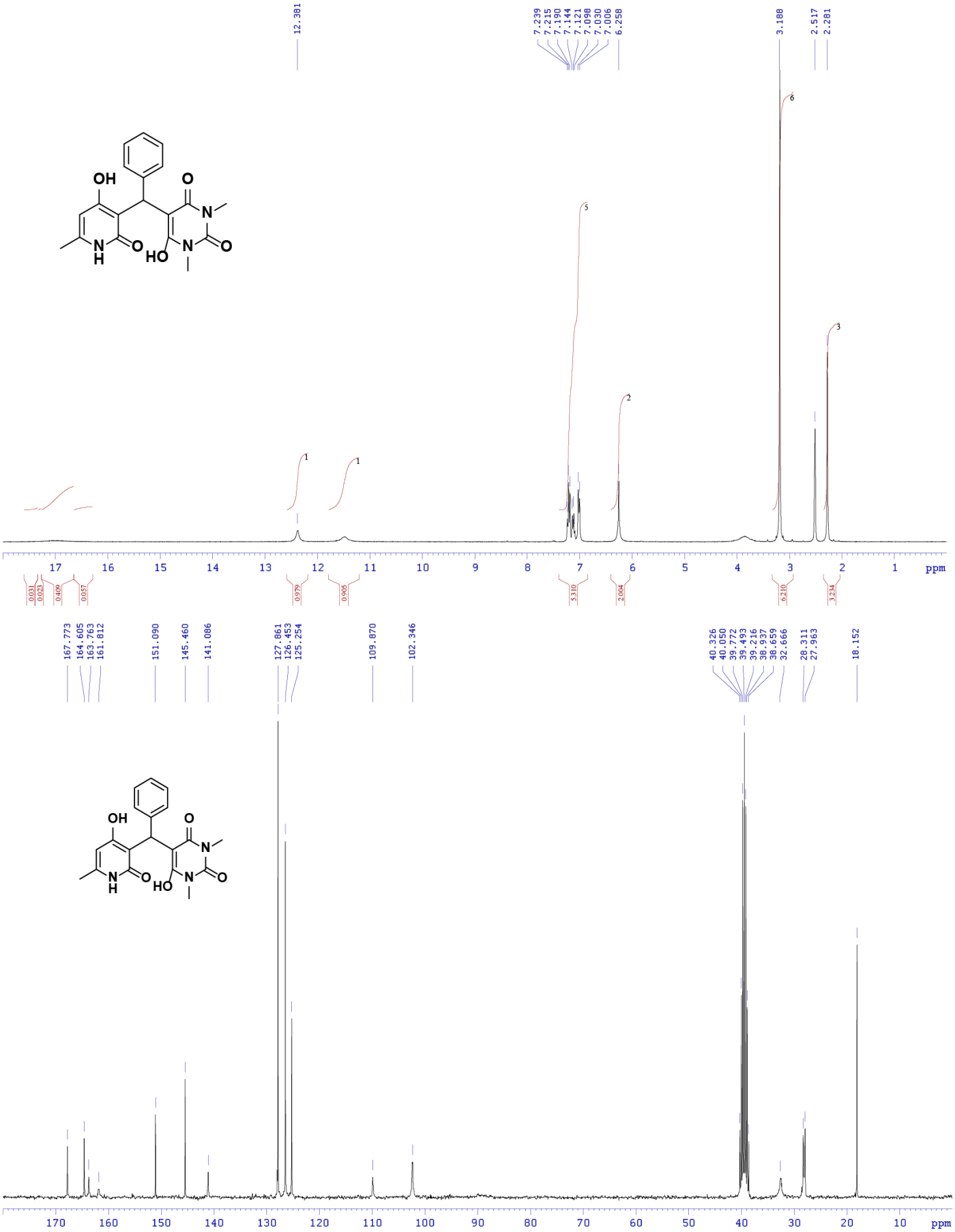
Yield 0.34 g (78%), mp: 246-247 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.23 (s, 3H, CH_3), 3.15 (s, 6H, 2 N-CH_3), 6.09 (s, 1H, CH), 6.13 (s, 1H, CH pyr), 7.18-7.32 (m, 2H, 2 CH Ar), 7.45 (d, ^{3}J = 6.6 Hz, 1H, CH Ar), 11.51 (br s, 1H, OH), 12.19 (s, 1H, NH), 13.65-14.59 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.2, 28.0 (br, 2C), 34.4, 78.4 (br), 101.5, 107.6, 126.9, 128.0, 129.4, 130.2, 131.5, 142.5, 145.8, 151.2, 163.5 (br, 2C), 164.5, 167.2 ppm. MS (*m/z* relative intensity %): 441 [M(^{37}Cl, ^{37}Cl)]$^{+}$] (2), 439 [M(^{37}Cl, ^{35}Cl)]$^{+}$] (16), 437 [M(^{35}Cl, ^{35}Cl)]$^{+}$ (27), 402 (16), 314 (7), 277 (41), 248 (33), 246 (100), 220 (12), 156 (13). IR (KBr) ν = 2696, 1694, 1621, 1581, 1469, 1448, 1377, 1300, 1045, 788 cm^{-1}. Anal. calcd for $C_{19}H_{17}Cl_2N_3O_5$: C, 52.07; H, 3.91; Cl, 16.18; N, 9.59 %. Found: C, 51.95; H, 3.87; Cl, 16.05; N, 9.45 %.

6-Hydroxy-5-((4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(4-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2j)

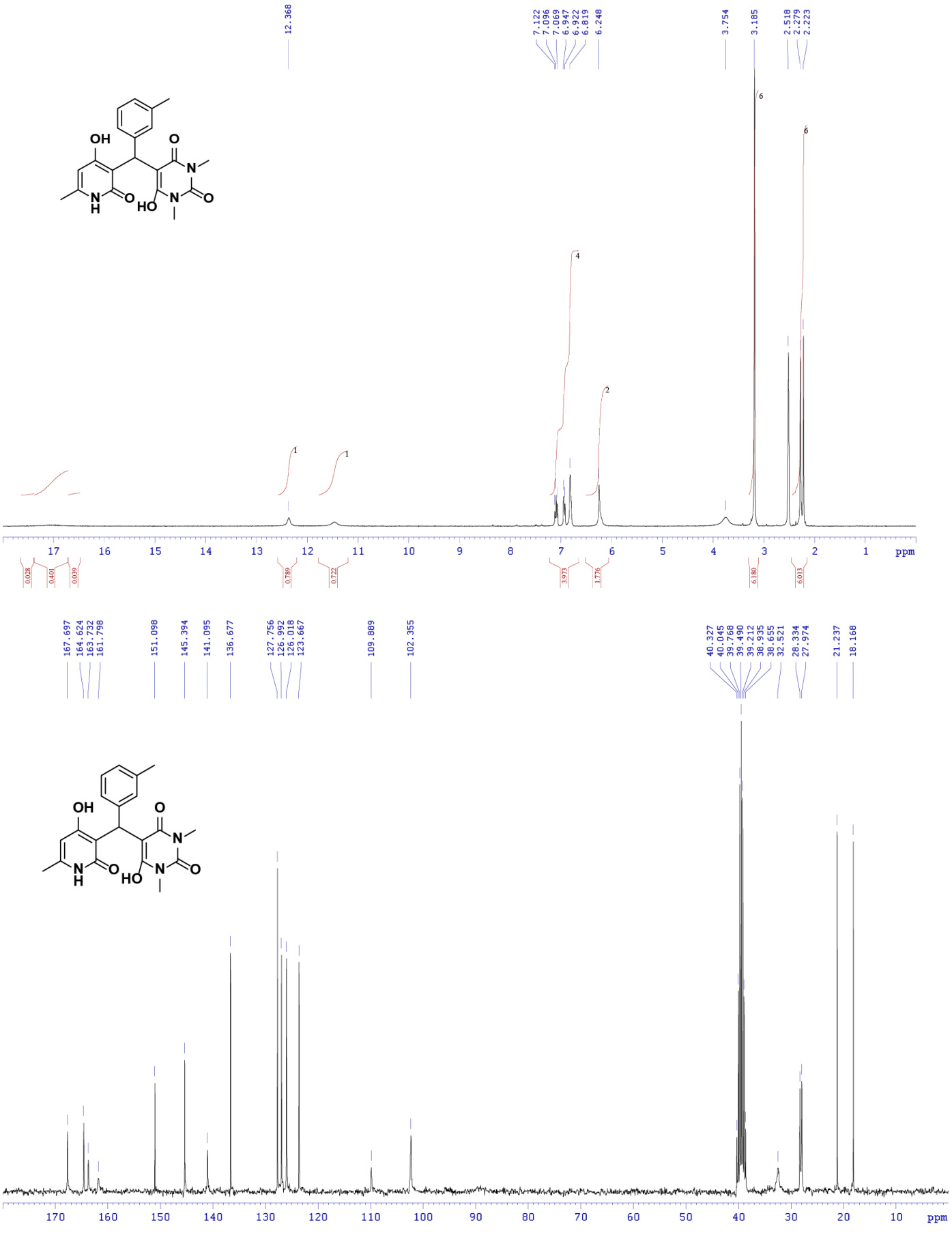
Yield 0.31 g (75%), mp: 228-229 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.30 (s, 3H, CH_3), 3.19 (s, 6H, 2 N-CH_3), 6.29 (s, 1H, CH), 6.36 (br s, 1H, CH pyr), 7.30 (d, ^{3}J = 8.5 Hz, 2H, 2 CH Ar), 8.11 (d, ^{3}J = 8.5 Hz, 2H, 2 CH Ar), 11.72 (br s, 1H, OH), 12.50 (s, 1H, NH), 16.76 (br s, 1H, OH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 18.2, 28.1 (br, 2C), 33.2, 88.2 (br), 102.5, 108.8, 123.2 (2C), 127.8 (2C), 145.6, 146.1, 150.2, 151.1, 162.1 (br), 163.5 (br), 164.5, 167.9 ppm. MS (*m/z* relative intensity %): 414 [M^{+}] (27), 290 (14), 289 (99), 288 (100), 272 (47), 259 (16), 242 (50), 231 (15), 175 (16) , 156 (39). IR (KBr) ν = 3085, 1704, 1628, 1515, 1347, 1308, 1255, 1198, 850 cm^{-1}. Anal. calcd for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38; N, 13.52 %. Found: C, 54.95; H, 4.33; N, 13.43 %.

2. ^{1}H and ^{13}C NMR spectra for compounds

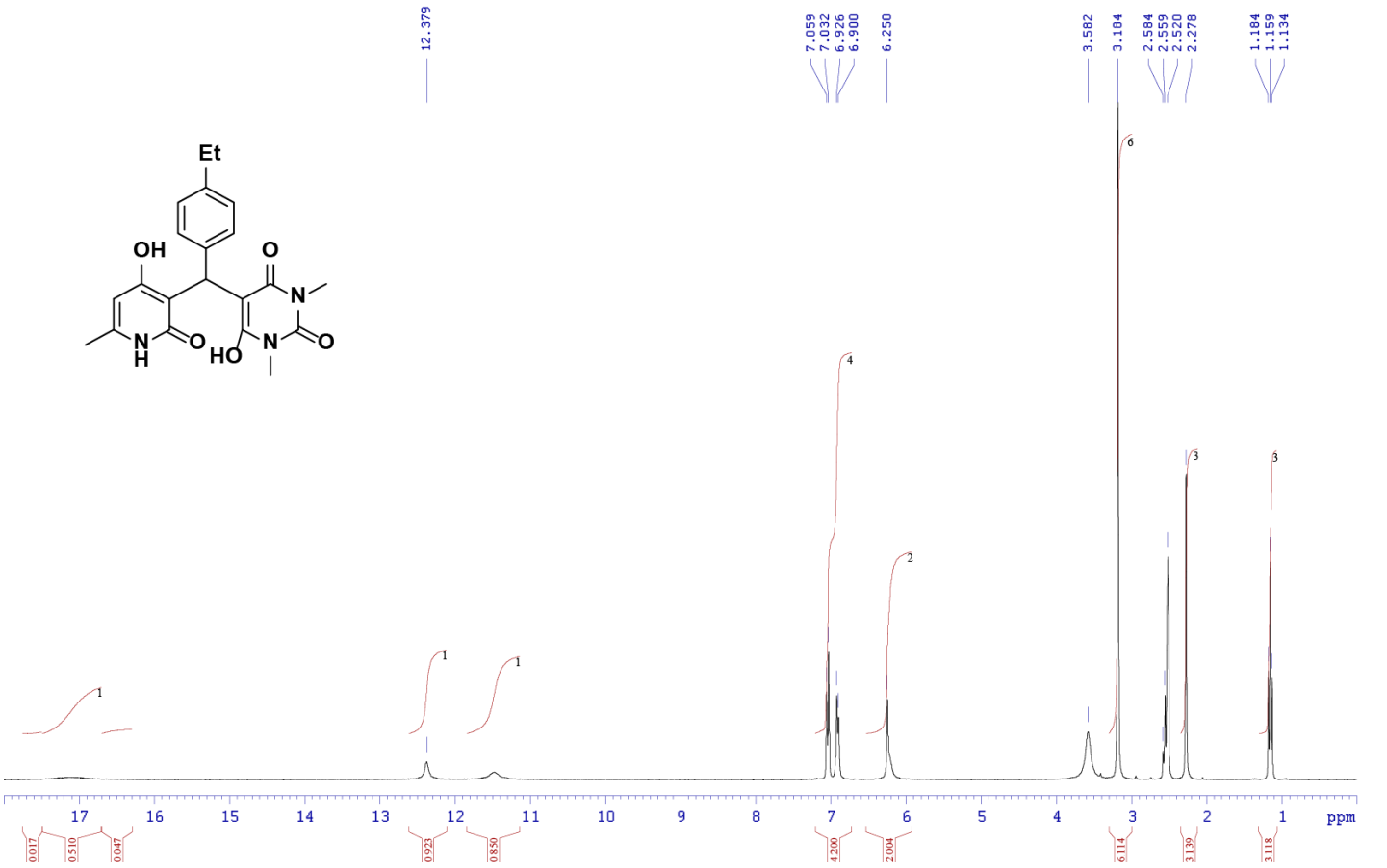
6-Hydroxy-5-((4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(phenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2a)

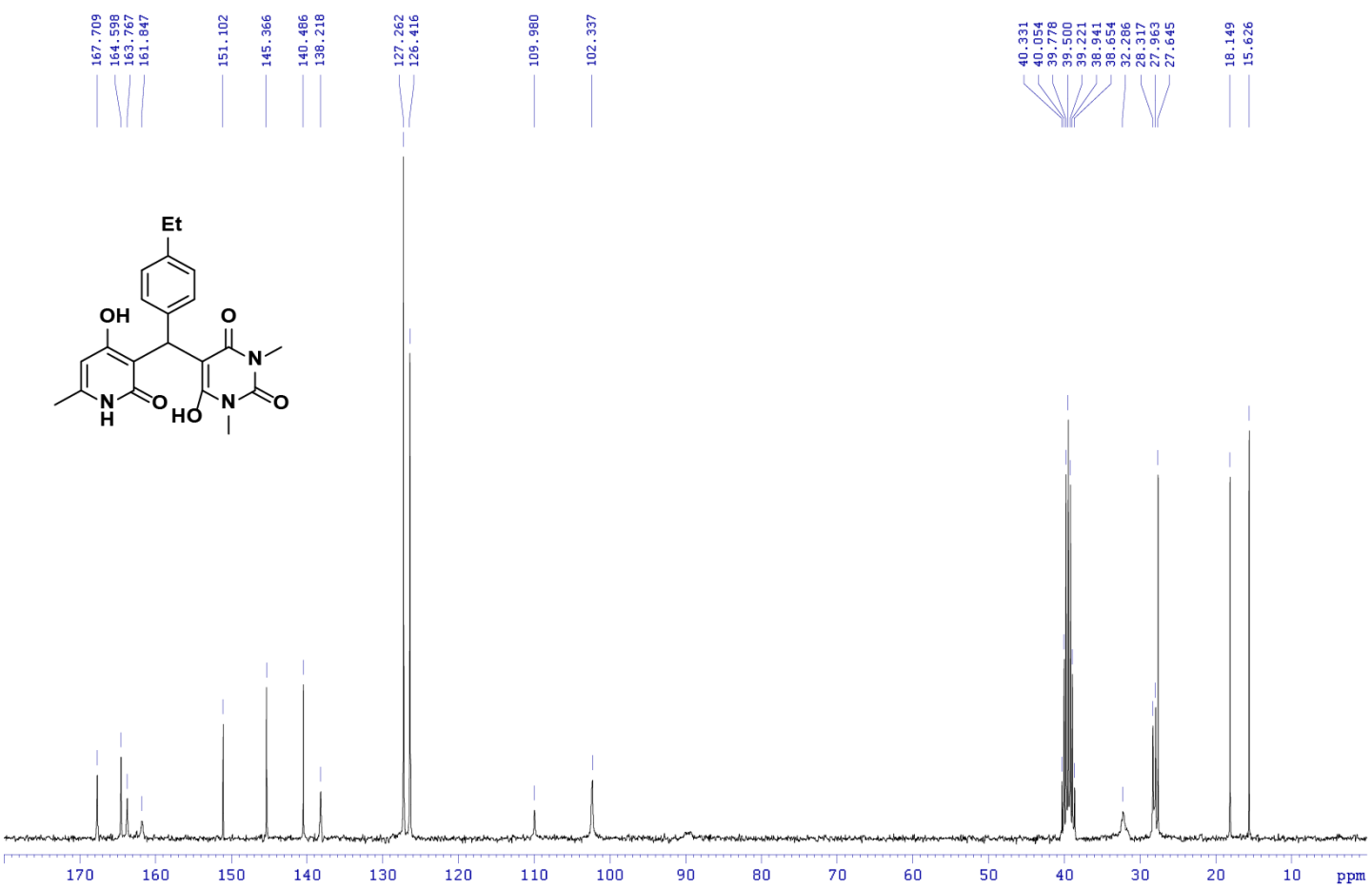


6-Hydroxy-5-((4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(*m*-tolyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2b)

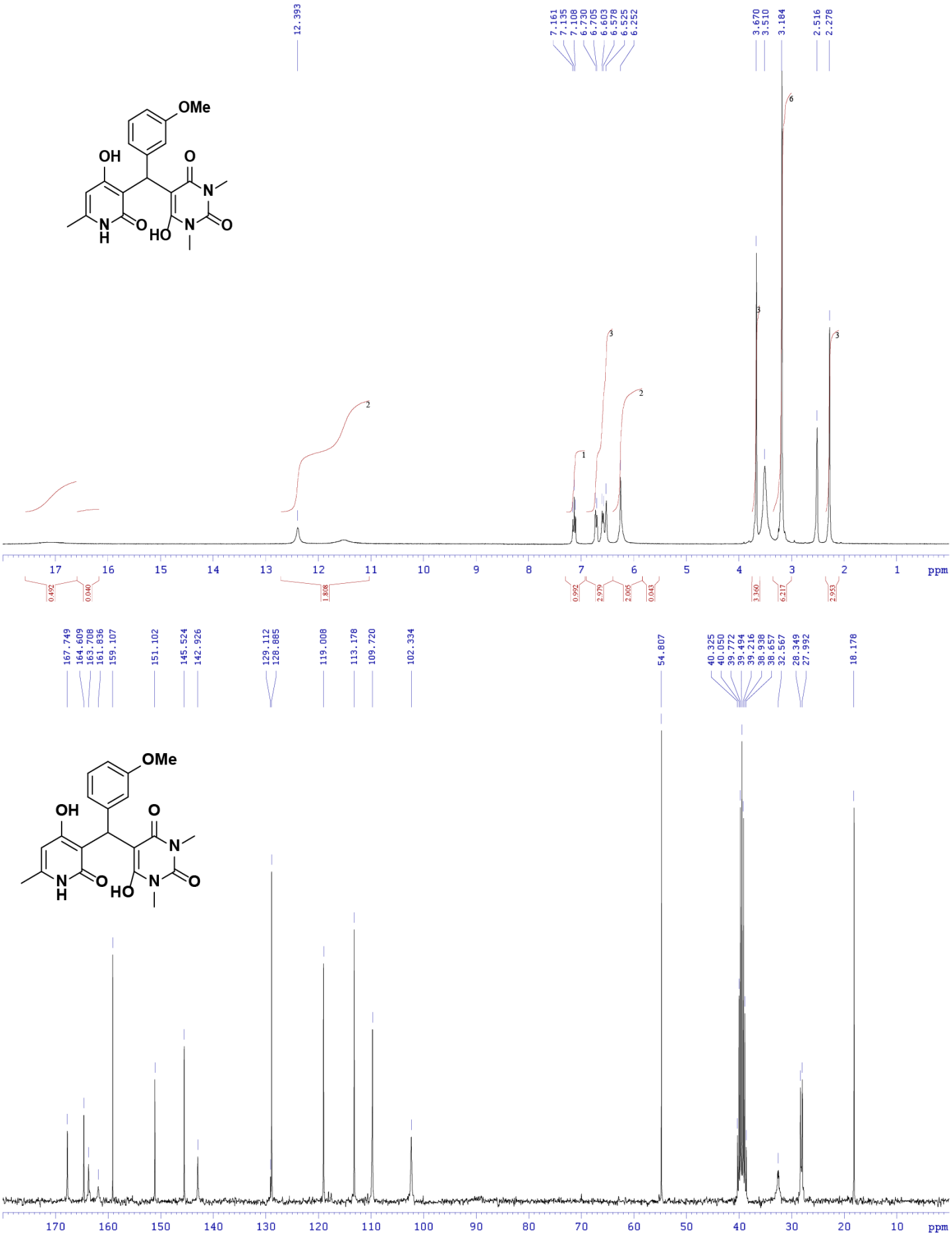


5-((4-Ethylphenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2c)

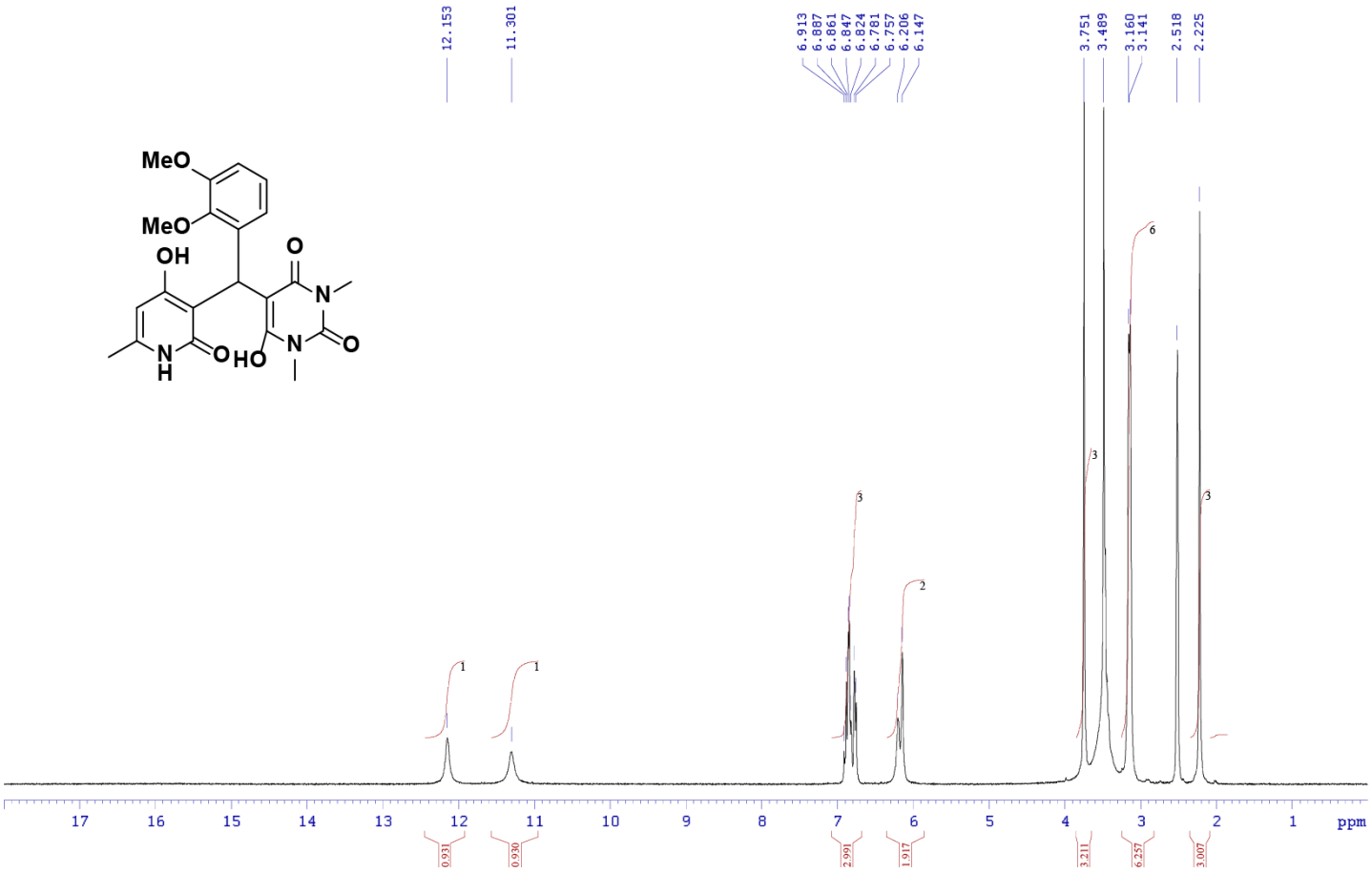


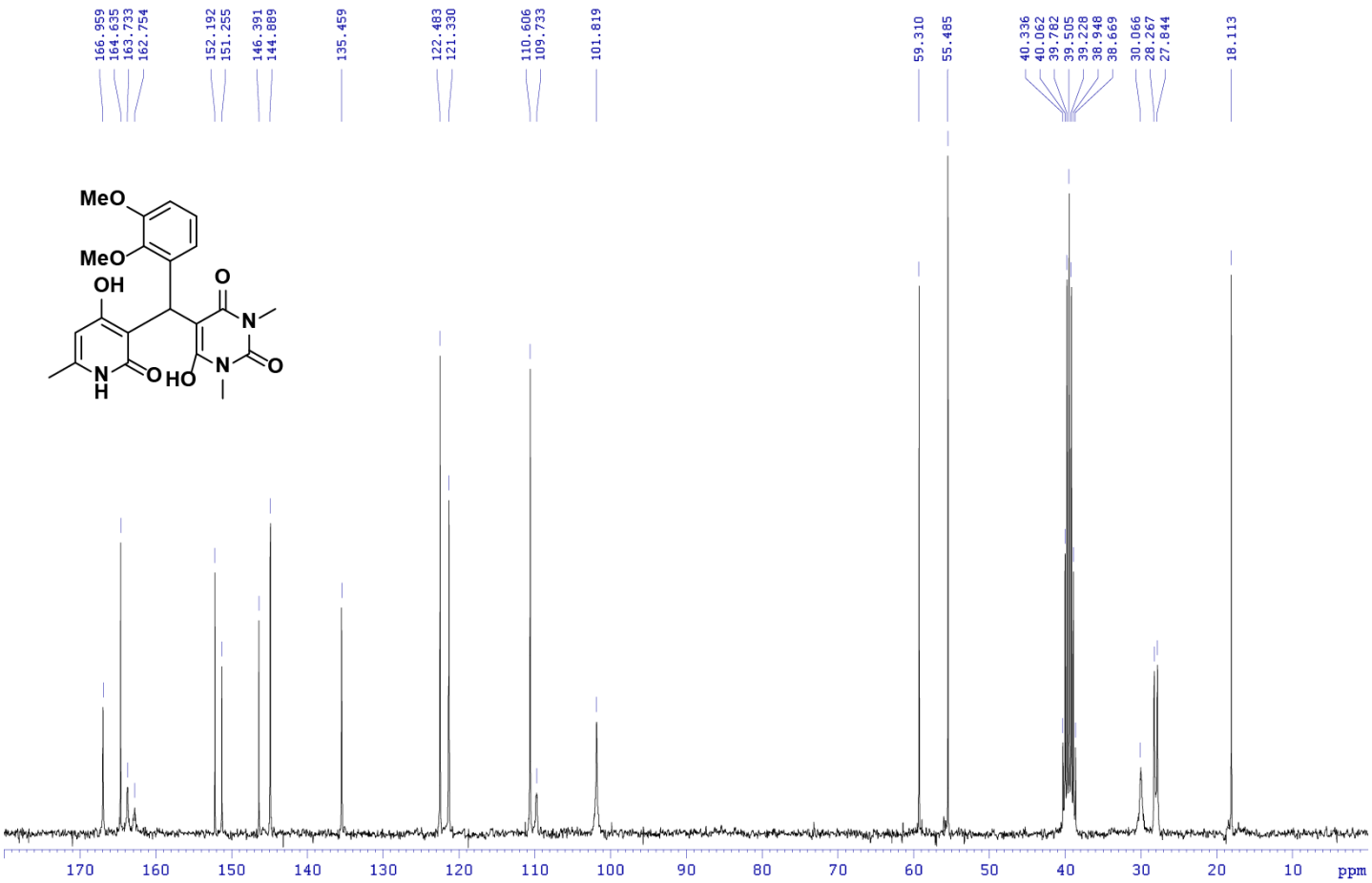


6-Hydroxy-5-((4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(3-methoxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2d)

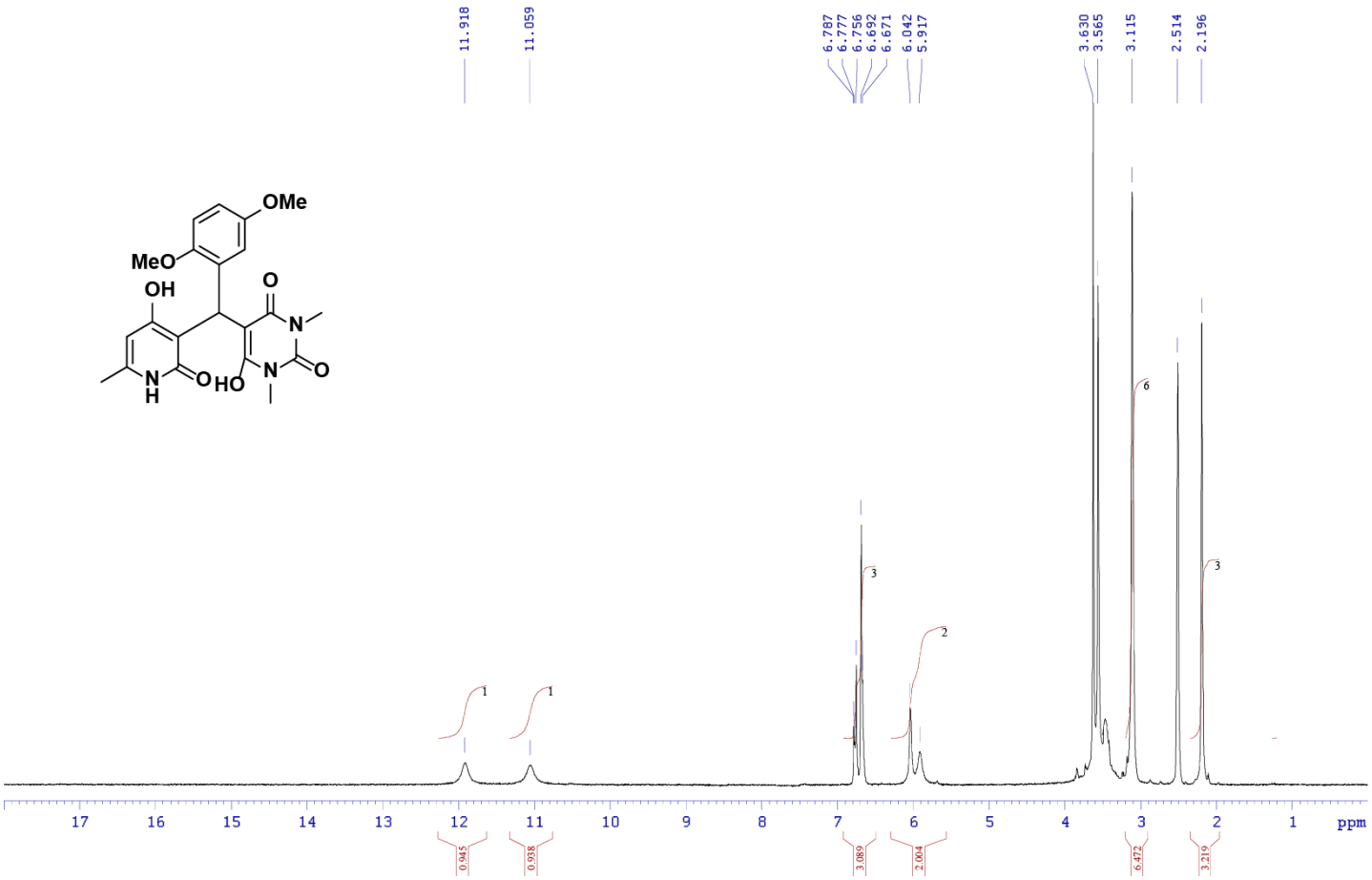


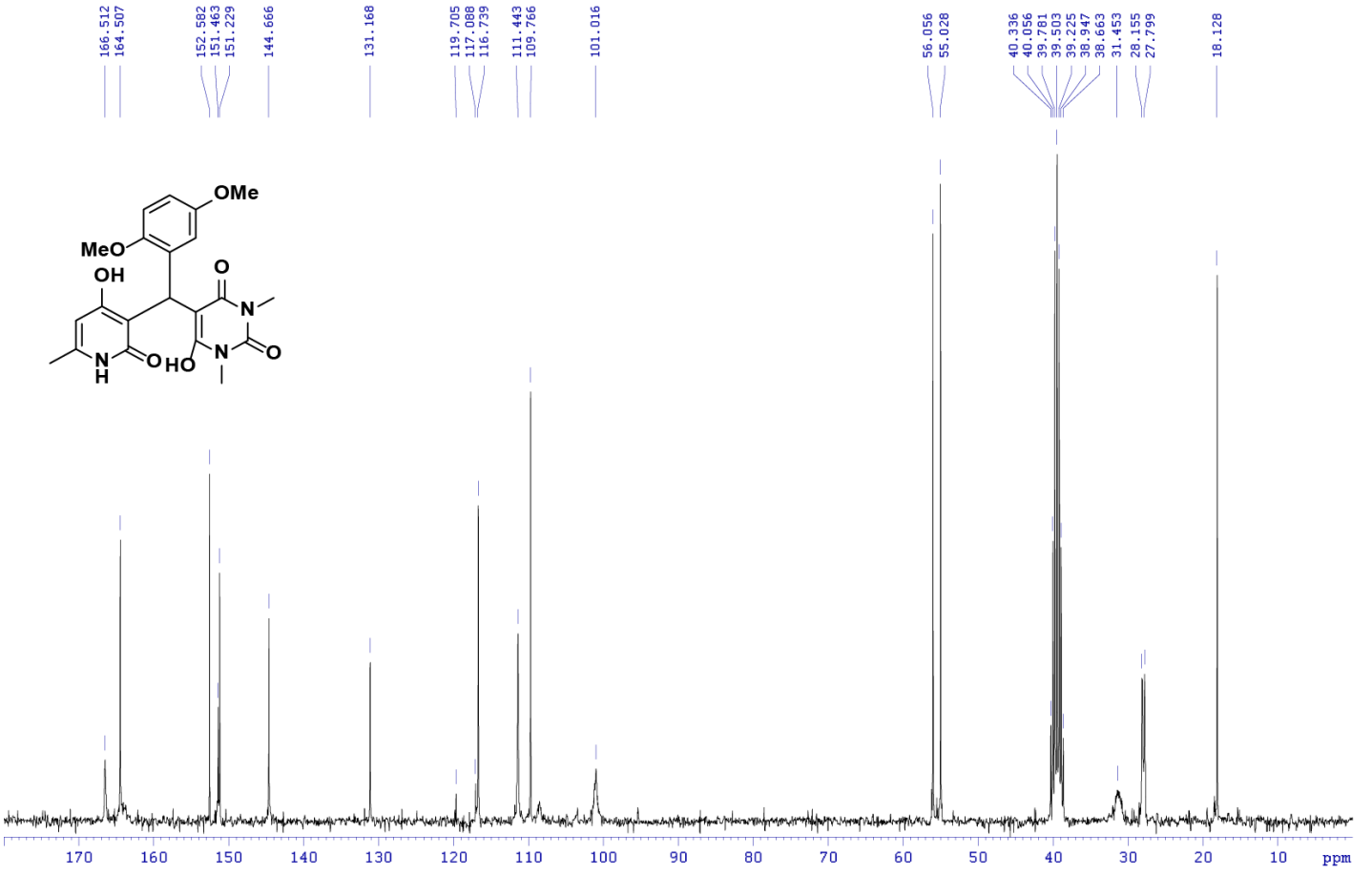
5-((2,3-Dimethoxyphenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2e)



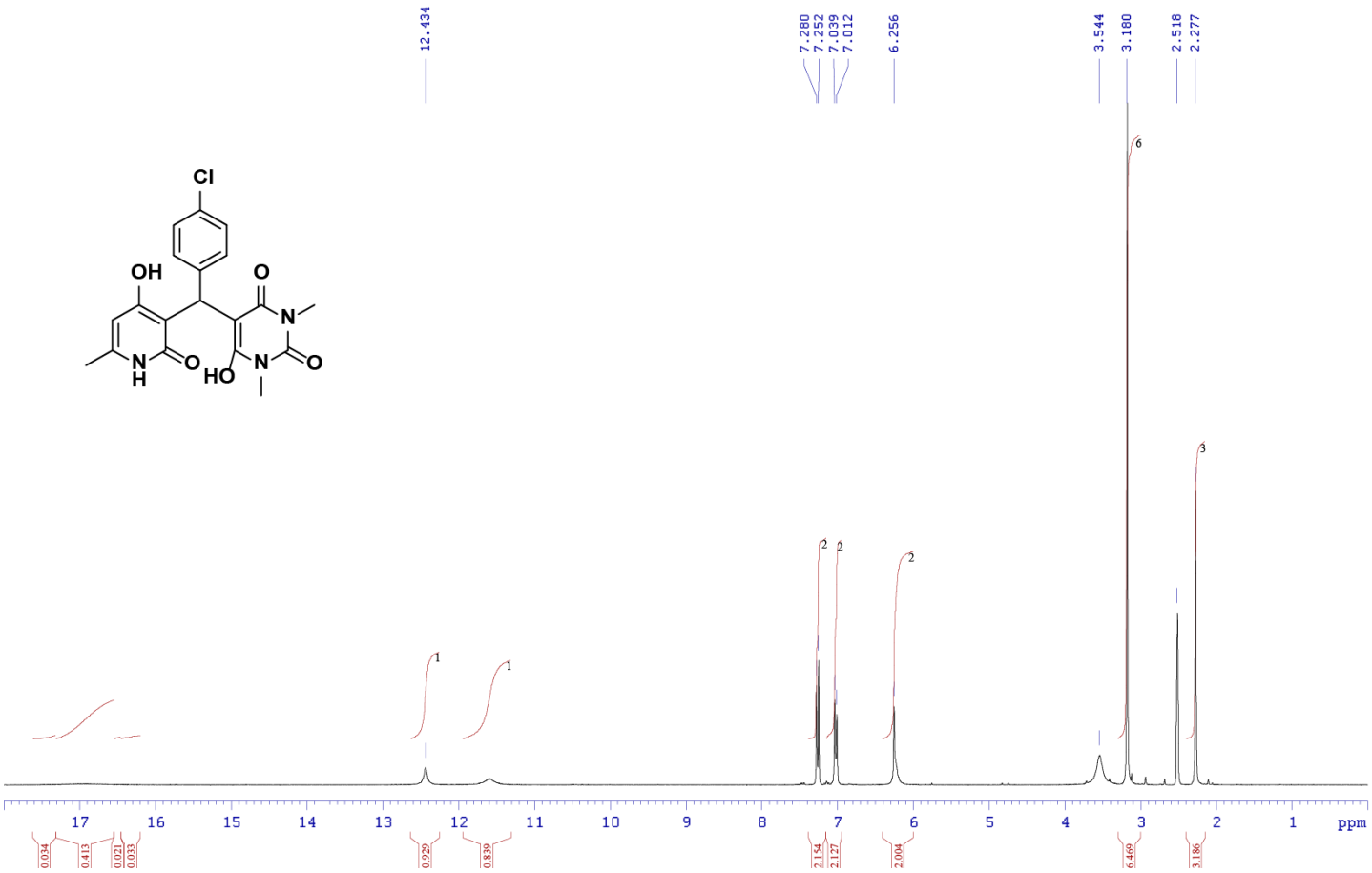


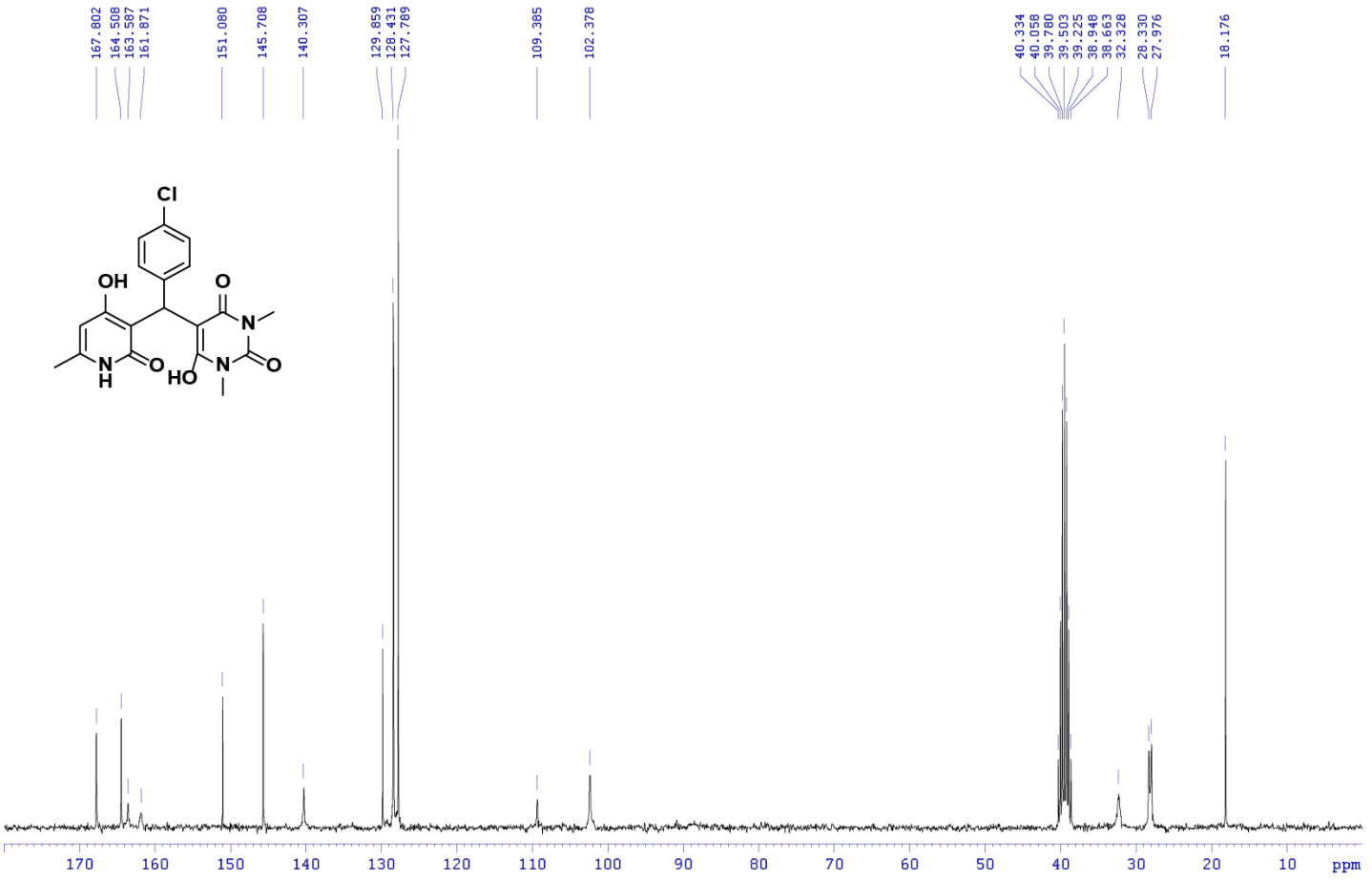
5-((2,5-Dimethoxyphenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2f)



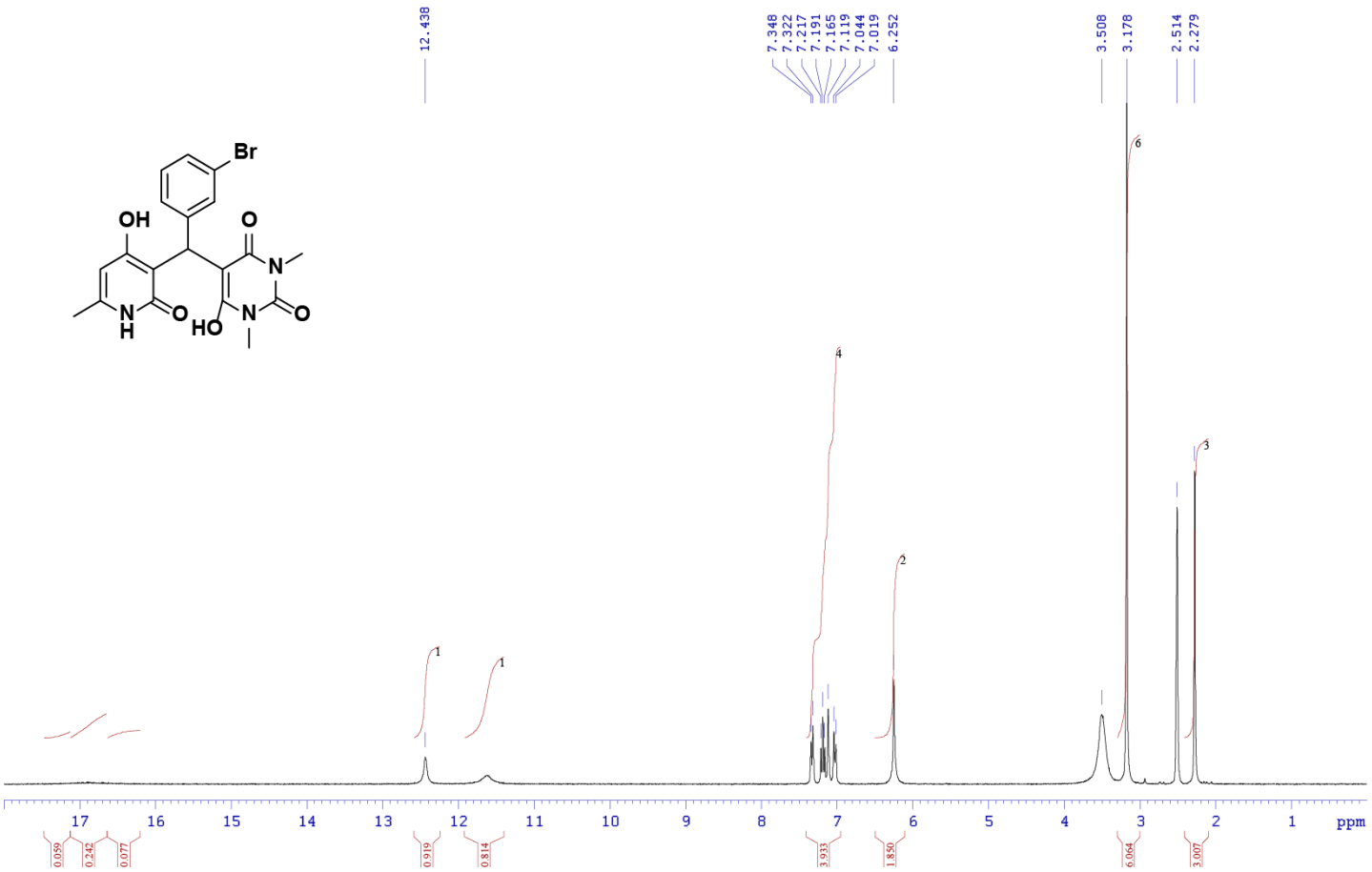


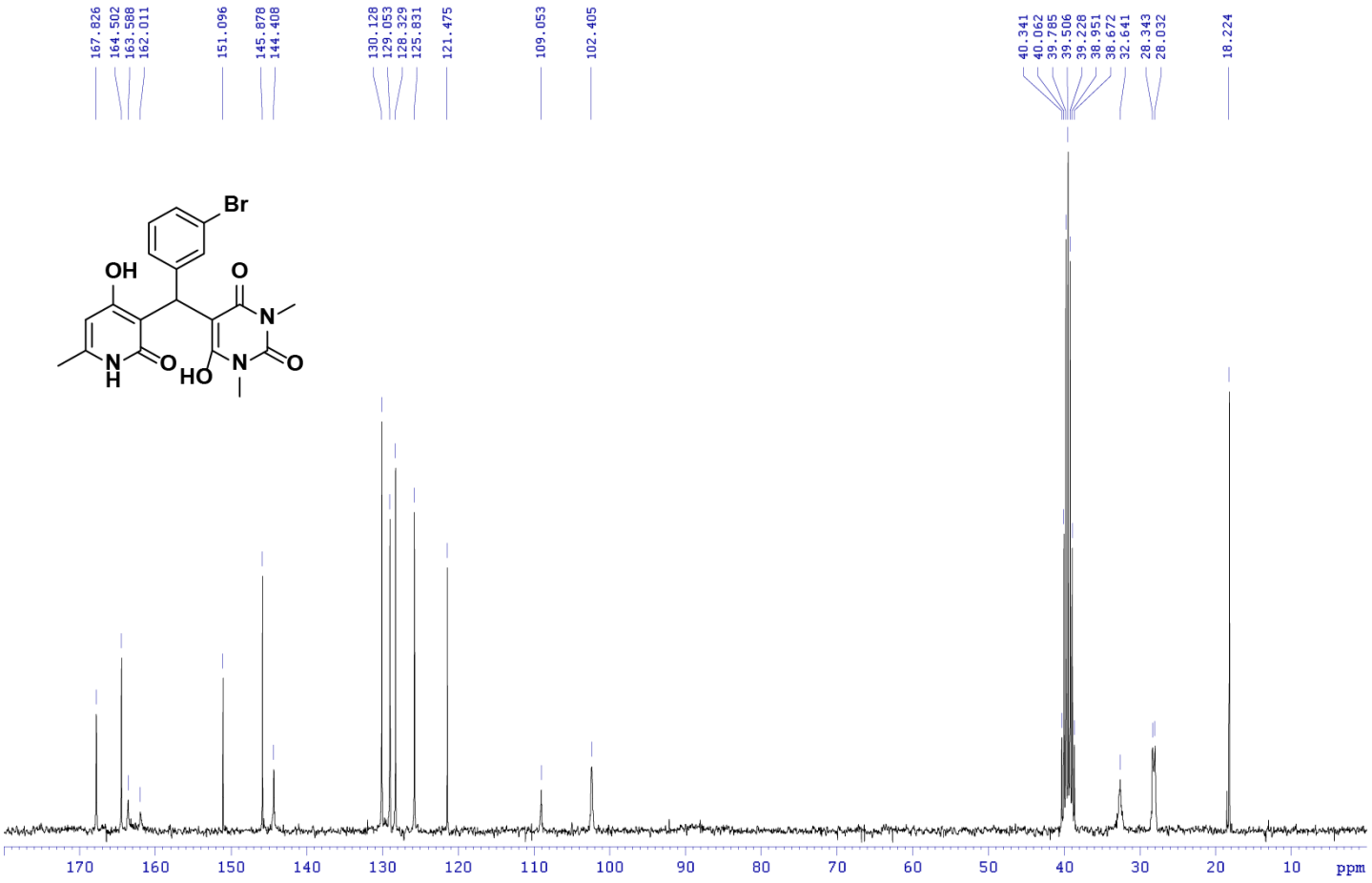
5-((4-Chlorophenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2g)



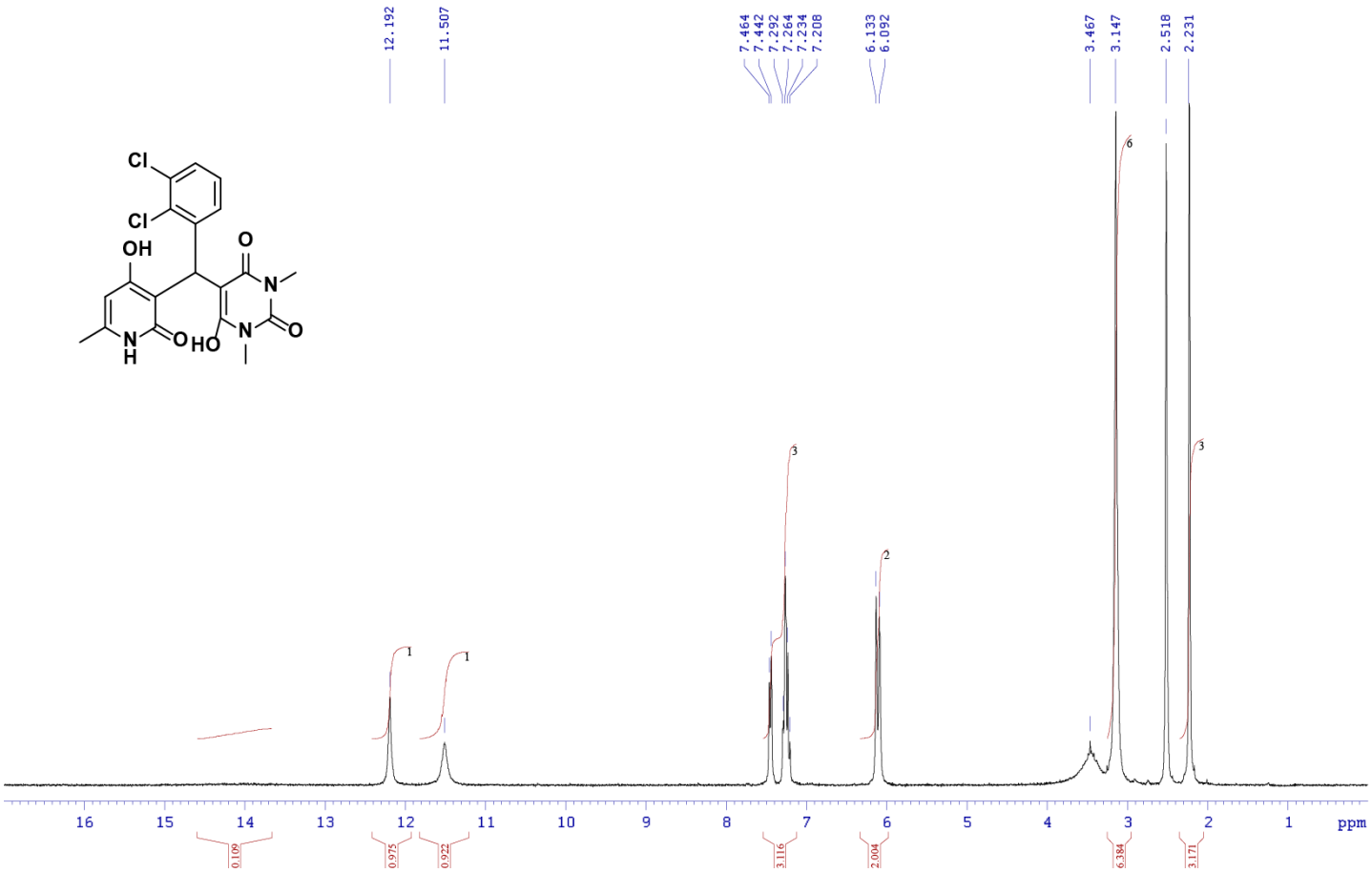


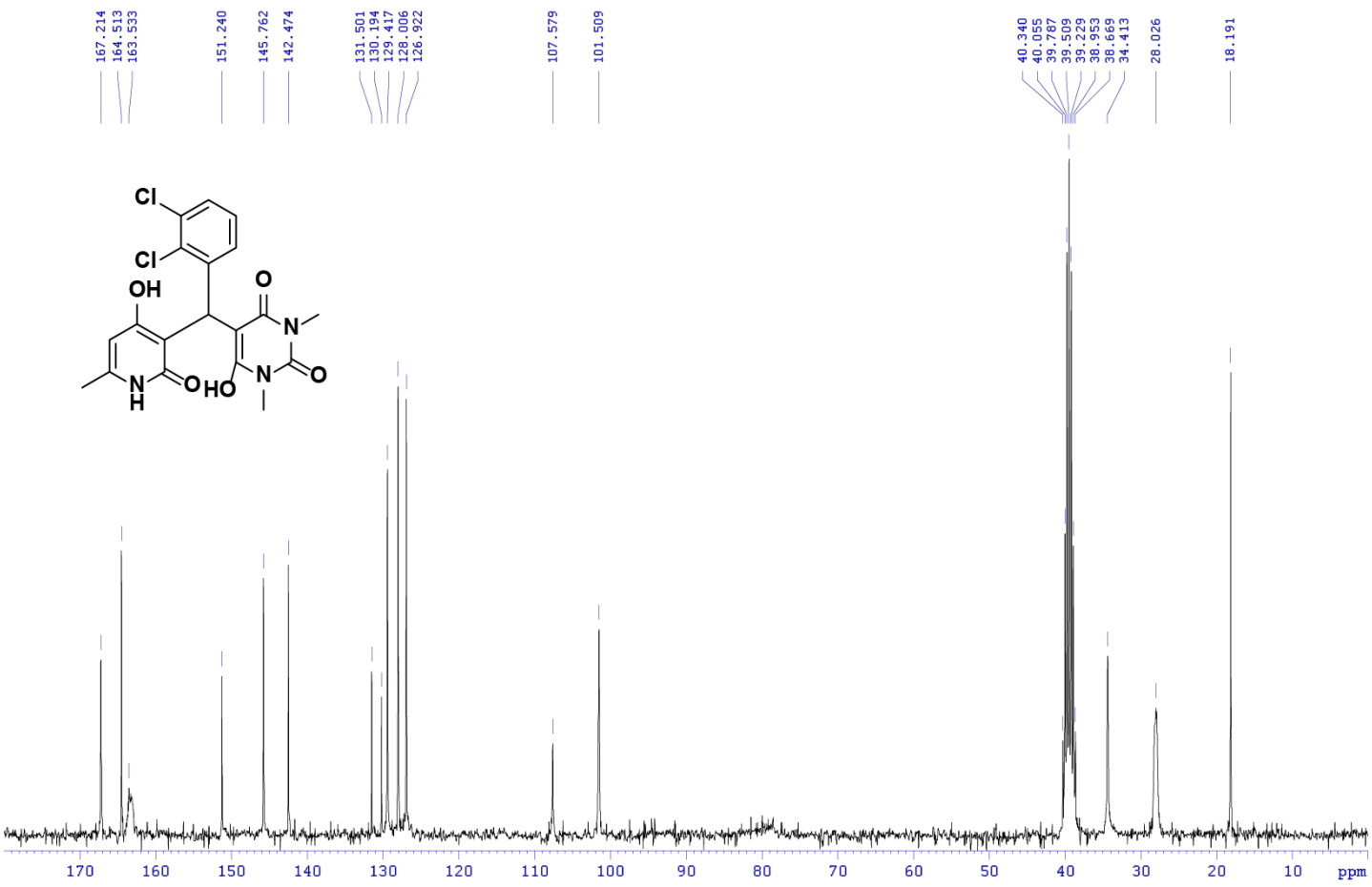
5-((3-Bromophenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2h)





5-((2,3-Dichlorophenyl)(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2i)





6-Hydroxy-5-((4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(4-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (2j)