
Palladium-catalyzed direct C-H arylation of 3-aryl-2*H*-benzo[1,2,4]thiadiazine
1,1-dioxides: an efficient strategy to the synthesis of benzothiadiazine-1,1-
dioxide derivatives

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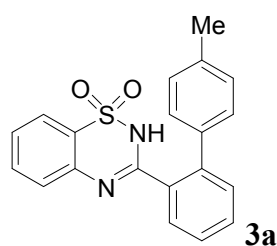
I General Information

All reactions were performed in air. Chemicals were purchased from Acros, or Alfa Aesar, and, unless otherwise noted, were used without further purification. Flash chromatography was performed on silica gel (silica gel, 200-300 mesh). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz and Bruker 100 MHz

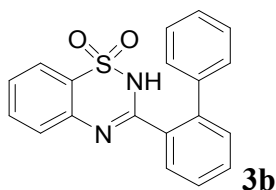
spectrometers with DMSO-d₆ or CDCl₃ as the solvent. High resolution mass spectrometry was performed on a Q-TOF mass spectrometer. Melting points were determined on an XT-4 electrothermal Micro-melting-point apparatus. The substrates **1a-d** was synthesized by the reaction of the corresponding aldehydes with 2-aminobenzenesulfonamide.^[12a,e]

II General procedure for Arylation Products 3

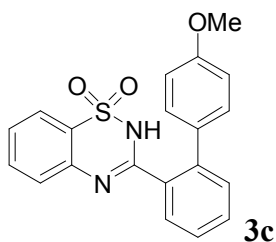
3-Aryl-2*H*-benzo[1,2,4]thiadiazine 1,1-dioxides **1** (0.5 mmol, 1.0 equiv), aryl iodides (1.0 mmol, 2.0 equiv), Pd(OAc)₂ (0.05 mmol, 10 mol %), and DMSO/TFA (0.5 mL, 4:1) was charged into a pressure tube. The reaction mixture was stirred at 130 °C under air for 6 h. After cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography using PE/EA to afford the desired product **3a-r**.



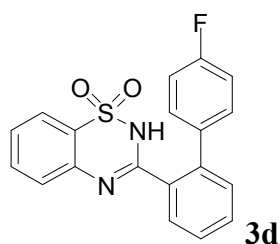
3-(4'-Methyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3a): Yellow powder (151 mg, 87 %); m.p. 242.6-243.8 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 12.11 (br, 1H), 8.81 (d, *J* = 8.0 Hz, 1H), 8.69 (d, *J* = 8.0 Hz, 2H), 7.63-7.56 (m, 3H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 3H), 2.26 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 156.98, 140.03, 136.83, 135.86, 135.23, 132.97, 132.27, 131.16, 130.28, 129.20, 129.00, 128.25, 127.28, 126.55, 123.30, 121.14, 117.61, 20.60. HRMS: [M + H]⁺ calcd. for C₂₀H₁₇N₂O₂S: 349.1012, found 349.1015.



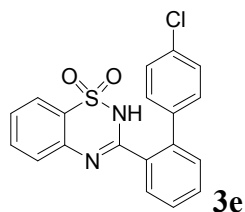
3-Biphenyl-2-yl-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3b): Yellow powder (146 mg 82 %); m.p. 236.5-236.8 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 12.17 (br, s, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.64 (m, 3H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.37-7.31 (m, 3H), 7.14 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ 156.82, 140.24, 138.74, 135.19, 132.98, 132.31, 131.27, 130.34, 129.27, 128.37, 127.56, 126.57, 123.28, 121.15, 117.55. HRMS: [M + Na]⁺ calcd. for C₁₉H₁₄ Na N₂O₂S: 357.0674, found 357.0677.



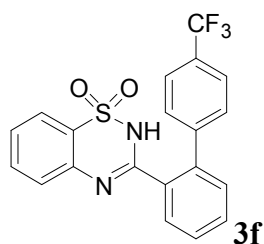
3-(4'-Methoxy-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3c): Yellow powder (168 mg, 92%); m.p. 236.5-237.8 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 12.12 (br, s, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 0.8 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 3.71 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 158.74, 157.03, 139.82, 135.24, 132.99, 131.18, 131.01, 130.22, 129.59, 129.25, 127.03, 126.56, 123.32, 121.13, 117.60, 113.89, 55.06. HRMS: [M + H]⁺ calcd. for C₂₀H₁₇N₂O₃S: 365.0962, found 365.0961.



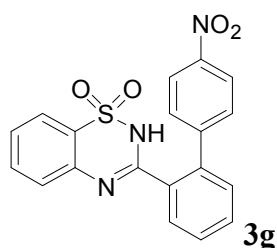
3-(4'-Fluoro-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3d): Yellow powder (120 mg, 68%); m.p. 228.5-229.8 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 12.27 (br, s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 3H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 8.0 Hz, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 161.65 (d, *J* = 243 Hz,), 156.58, 139.31, 135.19, 133.04, 132.27, 31.31, 13.48, 130.39, 130.35, 129.29, 127.65, 126.64, 123.30, 121.15, 117.60, 115.25 (d, *J* = 21 Hz). HRMS: [M + H]⁺ calcd. for C₁₉H₁₄FN₂O₂S: 353.0760, found 353.0757.



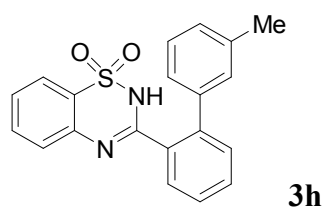
3-(4'-Chloro-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3e): Yellow powder (134 mg, 73%); m.p. 215.7-216.8 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 12.26 (br, s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.70-7.58 (m, 3H), 7.48-7.41 (m, 1H), 7.39-7.37 (m, 4H), 7.19 (d, *J* = 8.0 Hz, 1H); ¹³C NMR (100 MHz, DMSO-d₆): δ 156.48, 139.08, 137.68, 135.19, 133.05, 132.46, 132.19, 131.38, 130.32, 130.21, 129.36, 128.37, 127.89, 126.69, 123.31, 121.15, 117.63. HRMS: [M + H]⁺ calcd. for C₁₉H₁₄ClN₂O₂S: 369.0477, found 369.0480.



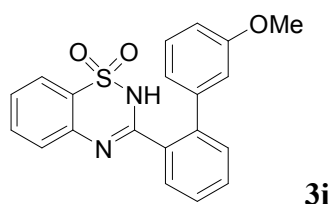
3-(4'-Trifluoromethyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3f): Yellow powder (135 mg, 67%); m.p. 215.7-216.8 °C; δ 12.36 (br, s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.76-7.66 (m, 2H), 7.63-7.61 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 156.24, 143.01, 139.06, 135.20, 133.01, 132.27, 131.50, 130.45, 129.50, 130.45, 129.28, 128.34, 128.07, 127.76, 126.71, 125.54, 125.22, 125.18, 123.30, 121.18, 117.64. HRMS: $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{14}\text{F}_3\text{N}_2\text{O}_2\text{S}$: 403.0730, found 403.0727.



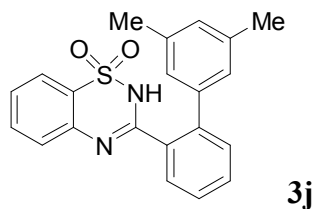
3-(4'-Nitro-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3g): Yellow powder (108 mg, 57%); m.p. 243.1-245.6 °C; δ 12.46 (br, s, 1H), 8.25 (d, J = 8.0 Hz, 2H), 7.89-7.83 (m, 3H), 7.82-7.66 (d, J = 8.0 Hz, 5H), 7.51 (t, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 155.95, 146.60, 145.80, 138.52, 135.21, 133.09, 132.20, 131.61, 130.45, 129.90, 129.65, 128.76, 126.78, 123.47, 123.31, 121.17, 117.80. HRMS: $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}_4\text{S}$: 380.0717, found 380.0718.



3-(3'-Methyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (**3h**): Yellow powder (136 mg, 78%); m.p. 243.1-245.6 °C; δ 12.08 (br, s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 2H), 7.62-7.55 (m, 3H), 7.45 (d, J = 8.0 Hz, 1H), 7.23-7.12 (m, 3H), 7.09 (t, J = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 157.57, 140.68, 139.05, 137.96, 135.77, 133.46, 132.81, 131.71, 130.68, 129.64, 128.80, 128.66, 127.94, 127.04, 126.00, 123.73, 121.64, 118.07. HRMS: $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$: 349.1012, found 349.1010.

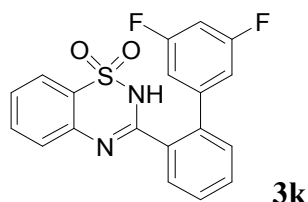


3-(3'-Methoxy-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (**3i**): Yellow powder (149 mg, 77%); m.p. 236.5-237.8 °C; ^1H NMR (400 MHz, DMSO- d_6): δ 12.10 (br, s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.72-7.61 (m, 4H), 7.58 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.25-6.22 (m, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.90 (s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 159.00, 156.82, 140.12, 140.07, 135.20, 133.01, 132.34, 131.21, 130.23, 129.47, 129.20, 127.63, 126.59, 123.29, 121.14, 120.74, 117.53, 113.90, 113.29, 55.00; HRMS: $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{16}\text{NaN}_2\text{O}_3\text{S}$: 387.0776, found 387.0773.

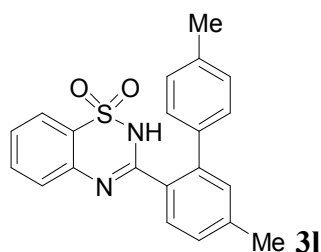


3-(3',5'-Dimethyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (**3j**): Yellow powder (127 mg, 70%); m.p. 187.5-188.6 °C; δ 12.11 (br, s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 8.0 Hz, 2H), 7.68-7.59 (m, 4H), 7.51 (t, J = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.06 (s, 2H), 6.95 (s, 1H), 2.21 (s, 6H); ^{13}C

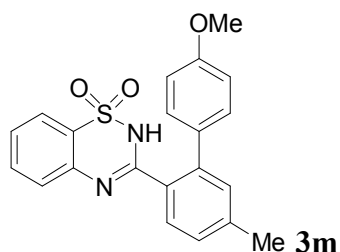
NMR (100 MHz, DMSO- d_6): δ 157.32, 140.14, 138.37, 137.32, 135.34, 132.93, 132.30, 130.02, 129.09, 128.91, 127.34, 126.51, 126.32, 123.18, 121.16, 117.58, 20.73. HRMS: $[M + H]^+$ calcd. for $C_{21}H_{19}N_2O_2S$: 363.1169, found 363.1174.



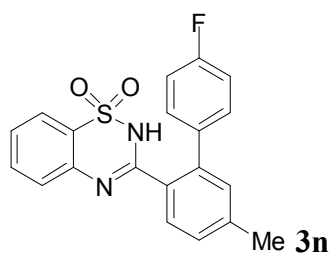
3-(3',5'-difluoro-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3k): Yellow oil (141 mg, 76%); 1H NMR (400 MHz, DMSO- d_6): δ 12.36 (br, s, 1H), 7.82-7.72 (m, 3H), 7.66 (dd, $J = 8.0$ Hz, $J = 4.0$ Hz, 3H), 7.48 (t, $J = 8.0$ Hz, 1H), 7.27 (d, $J = 8.0$ Hz, 1H), 7.21 (d, $J = 8.0$ Hz, 1H), 7.17-7.03 (m, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 163.32 (d, $J = 14$ Hz), 160.87 (d, $J = 14$ Hz), 156.05, 142.35, 138.09, 135.20, 133.11, 132.14, 131.48, 130.27, 129.42, 128.52, 126.77, 123.31, 121.18, 117.73, 111.86 (d, $J = 26$ Hz). HRMS: $[M + H]^+$ calcd. for $C_{19}H_{13}F_2N_2O_2S$: 371.0668, found 371.0669.



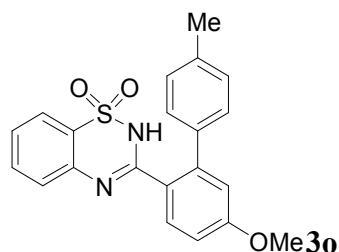
3-(5,4'-Dimethyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3l): Yellow powder (152 mg, 84%); m.p. 253.6-254.9 °C; 1H NMR (400 MHz, DMSO- d_6): δ 11.98 (br, s, 1H), 7.79 (d, $J = 8.0$ Hz, 1H), 7.43 (q, $J = 8.0$ Hz, 2H), 7.45-7.36 (m, 3H), 7.26 (d, $J = 8.0$ Hz, 2H), 3.77 (dd, $J = 12.0$ Hz, $J = 8.0$ Hz, 3H), 2.50 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 157.08, 141.15, 140.07, 136.71, 135.95, 135.23, 132.92, 130.80, 129.55, 129.29, 128.93, 128.24, 127.75, 126.48, 123.25, 121.11, 117.54, 20.91, 20.60. HRMS: $[M + H]^+$ calcd. for $C_{21}H_{19}N_2O_2S$: 363.1169, found 363.1179.



3-(4'-Methoxy-5-methyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3m): Yellow powder (144 mg, 76%); m.p. 226.3-227.8 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 12.02 (br, s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.59 (dd, *J* = 8.0 Hz, *J* = 12.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 12.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 3.72 (s, 3H), 2.46 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 158.68, 159.16, 141.15, 139.86, 135.28, 132.92, 131.12, 130.75, 129.58, 129.42, 129.35, 127.51, 126.47, 123.26, 121.13, 117.56, 113.82, 55.05, 20.92. HRMS: [M + H]⁺ calcd. for C₂₁H₁₉N₂O₃S: 379.1119, found 379.1124.

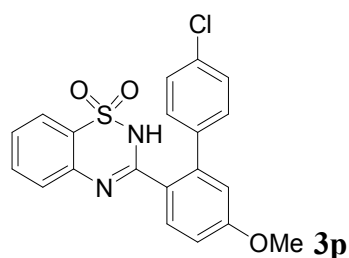


3-(4'-Fluoro-5-methyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3n): white powder (132 mg, 72%); m.p. 194.7-195.3 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 12.12 (br, s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.62 (q, *J* = 4.0 Hz, 2H), 7.47-7.37 (m, 5H), 7.19-7.14 (m, 3H), 2.46 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 162.82, 160.39, 156.70, 141.37, 139.37, 135.35, 135.32, 135.25, 132.96, 130.92, 130.46, 130.37, 129.57, 129.39, 128.09, 126.55, 123.26, 121.17, 117.57, 115.28, 115.07, 20.88. HRMS: [M + H]⁺ calcd. for C₂₀H₁₆FN₂O₂S: 367.0928, found 367.0928.



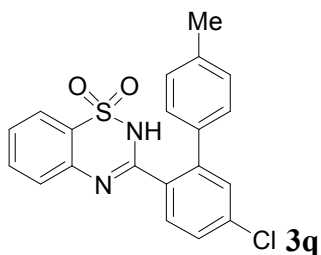
3-(5-Methoxy-4'-methyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3o):

Yellow powder (164 mg, 87%); m.p. 185.6-186.9 °C; ¹H NMR (400 MHz, DMSO-d₆): δ 12.65 (br, s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 4.0 Hz, 1H), 7.46-7.41 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.13 (q, *J* = 4.0 Hz, 3H), 3.77 (t, *J* = 4.0 Hz, 2H), 3.90 (s, 3H), 2.27 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 161.18, 156.87, 142.23, 136.91, 135.86, 135.29, 132.85, 131.28, 129.73, 128.91, 128.28, 126.40, 124.70, 123.56, 123.18, 121.15, 117.54. HRMS: [M + H]⁺ calcd. for C₂₁H₁₉N₂O₃S: 379.1118, found 379.1128.



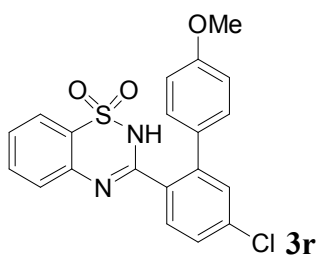
3-(4'-Chloro-5-methoxy-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3p):

Yellow powder (137 mg, 69%); m.p. 267.8-268.1; °C ¹H NMR (400 MHz, DMSO-d₆): δ 12.08 (br, s, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.47-7.44 (m, 1H), 7.38 (d, *J* = 4.0 Hz, 4H), 7.19-7.10 (m, 3H), 2.91 (s, 3H); ¹³C NMR (100 MHz, DMSO-d₆): δ 161.27, 156.35, 141.27, 137.69, 135.31, 132.94, 132.47, 131.50, 130.25, 128.28, 126.52, 124.55, 123.21, 121.17, 117.59, 115.59, 113.31, 55.69. HRMS: [M + H]⁺ calcd. for C₂₀H₁₆ClN₂O₃S: 399.0572, found 399.0577.



3-(5-Chloro-4'-methyl-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3q):

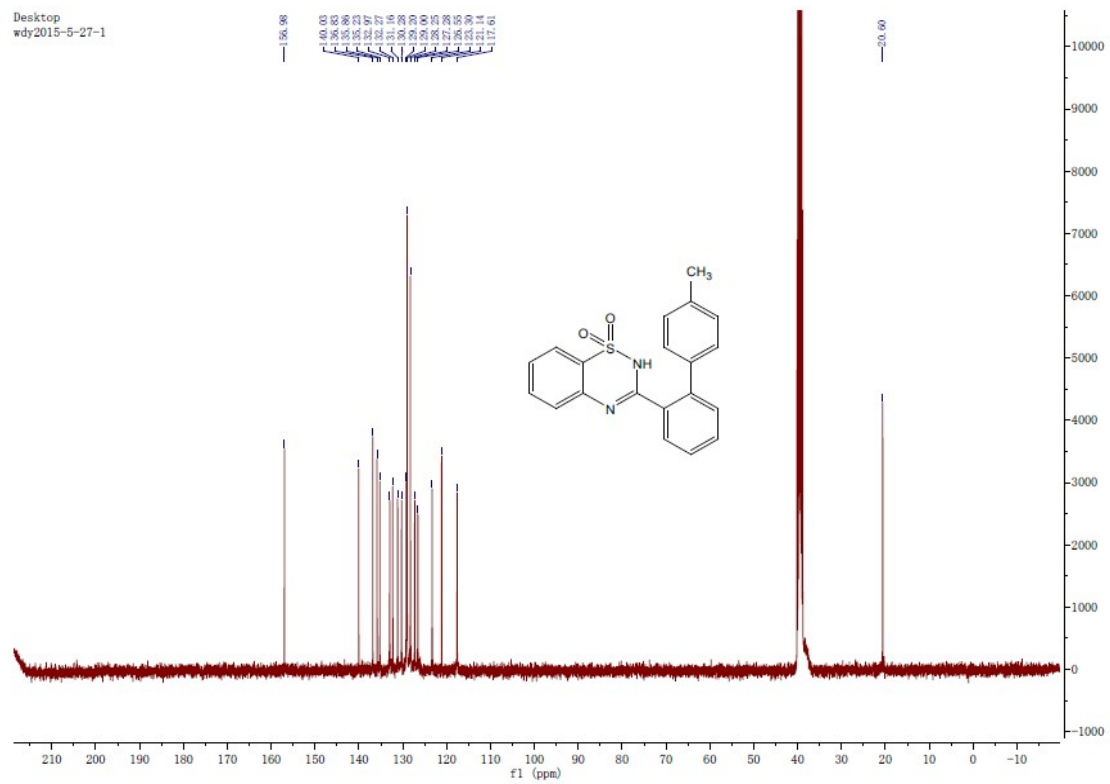
Yellow oil (132 mg, 68%); ^1H NMR (400 MHz, DMSO- d_6): δ 12.18 (br, s, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.74- 7.65(m, 1H), 7.62 (q, $J = 8.0$ Hz, 3H), 7.45 (t, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.13 (dd, $J = 16$ Hz, $J = 8$ Hz, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 155.99, 142.14, 137.52, 135.76, 135.10, 134.51, 131.18, 131.00, 129.76, 129.74, 129.10, 128.27, 127.22, 126.69, 123.55, 123.31, 121.13, 117.62. HRMS: $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}$: 383.0623, found 383.0623.

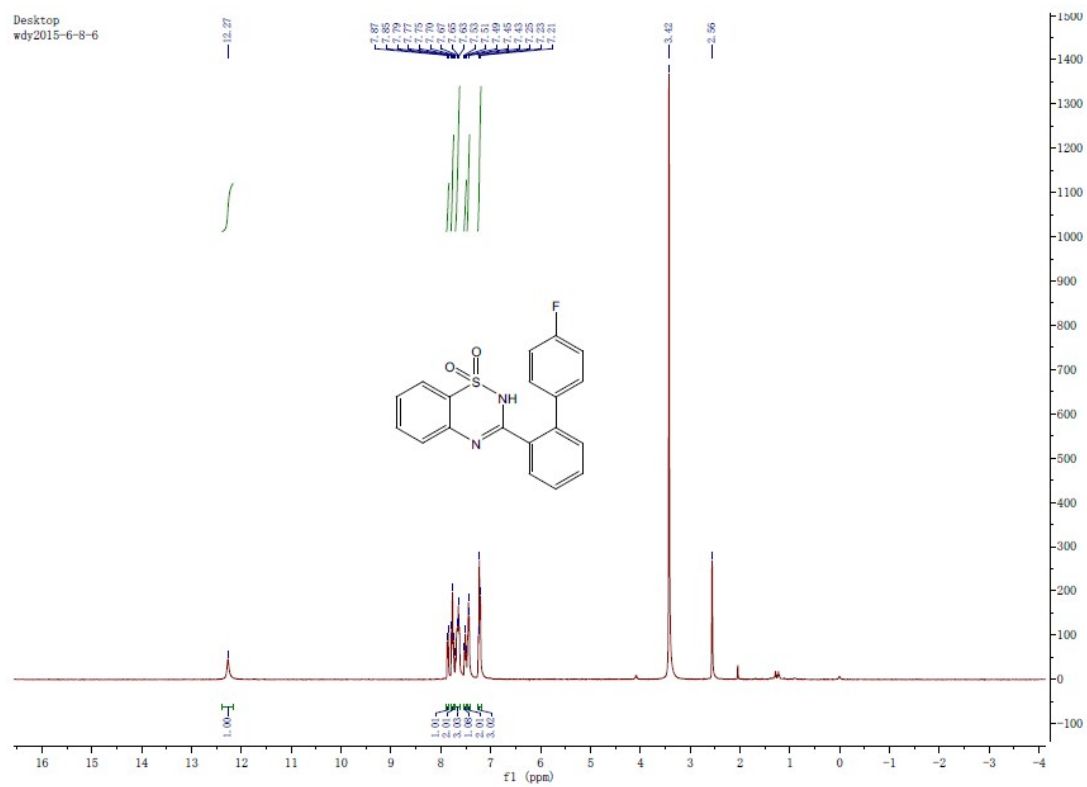


3-(5-Chloro-4'-methoxy-biphenyl-2-yl)-2H-benzo[1,2,4]thiadiazine 1,1-dioxide (3r):

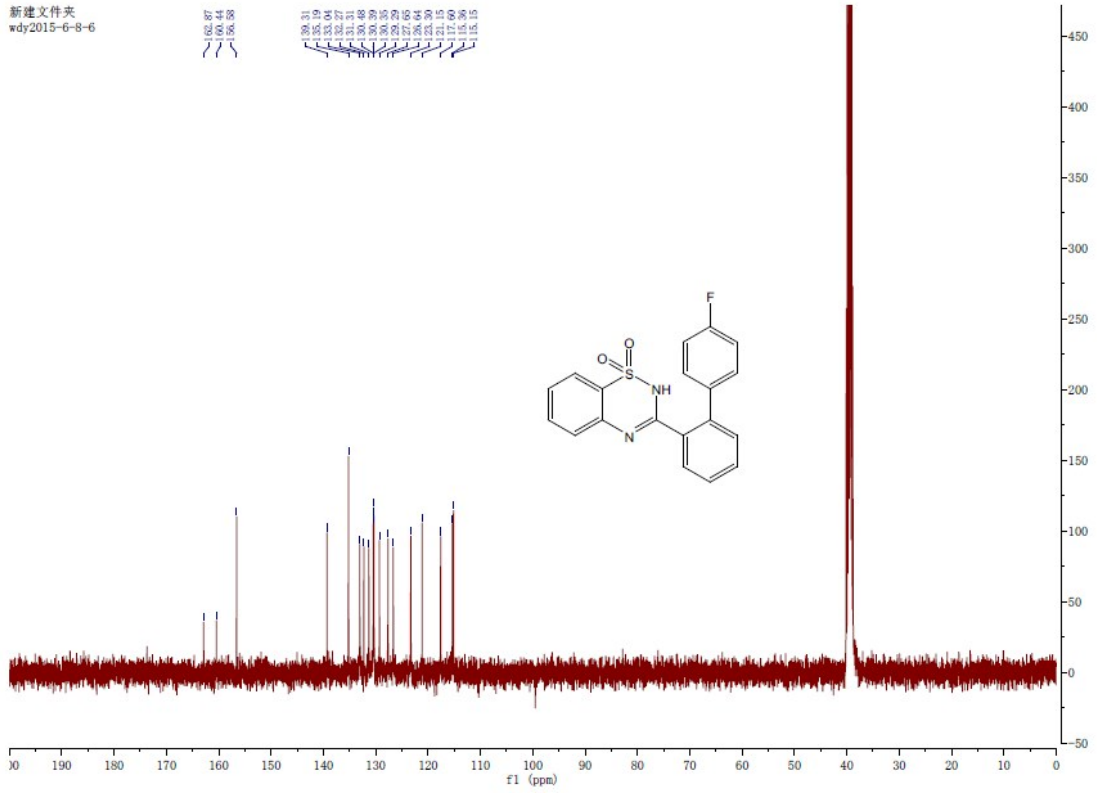
Yellow oil (143 mg, 72%); ^1H NMR (400 MHz, DMSO- d_6): δ 12.18 (br, s, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.72(d, $J = 8.0$ Hz, 1H), 7.64 (m, 3H), 7.46 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.14 (d, $J = 8.0$ Hz, 2H), 6.91 (d, $J = 12.0$ Hz, 1H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, DMSO- d_6): δ 159.63, 156.56, 142.42, 136.25, 135.63, 133.55, 131.73, 131.34, 130.19, 130.13, 127.44, 127.19, 123.82, 121.63, 118.12, 114.48, 55.62. HRMS: $[\text{M} + \text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{16}\text{ClN}_2\text{O}_3\text{S}$: 399.0572, found 399.0579.

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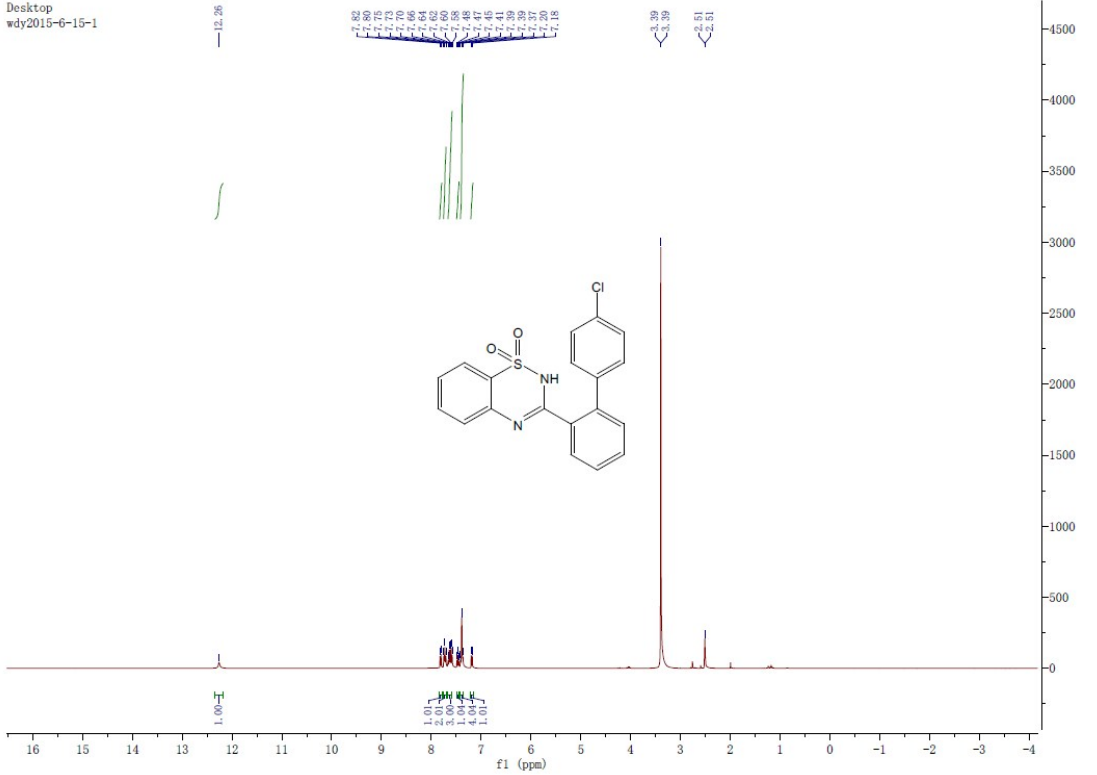




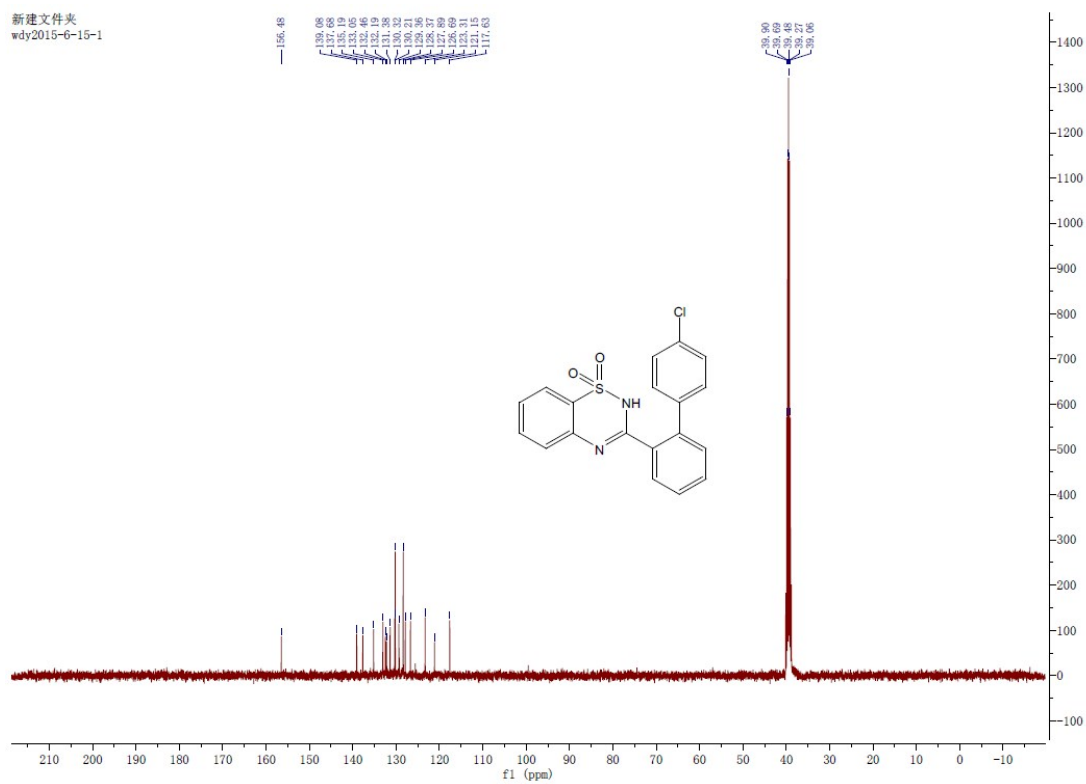
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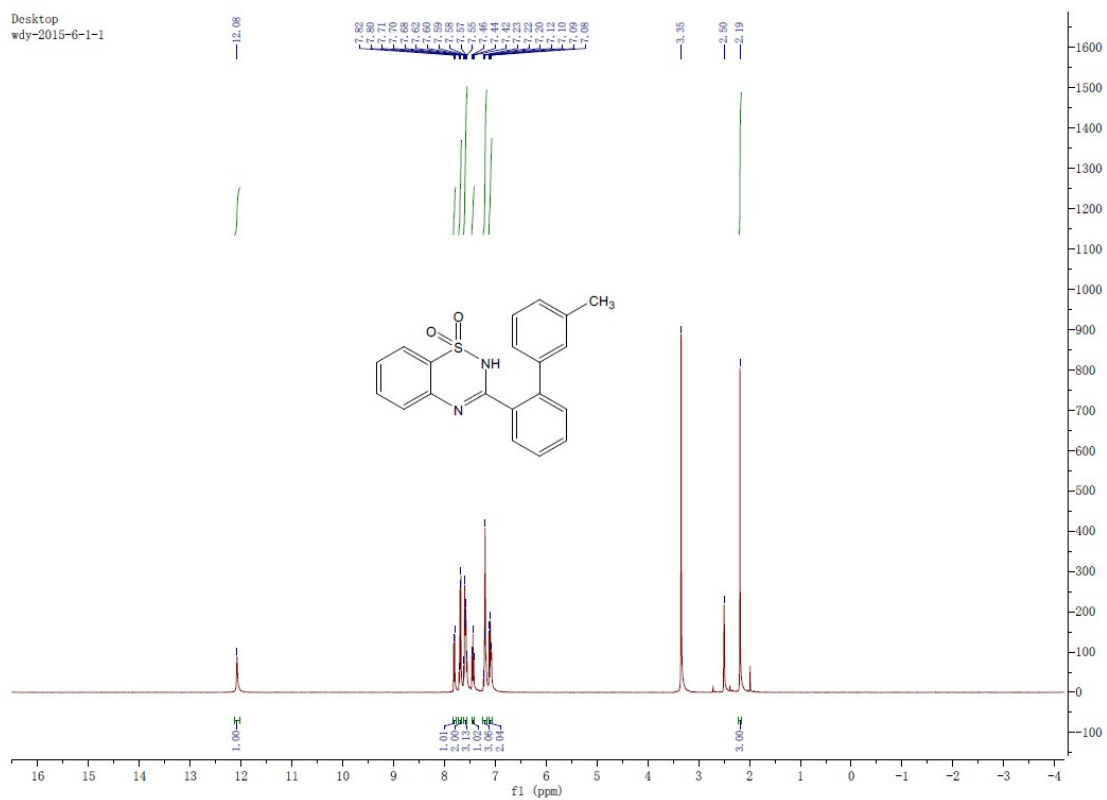
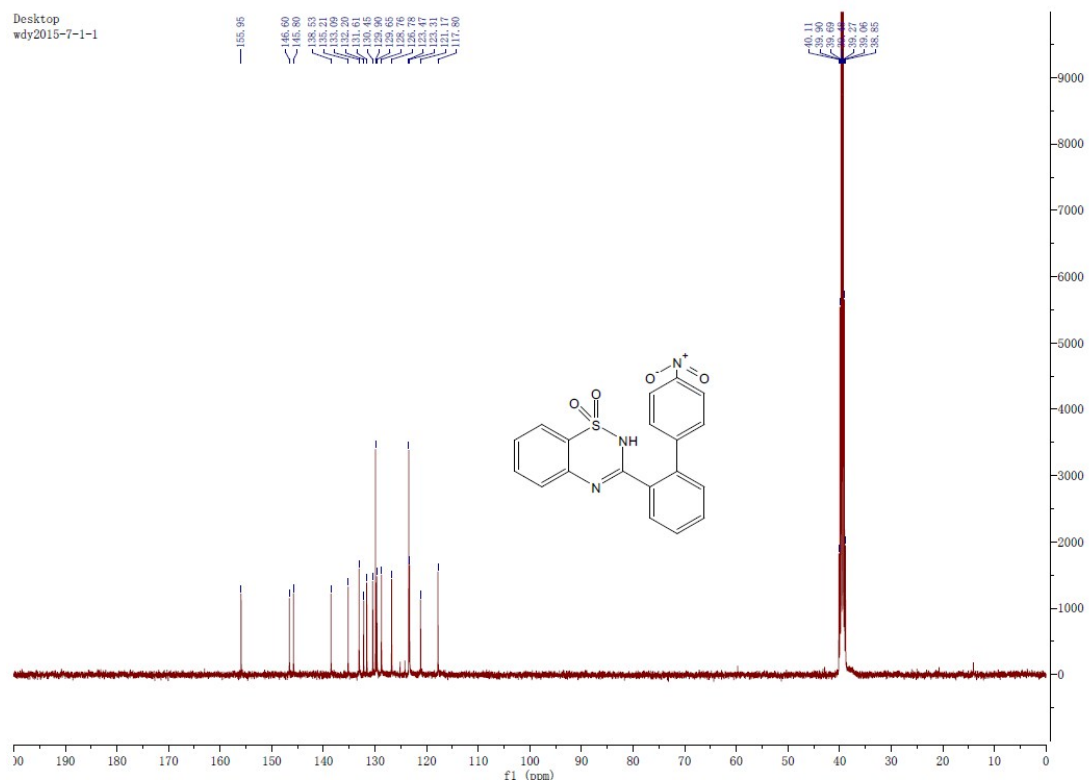


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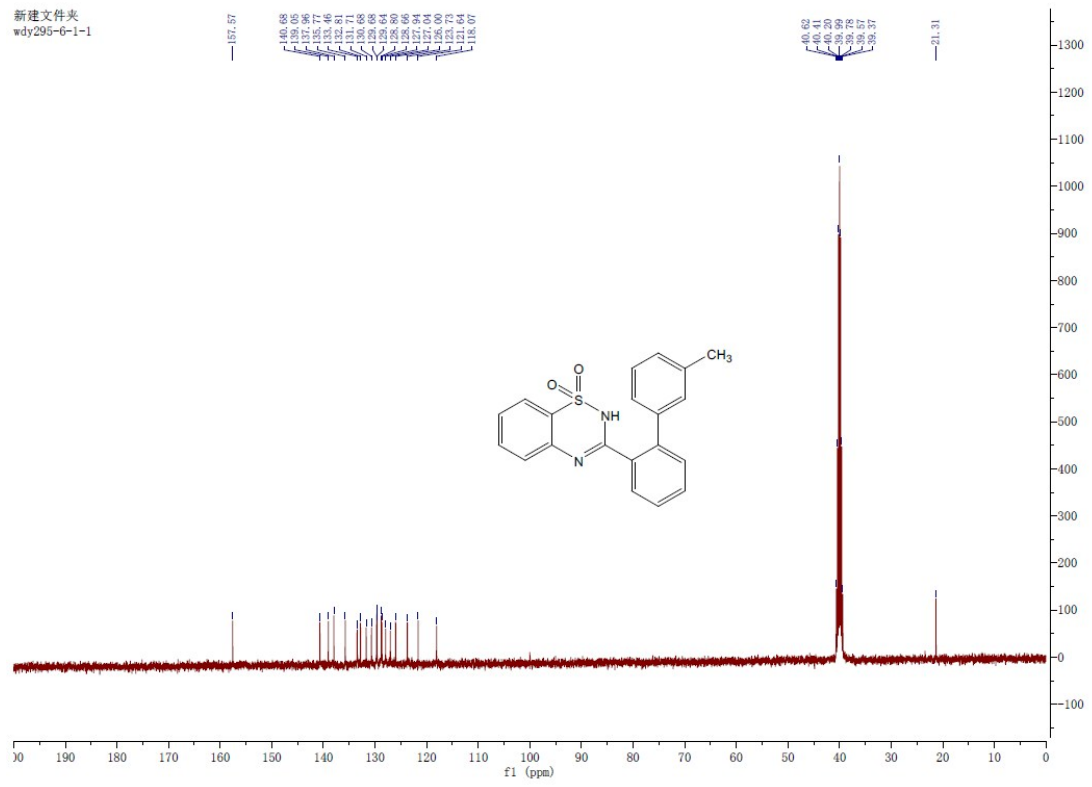


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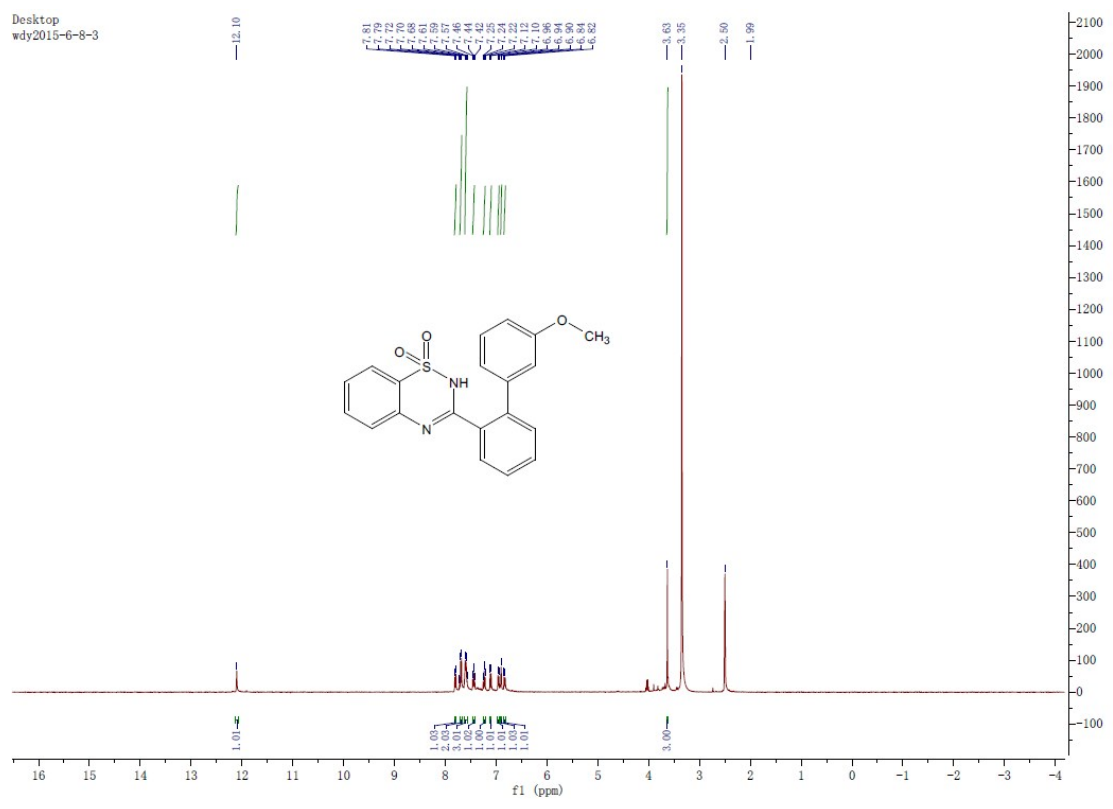




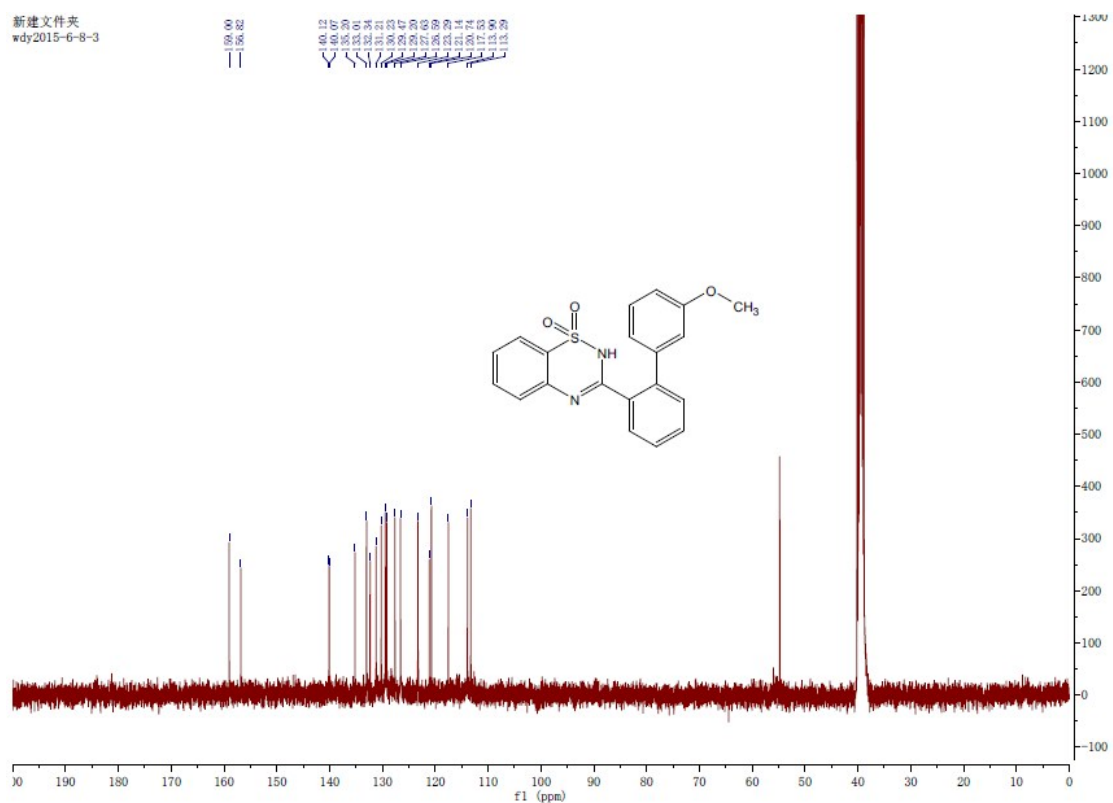
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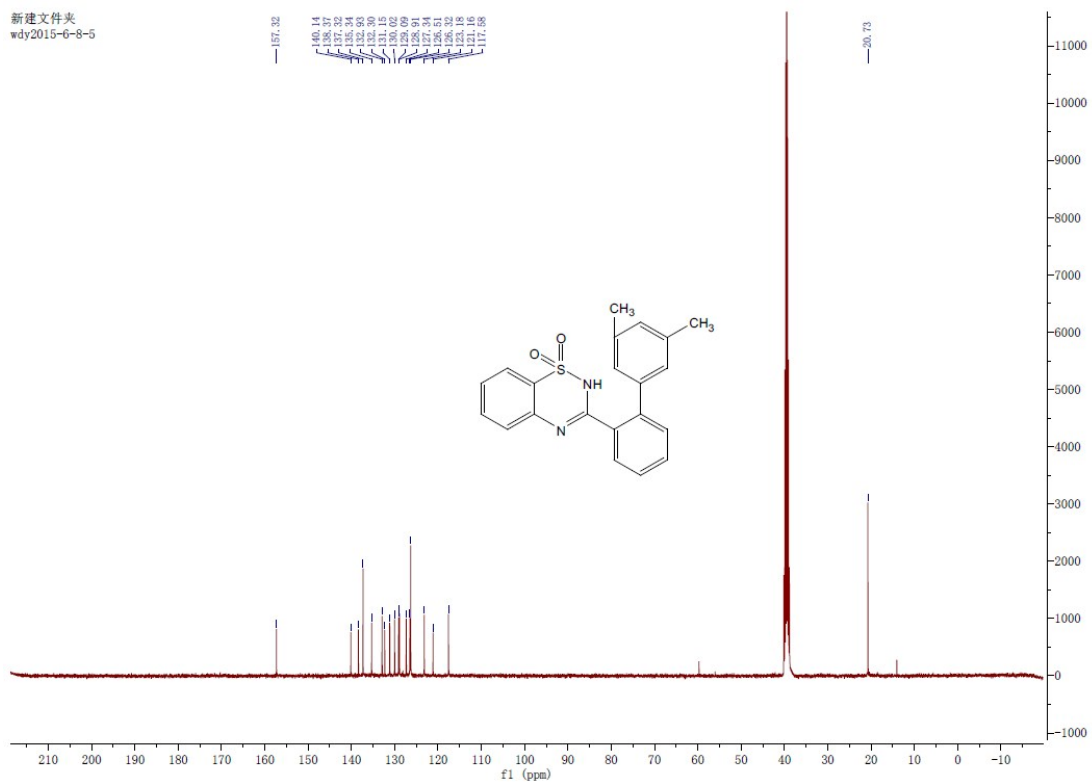
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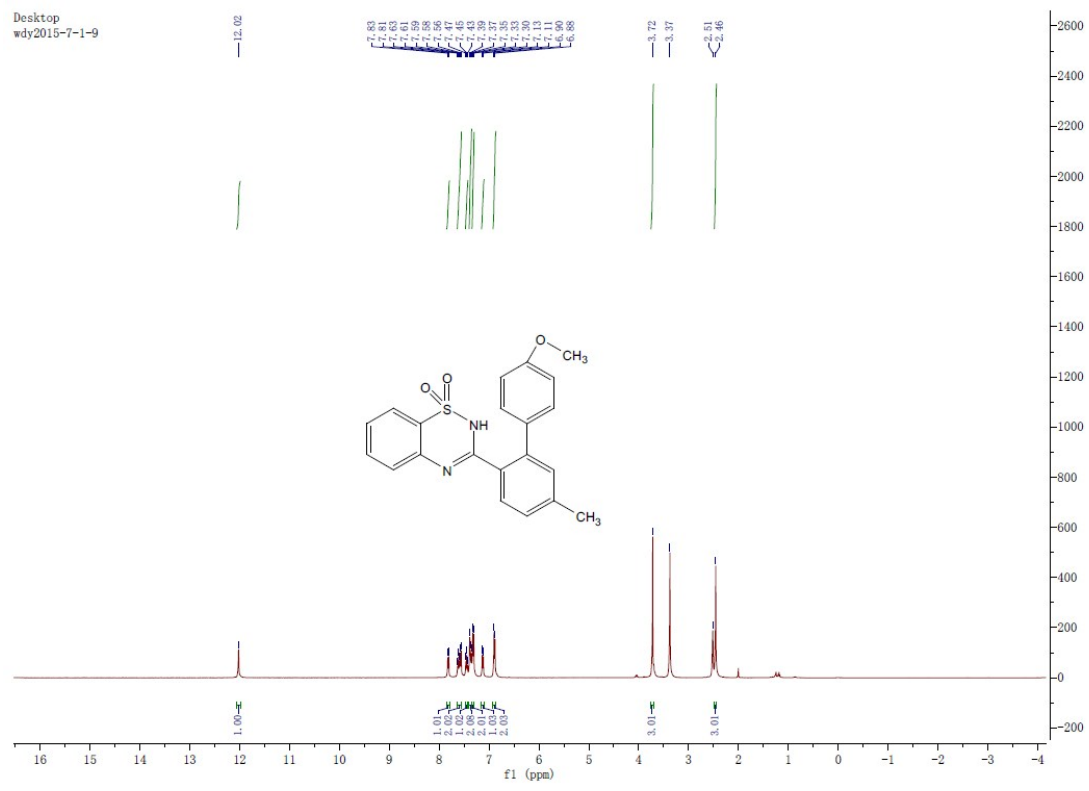
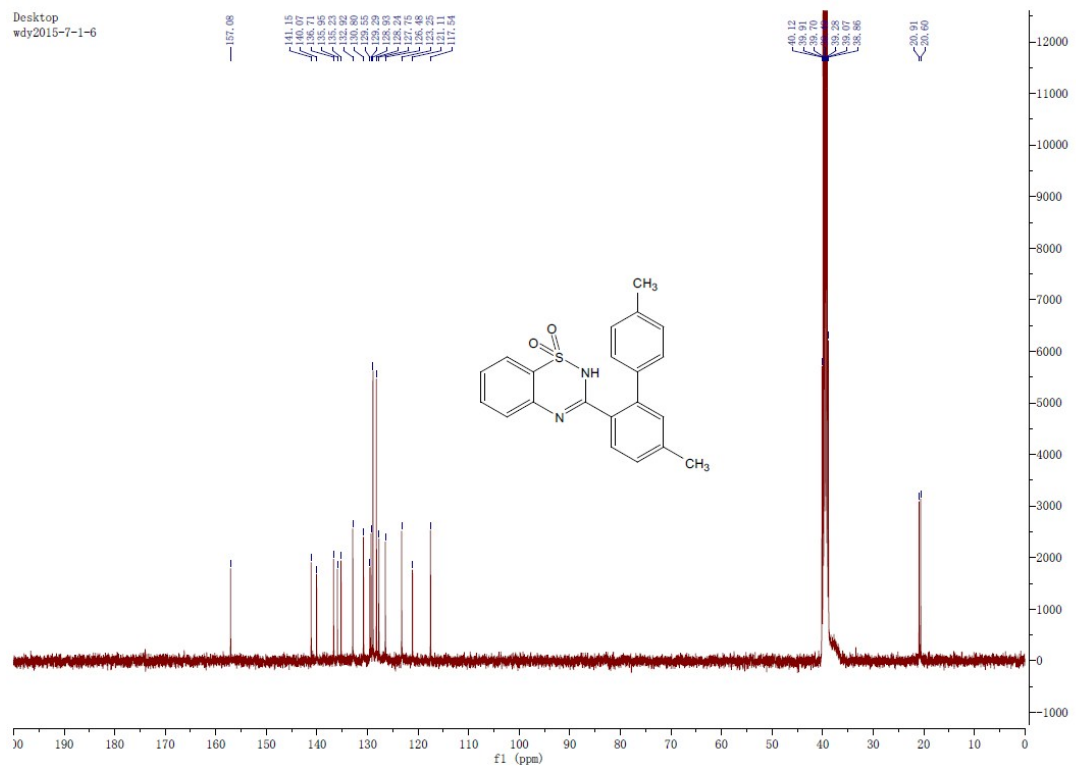


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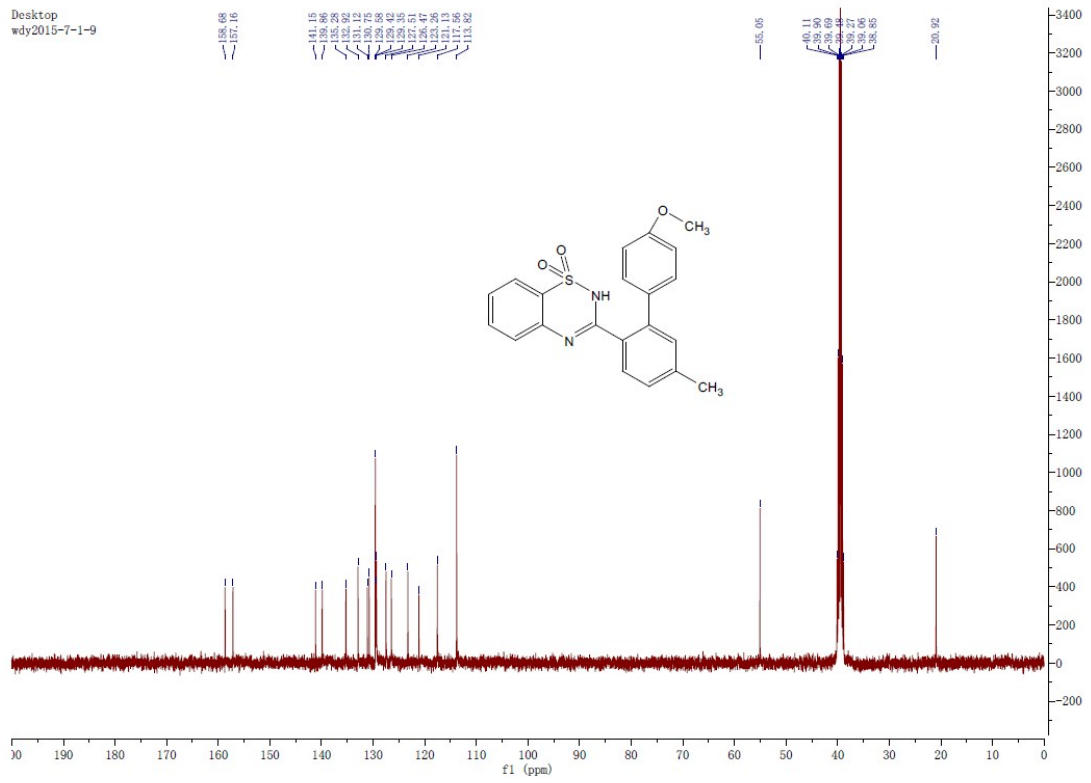


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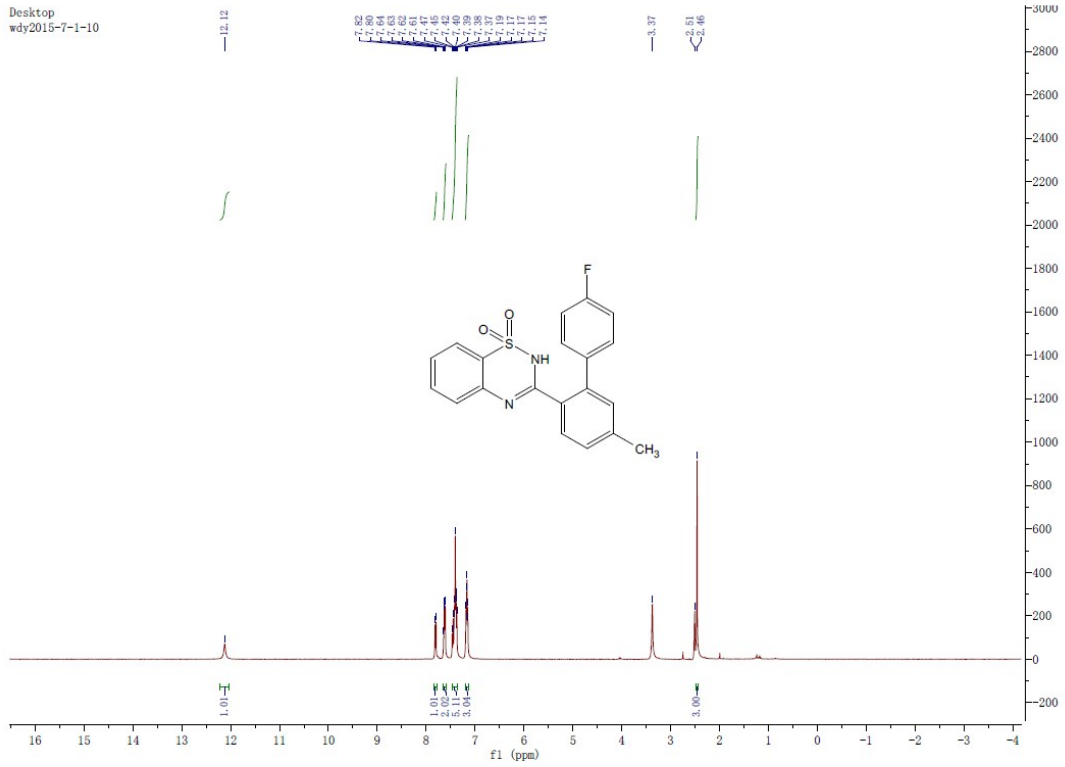




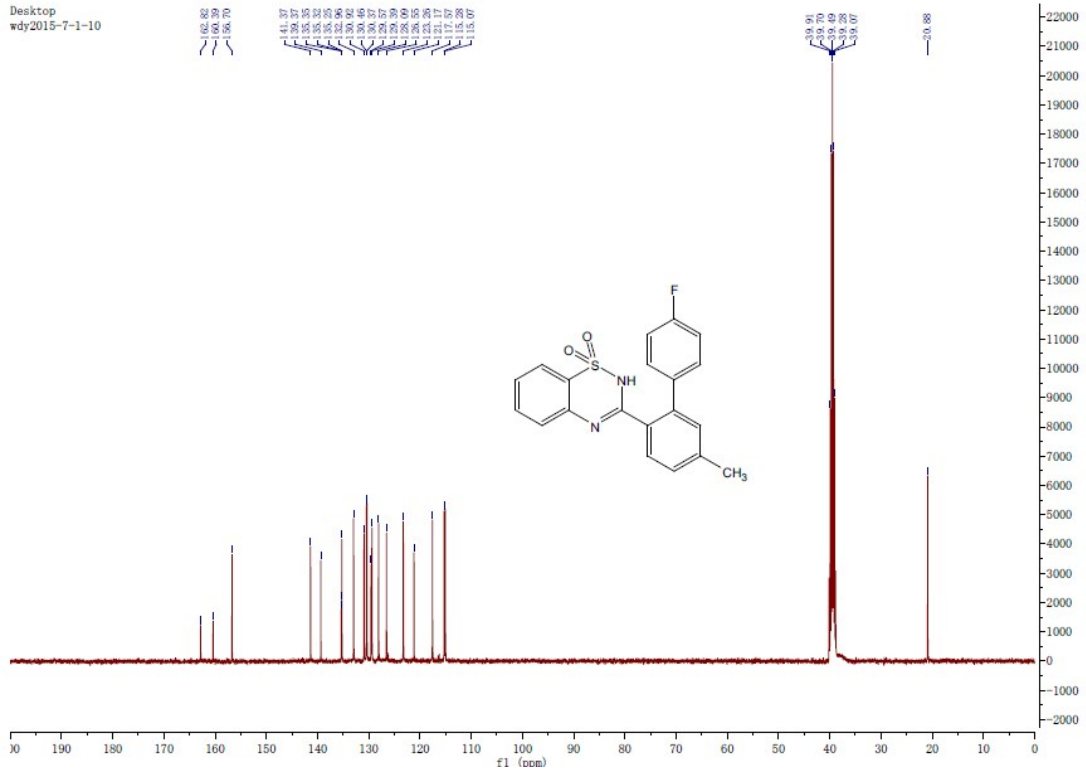
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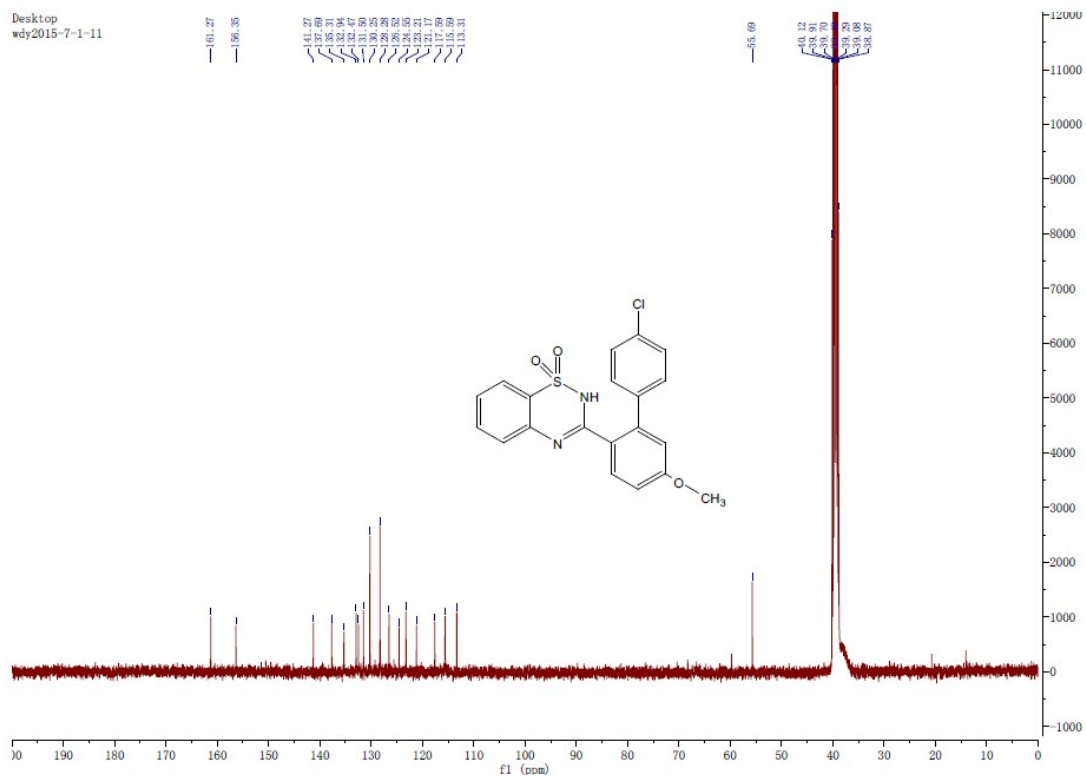
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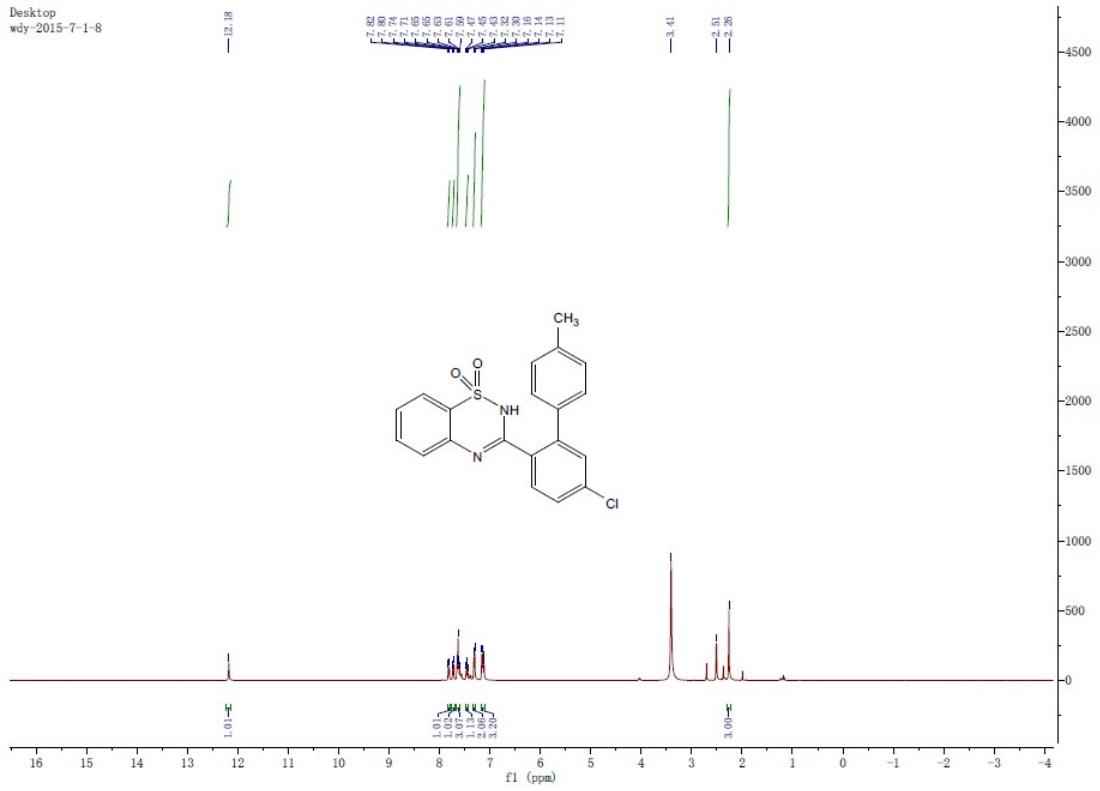
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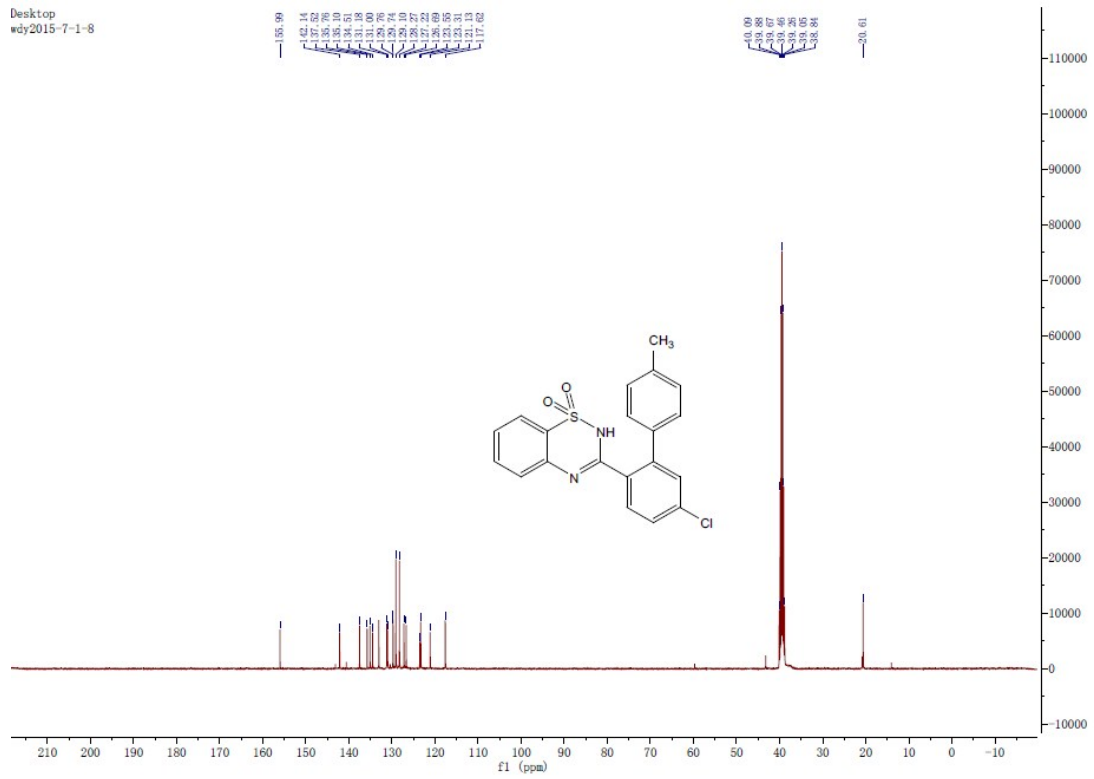
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