Electronic Supplementary Information (ESI)

One-pot synthesis of 5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives

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Context

Experimental

General Information.

All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F_{254} plates. The silica gel (200−300 meshes) for column chromatography was from the Qingdao Marine Chemical Factory in China. Unless otherwise stated, commercially obtained materials were used without further purification. Formic acid was Tianjin Guangfu Fine Chemical Research Institute, purified by refluxing with phthalic anhydride for 6 hs. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker AV400-MHz FT NMR instruments, and spectral data are reported in *ppm* relative to tetramethylsilane (TMS) as internal standard. MS were measured on a HP-5988 spectrometer by direct inlet at 70 eV, and signals were given in *m*/*z* with relative intensity (%) in brackets, high resolution mass spectrometry were measured with MICRO-TOF Q Ⅱ (ESI).

General procedure for the reactions

Typical preparation procedure for compounds 2-amino-5-substituted-[1,3,4]thiadiazoles 2a-o were synthesized by the method reported in previous communications.

The mixture of aryl carboxylic acid 1a-o (5 mmol) and phosphorus oxychloride (7 mL) was heated at 75-80 ^oC for 4 h, and then allowed to cool to room temperature. Water (10 mL) was added dropwise to the solution and the reaction mixture was heated at 105-110 ^oC for 10 h. After the reaction was completed, the mixture was basified to pH 8 with 10% potassium hydroxide, and the precipitated solid was collected by filtered, washed with water and finally crystallized from ethanol to give **2a-o.**

R= 2a 2-ethoxyphenyl[1]; **2b** 4-methylphenyl[2]; **2c** 3-methoxyphenyl[3]; **2d** 4-methoxyphenyl[2]; **2e** phenyl[2]; **2f** 4-chlorophenyl[2]; **2g** 4-bromophenyl[3]; **2h** furan-2-yl[4]; **2i** 2-chlorophenyl[2]; **2j** 3-methylphenyl[1]; **2k** 2-bromophenyl[1]; **2l** 2-fluorophenyl[5]; **2m** benzyl[5]; **2n** 2-methoxyphenyl[2]; **2o** 2-methylphenyl[2].

2a 50616-29-0 2b 26907-54-0 2c 247109-15-5 2d 1014-25-1 2e 2002-03-1 2f 28004-62-8 2g 13178-12-6 2h 447-45-4 2i 828-81-9 2j 76074-47-0 2k 108656-64-0 2l 59565-51-4 2m 16502-08-2 2n 28004-56-0 2o 59565-54-7

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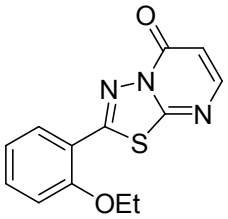
5. X.-H. Liu, Y.-X. Shi, Y. Ma, C.-Y. Zhang, W.-L. Dong, L. Pan, B.-L. Wang, B.-J. Li, Z.-M. Li, *Eur. J. Med. Chem*. **2009**, *44*, 2782–2786.

Typical synthesis procedure of 2-substituted-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives (3a-o)

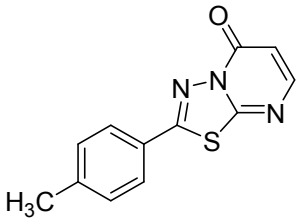
A mixture of **2a-o** (1.0 mmol) with ethyl cyanoacetate (1.0 mL), phosphorus pentoxide (20 mmol) and formic acid (10.0 mL) was heated at 100-105^{o} C for 12 h. The cooled reaction mixture was treated with ice-water and neutralized with 10% potassium hydroxide. Then the mixture liquid was extracted with $CHCl_3$ (3×15mL), dried with Na_2SO_4 and the residue was purified by silica gel chromatography using $CHCl_3$-ethyl acetate (4/1, v/v) to afford **3a-o**.

2-(2-Ethoxyphenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyridin-5-one (3a)



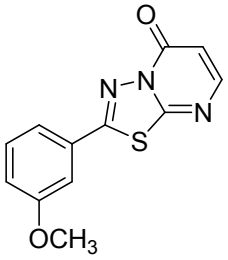
Yield(90%), white solid, m.p.: 191-193 ^{o}C; IR (KBr): 3372, 2980, 1698, 1598, 1492, 1460, 1397, 1298, 1124, 1035, 834, 785, 762, 609; ^{1}H NMR ($CDCl_3$): δ 8.49-8.46 (m, 1H, Ar-H), 7.98-7.97 (d, 1H, *J* = 6.8Hz, 6-CH), 7.54-7.49 (m, 1H, Ar-H), 7.12-7.02 (m, 2H, Ar-H), 6.47-6.45 (d, 1H, *J* = 6.8Hz, 7-CH), 4.32-4.26 (q, 2H, *J* = 20.8Hz, OCH_2), 1.62-1.59 (t, 3H, *J* = 14Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$): 163.2, 157.2, 156.6, 154.7, 152.3, 134.0, 128.7, 121.2, 117.0, 112.1, 108.9, 65.4, 14.6; MS(%): m/z 273(M^+, 39.5), 258(24.2), 245(23.8), 229(2.5), 217(4.3), 146(47.6), 121(24.3), 112(48.2), 98(100), 80(43.2), 69(44.0), 52(60.1). **HRMS** (ESI) calcd for $C_{13}H_{11}N_3O_2S$ $[M+H]^+$274.0645, found 274.0648.

2-(4-Methylphenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3b)



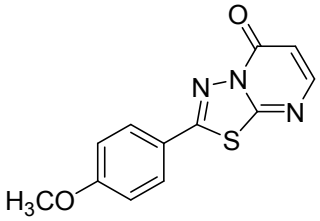
Yield(75%), white solid, m.p.: 213-215 ^{o}C; IR (KBr): 3400, 2913, 1789, 1670, 1596, 1550, 1469, 1383, 1255, 1219, 1148, 1103, 1039, 938, 804, 737, 678; ^{1}H NMR ($CDCl_3$): δ 7.95-7.93 (d, 1H, *J* = 6.4Hz, 6-CH), 7.86-7.84 (d, 2H, *J* = 8.4Hz, Ar-H), 7.34-7.28 (t, 2H, *J* = 8.4Hz, Ar-H), 6.49-6.48 (d, 1H, *J* = 6.4Hz, 7-CH), ^{13}C NMR ($CDCl_3$): 162.1, 159.2, 157.1, 152.1, 143.9, 130.0, 127.6, 125.5, 109.9, 21.6; MS(%): m/z 243(M^+, 60.0), 215(4.7), 135(39.2), 126(19.4), 119(33.9), 112(22.0), 98(100), 91(30.2), 80(19.8), 52(41.8), 39(25.9). **HRMS** (ESI) calcd for $C_{12}H_9N_3OS$ $[M+H]^+$244.0539, found 244.0545.

2-(3-Methoxyphenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3c)



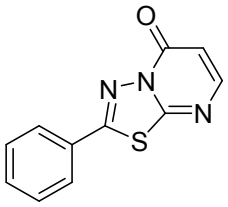
Yield(78.5%), yellow solid, m.p.: 135-137 °C; IR (KBr): 3509, 3066, 2939, 1708, 1495, 1287, 1236, 1169, 1045, 790, 686; ^{1}H NMR ($CDCl_3$): δ 7.96-7.94 (d, 1H, *J* = 6.4Hz, 6-CH), 7.53-7.53 (d, 1H, Ar-H), 7.47-7.40 (m, 2H, Ar-H), 7.15-7.12 (m, 1H, Ar-H), 6.50-6.49 (d, 1H, *J* = 6.4Hz, 7-CH), 3. 90 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): 162.1, 160.2, 159.1, 157.1, 152.2, 130.4, 129.4, 120.4, 119.4, 112.0, 110.0, 55.7; MS(%): m/z 259(M^+, 100), 231(2.2), 204(3.7), 188(2.6), 151(19.3), 133(25.9), 126(22.3), 108(59.2), 98(39.3), 69(31.9), 52(71.4), 39(35). **HRMS** (ESI) calcd for $C_{12}H_9N_3O_2S$ $[M+H]^+$260.0488, found 260.0495.

2-(4-Methoxyphenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3d)



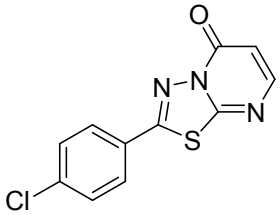
Yield(93%), white solid, m.p.: 189-191 °C; IR (KBr): 3522, 3027, 2928, 2842, 1704, 1602, 1487, 1261, 1173, 1014, 828, 723, 682, 601; ^{1}H NMR ($CDCl_3$): δ 7.93-7.92 (d, 1H, *J* = 6.4Hz, 6-CH), 7.91-7.88 (t, 2H, *J* = 8.8Hz, Ar-H), 7.02-6.99 (t, 2H, *J* = 7.6Hz, Ar-H), 6.48-6.46 (d, 1H, *J* = 6.4Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 163.3, 162.0, 158.7, 157.1, 152.0, 129.4, 120.6, 114.7, 109.8, 55.5; MS(%): m/z 259(M^+, 100), 231(3.3), 216(1.6), 204(1.4), 188(5.3), 151(36.2), 135(45.8), 126(16.8), 108(44.2), 98(99.2), 80(23.3), 52(53.5). **HRMS** (ESI) calcd for $C_{12}H_9N_3O_2S$ $[M+H]^+$260.0488, found 260.0491.

2-Phenyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3e)



Yield(30%): white solid, m.p.: 165-167 °C; IR (KBr): 3382, 3048, 2923, 1706, 1490, 1269, 1231, 1180, 829, 762, 688, 607; ^{1}H NMR ($CDCl_3$): δ 7.98-7.96 (d, 1H, *J* = 7.2Hz, 6-CH), 7.96-7.94 (d, 2H, *J* = 6.4Hz, Ar-H), 7.63-7.52 (m, 3H, Ar-H), 6.51-6.48 (d, 1H, *J* = 6.4Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 162.1, 159.1, 157.1, 152.2, 133.0, 128.4, 128.2, 127.7, 110.0; MS(%): m/z 229(M^+, 76.7), 201(6.4), 174(3.8), 126(17.6), 121(48.7), 112(22.9), 98(100), 77(67.0), 71(27.7), 52(51.1), 51(51.2), 39(30.2). **HRMS** (ESI) calcd for $C_{11}H_7N_3OS$ $[M+H]^+$230.0383, found 230.0380.

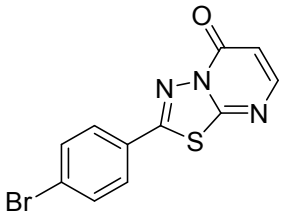
2-(4-Chlorophenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3f)



Yield(48%), white solid, m.p.: 176-178 °C; IR (KBr): 3059, 2921, 1986, 1707, 1494, 1272, 1184, 1066, 1040, 829, 757, 734, 607; ^{1}H NMR ($CDCl_3$): δ 8.31-8.29 (t, 1H, Ar-H), 8.00-7.99 (d, 1H, *J* = 6.4Hz, 6-CH), 7.57-7.23 (m, 3H,

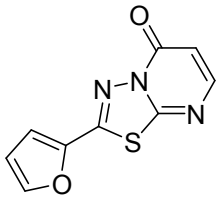
Ar-H), 6.51-6.49 (d, 1H, *J* = 6.8Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 162.5, 156.9, 156.3, 152.5, 133.3, 133.0, 131.3, 130.8, 127.6, 109.5; MS(%): m/z 263(M^+, 30.2), 235(3.8), 155(28.4), 139(15.9), 126(18.2), 112(26.0), 98(100), 71(27.5), 52(37.0). **HRMS** (ESI) calcd for $C_{11}H_6ClN_3OS$ $[M+H]^+$263.9993, found 263.9998.

2-(4-Bromophenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3g)



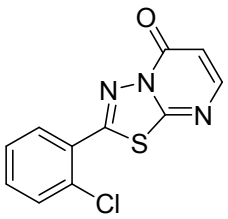
Yield(45%), white solid, m.p.: 214-216 °C; IR (KBr): 3549, 3023, 1708, 1684, 1559, 1496, 1395, 1272, 1003, 822, 704, 662; ^{1}H NMR ($CDCl_3$): δ 7.97-7.94 (m, 1H, 6-CH), 7.86-7.82 (m, 2H, Ar-H), 7.71-7.66 (m, 2H, Ar-H), 6.52-6.48 (m, 1H, 7-CH); ^{13}C NMR ($CDCl_3$): 161.9, 158.1, 157.0, 152.3, 132.8, 129.0, 127.9, 127.2, 110.2; MS(%): m/z 307(M^+, 19.8), 279(0.9), 201(17.1), 126(15.6), 120(46.5), 112(26.7), 102(15.6), 98(100), 80(27.3), 75(23.5), 52(61.4). **HRMS** (ESI) calcd for $C_{11}H_6BrN_3OS$ $[M+H]^+$307.9488, found 307.9485.

2-(Furan-2-yl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3h)



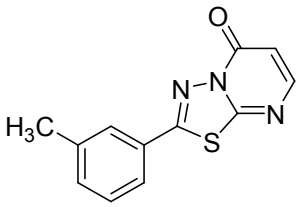
Yield(52.5%), white solid, m.p.: 218-220 °C; IR (KBr): 3094, 2922, 1675, 1591, 1555, 1470, 1266, 1145, 1034, 886, 809, 754, 672; ^{1}H NMR ($CDCl_3$): δ 7.96-7.94 (d, 1H, *J* = 6.4Hz, 6-CH), 7.69 (t, 1H, *J* = 0.8Hz, furan-H), 7.43 (d, 1H, *J* = 3.6Hz, furan-H), 6.69-6.67 (q, 1H, *J* = 5.2Hz, furan-H), 6.50-6.49 (d, 1H, *J* = 6.4Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 161.5, 157.1, 152.1, 149.5, 146.7, 143.6, 114.4, 113.3, 109.9; MS(%): m/z 219(M^+, 77.1), 191(5.1), 111(48.5), 98(83.1), 84(14.4), 71(17.9), 57(19.2), 52(43.8), 39(100). **HRMS** (ESI) calcd for $C_9H_5N_3O_2S$ $[M+H]^+$220.0175, found 220.0180.

2-(2-Chlorophenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3i)



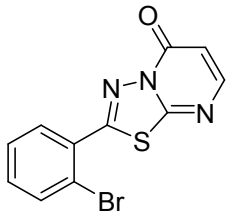
Yield(69.5%), white solid, m.p.: 169-171 °C; IR (KBr): 3381, 3060, 2922, 1710, 1560, 1497, 1273, 1186, 1068, 1042, 832, 757, 734, 606; ^{1}H NMR ($CDCl_3$): δ 8.32-8.29 (m, 1H, Ar-H), 8.01-7.99 (d, 1H, *J* = 6.8Hz, 6-CH), 7.58-7.44 (m, 3H, Ar-H), 6.52-6.49 (m, 1H, *J* = 6.4Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 162.6, 157.0, 156.1, 152.6, 133.3, 133.1, 131.4, 130.9, 127.7, 127.1, 109.6; MS(%): m/z 263(M^+, 21.5), 235(2.5), 208(0.8), 155(23.9), 139(11.7), 112(21.4), 98(100), 75(18.8), 52(21.7). **HRMS** (ESI) calcd for $C_{11}H_6ClN_3OS$ $[M+H]^+$263.9993, found 263.9995.

2-(3-Methylphenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3j)



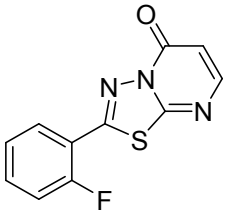
Yield(82%), white solid, m.p.: 150-152 °C; IR (KBr): 3390, 3062, 2923, 1697, 1493, 1274, 1232, 1172, 1050, 831, 789, 687, 568; ^{1}H NMR ($CDCl_3$): δ7.93-7.91 (q, 1H, *J* = 9.2Hz, 6-CH), 7.81 (s, 1H, Ar-H), 7.68-7.67 (d, 1H, *J* = 3.2Hz, Ar-H), 7.38-7.37 (d, 2H, *J* = 4.4Hz, Ar-H), 5.48-5.45 (q, 1H, *J* = 8.8Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 162.1, 159.3, 157.1, 152.1, 138.5, 133.8, 129.2, 128.1, 128.0, 125.0, 110.0, 21.1; MS(%): m/z 243(M^+, 44.6), 215(6.1), 135(37.5), 126(19.4), 119(22.5), 112(21.7), 98(100), 91(26.1), 71(22.1), 65(24.5), 52(42.0), 39(34.3). **HRMS** (ESI) calcd for $C_{12}H_9N_3OS$ $[M+H]^+$244.0539, found 244.0543.

2-(2-Bromophenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3k)



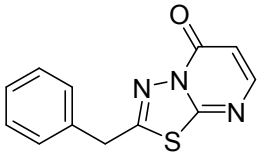
Yield(56%), white solid, m.p.: 179-181 °C; IR (KBr): 3372, 3061, 2922, 1709, 1563, 1495, 1271, 1189, 1064, 1029, 837, 759, 707, 572; ^{1}H NMR ($CDCl_3$): δ 8.15-8.13 (q, 1H, Ar-H), 8.01-7.99 (d, 1H, *J* = 6.8Hz, 6-CH), 7.76-7.74 (t, 1H, Ar-H), 7.52-7.43 (m, 2H, Ar-H), 6.52-6.50 (d, 1H, *J* = 6.8Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 162.6, 157.7, 157.0, 152.6, 134.3, 133.3, 132.1, 129.2, 128.1, 122.3, 109.7; MS(%): m/z 307(M^+, 25.5), 279(2.5), 201(12.8), 126(15.3), 120(29.2), 112(19.0), 98(100), 80(22.4), 75(25.2), 52(67.1), 40(28.6). **HRMS** (ESI) calcd for $C_{11}H_6BrN_3OS$ $[M+H]^+$307.9488, found 307.9494.

2-(2-Fluorophenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3l)



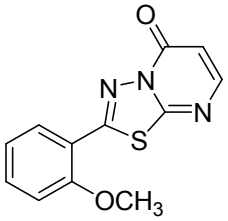
Yield(62%), white solid, m.p.: 178-180 °C; IR (KBr): 3699, 3380, 3053, 2921, 1588, 1406, 1096, 1032, 822, 757, 676; ^{1}H NMR ($CDCl_3$): δ 8.41-8.37 (m, 1H, Ar-H), 7.99-7.98 (d, 1H, *J* = 6.4Hz, 6-CH), 7.64-7.58 (m, 1H, Ar-H), 7.38-7.26 (m, 2H, Ar-H), 6.50-6.49 (d, 1H, *J* = 6.4Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 162.3, 159.2, 156.9, 152.4, 134.6, 134.49, 128.9, 125.1, 125.1, 116.4, 109.5; MS(%): m/z 247(M^+, 38.5), 219(5.2), 139(62.6), 126(14.7), 112(27.2), 98(100), 95(30.5), 80(21.0), 71(32.1), 57(22.4), 52(45.4). **HRMS** (ESI) calcd for $C_{11}H_6FN_3OS$ $[M+H]^+$248.0288, found 248.0285.

2-Benzyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3m)



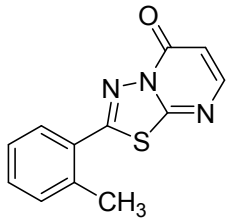
Yield(67%), white solid , m.p.: 119-121 °C; IR (KBr): 3494, 3063, 3029, 2924, 2234, 1697, 1549, 1495, 1293, 1238, 1123, 821, 708, 666; ^{1}H NMR ($CDCl_3$): δ 7.92-7.88 (m, 1H, *J* = 6.4Hz, 6-CH), 7.40-7.33 (m, 5H, Ar-H), 6.47-6.43 (m, 1H, *J* = 6.4Hz, 7-CH), 4.37-4.35 (t, 2H, *J* = 6.4Hz, Ph-CH_2); ^{13}C NMR ($CDCl_3$): 162.8, 162.6, 157.1, 152.3, 134.3, 129.4, 128.9, 128.3, 109.8, 37.8; MS(%): m/z 243(M^+, 48.7), 215(6.4), 149(25.6), 112(19.6), 98(79.6), 91(100), 80(21.7), 71(40.5), 65(38.6), 52(51.2), 39(49.5). **HRMS** (ESI) calcd for $C_{12}H_9N_3OS$ $[M+H]^+$244.0539, found 244.0540.

2-(2-Methoxyphenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3n)



Yield(85%), white solid, m.p.: 225-227 °C; IR (KBr): 3404, 2991, 2993, 1784, 1674, 1446, 1290, 1227, 1160, 1113, 991, 822, 759, 686; ^{1}H NMR ($CDCl_3$): δ 8.47-8.44 (q, 1H, Ar-H), 7.98-7.97 (d, 1H, *J* = 6.4Hz, 6-CH), 7.56-7.52 (m, 1H, Ar-H), 7.14-7.05 (m, 2H, Ar-H), 6.47-6.45 (d, 1H, *J* = 6.8Hz, 7-CH), 4.05(s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$): 163.1, 157.2, 157.1, 154.7, 152.4, 134.1, 128.7, 121.4, 117.0, 111.5, 109.0, 55.9; MS(%): m/z 259(M^+, 49.6), 151(11.6), 141(19.9), 132(20.9), 108(57.5), 84(27.2), 77(33.7), 69(33.6), 52(100), 39(30.1). **HRMS** (ESI) calcd for $C_{12}H_9N_3O_2S$ $[M+H]^+$260.0488, found 260.0494.

2-(2-Methylphenyl)-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3o)



Yield(76%), white solid, m.p.: 157-159 °C; IR (KBr): 3368, 3059, 2965, 1694, 1497, 1469, 1289, 1231, 1182, 834, 771, 711; ^{1}H NMR ($CDCl_3$): δ 7.96-7.92 (m, 1H, *J* = 6.4Hz, 6-CH), 7.63-7.61 (t, 1H, Ar-H), 7.47-7.42 (m, 1H, Ar-H), 7.35-7.26 (m, 2H, Ar-H), 6.49-6.45 (m, 1H, *J*=6.4Hz, 7-CH); ^{13}C NMR ($CDCl_3$): 162.4, 158.1, 157.0, 152.2, 137.9, 132.0, 131.9, 130.4, 127.3, 126.5, 109.9, 21.4; MS(%): m/z 243(M^+, 72.5), 215(4.3), 184(17.1), 149(39.8), 134(32.8), 116(55.9), 95(100), 89(35.3), 80(20.8), 63(25.1), 52(55.9), 39(49.4). **HRMS** (ESI) calcd for $C_{12}H_9N_3OS$ $[M+H]^+$244.0539, found 244.0546.

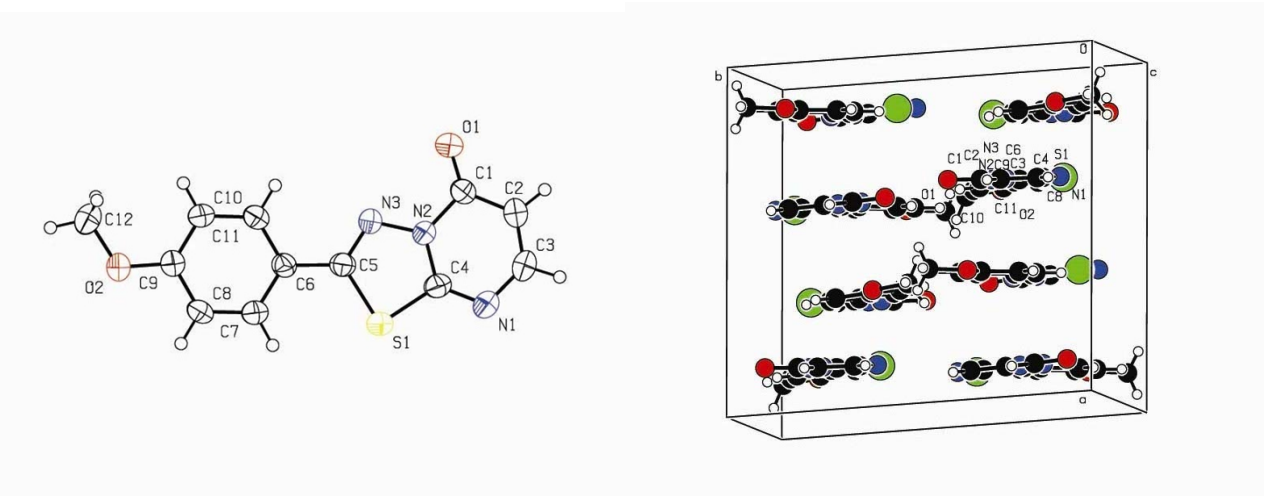
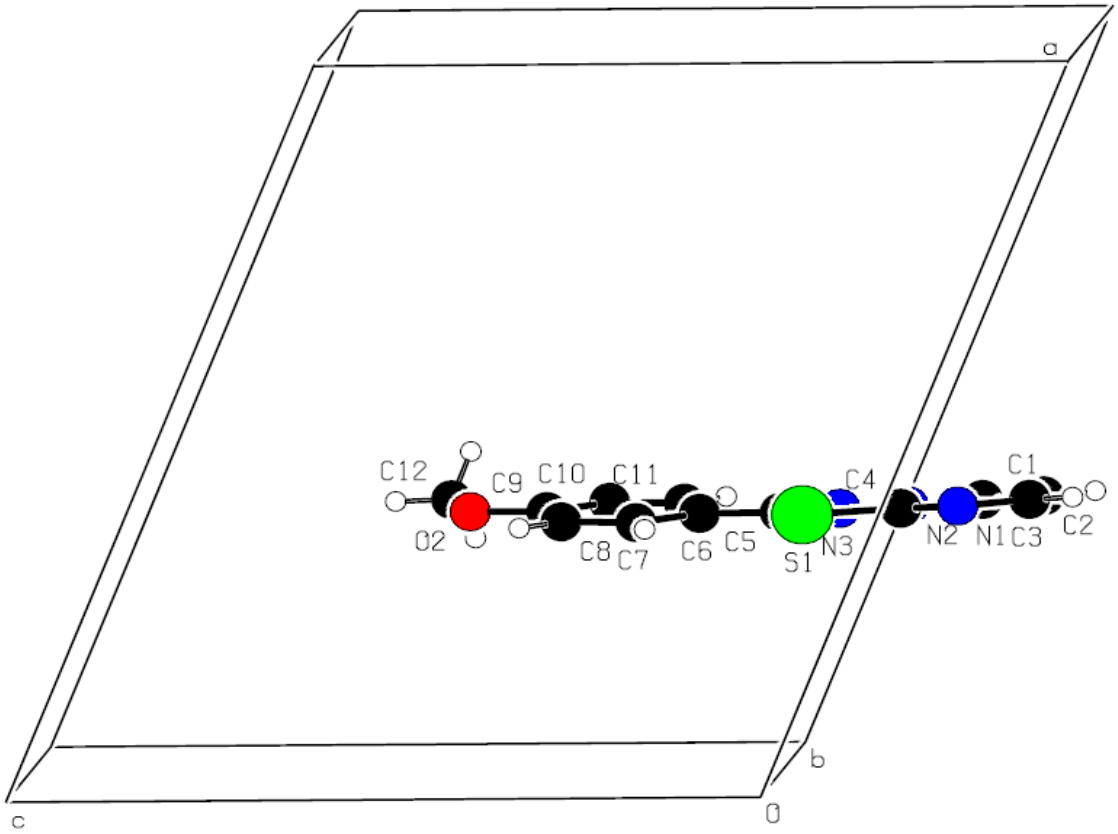
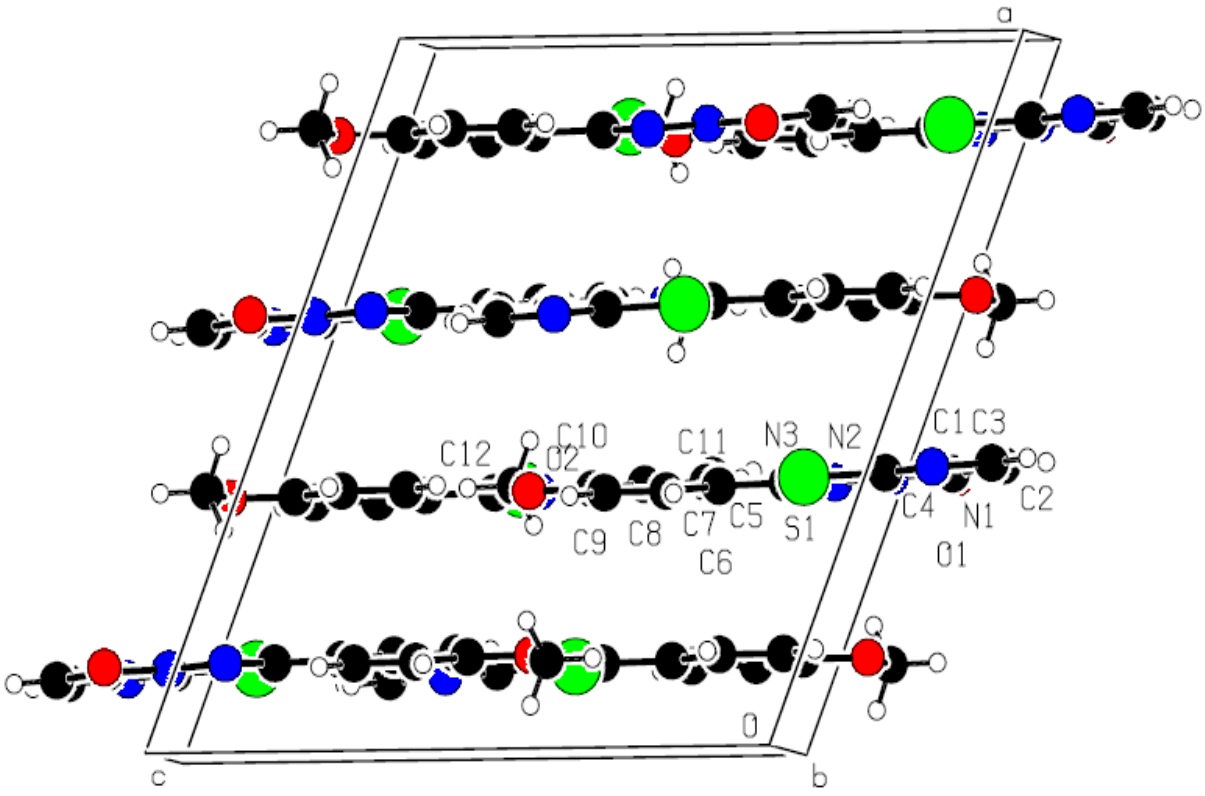


Figure 1 A Mercury (1.4, CCDC, 2005) view of the molecular structure of **3d**

X-ray structure determination of **3d.** Colorless Block, $C_{12}H_9N_3O_2S$, *Mr*=259.28, Monoclinic, space group *C*2/*c*, *a*=14.1942 (13), *b*=13.4679 (13), *c*=12.8940 (12) Å, α=90.00, β=112.384(7), γ=90.00°, *V*=2279.2(4) Å^{3,} *Z*=8, D_x=1.511 Mg m^{-3}, F_{000}=1072, μ=0.28 mm^{-1}. Intensity data were collected using a Siemens SMART diffractometer at 296(2) K, graphite monochromator MoKa radiation (λ=0.71073 Å), using the *φ*-*ω* scan technique to a maximun 2.2-25.5°. A total of 5973 reflections were collected with 2116 unique ones(*R* = 0.0422), of which 1458 reflections with *I* > 2σ(*I*). The final int *R* and *wR* values were 0.0336 and 0.1009, *s*=1.026, $(\Delta/\sigma)_{max}$ = 0.000. The maximum peak and minimum peak in the final difference map is 0.21 and -0.22 e Å^{-3}.

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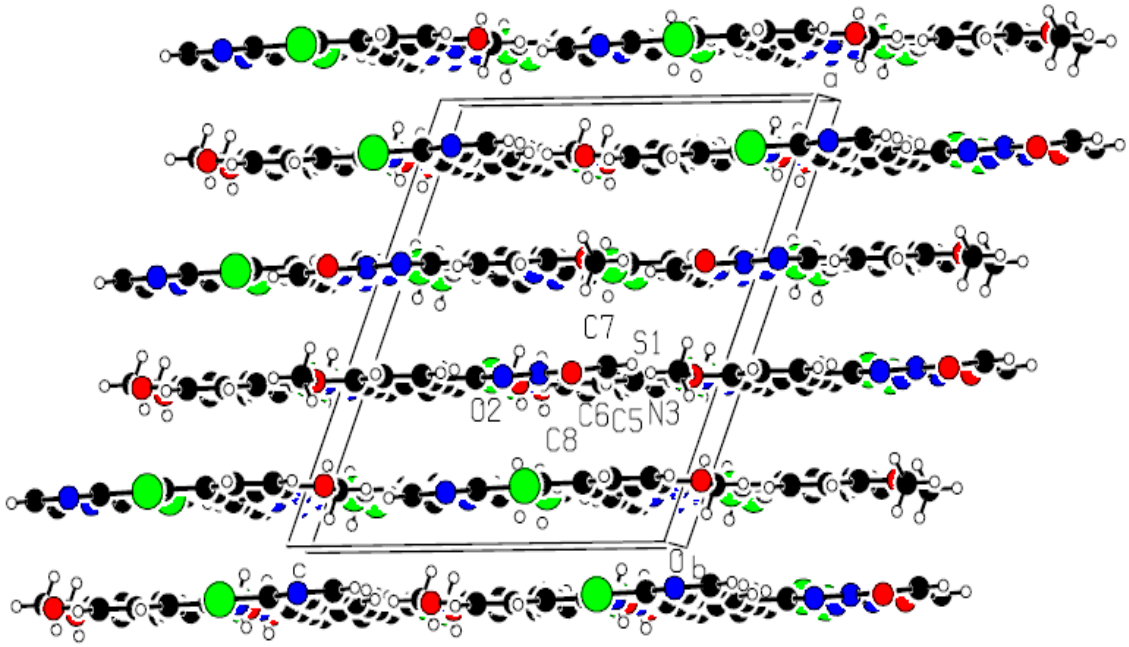
C12
C10
O2
C11
N3
N2
C1
C3
C4
N1
C2
C9
C8
C7
C5
S1
C6
O1
O
c
b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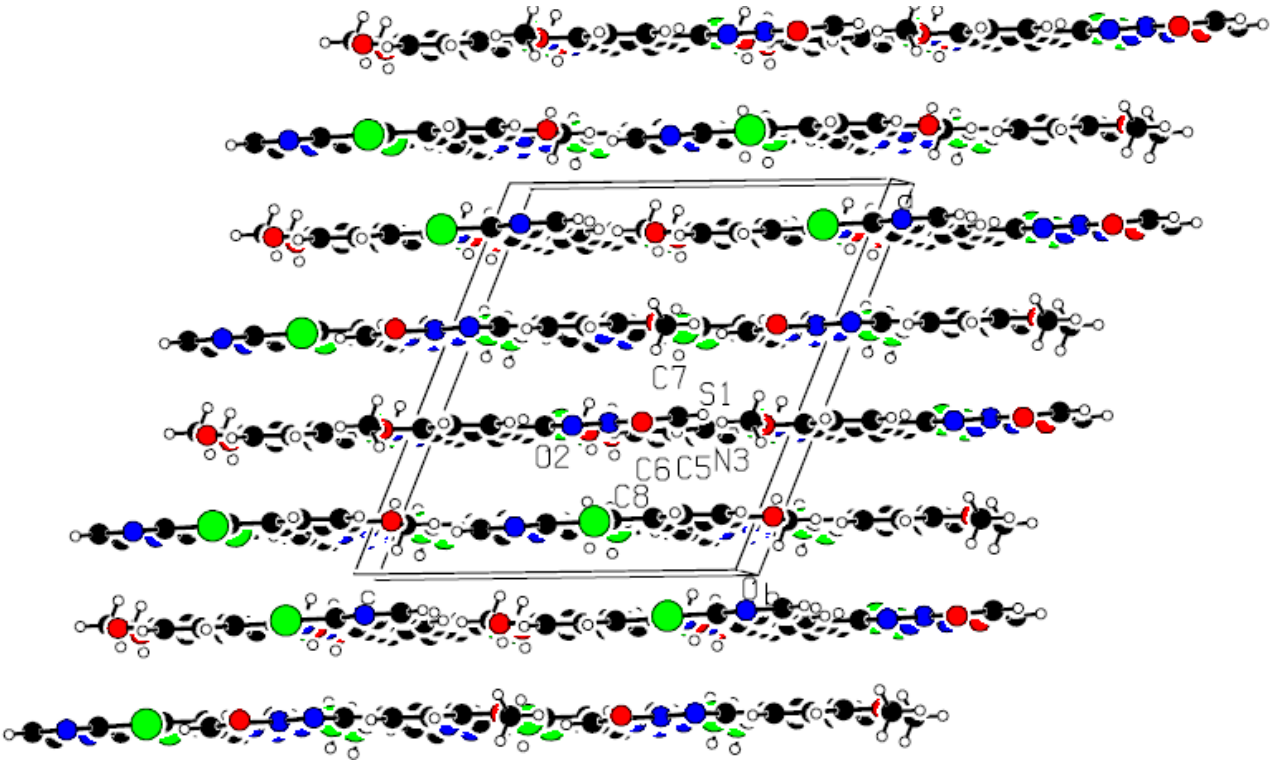
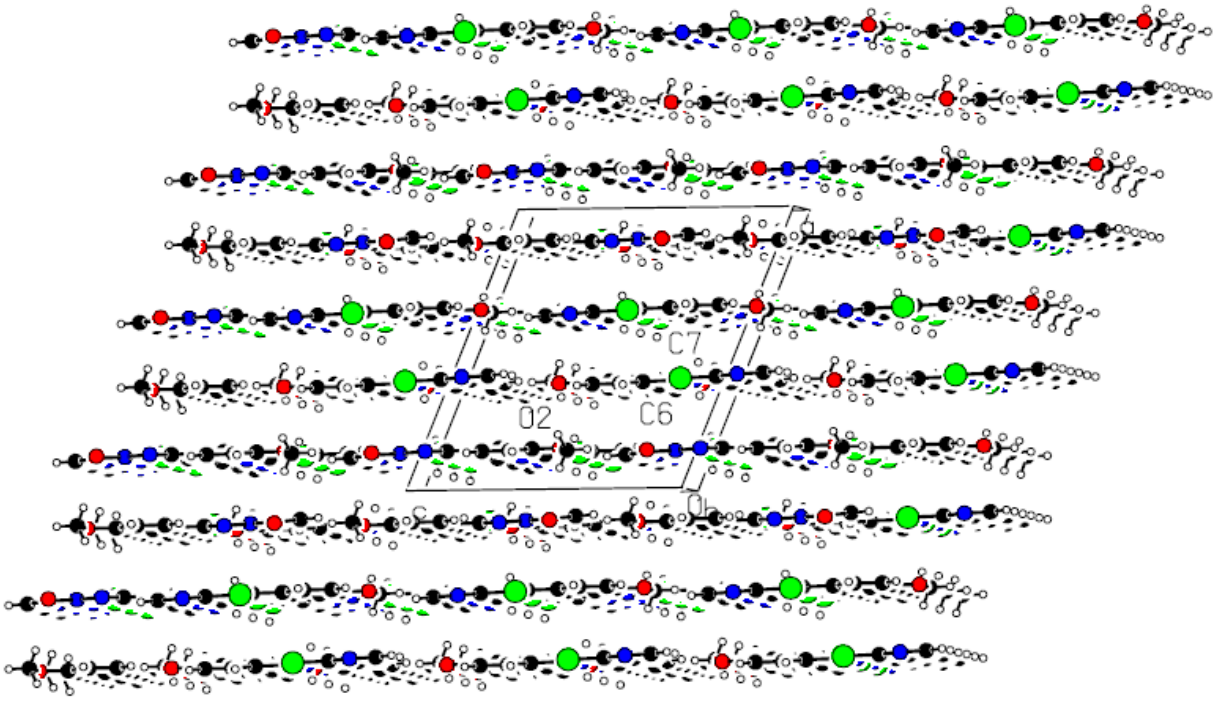
C7
S1
O2
C6
C5
N3
C8
O
c
b


C7
S1
O2
C6
C5
N3
C8
O1


C7
O2
C6
O1

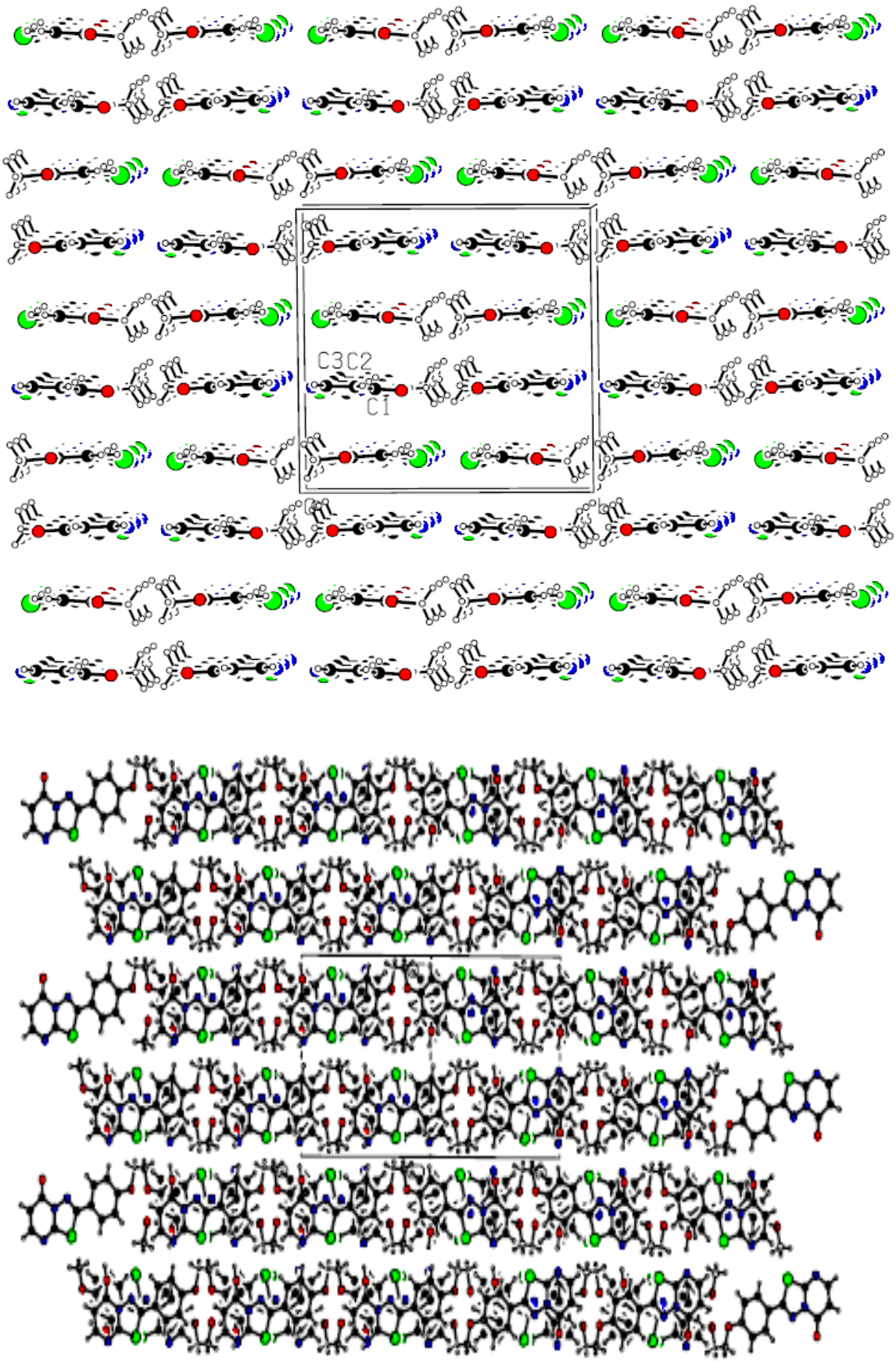


Figure 2. The π-π accumulation structure of 3d supramolecular self-assembly.

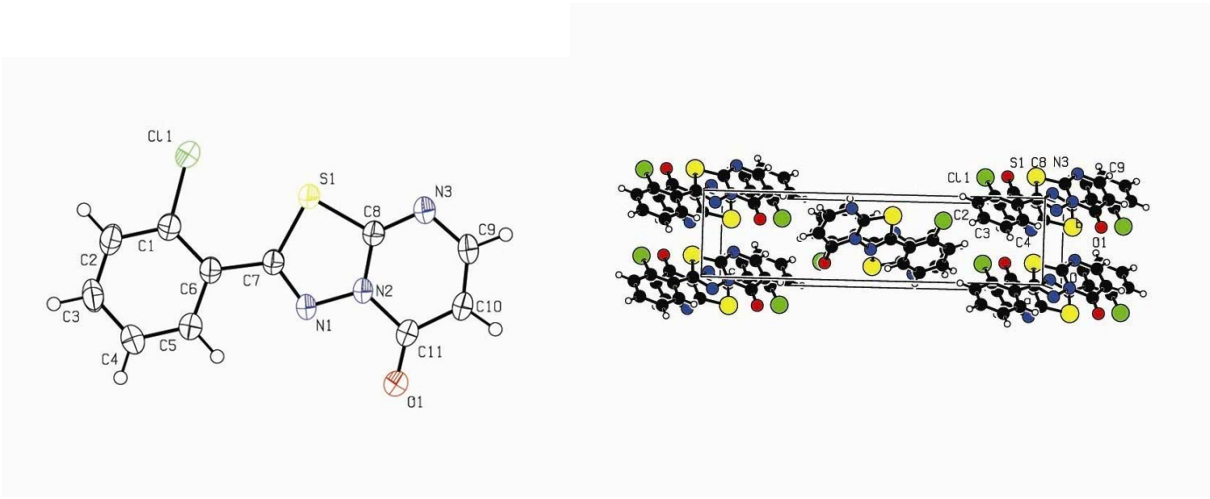
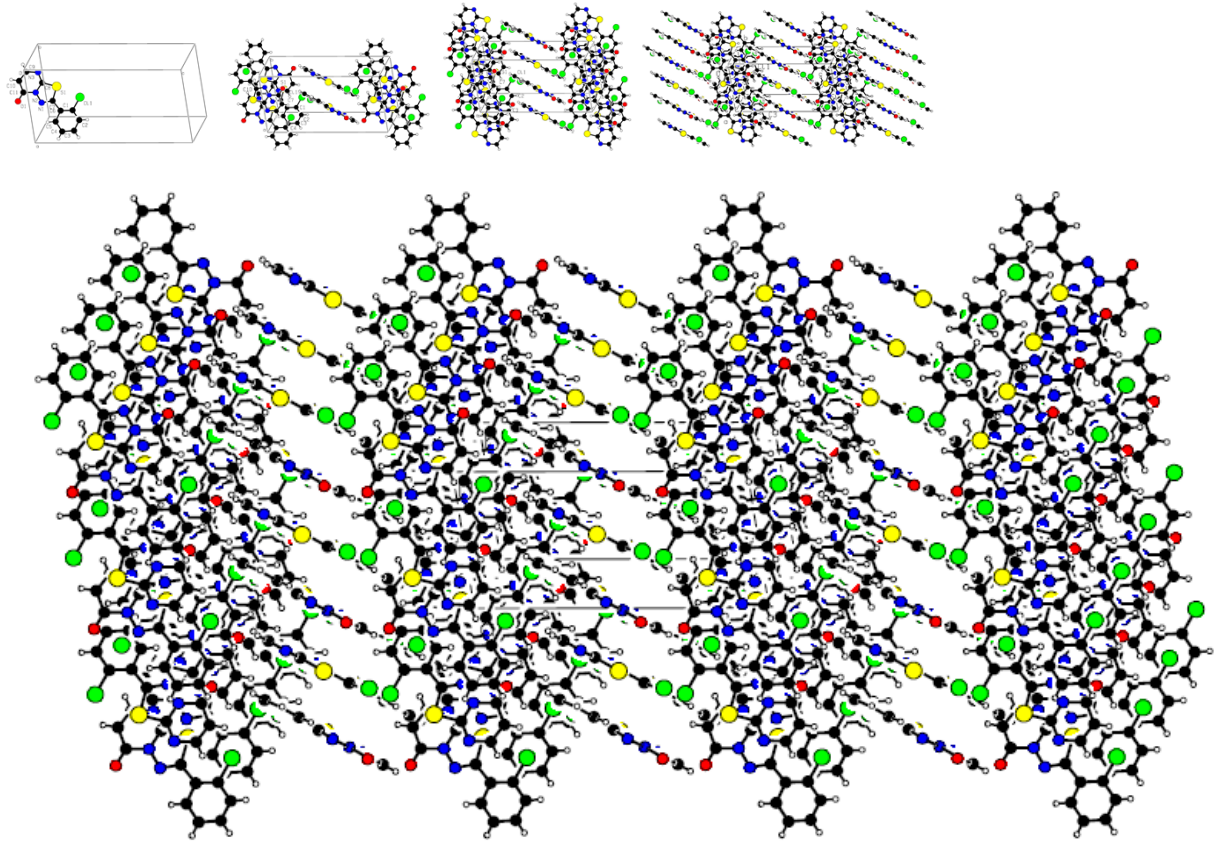


Figure 3 A Mercury (1.4, CCDC, 2005) view of the molecular structure of **3i**

X-ray structure determination of **3i**. Colorless Block, $C_{11}H_6ClN_3OS$, *Mr*=263.70, Monoclinic, space group *P*2(1)/*n*, *a*=10.838 (4), *b*=4.9244 (19), *c*=20.011 (7) Å, α=90.00, β=98.505(6), γ=90.00°, *V*= 1056.3(7) Å^3, *Z*=4, D_x=1.658 Mg m^{-3}, F_{000}=536, μ=0.54 mm^{-1}. Intensity data were collected using a Siemens SMART diffractometer at 296(2) K, graphite monochromator MoKa radiation (λ=0.71073 Å), using the *φ*-*ω* scan technique to a maximun 2.1-26.0°. A total of 5348 reflections were collected with 2061 unique ones(*R* = 0.0330), of which 1745 reflections with $I > 2\sigma(I)$. The final int *R* and *wR* values were 0.0237 and 0.0902, *s*=1.027, $(\Delta/\sigma)_{max}$ = 0.000. The maximum peak and minimum peak in the final difference map is 0.22 and -0.29 e Å^{-3}.



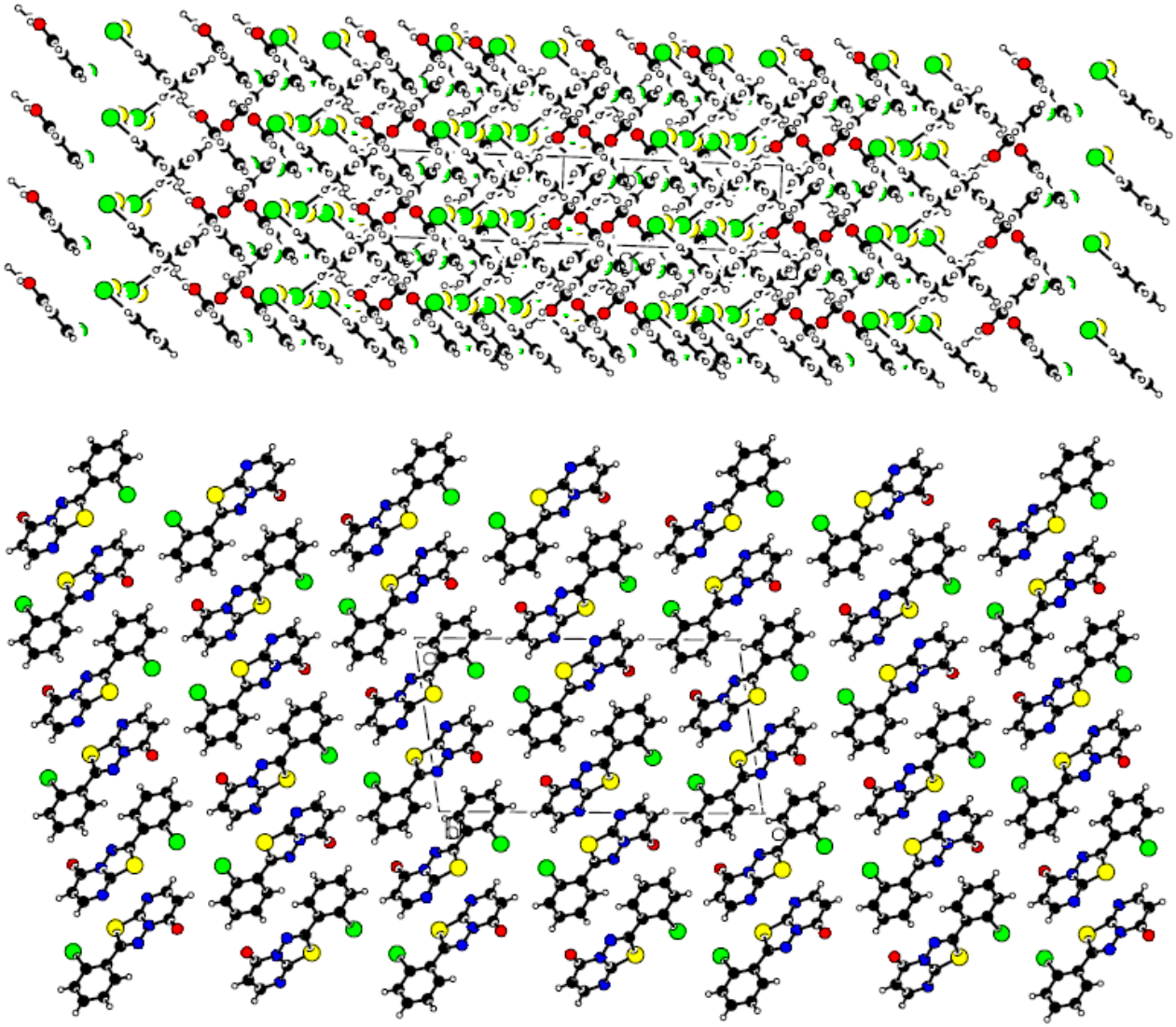
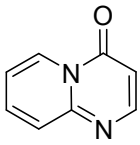


Figure 4. The π-π accumulation structure of **3i** supramolecular self-assembly.

Typical synthesis procedure of substituted-4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives (4a-c)

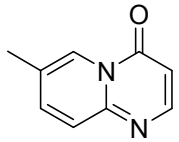
A mixture of (un)substituted-2-aminopyridine (1.0 mmol) with ethyl cyanoacetate (1.0 mL), phosphorus pentoxide (20 mmol) and formic acid (10.0 mL) was heated at 100-105° C for 12 h. The cooled reaction mixture was treated with ice-water and neutralized with 10% potassium hydroxide. Then the mixture liquid was extracted with $CHCl_3$ (3×15mL), dried with Na_2SO_4 and the residue was purified by silica gel chromatography using $CHCl_3$-ethyl acetate (4/1, v/v) to afford **4a-c**.

4*H*-Pyrido[1,2-*a*]pyrimidin-4-one (4a)



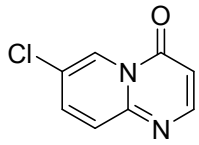
Yield(20%), white needle solid, m.p.: 127-128 °C (Lit. 127 °C [1]); ^{1}H NMR ($CDCl_3$): δ 9.10-9.09 (d, 1H, *J* = 7.2 Hz), 8.31-8.30 (d, 1H, *J* = 6.4 Hz), 7.79-7.75 (m, 1H), 7.69-7.67 (d, 1H, *J* = 8.0 Hz), 7.21-7.17 (m, 1H), 6.47-6.46 (d, 1H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$): δ 158.0, 154.9, 152.0, 136.3, 127.5, 126.7, 115.8, 105.0.

7-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (4b)



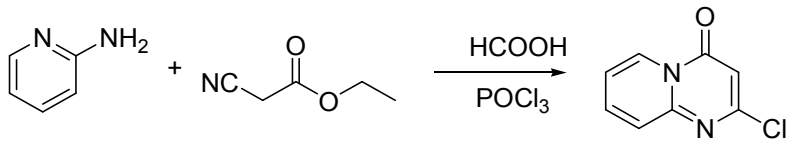
Yield(37.5%), white needle solid, m.p.: 97-98 °C (Lit. 98-99 °C); ^{1}H NMR ($CDCl_3$): δ 8.90 (s, 1H), 8.28-8.27 (d, 1H, *J* = 6.4 Hz), 7.62 (s, 2H), 6.44-6.43 (d, 1H, *J* = 6.4 Hz), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 157.9, 154.5, 150.9, 139.3, 126.1, 125.0, 109.4, 104.6, 18.5.

7-Chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (4c)[4]



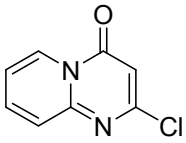
Yield(33%), white needle solid, m.p.: 121-122 °C; ^{1}H NMR ($CDCl_3$): δ 9.11 (d, 1H, *J* = 6.0 Hz), 8.31-8.30 (d, 1H, *J* = 6.0 Hz), 7.71-7.68 (m, 1H), 7.65-7.61 (m, 1H), 6.50-6.49 (d, 1H, *J* = 6.0 Hz); ^{13}C NMR ($CDCl_3$): ^{13}C NMR (CD_3OD): δ 157.0, 154.8, 150.4, 137.6, 127.8, 125.4, 124.5, 105.6.

Synthesis procedure of 2-chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one



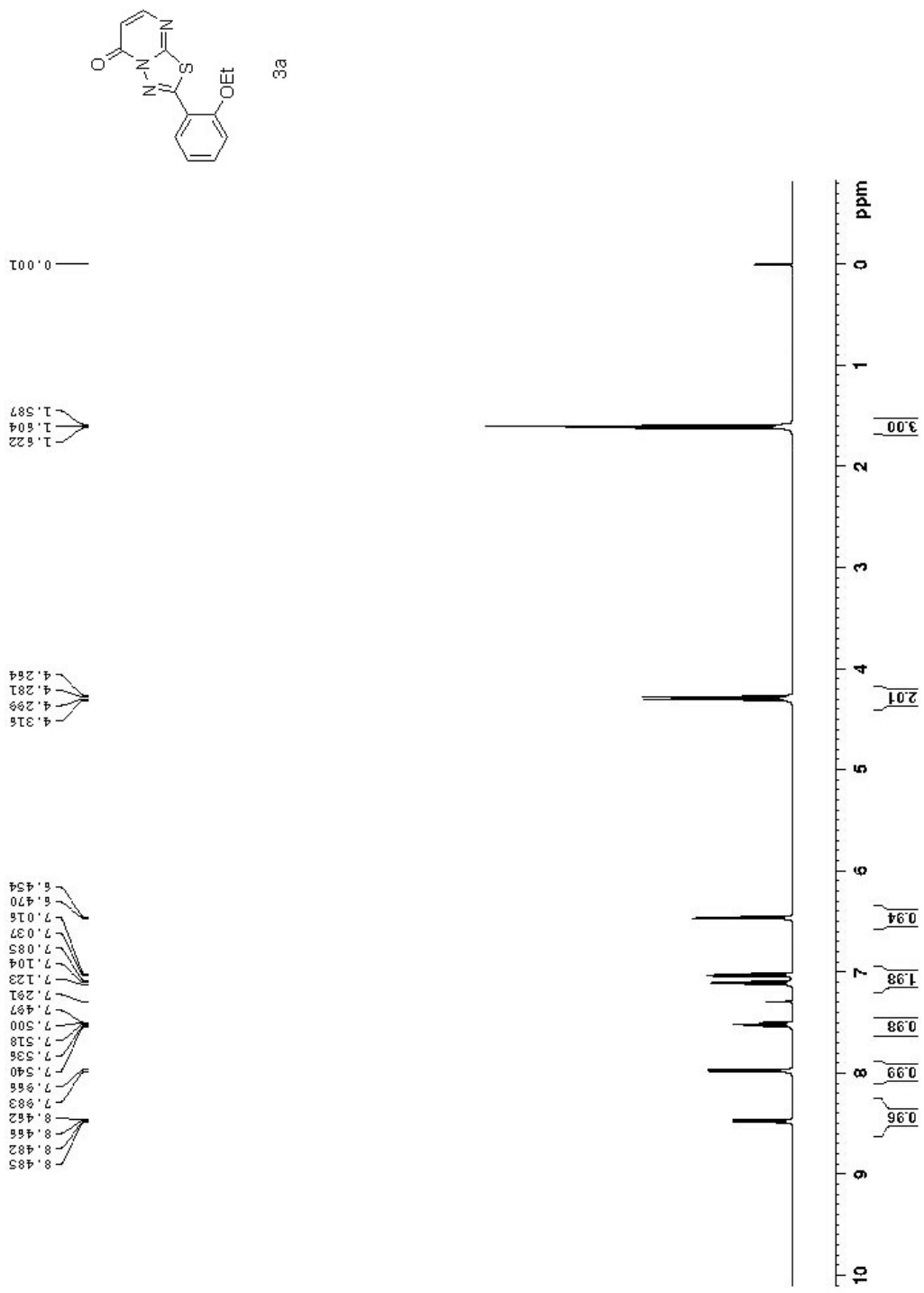
A mixture of 2-aminopyridine (1.0 mmol) with ethyl cyanoacetate (1.0 mL), phosphorus oxychloride (20 mmol) and formic acid (10.0 mL) was heated at 100-105° C for 12 h. The cooled reaction mixture was treated with ice-water and neutralized with 10% potassium hydroxide. Then the mixture liquid was extracted with $CHCl_3$ (3×15mL), dried with Na_2SO_4 and the residue was purified by silica gel chromatography using $CHCl_3$-ethyl acetate (4/1, v/v) to afford **4d**.

2-Chloro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4d**)



Yield(42.5%), white needle solid, m.p.: 157-158 °C (Lit. 159 °C) [5]; ^{1}H NMR ($CDCl_3$): δ 9.08-9.06 (d, 1H, *J* = 6.8 Hz), 7.92-7.87 (m, 1H), 7.70-7.87 (d, 1H, *J* = 6.8 Hz), 7.28-7.26 (d, 1H, *J* = 6.8 Hz), 6.50 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 158.7, 157.3, 150.6, 138.4, 127.9, 126.0, 116.6, 102.7.

1. R. Adams, I. J. Pachter, *J. Am. Chem. Soc.*, **1952**, *74 (21)*, 5491–5497.
2. N. Katagiri, R. Niwa, T. Kato, *Heterocycles,* **1983**, *20(4)*, 597-600.
3. K. A. Suri, O. P. Suri, M. Amina, B. P. Wakhloo, N. K. Satti, *Mag. Res. Chem*., **2003**, *41* (9), 747-749.
4. A. Molnar, F. Faigl, B. Podanyi, Z. Finta, L. Balazs, I. Hermecz, *Heterocycles*, **2009**, *78*(10), 2477-2488.
5. V. Oakes, H. N. Rydon, *J. Chem. Soc.*, **1958**, 209-11.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7.037
7.085
7.104
7.123
7.291
7.497
7.500
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7.536
7.540
7.966
7.983
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8.485
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0
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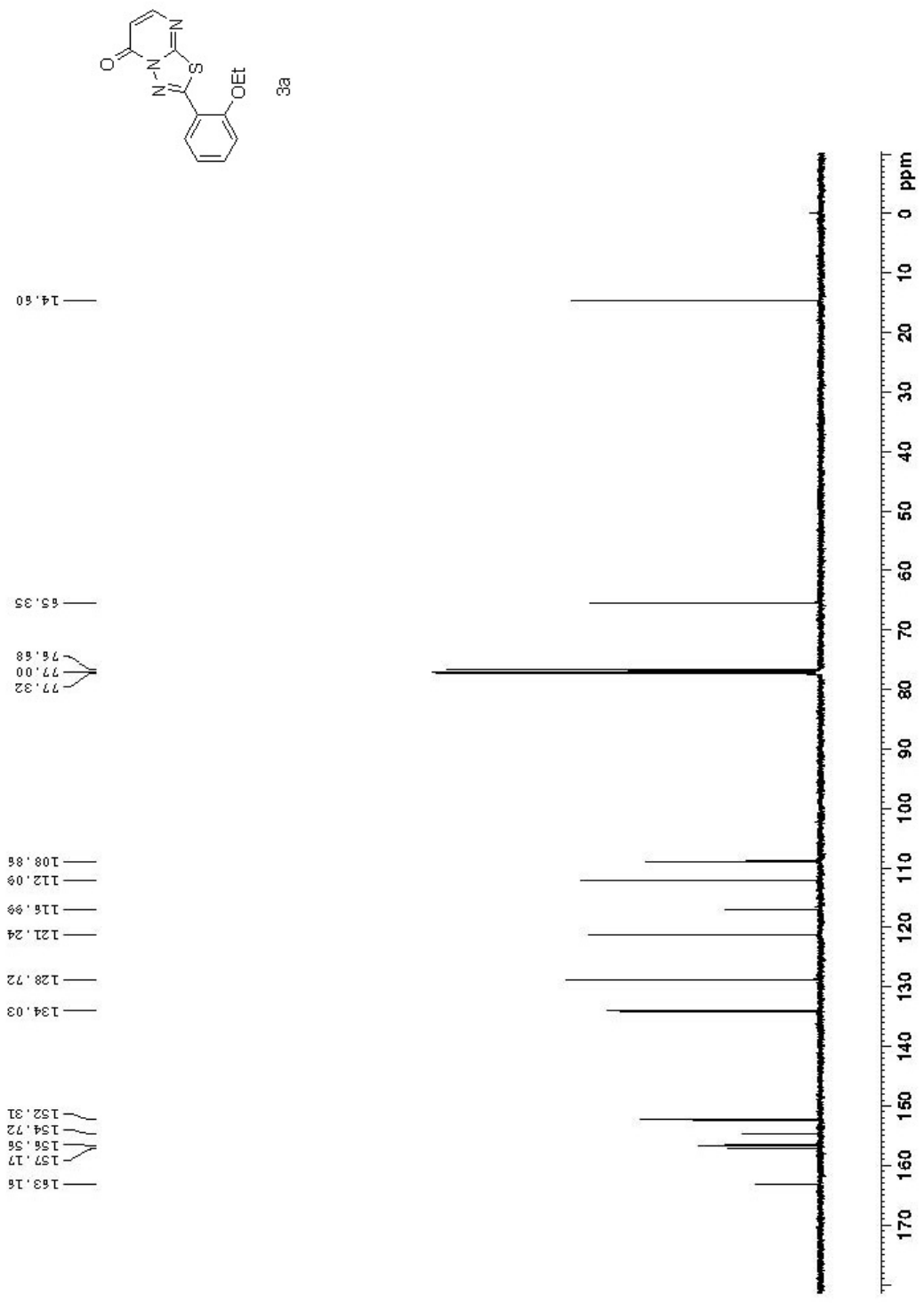
0.96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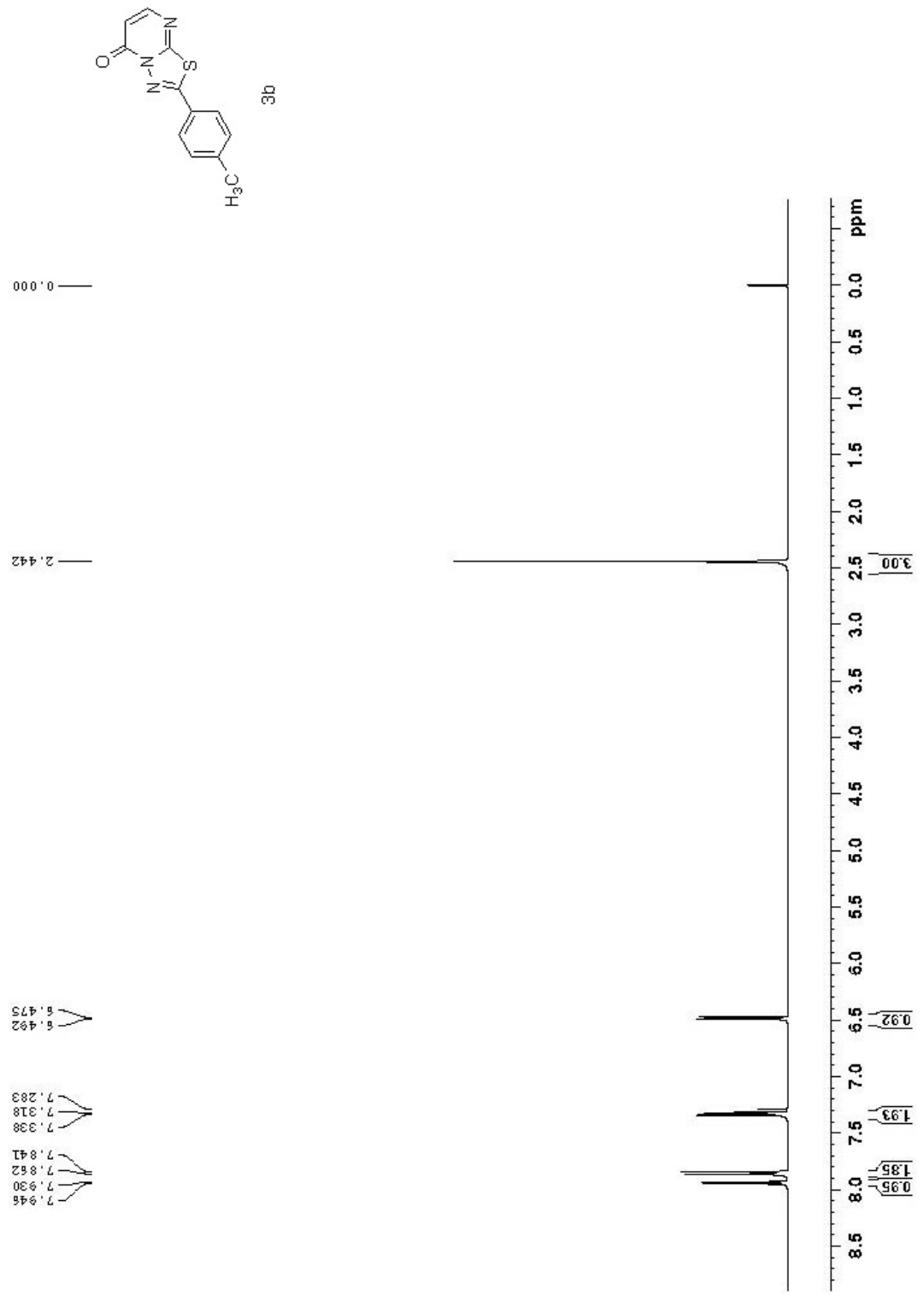
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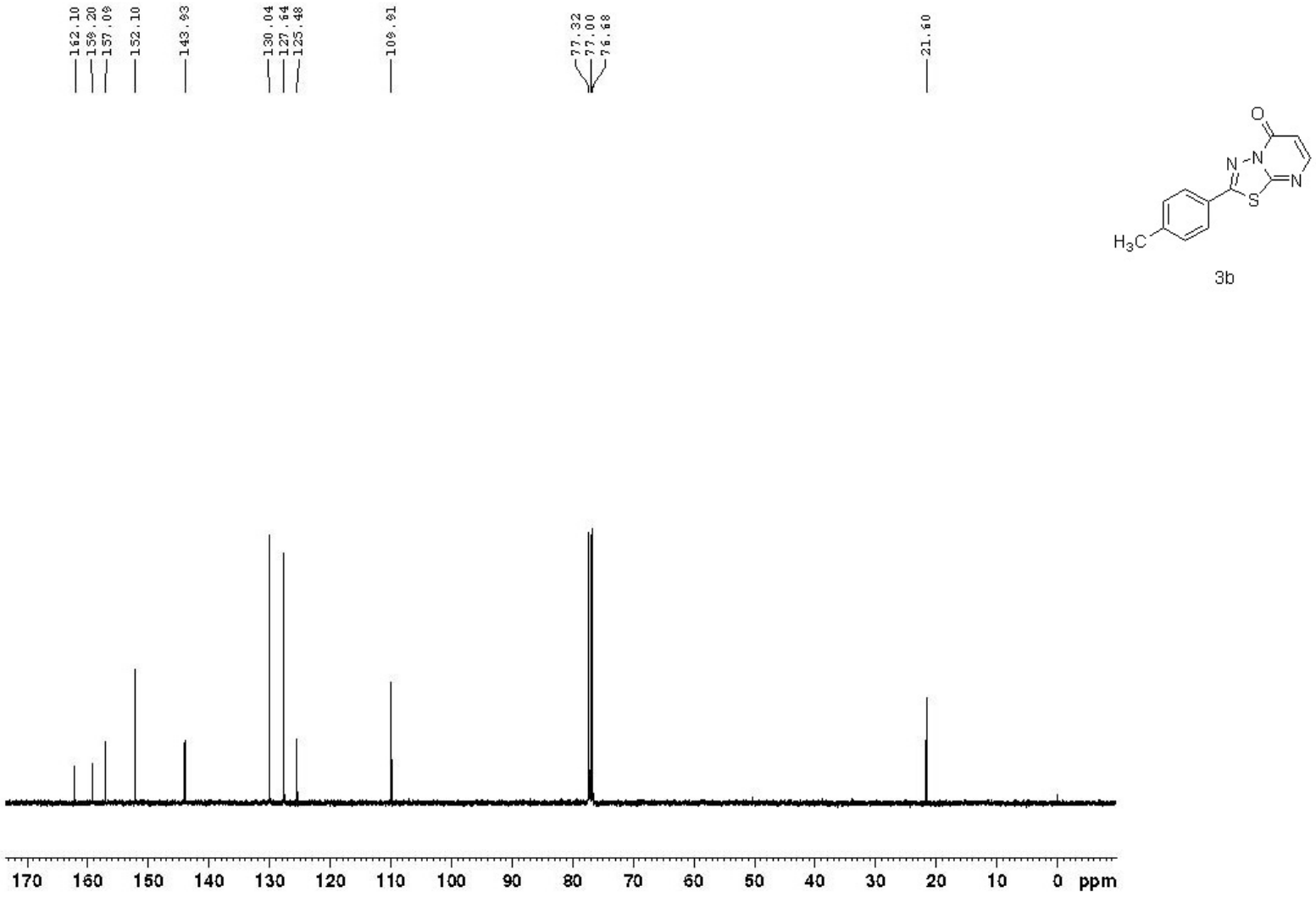
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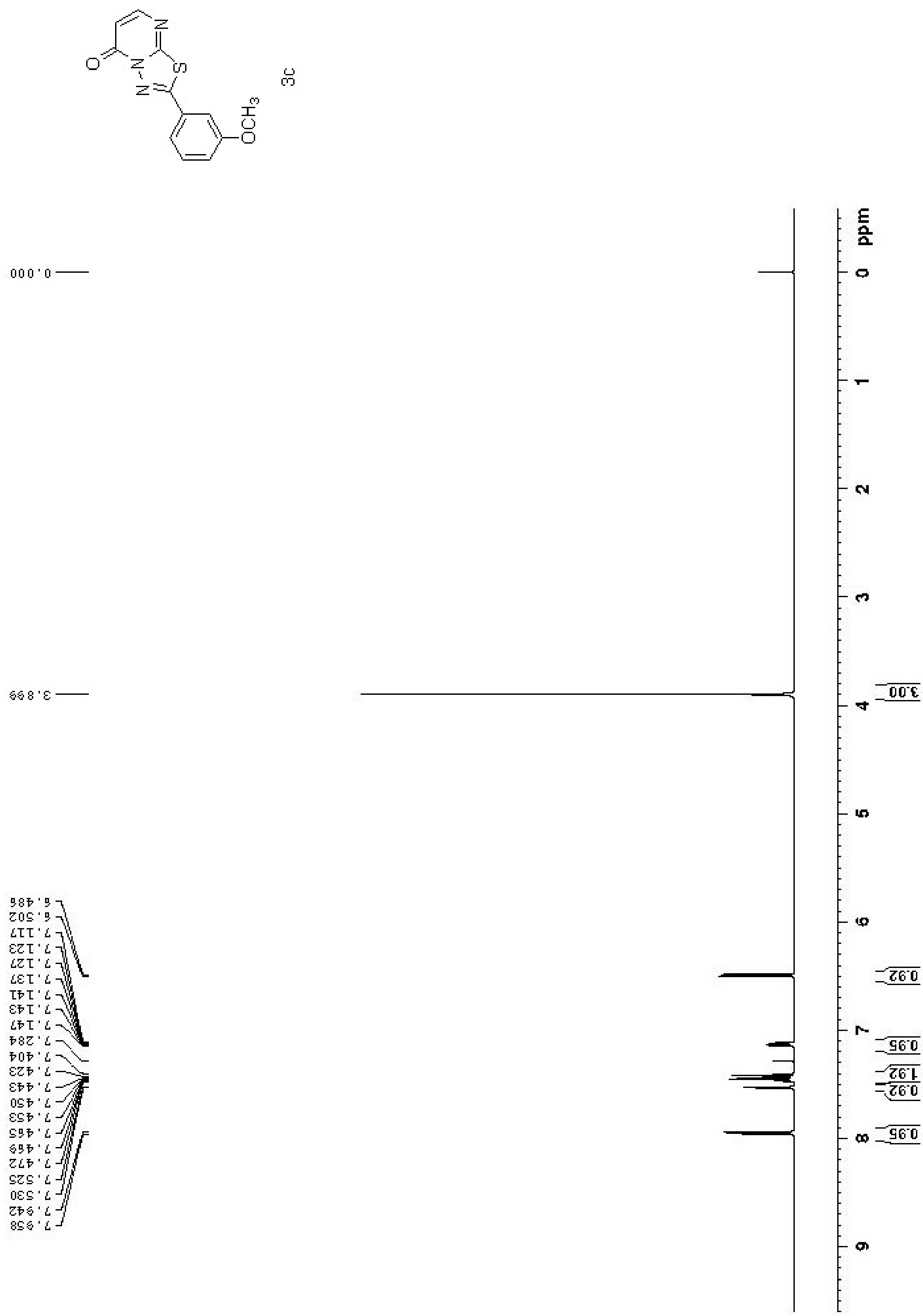

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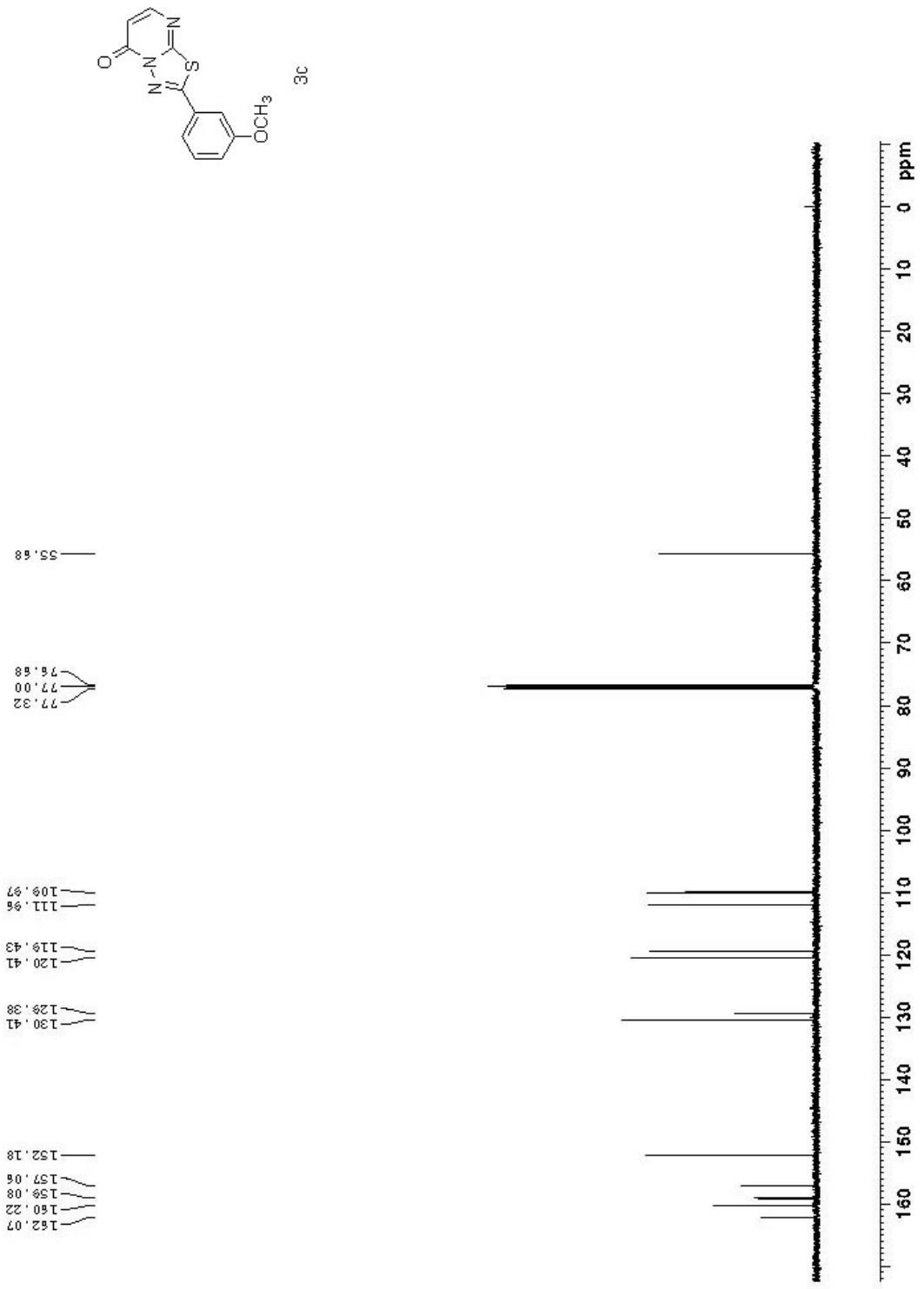
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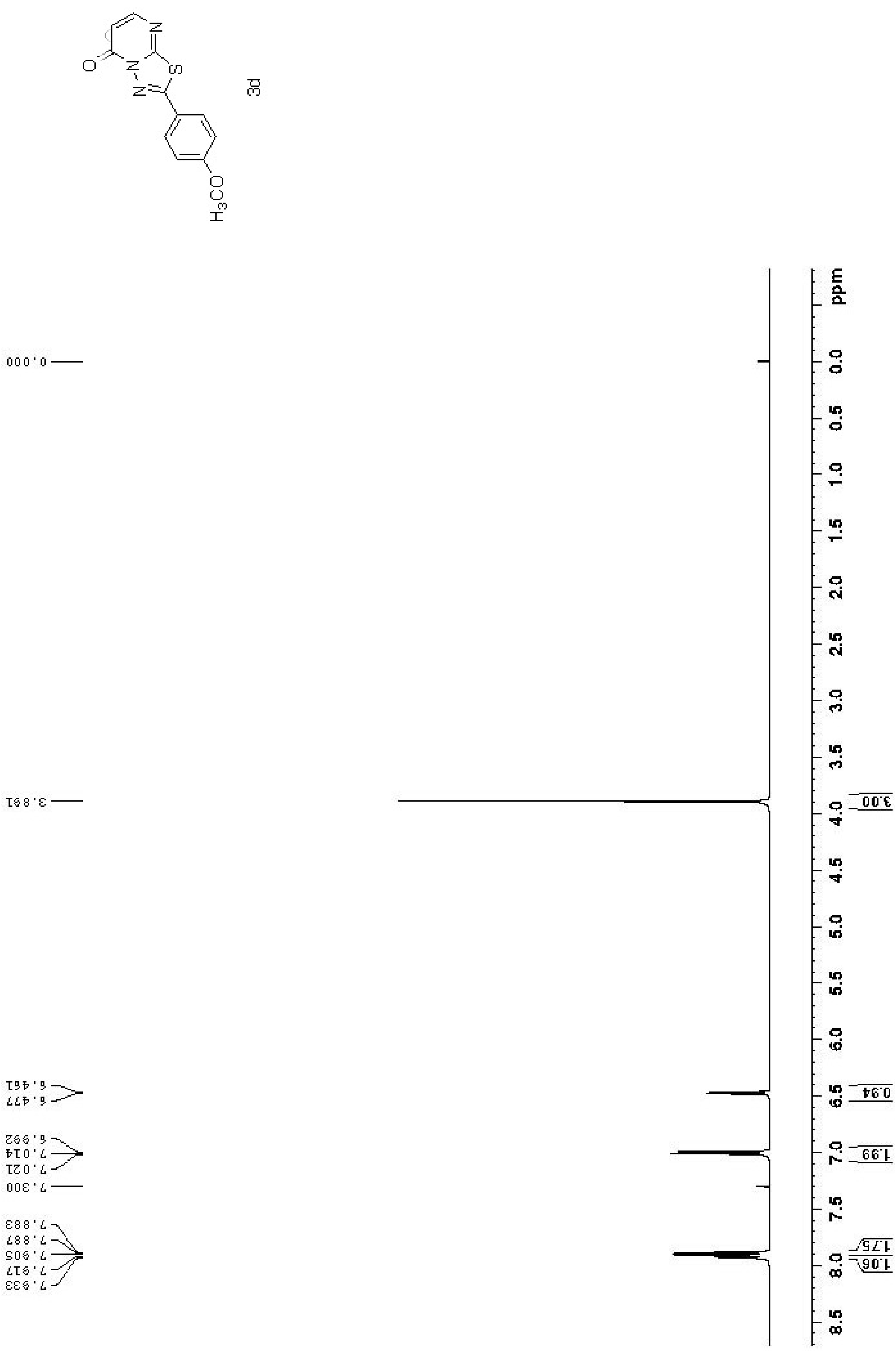
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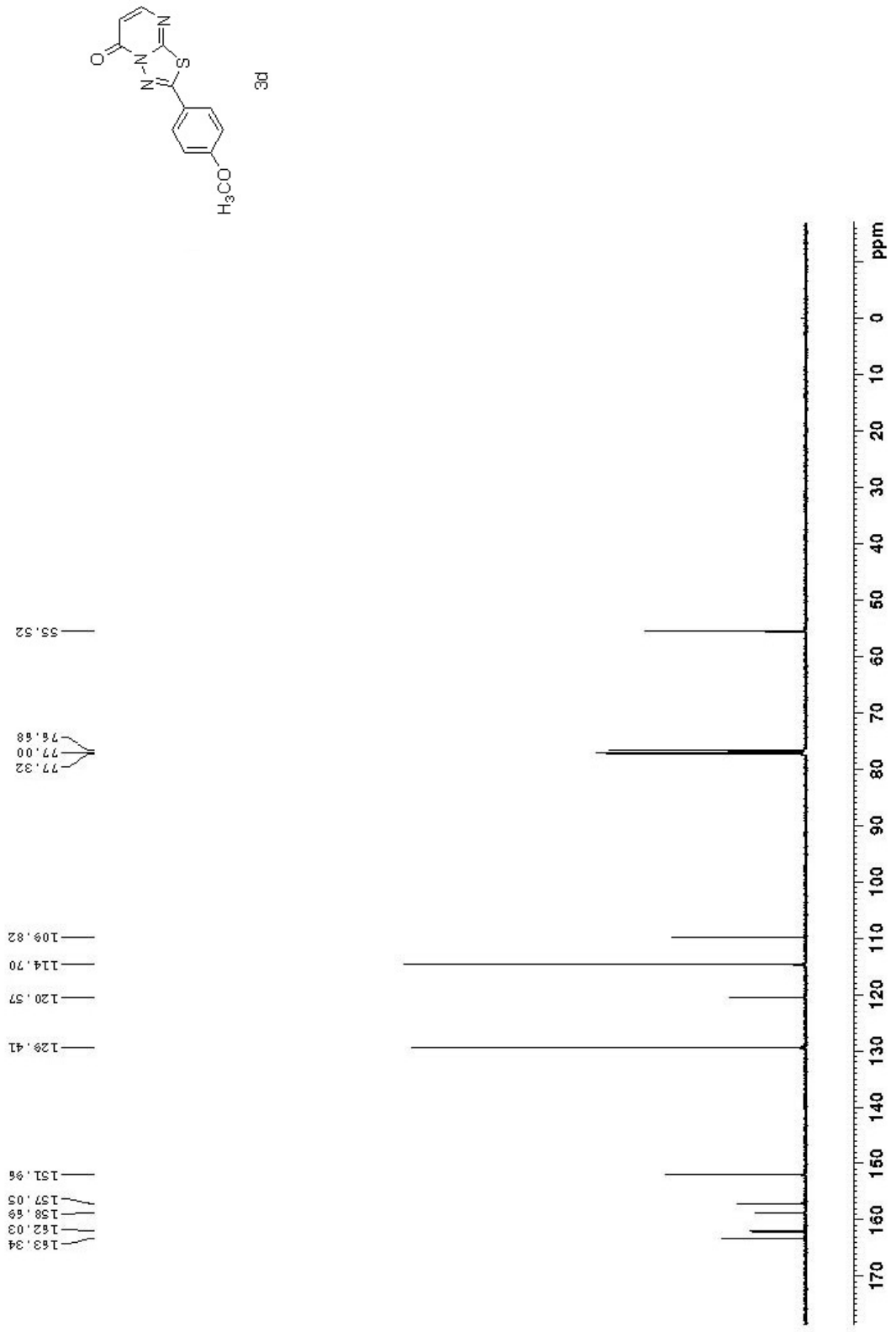
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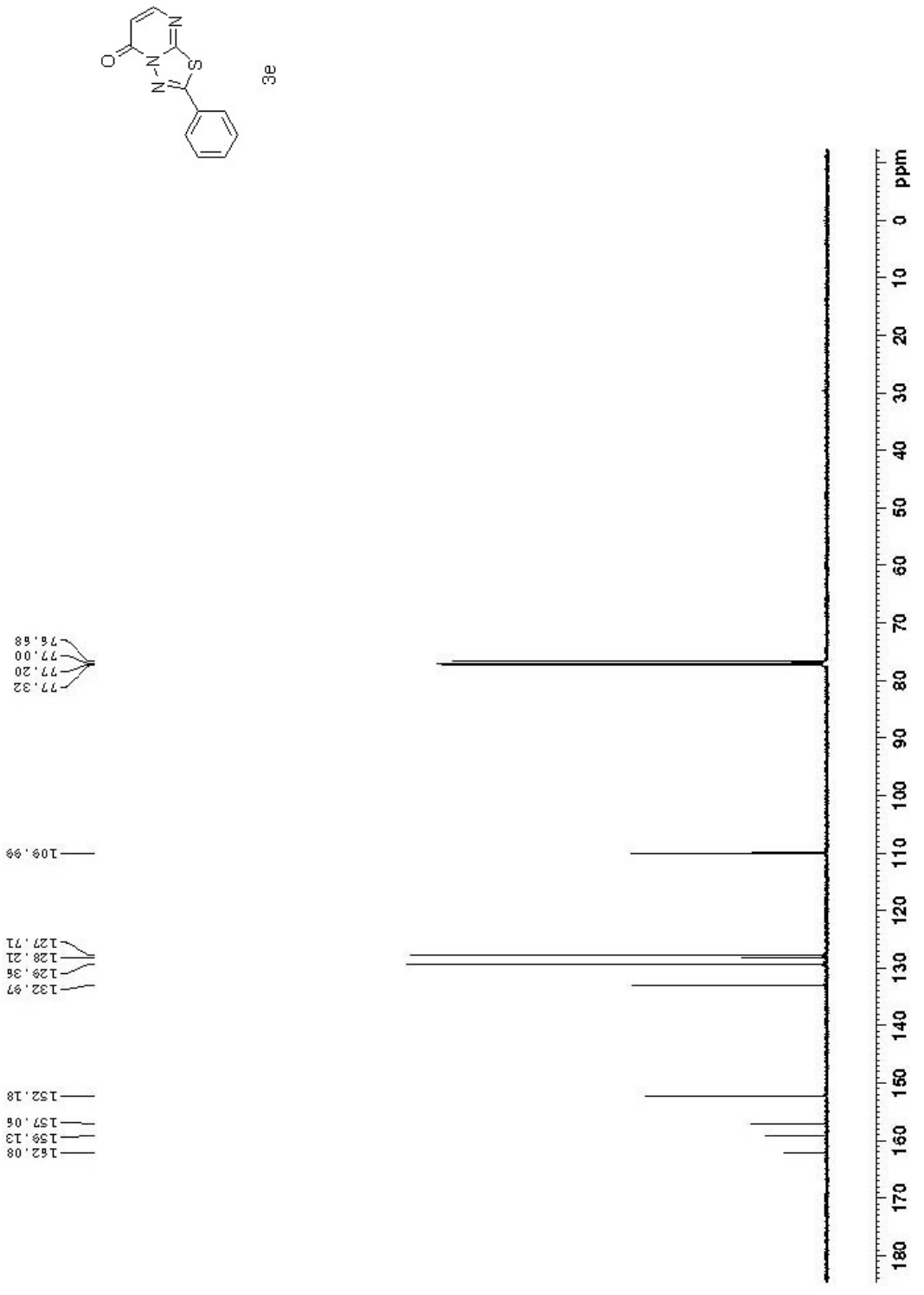
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ppm

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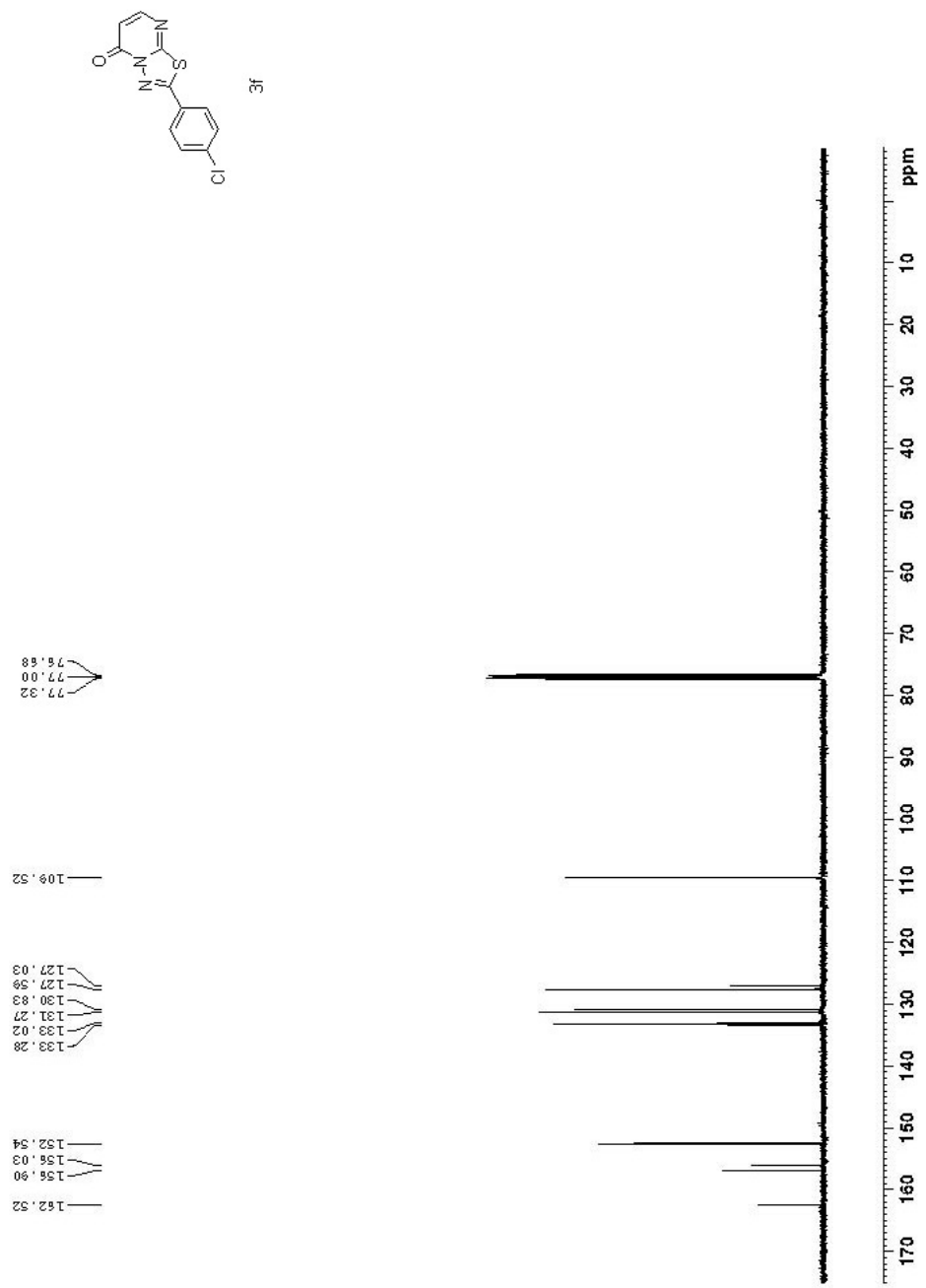
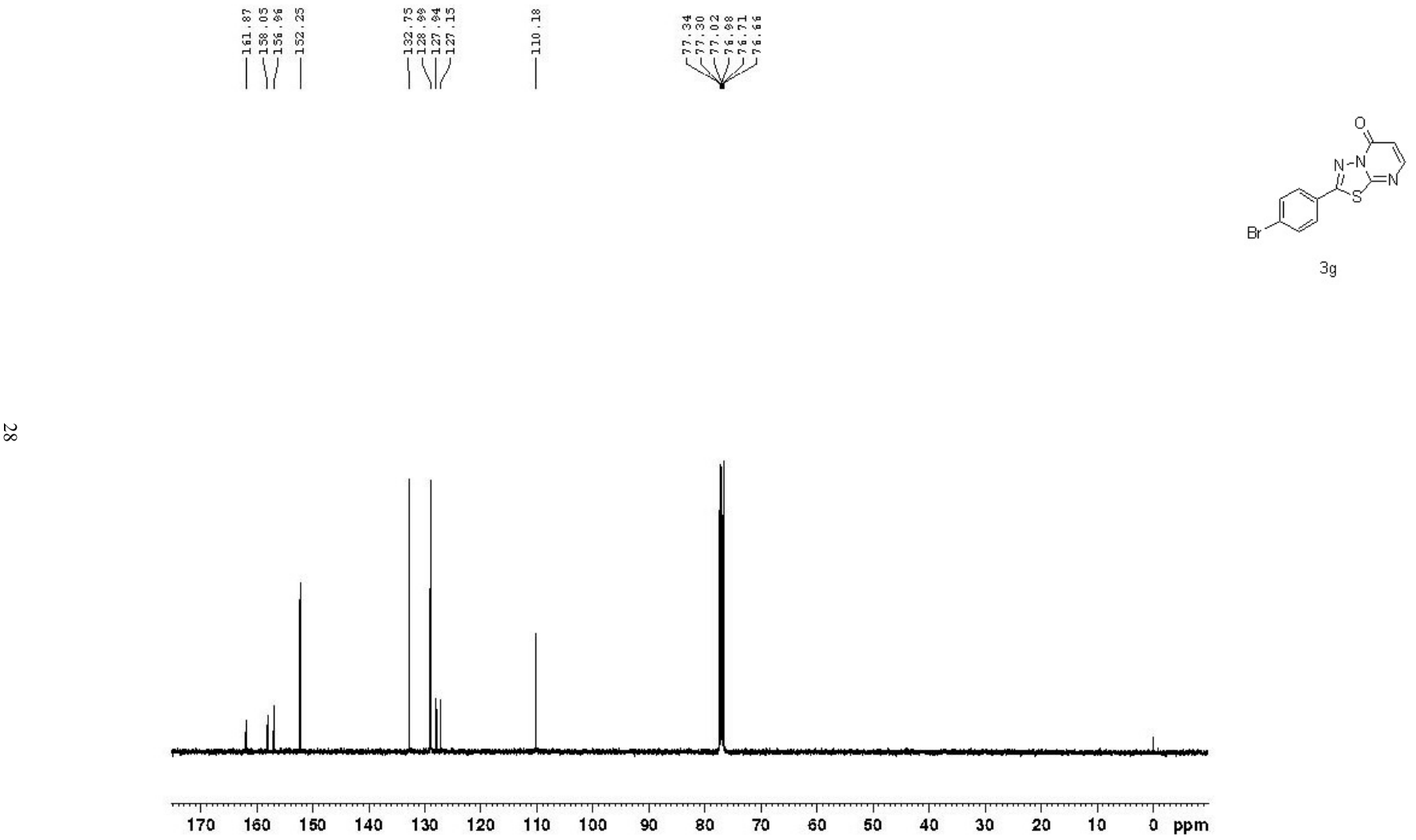
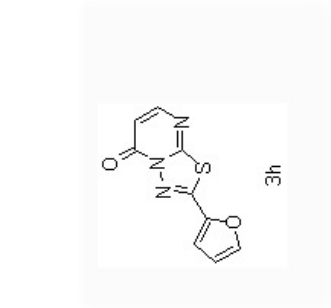
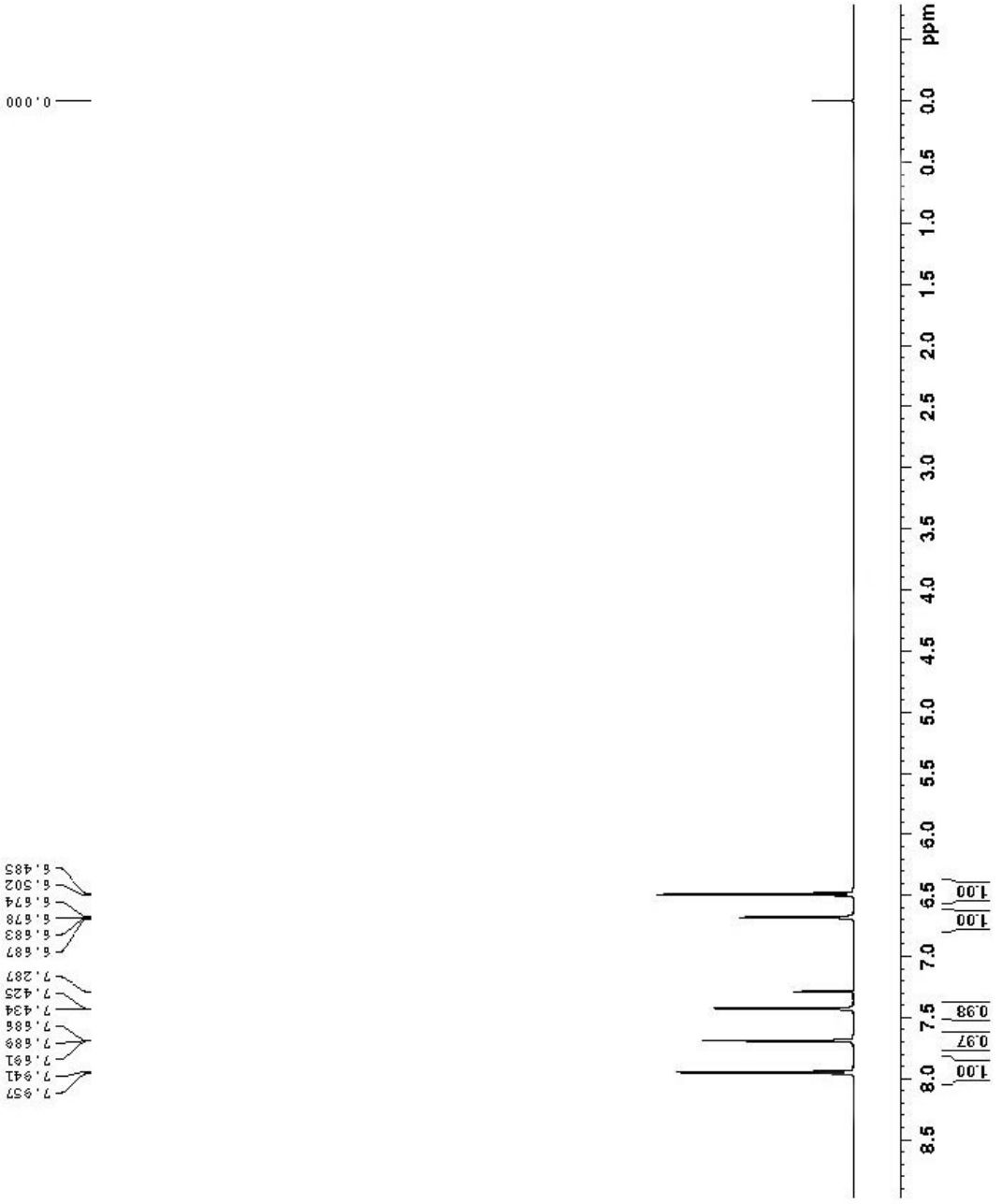
7.554
7.551
7.538
7.534
7.518
7.514
7.482
7.476
7.462
7.457
7.446
7.441
7.293
6.509
6.492
1.00
1.01
3.06
0.99
ppm

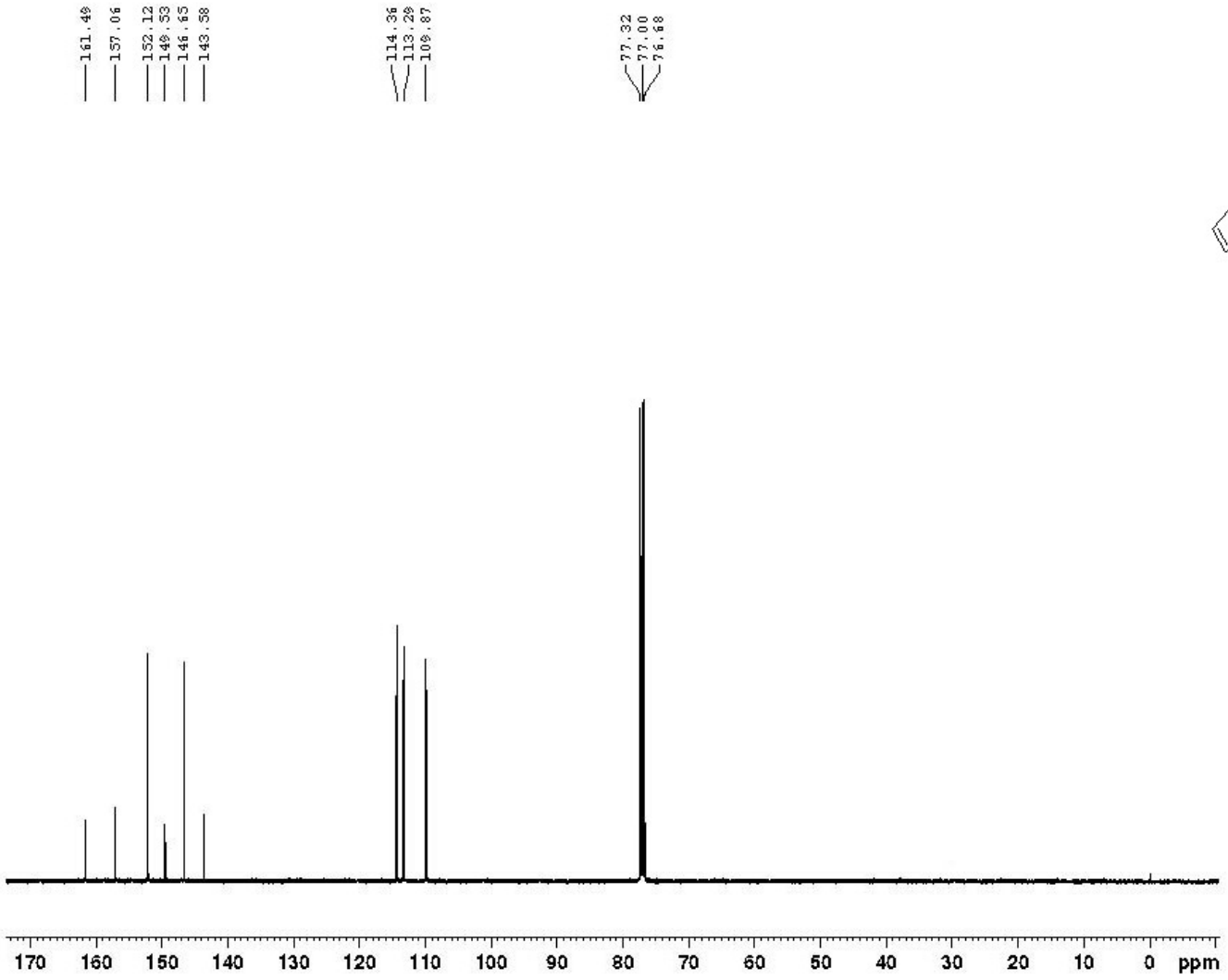

3f
Cl
O
N
S
77.32
77.00
76.68
109.52
127.03
127.59
130.83
131.27
133.02
133.28
152.54
156.03
156.90
162.52
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

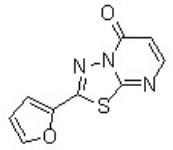
3g
Br
O
N
S
N
N
0.008
-0.002
-0.008
7.971
7.952
7.943
7.935
7.860
7.840
7.829
7.823
7.819
7.705
7.685
7.674
7.658
7.564
7.275
6.522
6.506
6.498
6.492
6.482
1.00
2.11
2.06
1.04
ppm
9
8
7
6
5
4
3
2
1
0


161.87
158.05
156.96
152.25
132.75
128.99
127.94
127.15
110.18
77.34
77.30
77.02
76.98
76.71
76.66
O
N
N
S
N
Br
3g
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


3h


0.000
7.957
7.941
7.691
7.689
7.686
7.434
7.425
7.287
6.887
6.883
6.878
6.874
6.502
6.485
1.00
1.00
0.98
0.97
1.00
ppm
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5


161.49
157.06
152.12
149.53
146.65
143.58
114.36
113.29
109.87
77.32
77.00
76.68
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



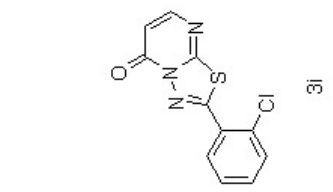
3h

3i

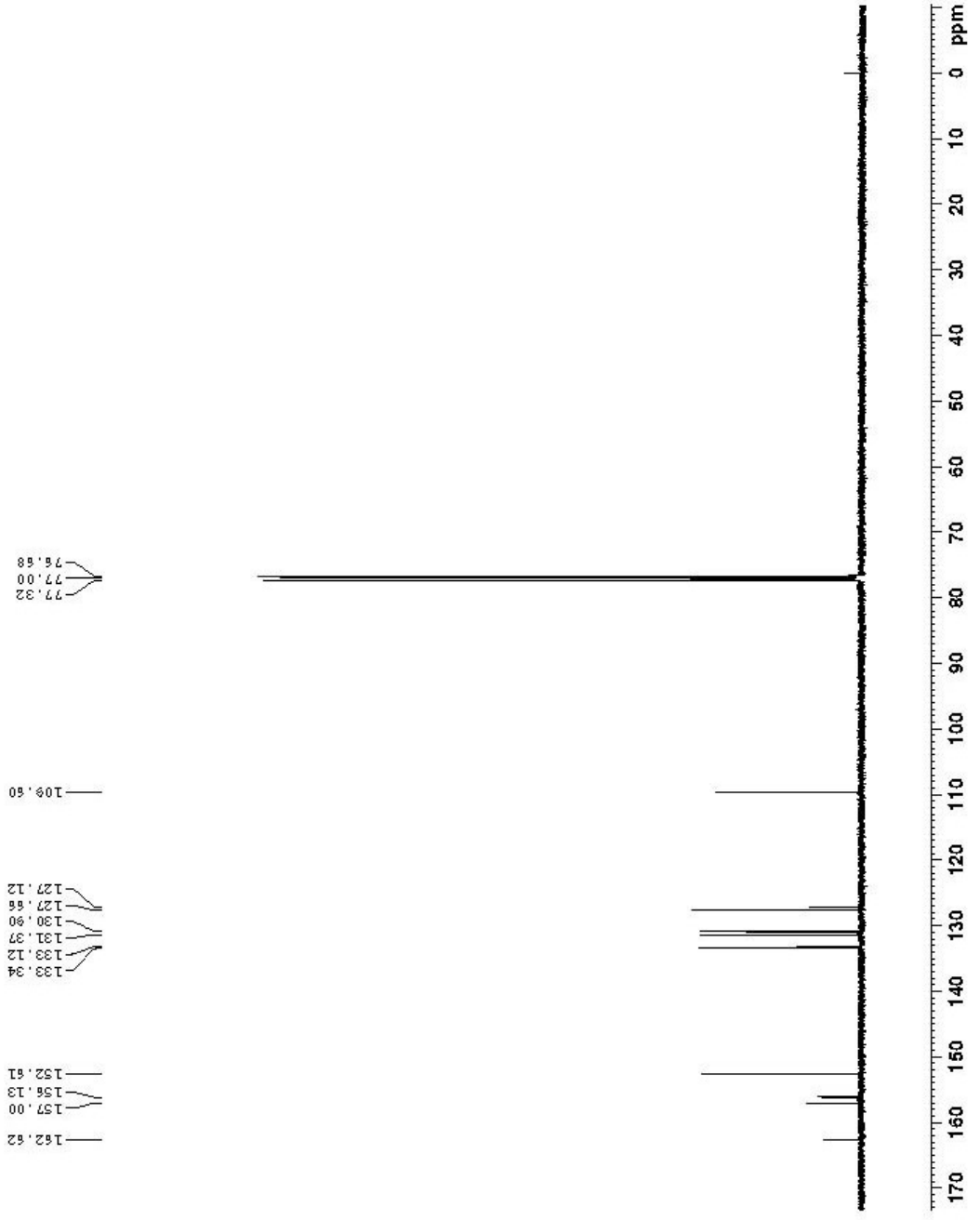
0.001
0.000

8.316
8.314
8.312
8.296
8.293
8.006
7.999
7.989
7.580
7.573
7.560
7.555
7.539
7.537
7.536
7.519
7.516
7.516
7.486
7.485
7.481
7.479
7.465
7.462
7.449
7.448
7.444
7.443
7.270
6.516
6.514
6.507
6.499
6.498
6.490

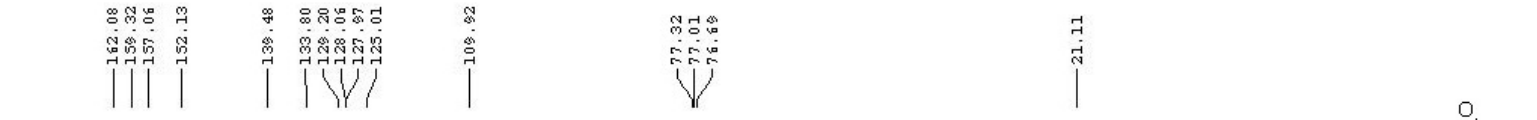
ppm
0
1
2
3
4
5
6
7
8
9
10
1.00
1.01
3.11
1.00

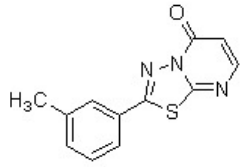

O
N
N
S
Cl

3i

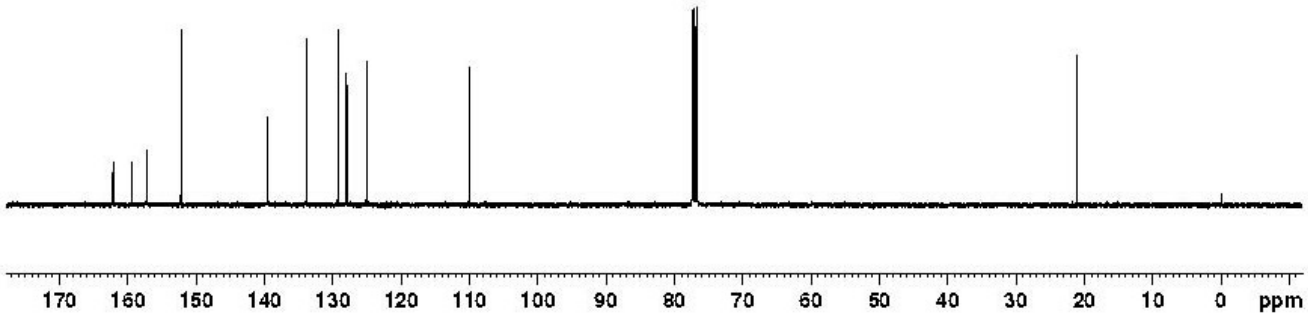

77.32
77.00
76.68
109.60
127.12
127.66
130.90
131.37
133.12
133.34
152.61
156.13
157.00
162.62
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
ppm

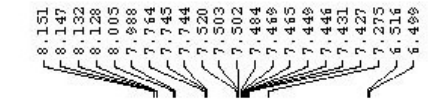
3j
7.930
7.923
7.915
7.907
7.806
7.682
7.674
7.378
7.367
7.260
6.476
6.468
6.464
6.452
2.418
2.411
0.030
1.00
0.96
0.98
2.01
0.96
3.08
ppm


162.08
159.32
157.06
152.13
139.48
133.80
129.20
128.06
127.97
125.01
109.92
77.32
77.01
76.69
21.11

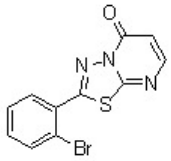

O
N
N
S
N
H3C

3j

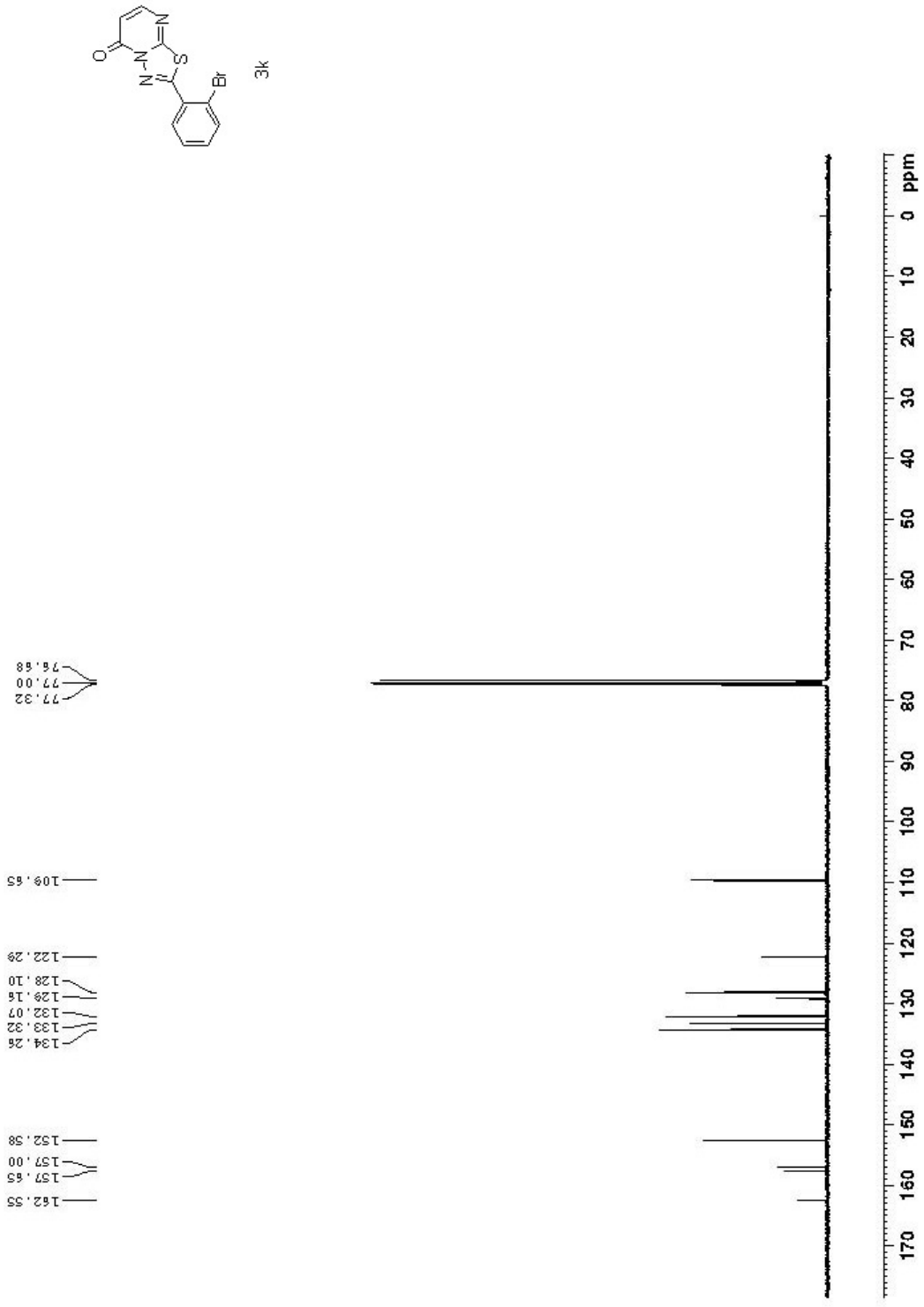

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


8.151
8.147
8.132
8.128
8.005
7.988
7.764
7.745
7.744
7.520
7.503
7.502
7.484
7.469
7.465
7.449
7.446
7.431
7.427
7.275
6.516
6.499

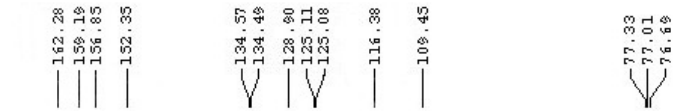

0.000
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.02
0.98
2.07
1.00

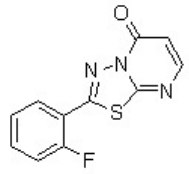

O
N
N
S
N
Br

3k

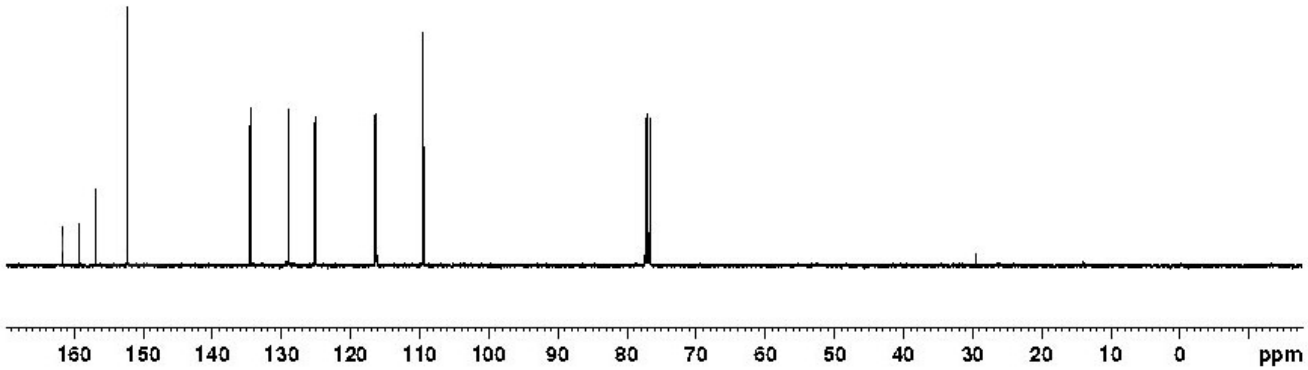

3k
Br
O
N
S
162.55
157.65
157.00
152.58
134.26
133.32
132.07
129.16
128.10
122.29
109.65
77.32
77.00
76.68
ppm

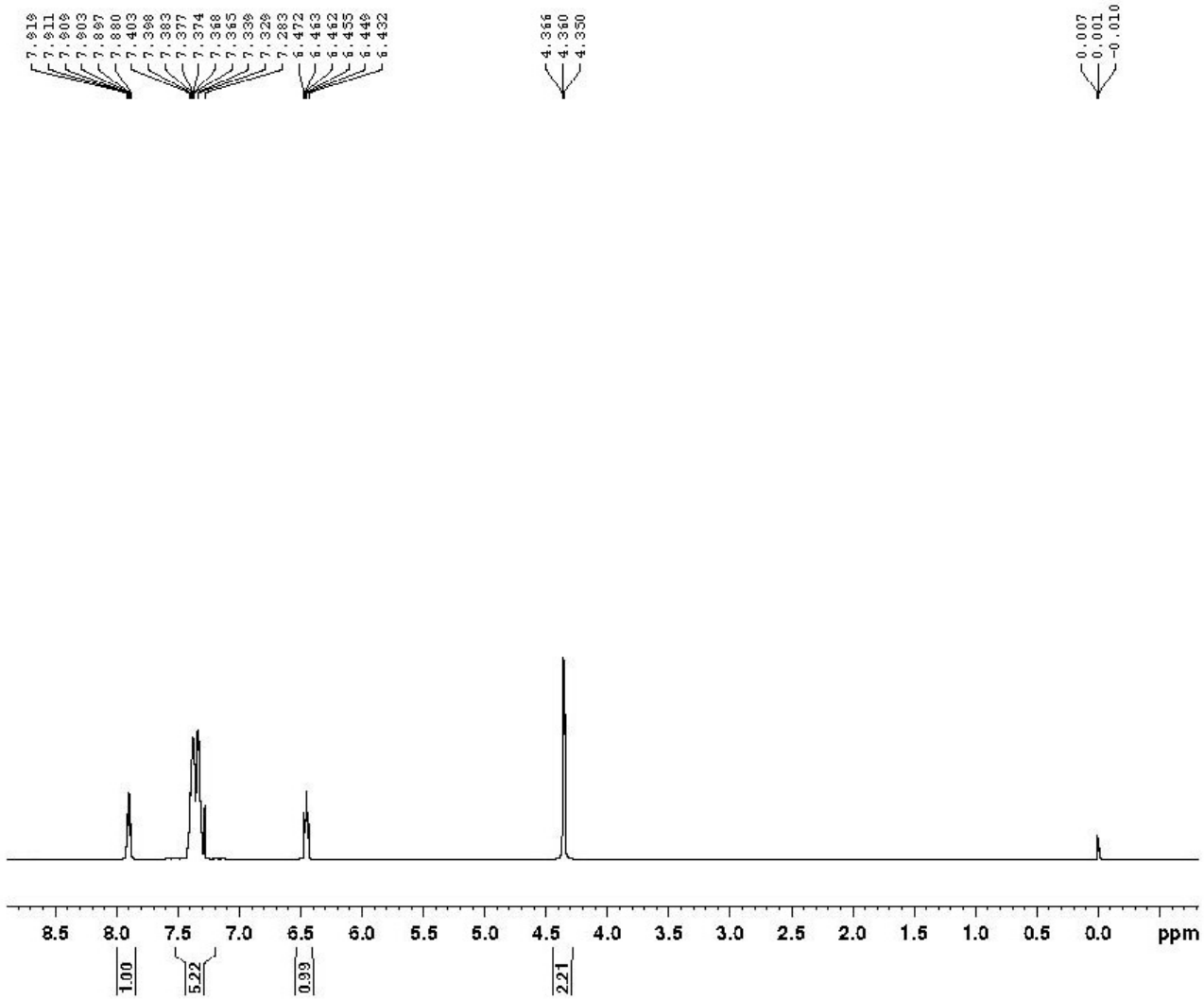
3l
-0.000
8.412
8.407
8.393
8.389
8.374
8.369
7.993
7.977
7.642
7.637
7.628
7.623
7.620
7.619
7.616
7.609
7.607
7.605
7.603
7.598
7.589
7.584
7.378
7.375
7.358
7.339
7.337
7.328
7.305
7.284
7.277
7.267
7.256
6.501
6.485
1.00
2.16
1.02
1.02
1.00
ppm

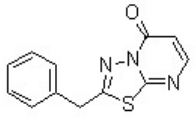

162.28
159.19
156.85
152.35
134.57
134.49
128.90
125.11
125.08
116.38
109.45
77.33
77.01
76.68


O
N
N
N
S
F

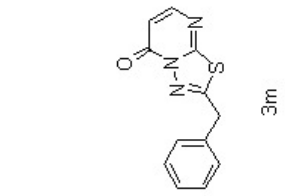
3l

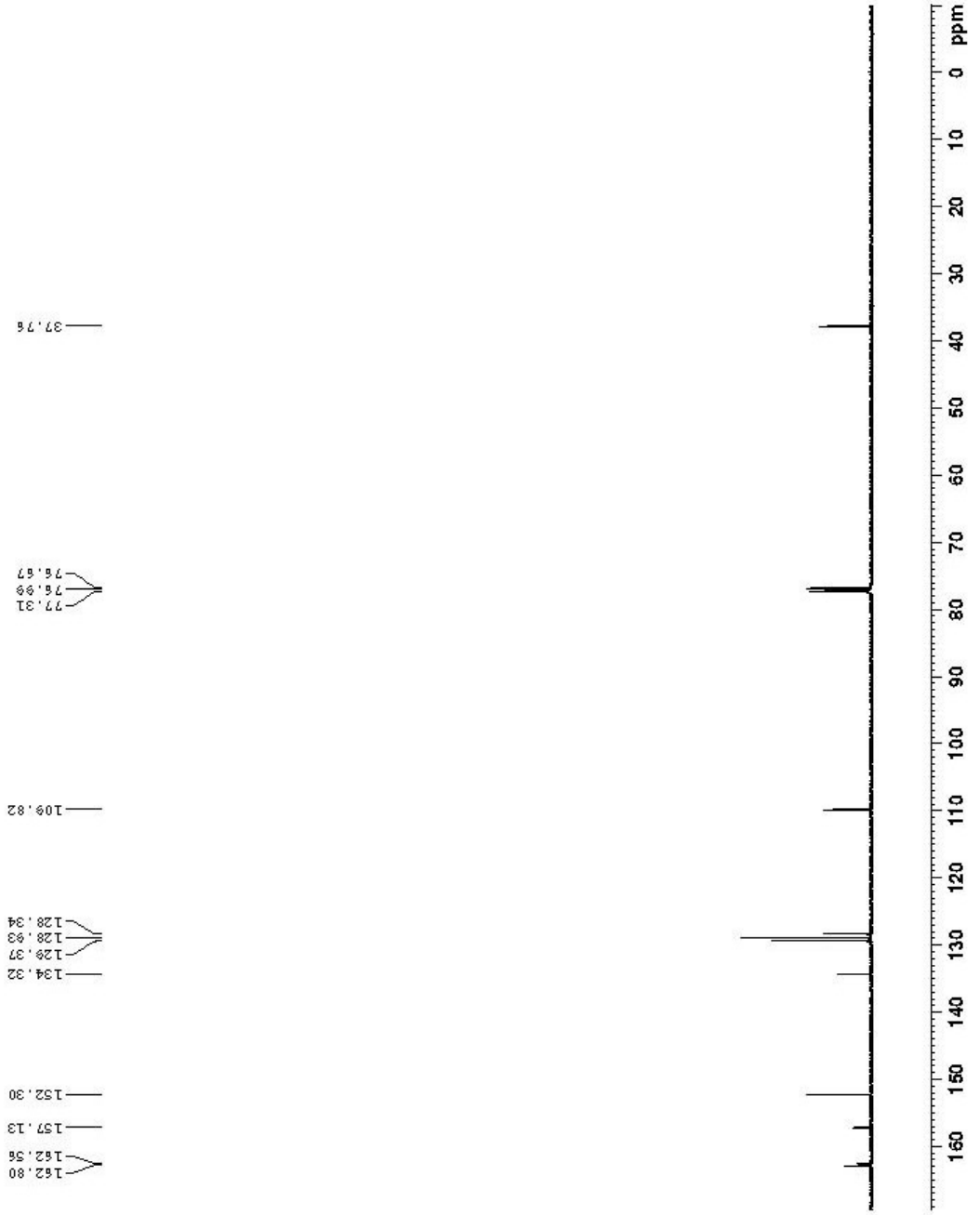

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

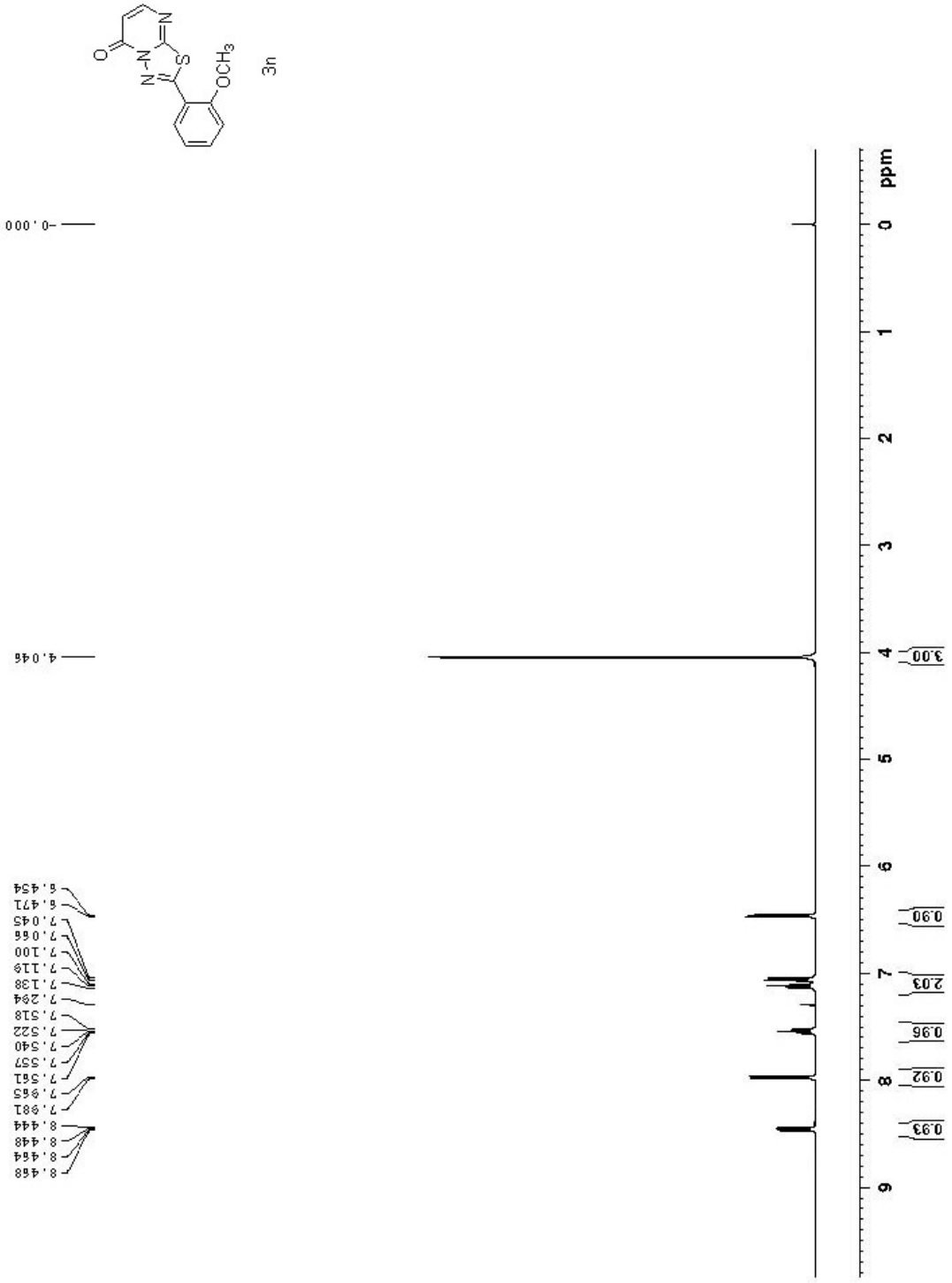

7.919
7.911
7.909
7.903
7.897
7.880
7.403
7.398
7.383
7.377
7.374
7.368
7.365
7.339
7.329
7.283
6.472
6.463
6.462
6.455
6.448
6.432
4.366
4.360
4.350
0.007
0.001
-0.010
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.00
5.22
0.99
2.21

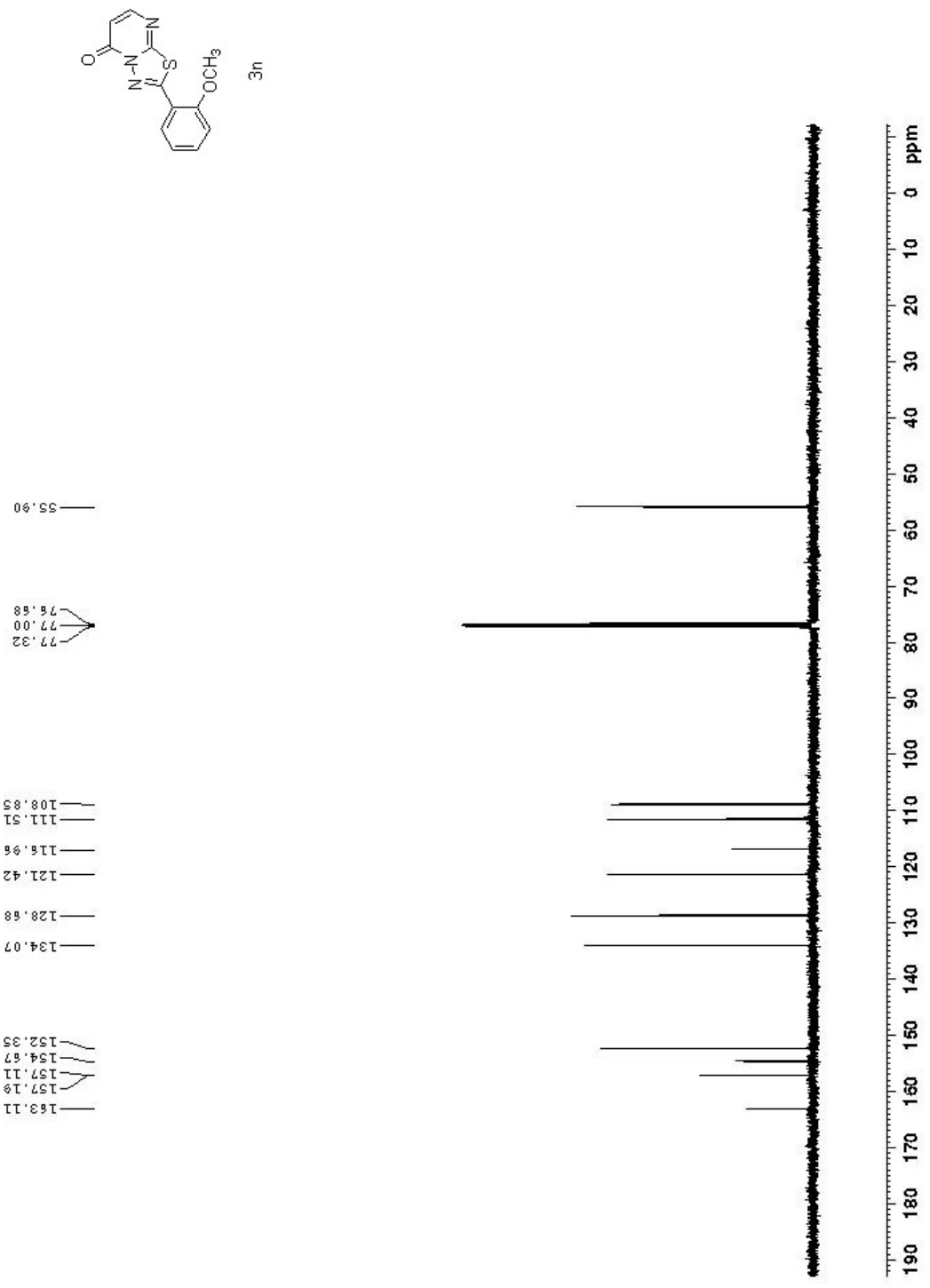

O
N
N
S
N

3m

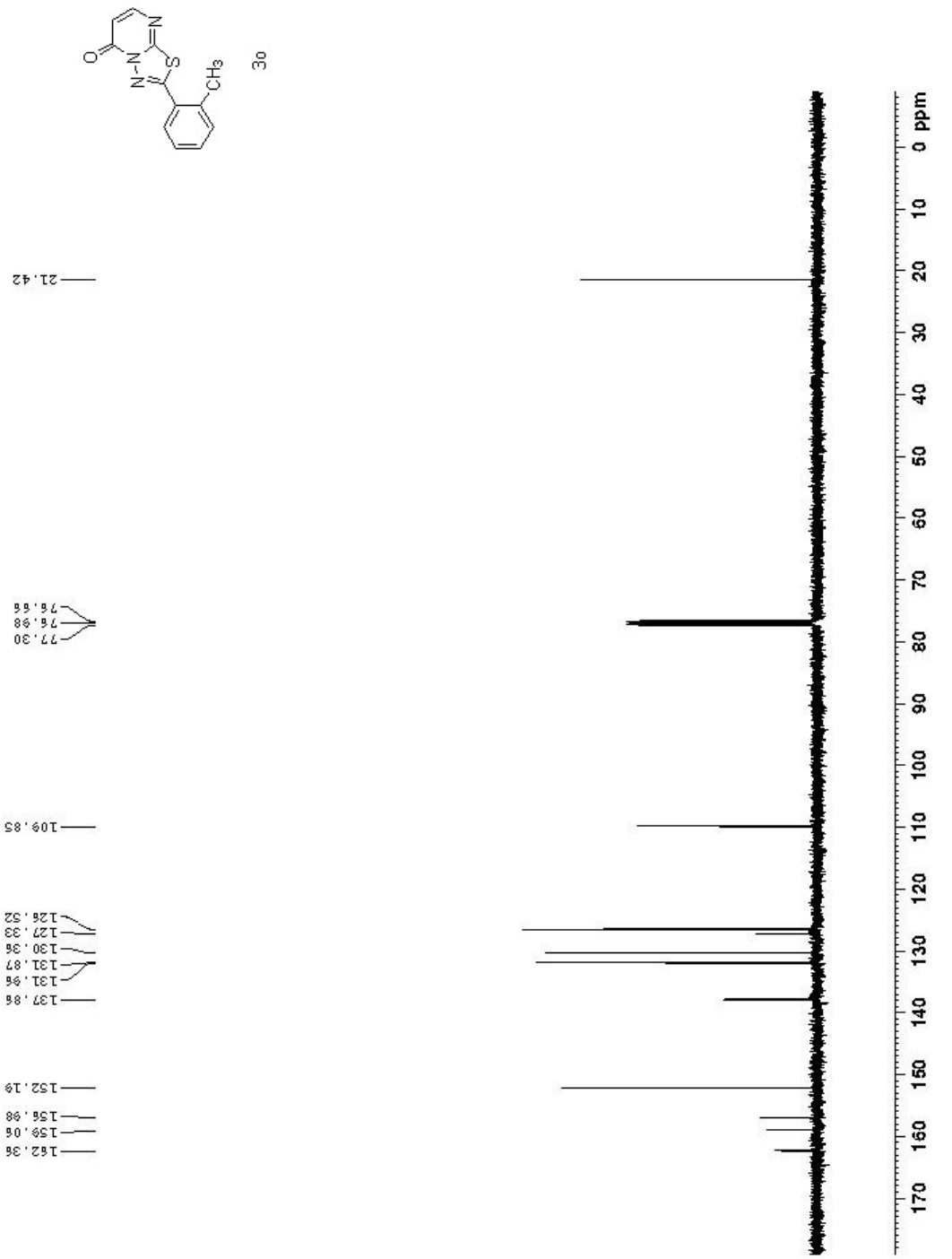

3m


162.80
162.56
157.13
152.30
134.32
129.37
128.93
128.34
109.82
77.31
76.99
76.67
37.76
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
ppm

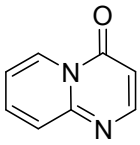

3n
8.458
8.464
8.468
8.484
7.965
7.981
7.561
7.557
7.540
7.522
7.518
7.294
7.138
7.119
7.100
7.066
7.045
6.471
6.454
4.046
-0.000
ppm
0
1
2
3
4
5
6
7
8
9
3.00
0.90
2.03
0.96
0.92
0.93

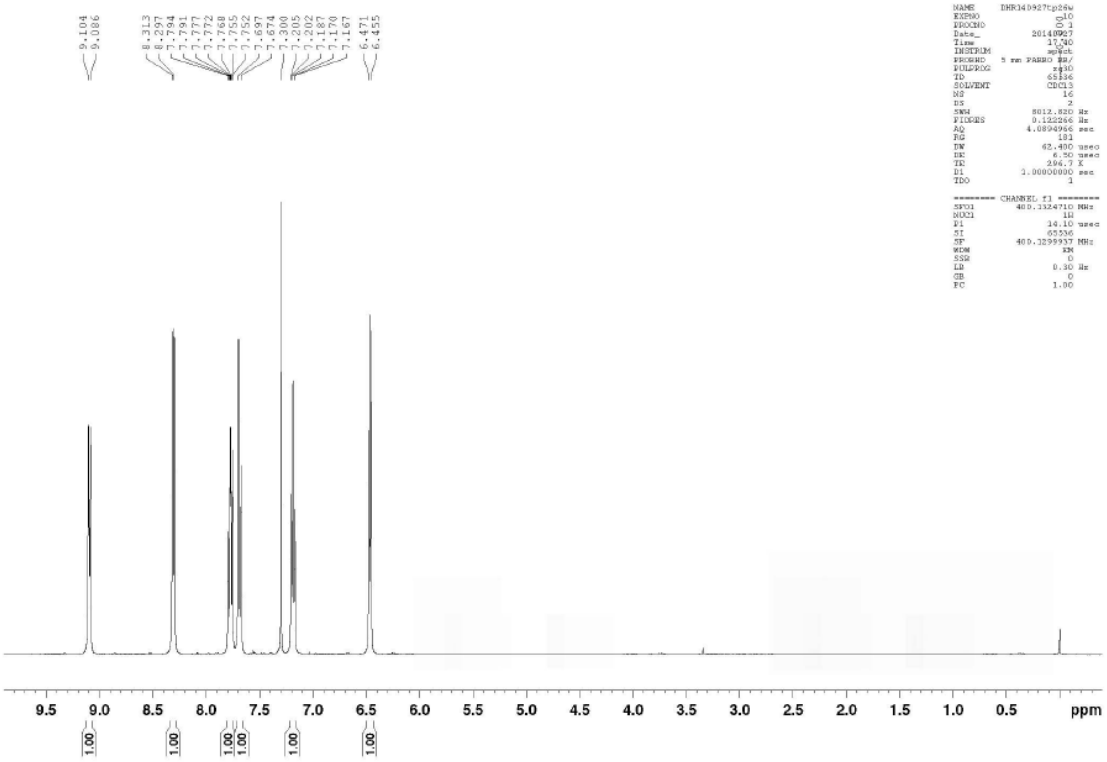

3n
55.90
76.68
77.00
77.32
108.85
111.51
116.96
121.42
128.68
134.07
152.35
154.67
157.11
157.19
163.11
ppm

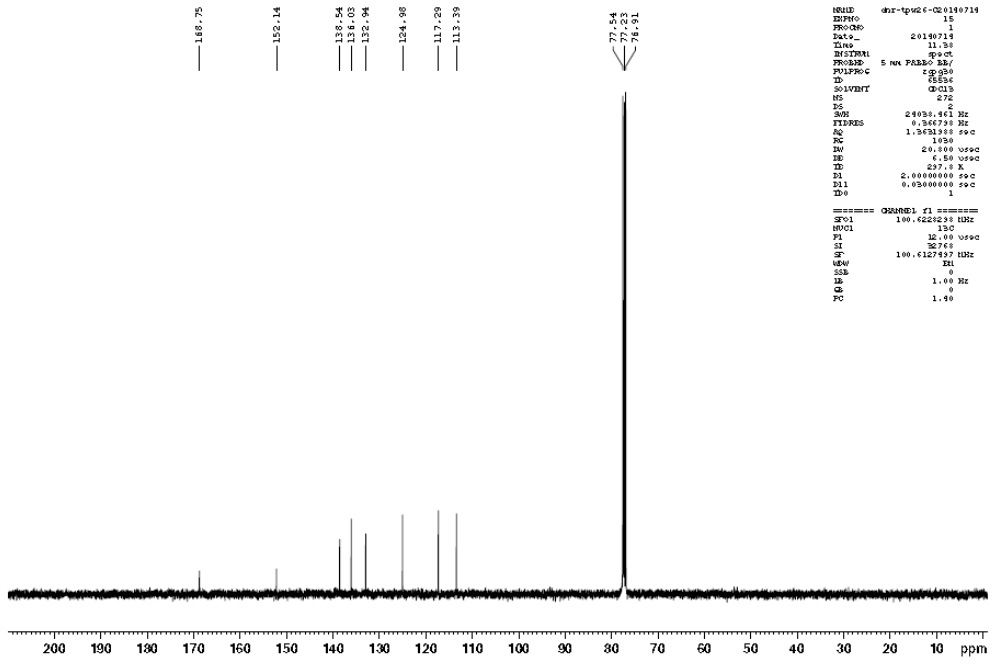
3o
2.648
2.640
7.955
7.946
7.944
7.938
7.930
7.928
7.926
7.921
7.630
7.622
7.611
7.466
7.447
7.438
7.432
7.424
7.420
7.415
7.349
7.336
7.331
7.317
7.312
7.299
7.260
6.487
6.483
6.478
6.471
6.468
6.462
6.460
6.457
6.451
3.00
0.94
1.97
0.97
0.96
0.96
ppm


3o
21.42
77.30
76.98
76.66
109.85
128.52
127.33
130.36
131.87
131.96
137.86
152.19
156.98
159.06
162.36
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

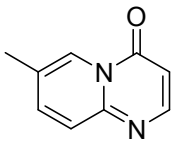
4a

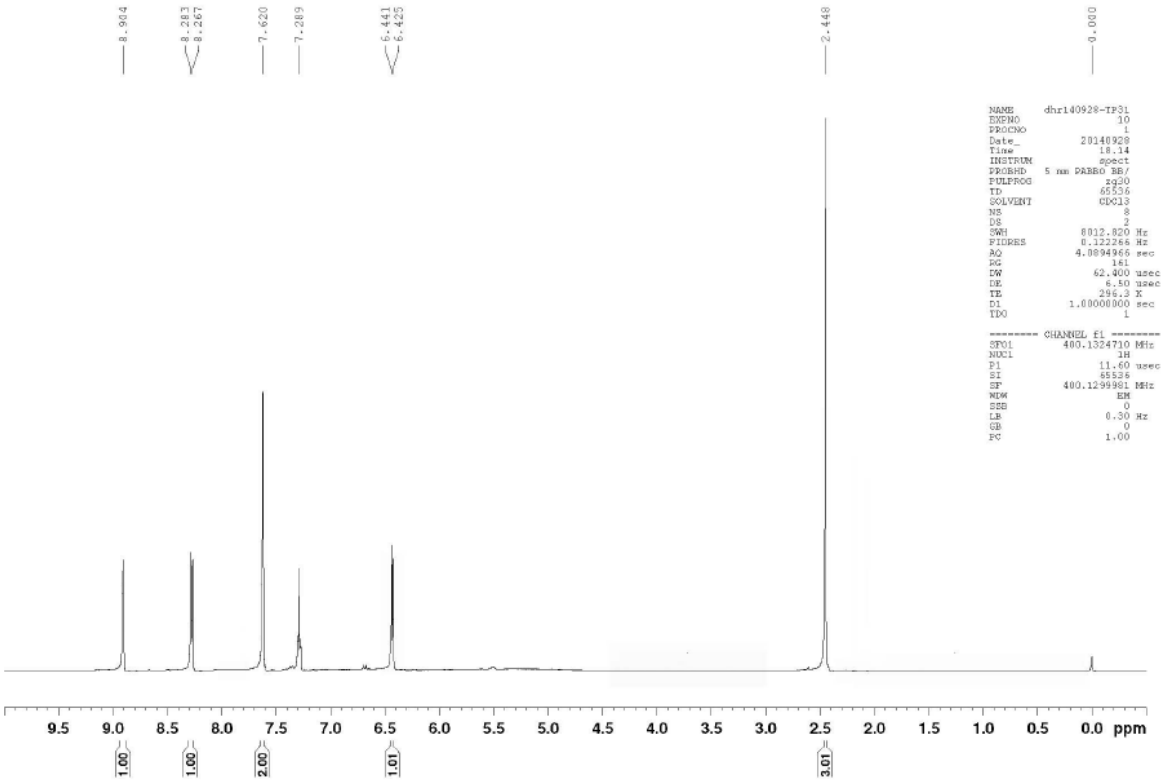

O
N
N

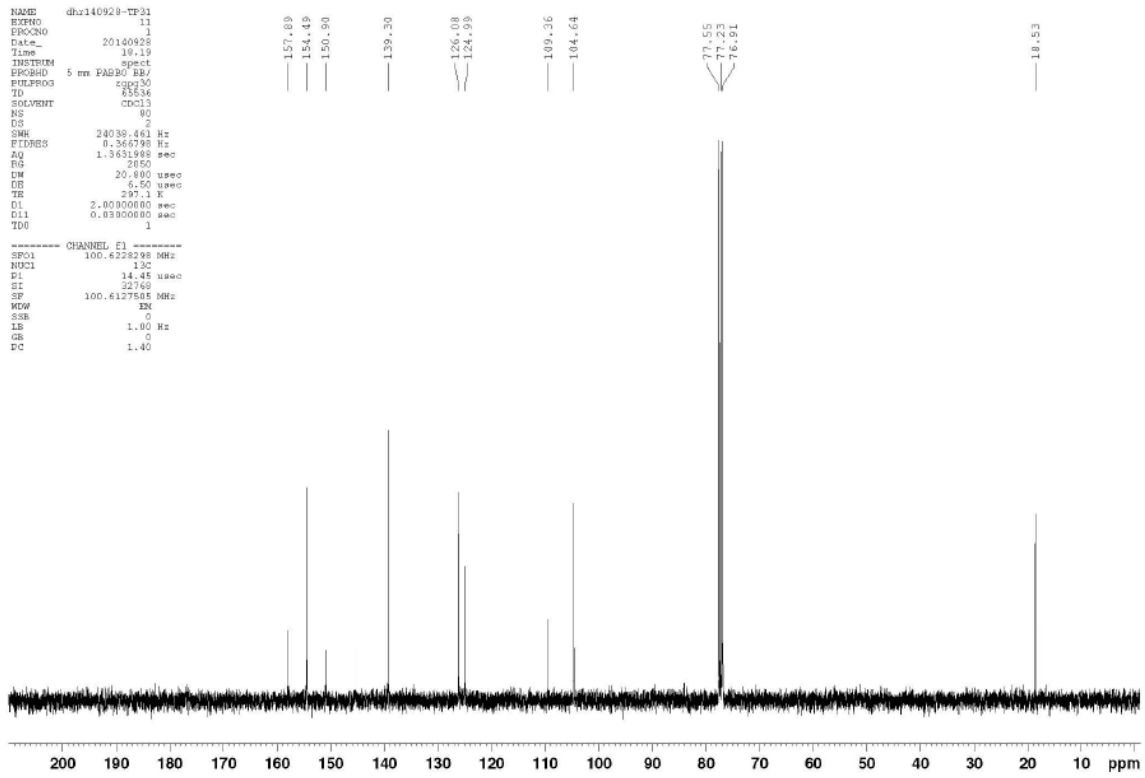

9.104
9.086
8.313
8.297
7.794
7.791
7.777
7.772
7.768
7.755
7.752
7.697
7.674
7.300
7.295
7.202
7.187
7.170
7.167
6.471
6.455
1.00
1.00
1.00
1.00
1.00
1.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


148.75
152.14
138.54
136.03
132.94
124.98
117.29
113.39
77.54
77.23
76.91
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

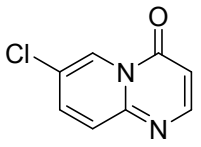
4b

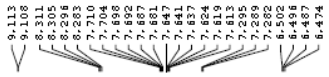

O
N
N

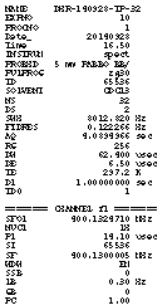

8.964
8.283
8.267
7.620
7.289
6.441
6.425
2.448
0.000
NAME dhr140928-TP31
EXPNO 10
PROCNO 1
Date_ 20140928
Time 18.14
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894966 sec
RG 161
DW 62.400 usec
DE 6.50 usec
TE 296.3 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 11.60 usec
SI 65536
SF 400.1299981 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
1.00
2.00
1.01
3.01

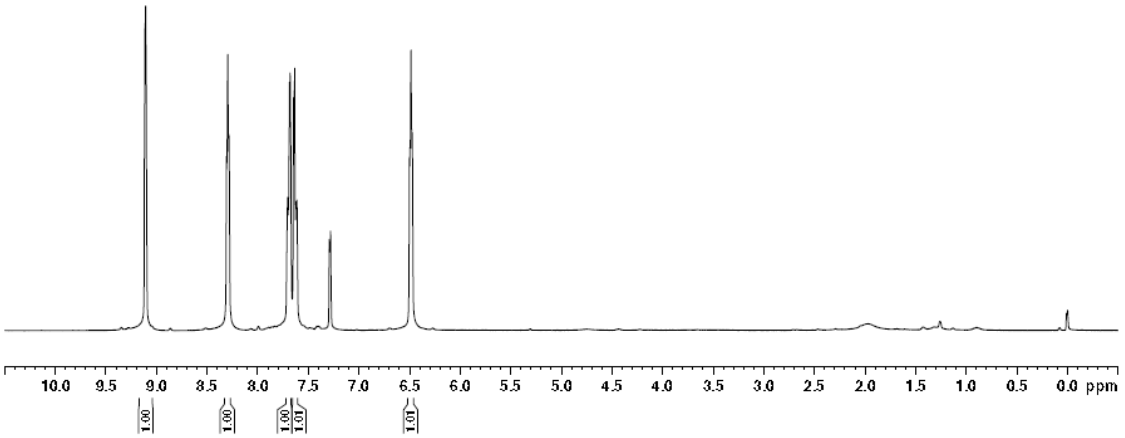

NAME dhr140928-TP31
EXPNO 11
PROCNO 1
Date_ 20140928
Time 19.19
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 80
DS 2
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 2050
DW 20.800 usec
DE 6.50 usec
TE 297.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 100.6228298 MHz
NUC1 13C
P1 14.45 usec
SI 32768
SF 100.6127505 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
157.89
154.49
150.90
139.30
126.08
124.99
109.36
104.64
77.55
77.23
76.91
18.53
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

4c

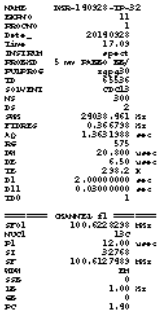

Cl
O
N
N

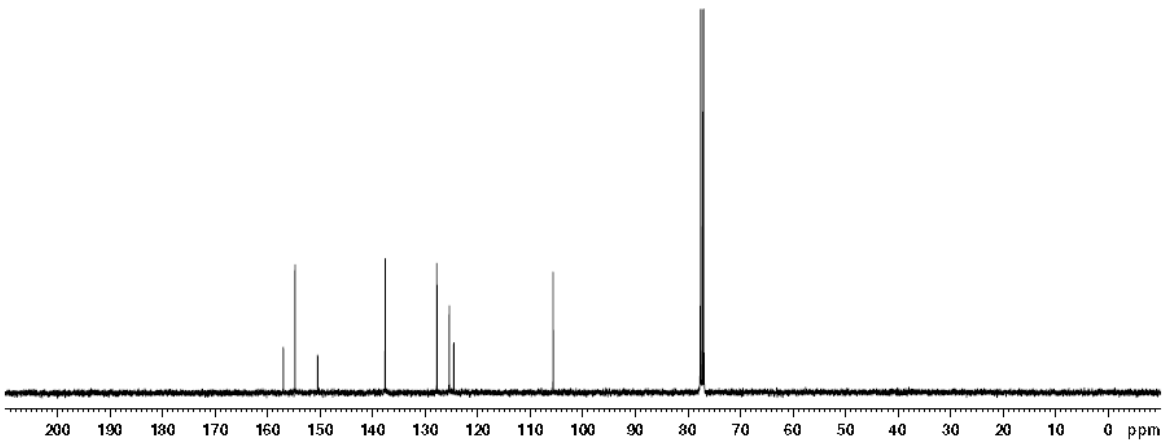

9.113
9.108
8.311
8.305
8.298
8.293
7.710
7.704
7.698
7.692
7.687
7.681
7.647
7.641
7.637
7.624
7.619
7.613
7.295
7.289
7.282
6.502
6.498
6.487
6.474


NAME INER-140328-IP-32
EXPNO 10
PROCNO 1
Date_ 20140328
Time 16.50
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894366 sec
RG 256
DW 62.900 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
SF01 900.1324710 MHz
NUC1 1H
P1 14.10 usec
SI 65536
SF 900.1300005 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

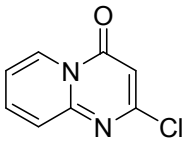

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
1.00
1.00
1.01
1.01

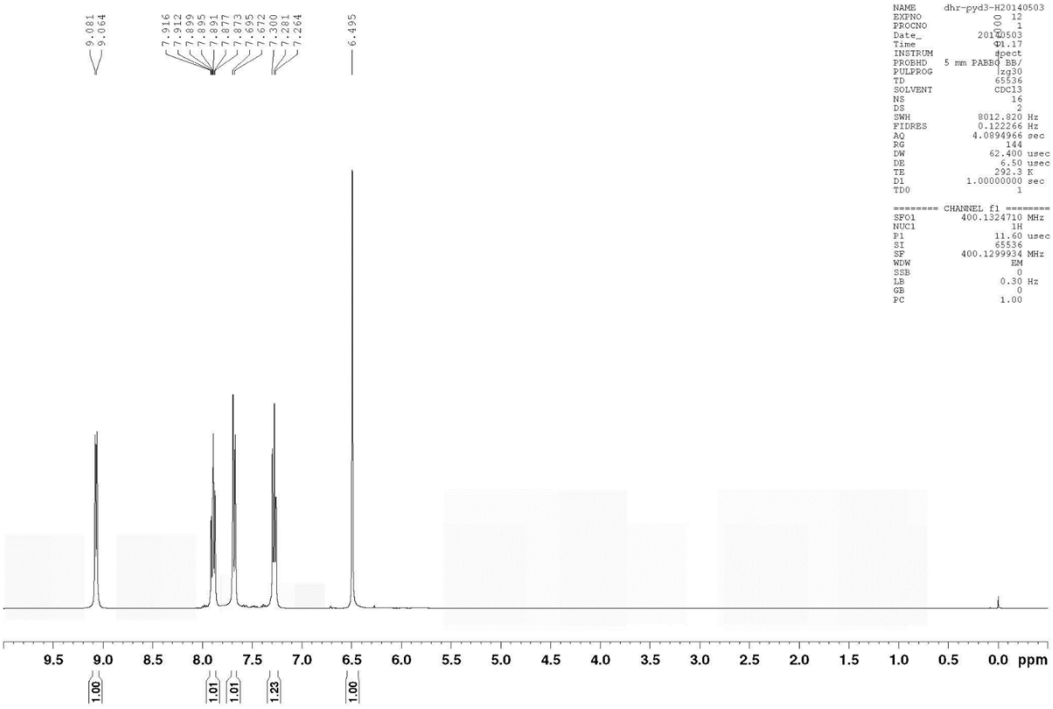

156.97
154.75
150.43
137.56
127.75
125.37
124.53
105.61
77.55
77.24
76.92

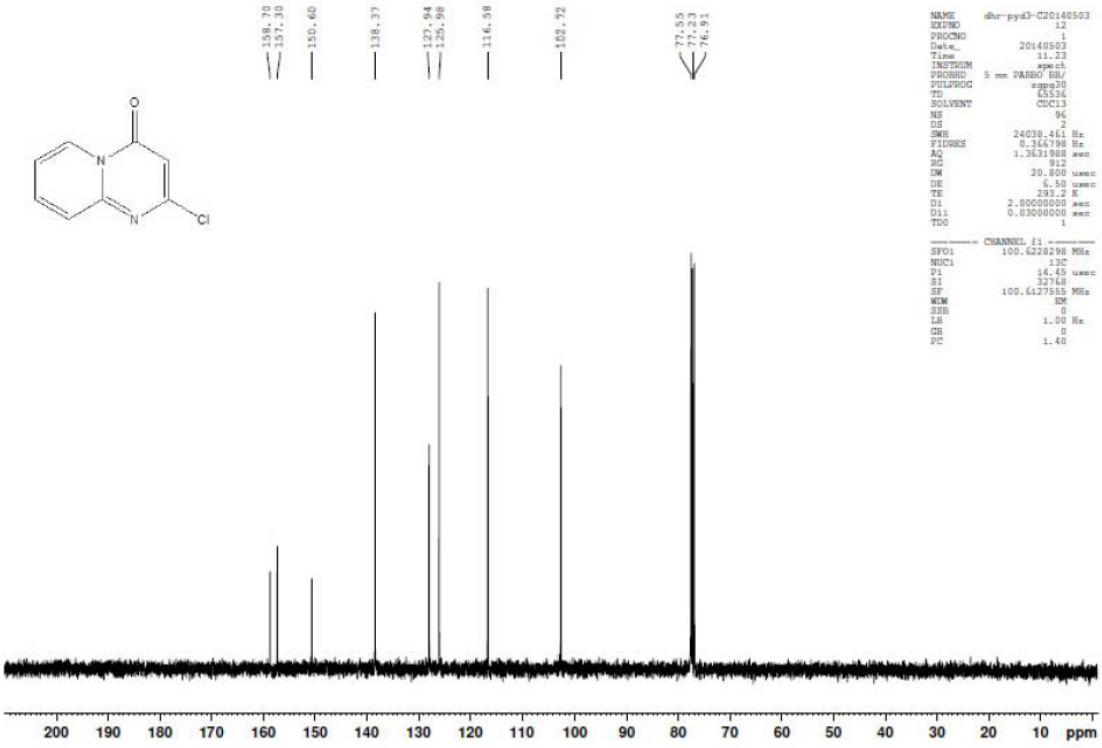

NAME INER-140328-IP-32
EXPNO 11
PROCNO 1
Date_ 20140328
Time 17.03
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 300
DS 2
SWH 29038.961 Hz
FIDRES 0.886738 Hz
AQ 1.1631988 sec
RG 575
DW 20.800 usec
DE 6.50 usec
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SF01 100.6228298 MHz
NUC1 13C
P1 12.00 usec
SI 32768
SF 100.6127989 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

4d


O
N
N
Cl


9.081
9.064
7.916
7.912
7.899
7.895
7.891
7.877
7.873
7.695
7.692
7.300
7.281
7.264
6.495
NAME dhr-pyd3-H20140503
EXPNO 12
PROCNO 1
Date_ 20140503
Time 11.17
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894966 sec
RG 144
DW 62.400 usec
DE 6.50 usec
TE 292.3 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
SFO1 400.1324710 MHz
NUC1 1H
P1 11.60 usec
SI 65536
SF 400.1299934 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
1.01
1.01
1.23
1.00


158.70
157.30
150.60
138.37
127.94
125.98
116.58
102.72
77.55
77.23
76.91
O
N
N
Cl
NAME dhr-pyd3-C20140503
EXPNO 12
PROCNO 1
Date_ 20140503
Time 11.23
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 96
DS 2
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631988 sec
RG 912
DW 20.800 usec
DE 6.50 usec
TE 293.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 100.6228298 MHz
NUC1 13C
P1 14.45 usec
SI 32768
SF 100.6127555 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm