Supporting Information

A Novel and Versatile Entry to Asymmetrically Substituted Pyrazines

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General experimental methods.

^{1}H NMR spectra were recorded on 300 MHz instrument using $CDCl_3$ as solvent unless otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as an internal reference. Mass spectra were recorded by using ion source temperature was 150-250°C, as required. High-resolution EI-mass spectra were performed with a resolution of 10,000. Purification of compounds using preparative HPLC was carried out in system equipped with a Photo Diode Array detector. Analytical C18 column, 150 x 21.20 mm, 5 micron. For thin-layer chromatography, analytical TLC plates (SIL G/UV_{254}) and 70-230 mesh silica gel were used. Melting points of the compounds were determined and are uncorrected.

Microwave Irradiation Experiments. All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300W maximum power. The reactions were carried out in 10-mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. Initially, microwave irradiation of required watts was used and the temperature is being ramped from room temperature to the desired temperature. Once this was reached the reaction mixture was held at this temperature for the required time. The reaction mixture was continuously stirred during the reaction. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, gas jet cooling cooled the reaction vessel rapidly to ambient temperature.

1-(4-methoxybenzyl)-5-chloro-3-methoxypyrazin-2(1H)-one (2a): 100 % yield. white crystalline solid. m.p. 134- 135 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 10.0 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.80 (s, 1H), 4.99 (s, 2H), 3.99 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 155.5, 150.4, 130.3, 126.7, 123.1, 118.6, 114.6, 55.4, 51.6. HR-MS (EI): $C_{13}H_{13}ClN_2O_3$ calcd. 280.0615, found 280.0614.

1-(4-methoxybenzyl)-5-chloro-3-methoxy-6-(4-methoxyphenyl)pyrazin-2(1H)-one (2b): 100% yield. white crystalline solid. m.p. 123- 125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 9.1 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 2H), 6.70 (d, *J* = 9.1 Hz, 2H), 4.99 (s, 2H), 4.05 (s, 3H), 3.87 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 159.2, 154.6, 151.4, 131.7, 130.6, 129.3, 127.8, 123.5, 123.3, 114.2, 113.8, 55.5, 55.3, 49.2. HR-MS (EI): $C_{20}H_{19}ClN_2O_4$ calcd. 386.1033, found 386.1056.

1-(4-methoxybenzyl)-5-chloro-3-methylpyrazin-2(1H)-one (2c): 92% yield. Colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 10.1 Hz, 2H), 7.06 (s, 1H), 6.89 (d, *J* = 10.1 Hz, 2H), 4.98 (s, 2H), 3.81 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 158.5, 155.2, 130.4, 126.3, 125.8, 124.1, 114.7, 55.5, 52.1, 21.1. HR-MS (EI): $C_{13}H_{13}ClN_2O_2$ calcd. 264.0666, found 264.0670.

1-(4-methoxybenzyl)-5-chloro-3-methoxypyrazin-2(1H)-thione (3a): 85% yield. yellow crystalline solid. m.p. 130 - 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, *J* = 10.1 Hz, 2H), 7.12 (s, 1H), 6.91 (d, *J* = 9.2 Hz, 2H), 5.57 (s, 2H), 4.06 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 161.2, 160.3, 130.7, 130.2, 128.5, 125.4, 121.9, 114.8, 114.4, 58.8, 56.7, 55.5. HR-MS (EI): $C_{13}H_{13}ClN_2O_2S$ calcd. 296.0386, found 296.0394.

1-(4-methoxybenzyl)-5-chloro-3-methoxy-6-(4-methoxyphenyl)pyrazin-2(1H)-thione (3b): 81% yield. yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 – 6.73 (m, 8H), 5.71 (bs, 2H), 4.11 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 160.2, 159.3, 134.8, 131.6, 130.5, 128.5, 126.6, 123.9, 114.6, 114.2, 60.8, 56.7, 55.8, 55.6. HR-MS (EI): $C_{20}H_{19}ClN_2O_3S$ calcd. 402.0805, found 402.0812.

1-(4-methoxybenzyl)-5-chloro-3-methylpyrazin-2(1H)-one (3c): 92% yield. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.28 (d, *J* = 9.1 Hz, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 5.53 (s, 2H), 3.83 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 166.3, 160.4, 132.6, 130.9, 127.1, 125.0, 114.9, 59.6, 55.5, 26.6. HR-MS (EI): $C_{13}H_{13}ClN_2OS$ calcd. 280.0437, found 280.0478.

5-chloro-3-methoxy-2-(methylthio)pyrazine (4a): 71% yield. Yellow crystalline solid. m.p. 76-78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (s, 1H), 4.04 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5, 145.3, 139.9, 134.2, 54.9, 12.3. HR-MS (EI): $C_6H_7ClN_2OS$ calcd. 189.9968, found 189.9954.

2-chloro-6-methoxy-3-(4-methoxyphenyl)-5-(methylthio)pyrazine (4b): 73% yield. Yellow crystalline solid. m.p. 115-117 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 9.8 Hz, 2H), 6.96 (d, *J* = 9.8 Hz, 2H), 4.05 (s, 3H), 3.85 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 153.2, 144.2, 142.6, 136.7, 130.8, 129.8, 129.0, 113.5, 55.4, 54.9, 12.2. HR-MS (EI): $C_{13}H_{13}ClN_2O_2S$ calcd. 296.0368, found 296.0380.

5-iodo-3-methyl-2-(methylthio)pyrazine (4c): 67% yield. White crystalline solid. m.p. 65-67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (s, 1H), 2.52 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 148.8, 113.9, 109.0, 21.4, 13.0. HR-MS (EI): $C_6H_7IN_2S$ calcd. 265.9375, found 265.9373.

A typical procedure for the Suzuki Coupling to generate compound 5a-h.

In a 10 mL microwave vial were successively dissolved in Dioxane/H_2O (1:1, 3 mL) halopyrazine **4a-c** (0.3 mmol), boronic acid **6a-g** (0.36 mmol, 1.2 equiv), $Pd(PPh_3)_4$ (8 mg, 2 mol %) and K_2CO_3 (84 mg, 2 equiv). The reaction tube was sealed and irradiated at a ceiling temperature of 120 °C using 150 W maximum power for 10 min. After the reaction mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2×50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to preparative HPLC column chromatography. All the compounds were purified by reversed phase preparative HPLC using acetonitrile/water (with 0.1% HCOOH) as the eluent. All gradients ran between 80:20:0.01 (water:acetonitrile:HCOOH) and 0:100:0.01 (water:acetonitrile:HCOOH) for 20 min, with the UV detector set at λ = 215 and 254 nm to afford compounds **5a-h**.

3-methoxy-5-(4-methoxyphenyl)-2-(methylthio)pyrazine (5a): 92% yield. white crystalline solid. m.p. 95-97 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.92 (d, *J* = 9.9 Hz, 2H), 6.97 (d, *J* = 9.9 Hz, 2H), 4.09 (s, 3H), 3.85 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 155.8, 143.8, 143.6, 131.6, 129.0, 127.6, 114.3, 55.5, 53.8, 12.1. HR-MS (EI): $C_{13}H_{14}N_2O_2S$ calcd. 262.0776, found 262.0772.

3-methoxy-2-(methylthio)-5-p-tolylpyrazine (5b): 91% yield. yellow crystalline solid. m.p. 90-92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.88 (d, *J* = 8.9 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 4.11 (s, 3H), 2.57 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 144.5, 143.8, 139.1, 133.7, 132.1, 129.7, 126.2, 53.9, 21.4, 12.2. HR-MS (EI): $C_{13}H_{14}N_2OS$ calcd. 246.0827, found 246.0831.

2-methoxy-5-(4-methoxyphenyl)-3-(methylthio)-6-(naphthalen-2-yl)pyrazine (5c): 94% yield. colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.80 – 7.76 (m, 2H), 7.69 (d, *J* = 9.5 Hz, 2H), 7.47 – 7.43 (m, 3H), 7.41 (d, *J* = 9.6 Hz, 2H), 6.77 (d, *J* = 9.6 Hz, 2H), 4.12 (s, 3H), 3.77 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 154.2, 143.6, 141.9, 136.5, 133.4, 133.0, 131.4, 131.1, 129.2, 128.6, 127.7, 127.6, 127.5, 126.4, 126.2, 113.7, 55.3, 54.2, 12.1. HR-MS (EI): $C_{23}H_{20}N_2O_2S$ calcd. 388.1245, found 388.1243.

2-(4-tert-butylphenyl)-6-methoxy-3-(4-methoxyphenyl)-5-(methylthio)pyrazine (5d): 87% yield. Yellow solid. m.p. 120 - 122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.38 (m, 4H), 7.28 (d, *J* = 9.2 Hz, 2H), 6.81 (d, *J* = 9.8 Hz, 2H), 4.08 (s, 3H), 3.81 (s, 3H), 2.60 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 154.3, 151.1, 143.3, 142.9, 142.1, 135.8, 131.7, 131.1 (x 2C), 129.4 (x 2C), 125.2, 113.6, 55.4, 54.1, 34.8, 31.4 (x 3C), 12.1. HR-MS (EI): $C_{23}H_{26}N_2O_2S$ calcd. 394.1715, found 394.1717.

5-(3-(trifluoromethyl)phenyl)-3-methyl-2-(methylthio)pyrazine (5f): 68% yield. yellow solid m. p. 59-61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.15 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.67 – 7.56 (m, 2H), 2.61 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 150.9, 150.0, 144.8, 138.3, 137.6, 131.7, 131.3, 129.5, 126.7, 126.0, 125.7, 125.6, 123.4, 116.5, 21.7, 13.0. HR-MS (EI): $C_{13}H_{11}F_3N_2S$ calcd. 284.0595, found 284.0596.

Ethyl-4-(6-methyl-5-(methylthio)pyrazin-2-yl)benzoate (5g): 99% yield. Yellow solid. m.p. 242 - 244 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.13 (d, *J* = 9.3 Hz, 2H), 8.04 (d, *J* = 9.4 Hz, 2H), 4.44 – 4.36 (m, 2H), 2.60 (s, 3H), 2.58 (s, 3H), 1.44 – 1.39 (t, *J* = 7.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 155.3, 150.9, 145.1, 140.9, 138.4, 134.0, 133.7, 130.7 (x 2C), 126.2 (x 2C), 61.2, 54.1, 21.8, 14.5, 12.9. HR-MS (EI): $C_{15}H_{16}N_2O_2S$ calcd. 288.0932, found 288.0935.

5-(4-tert-butylphenyl)-3-methyl-2-(methylthio)pyrazine (5h): 89% yield. white crystalline solid. m.p. 110 - 111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.89 (d, *J* = 9.2 Hz, 2H), 7.49 (d, *J* = 9.2 Hz, 2H), 2.59 (s, 3H), 2.56 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 152.3, 150.6, 146.6, 138.0, 134.0, 126.3 (x 2C), 126.0 (x 2C), 34.8, 31.4, 21.8, 12.9. HR-MS (EI): $C_{16}H_{20}N_2S$ calcd. 272.1347, found 272.1351.

Sonogashira coupling reaction on 4a, 4c. A typical procedure. In a 10 mL microwave vial were successively dissolved in DMF/Et_3N (1:1, 3 mL) compound **4a, 4c** (0.31 mmol), acetylene (0.37 mmol, 1.2 equiv.), $Pd(PPh_3)Cl_2$ (5 mg, 2 mol %), TBAB (1.2 equiv.) and CuI (3 mg, 5 mol %). The reaction tube was sealed, and irradiated in microwave at a ceiling temperature of 90 °C using 50 W maximum power for 20 min. After the reaction mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2×150 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to preparative HPLC column chromatography. All the compounds were purified by reversed phase preparative HPLC using acetonitrile/water (with 0.1% HCOOH) as the eluent. All gradients ran between 80:20:0.01 (water:acetonitrile:HCOOH) and 0:100:0.01 (water:acetonitrile:HCOOH) for 20 min, with the UV detector set at λ = 215 and 254 nm to afford compounds **7a-c**.

3-methoxy-2-(methylthio)-5-(2-phenylethynyl)pyrazine (7a): 69% yield. yellow oil.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.60 – 7.57 (m, 2H), 7.39 – 7.37 (m, 3H), 4.07 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (75

MHz, $CDCl_3$): δ 155.7, 147.0, 139.1, 131.9, 129.6, 129.1, 128.5, 122.2, 116.5, 91.5, 86.3, 54.4, 12.1. HR-MS (EI): $C_{14}H_{12}N_2OS$ calcd. 256.0670, found 256.0675.

3-methoxy-2-(methylthio)-5-(2-p-tolylethynyl)pyrazine (7b): 74% yield. yellow oil.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.48 (d, *J* = 9.1 Hz, 2H), 7.18 (d, *J* = 9.1 Hz, 2H), 4.06 (s, 3H), 2.55 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 144.9, 139.4, 132.3, 129.9, 129.5, 128.3, 122.8, 116.9, 99.4, 86.2, 54.3, 21.5, 12.3. HR-MS (EI): $C_{15}H_{14}N_2OS$ calcd. 270.0827, found 270.0834.

3-methyl-2-(methylthio)-5-(2-phenylethynyl)pyrazine (7c): 81% yield. yellow oil.^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.61 – 7.58 (m, 2H), 7.38 – 7.36 (m, 3H), 2.59 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 151.2, 144.1, 133.0, 132.1, 129.2, 128.5, 122.2, 92.0, 6.3, 21.6, 13.0. HR-MS (EI): $C_{14}H_{12}N_2S$ calcd. 240.0721, found 240.0728.

A typical procedure for the preparation of 7d.

In a 10 mL microwave vial was taken 1,4-dioxane (3 mL) **4a** (0.3 mmol), morpholine (0.375 mmol, 1.25 equiv), $Pd(OAc)_2$ (3.5 mg, 3 mol %) and (±)-BINAP (11 mg, 3.3 mol %), tetrabutylammonium bromide (1.0-1.2 equiv) and of NaO^tBu (1.5 equiv). The reaction tube was sealed and irradiated at a ceiling temperature of 130 °C at 300 W maximum power for 25 min. After the reaction mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2×50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to preparative HPLC column chromatography. The compound was purified by reversed phase preparative HPLC using acetonitrile/water (with 0.1% HCOOH) as the eluent. All gradients ran between 80:20:0.01 (water:acetonitrile:HCOOH) and 0:100:0.01 (water:acetonitrile:HCOOH) for 20 min, with the UV detector set at λ = 215 and 254 nm to afford compound **7d**.

3-methoxy-2-(methylthio)-5-morpholinopyrazine (7d): 62% yield. yellow oil.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 1H), 3.96 (s, 3H), 3.86 - 3.82 (m, 4H), 3.46 - 3.42 (m , 4H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.1, 151.2, 131.9, 119.7, 66.6, 53.7, 43.7, 12.7. HR-MS (EI): $C_{16}H_{20}N_2S$ calcd. 241.0885 found 241.0878.

A typical procedure for the Leibeskind - Srogl coupling to generate compound 8a-e.

In a 10 mL microwave vial were successively added compound **5a-d, 5g** (0.2 mmol), THF (3 mL), boronic acid **6a-d** (0.6 mmol, 3.0 equiv), $Pd(PPh_3)_4$ (11 mg, 5 mol %) and CuTC (76 mg, 2 equiv). The reaction tube was sealed and irradiated at a ceiling temperature of 110 °C using 200 W maximum power for 50 min. After the reaction mixture was cooled with an air flow for 15 min, extracted with dichloromethane (2×50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to preparative HPLC column chromatography. The compound was purified by reversed phase preparative HPLC using acetonitrile/water (with 0.1% HCOOH) as the eluent. All gradients ran between 80:20:0.01 (water:acetonitrile:HCOOH) and 0:100:0.01 (water:acetonitrile:HCOOH) for 25 min, with the UV detector set at λ = 215 and 254 nm to afford compound **8a-e**.

2-(3-ethoxyphenyl)-3-methoxy-5-(4-methoxyphenyl)pyrazine (8a): 82% yield. white crystalline solid. m.p. 102 - 104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.04 (d, *J* = 9.5 Hz, 2H), 7.71 – 7.67 (m, 2H), 7. 39 – 7.34 (t, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 9.9 Hz, 2H), 6.97 – 6.93 (dd, 1H), 4.15- 4.08 (m, 2H), 4.12 (s, 3H), 3.86 (s, 3H), 1.46- 1.41 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0, 158.9, 157.1, 147.3, 139.9, 137.3, 132.1, 129.2, 128.7, 128.1 (x 2C), 121.5, 115.5, 114.9, 114.4 (x 2C), 63.6, 55.5, 53.5, 14.9. HR-MS (EI): $C_{20}H_{20}N_2O_3$ calcd. 336.1474, found 336.1470.

2-(3-ethoxyphenyl)-3-methoxy-5-p-tolylpyrazine (8b): 91% yield. yellow solid. m. p. 130 – 132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.85 – 7.80 (m, 3H), 7.73 (d, *J* = 9.6 Hz, 2H), 7.52 – 7.47 (m, 3H), 7.42 (d, *J* = 9.8 Hz, 2H), 7.25 (bs, 1H), 6.82 (d, *J* = 9.4 Hz, 2H), 4.19 (s, 3H), 3.79 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0, 159.2, 156.3, 147.3, 139.5, 139.2, 136.9, 135.4, 133.4, 133.2, 131.4, 131.1, 130.6 (x 2C), 129.7, 129.2, 128.7, 127.8, 127.2, 127.1, 126.9, 126.4, 113.9 (x 2C), 55.4, 54.4, 19.9. HR-MS (EI): $C_{20}H_{20}N_2O_2$ calcd. 320.1525, found 320.1522.

2-methoxy-5-(4-methoxyphenyl)-3-(3,4-dimethylphenyl)-6-(naphthalen-2-yl)pyrazine (8c): 94% yield. yellow solid m.p. 154-156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 9.6 Hz, 2H), 7.49 (d, *J* = 9.4 Hz, 2H), 7.46 – 7.41 (m, 4H), 7.33 (d, *J* = 9.2 Hz, 2H), 6.84 (d, *J* = 9.7 Hz, 2H), 4.14 (s, 3H), 3.83 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 154.2, 151.8, 146.5, 143.8, 137.6, 135.1, 134.4, 131.6 (x 2C), 131.1 (x 2C), 129.5, 128.5 (x 2C), 125.3 (x 2C), 113.7 (x 2C), 55.4, 53.9, 34.8, 31.4 (x 3C). HR-MS (EI): $C_{30}H_{26}N_2O_2$ calcd. 446.1994, found 446.1994.

2-(4-tert-butylphenyl)-5-(4-chlorophenyl)-6-methoxy-3-(4-methoxyphenyl)pyrazine (8d): 89% yield. yellow solid. m.p. 85-86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.72 – 7.67 (m, 2H), 7. 39 – 7.34 (t, *J* = 8.9 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.97 – 6.94 (dd, 1H), 4.15- 4.08 (m,

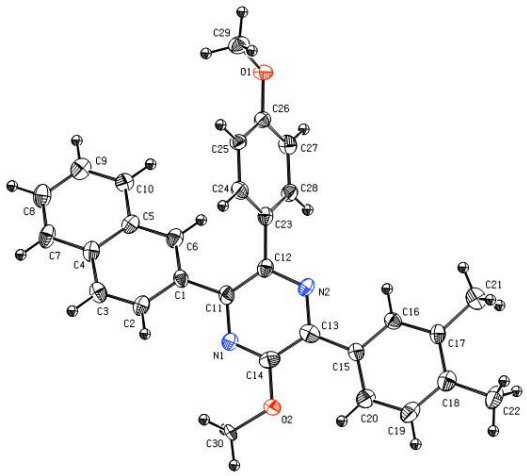
2H), 4.13 (s, 3H), 2.42 (s, 3H), 1.46 - 1.42 (t, J = 7.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 157.1, 147.5, 140.5, 139.9, 137.3, 133.5, 132.5, 129.7 (x 2C), 129.3, 126.7, 121.5, 115.6, 114.9 (x 2C), 63.6, 53.5, 21.5, 15.0. HR-MS (EI): $C_{28}H_{27}ClN_2O_2S$ calcd. 458.1761, found 458.1763.

Ethyl 4-(6-methyl-5-p-tolylpyrazin-2-yl)benzoate (8e): 78% yield. yellow crystalline solid. m.p. 140-141 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.18 (d, J = 9.5 Hz, 2H), 8.14 (d, J = 9.5 Hz, 2H), 7.54 (d, J = 8.9 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 4.46 – 4.39 (m, 2H), 2.74 (s, 3H), 2.44 (s, 3H), 1.46 – 1.41 (t, J = 7.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 155.8, 151.2, 148.5, 140.8, 139.0, 135.6, 131.3, 130.3 (x 2C), 129.3 (x 2C), 129.1 (x 2C), 126.8 (x 2C), 61.3, 23.7, 21.5, 14.5. HR-MS (EI): $C_{21}H_{20}N_2O_2$ calcd. 332.1525, found 332.1516.

Description of the compound **8c.**

The naphtyl moiety is torsioned with respect to the dimethoxypyrazine ring (angle of 28.5(2)° between planes through the component aromatic rings). This dimethoxypyrazine ring is almost planar with the dimethylphenyl ring (angle of 5.4(2)° between planes through the aromatic rings). The methoxyphenyl ring is also torsioned with respect to the rest of the molecule (angle of 68.5(2)° between the methoxyphenyl and pyrazine rings). A torsion angle C11-C12-C23-C24 of 67.4(4)° is observed. As the compound crystallized in the centrosymmetric space group P $\bar{1}$ (No. 2), an inverse conformer is present in the unit cell, due to the rotational freedom around the C1-C11, C13-C15 and C12-C23 single bonds. π-π stacking is observed in the packing between the pyrazine ring and the dimethylphenyl ring of a symmetry equivalent molecule (centroids distance of 3.755(2) Å).

Figure 2. Molecular structure of **8c**, showing atom-labelling and 50% probability displacement ellipsoids.



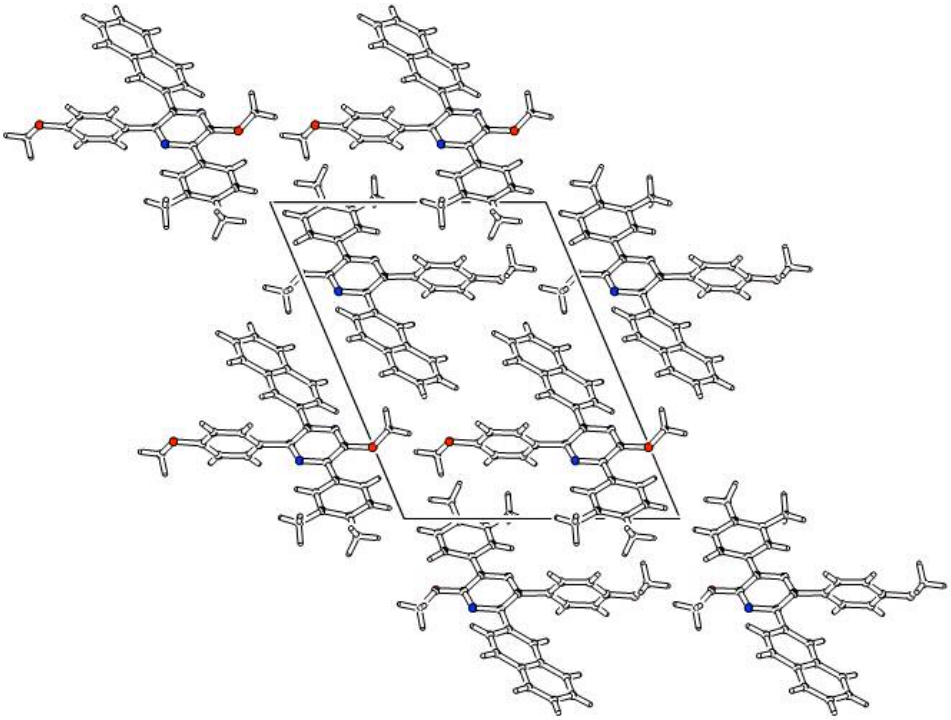
Crystallography (experimental)

Compound **8c**: needle-shaped crystals grown, by vapor diffusion, from a 1:1 dichloromethane/heptane mixture at room temperature, $C_{30}H_{26}N_2O_2$, M = 446.53, triclinic, P $\bar{1}$ (No. 2), a = 5.641(2), b = 13.376(2), c = 16.672(3) Å, α = 112.058(8)°, β = 96.477(9), γ = 95.546(10), V = 1145.2(4) Å^3, T = 100(2) K, Z = 2, D_c = 1.295 g cm^{-3}, μ(Cu-Kα) = 0.641 mm^{-1}, F(000) = 472, crystal size 0.5 × 0.1 × 0.1 mm, 3083 independent reflections (R_{int} = 0.1876). Final R = 0.0719 for 1582 reflections with $I > 2\sigma(I)$ and $\omega R2$ = 0.1563 for all data.
Intensity data were collected on a SMART 6000 diffractometer equipped with CCD detector using Cu-Kα radiation (λ = 1.54178 Å). The images were interpreted and integrated with the program SAINT from Bruker[1] The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using the SHELXTL program package.[2] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode with isotropic temperature factors fixed at 1.2 times

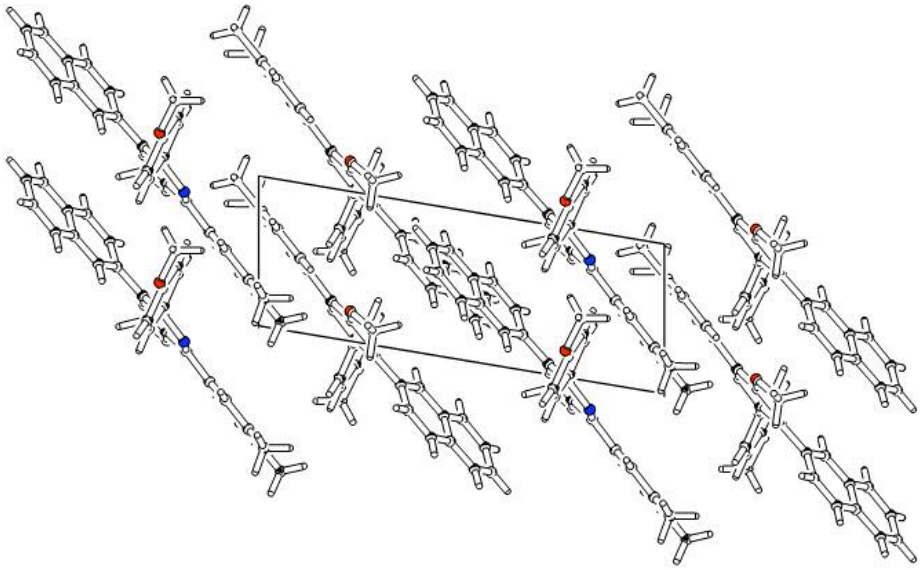
U(eq) of the parent atoms (1.5 times for methyl groups). CCDC -666941 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

[1] SAINT, Manual Version 5/6.0, Bruker Analytical X-ray Systems Inc.: Madison, Wisconsin, 1997.

[2] SHELXTL-NT, Manual Version 5.1, Bruker Analytical X-ray Systems Inc.: Madison, Wisconsin, 1997.

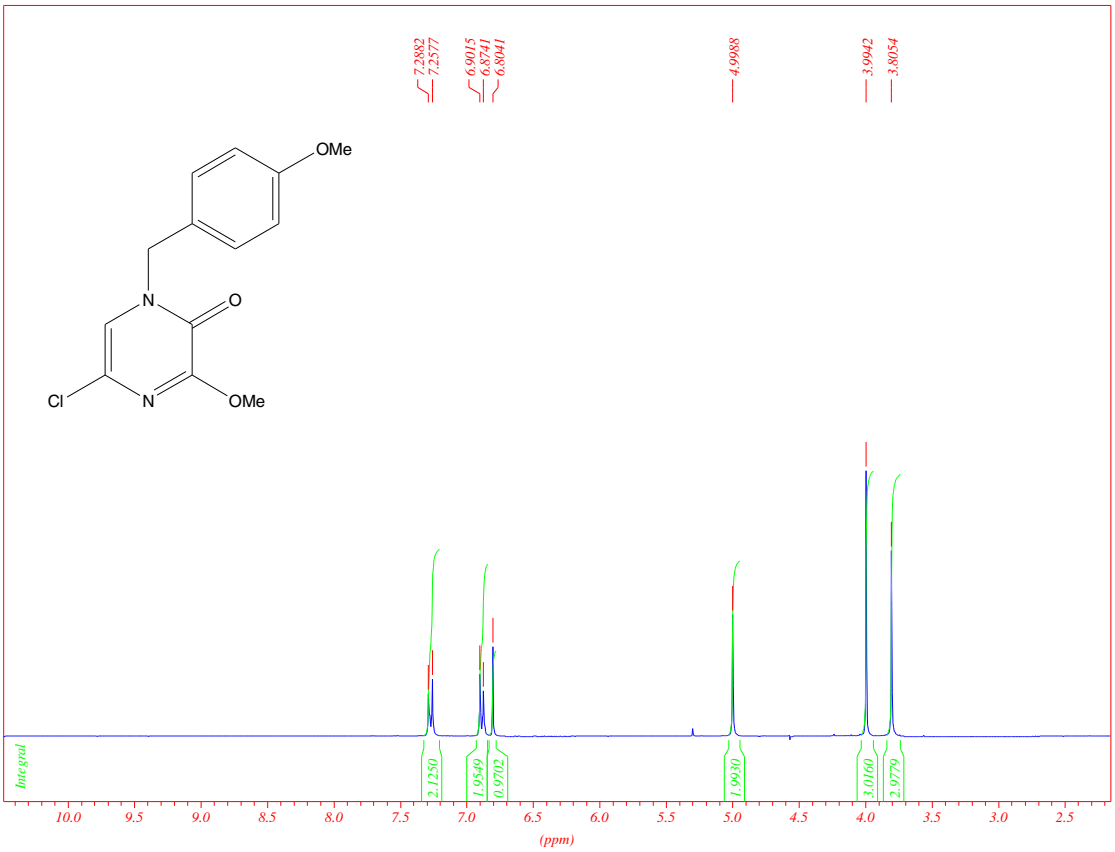


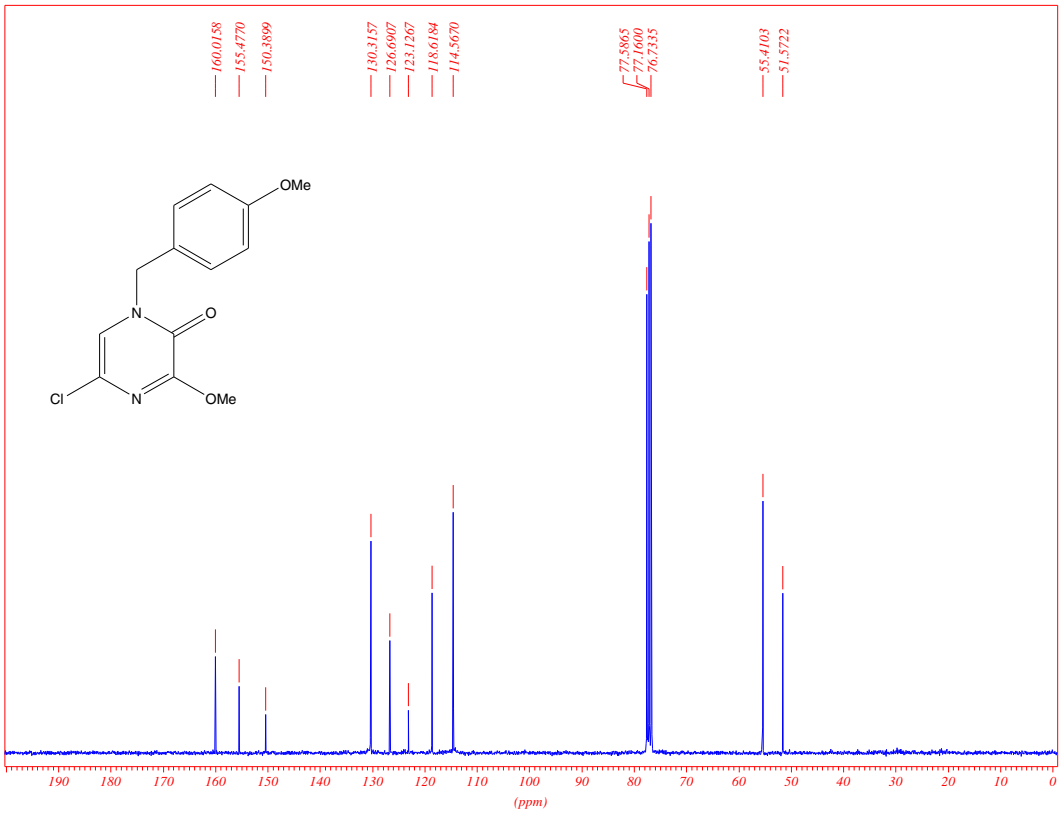
Packing of molecule through plane bc.



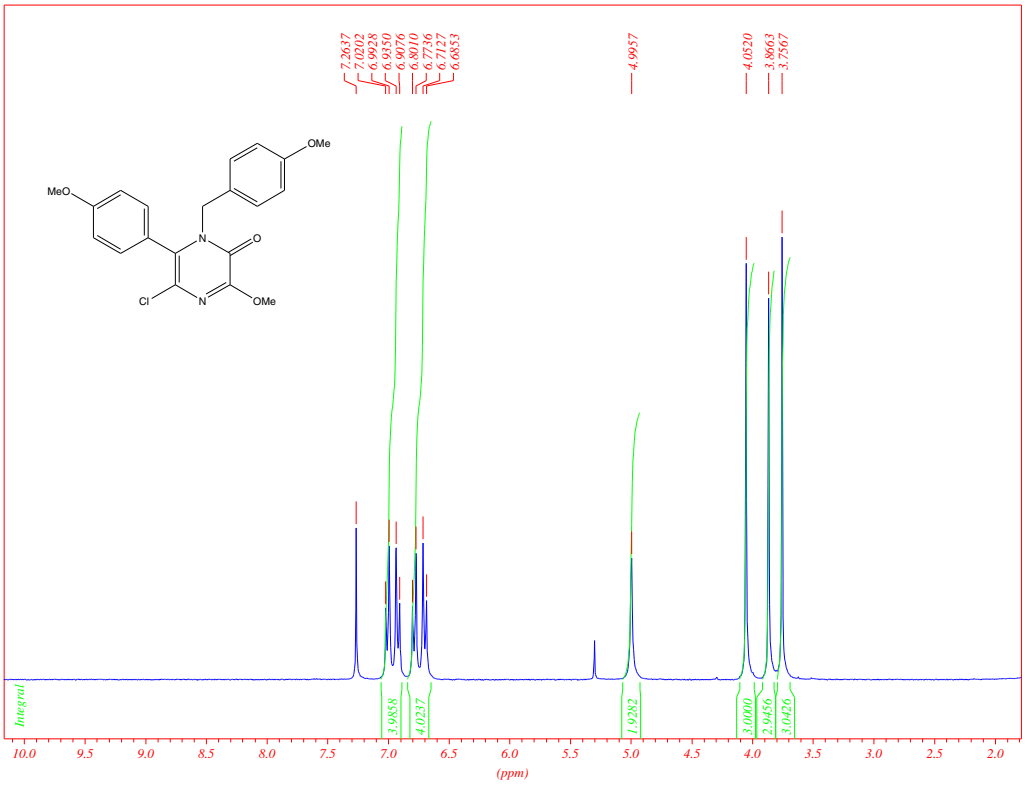
Packing of molecule through plane ac.

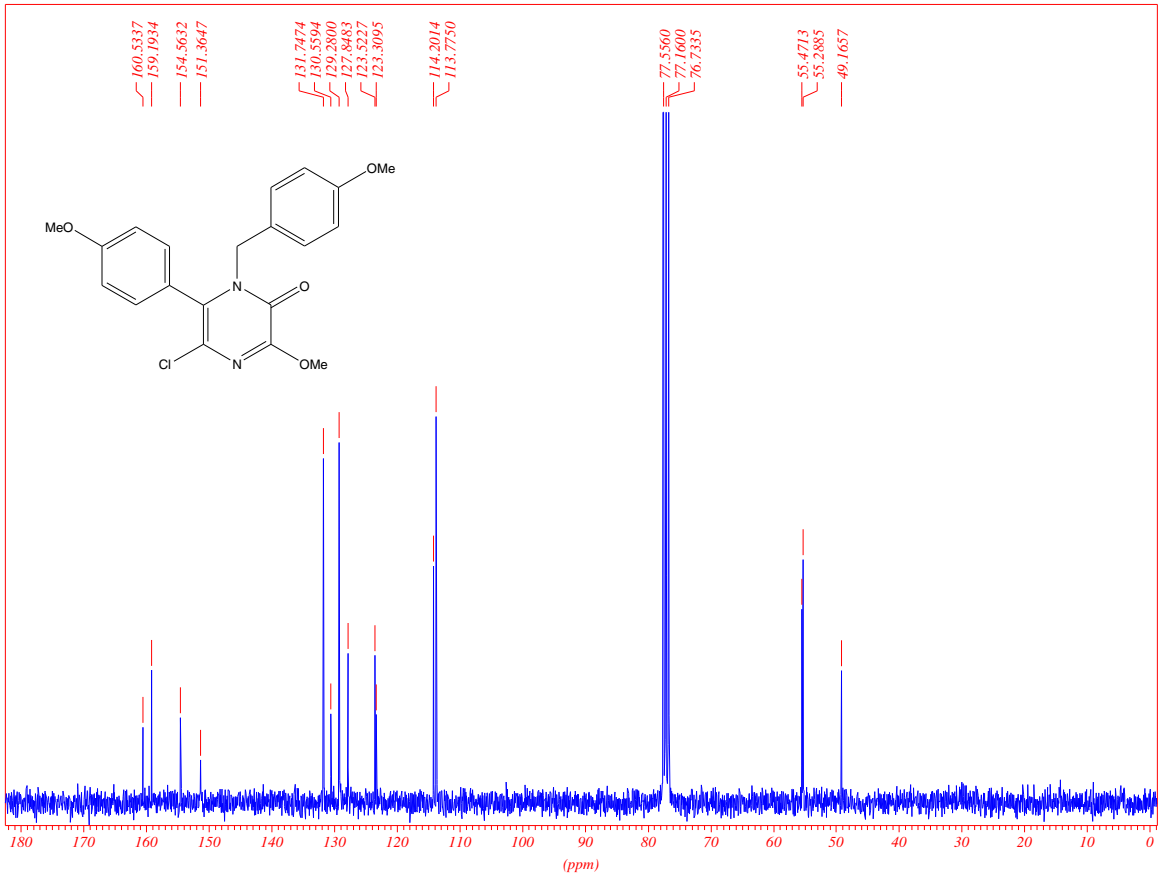
^{1}H and ^{13}C Spectra of compound 2a (300 MHz, $CDCl_3$).



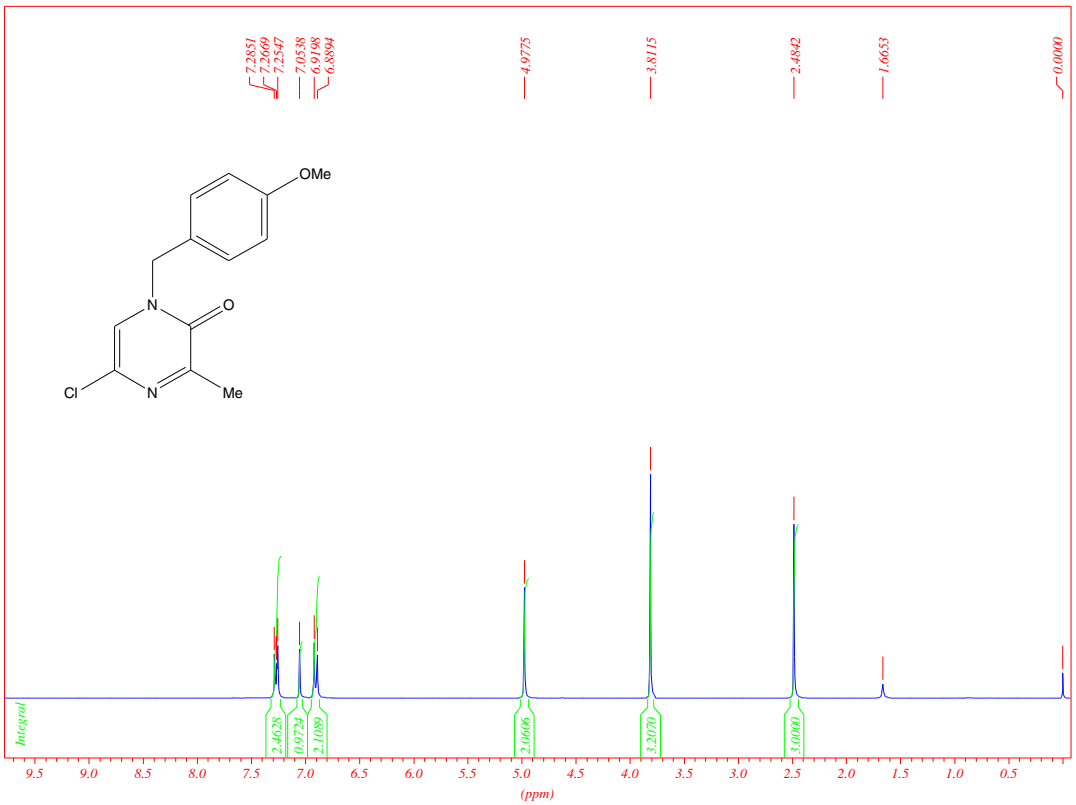


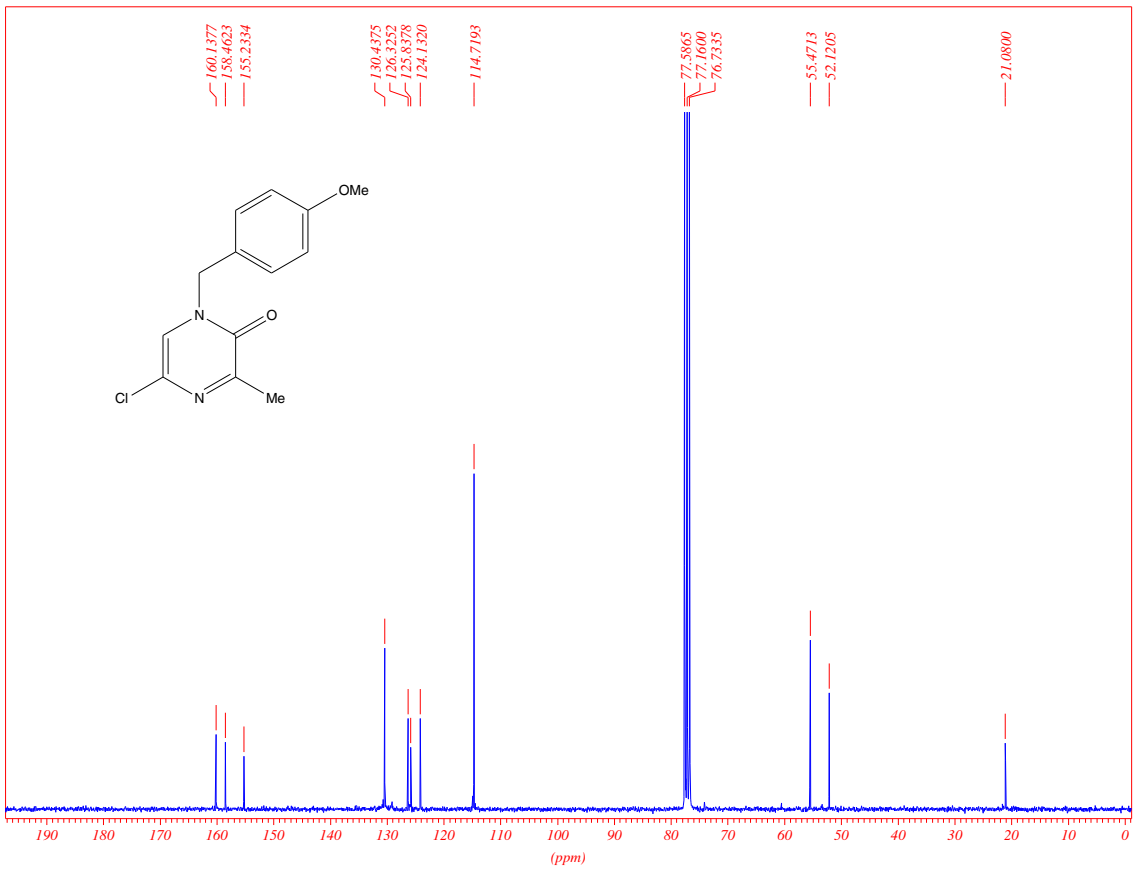
^{1}H and ^{13}C Spectra of compound 2b (300 MHz, $CDCl_3$).



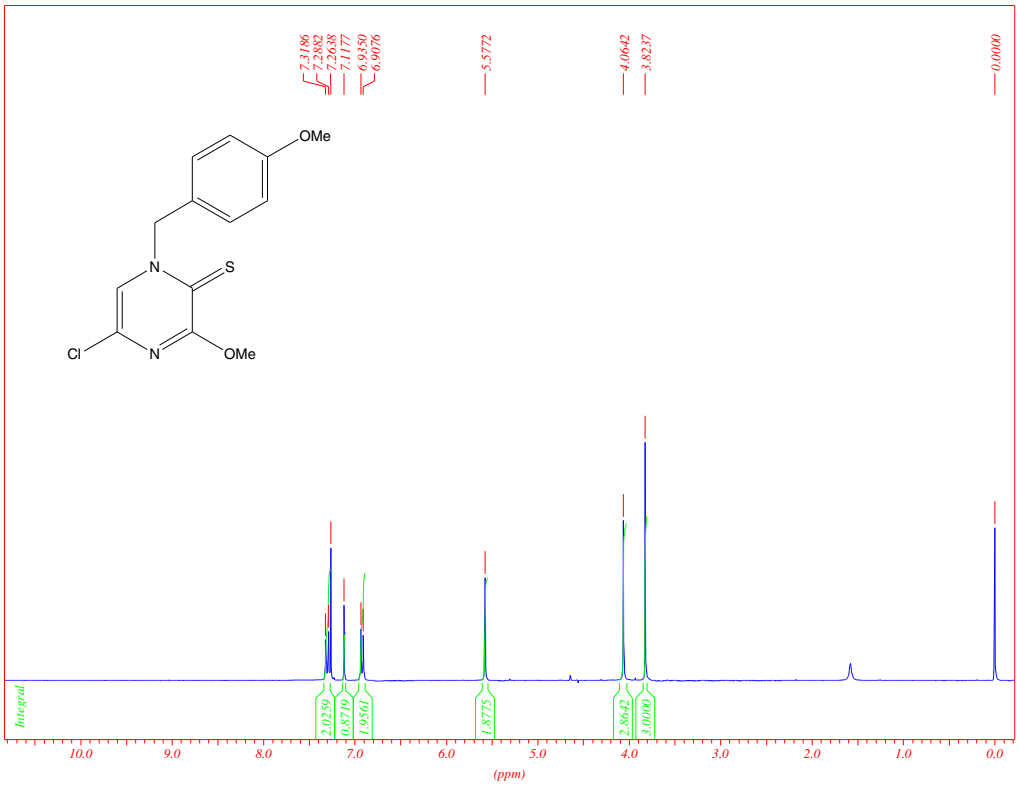


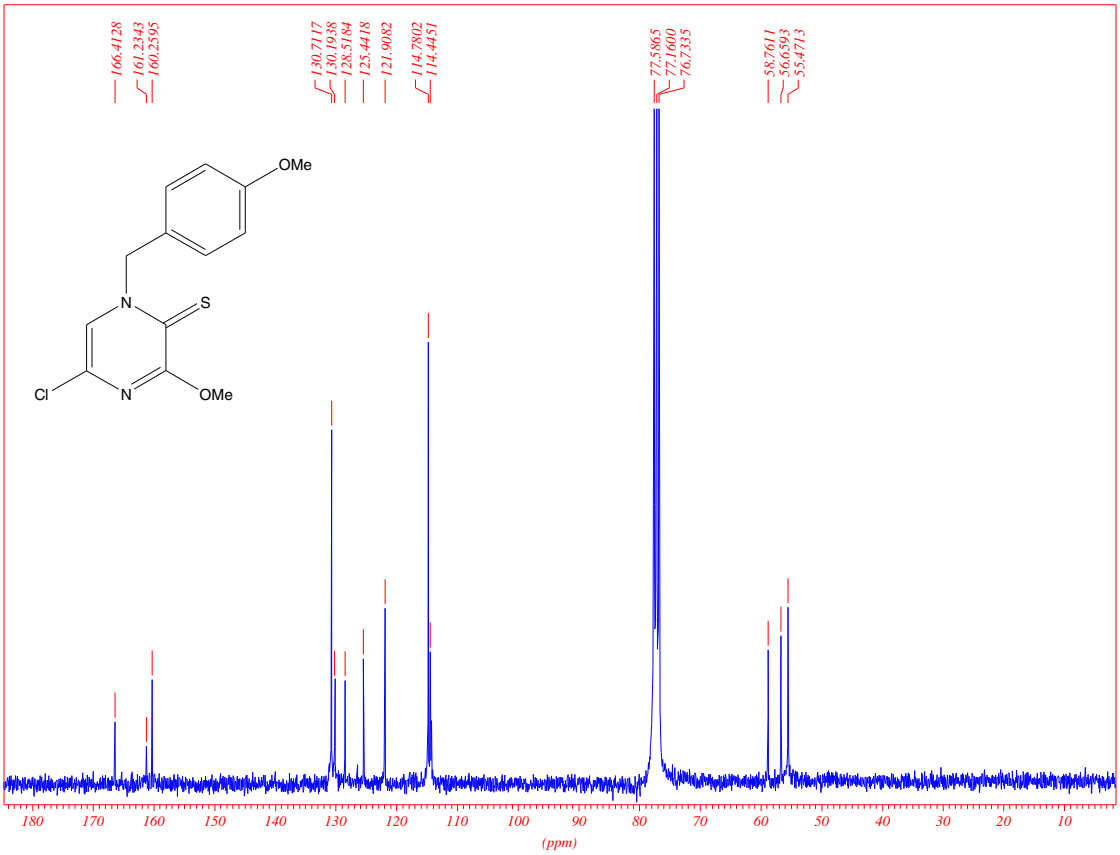
^{1}H and ^{13}C Spectra of compound 2c (300 MHz, $CDCl_3$).





^{1}H and ^{13}C Spectra of compound 3a (300 MHz, $CDCl_3$).





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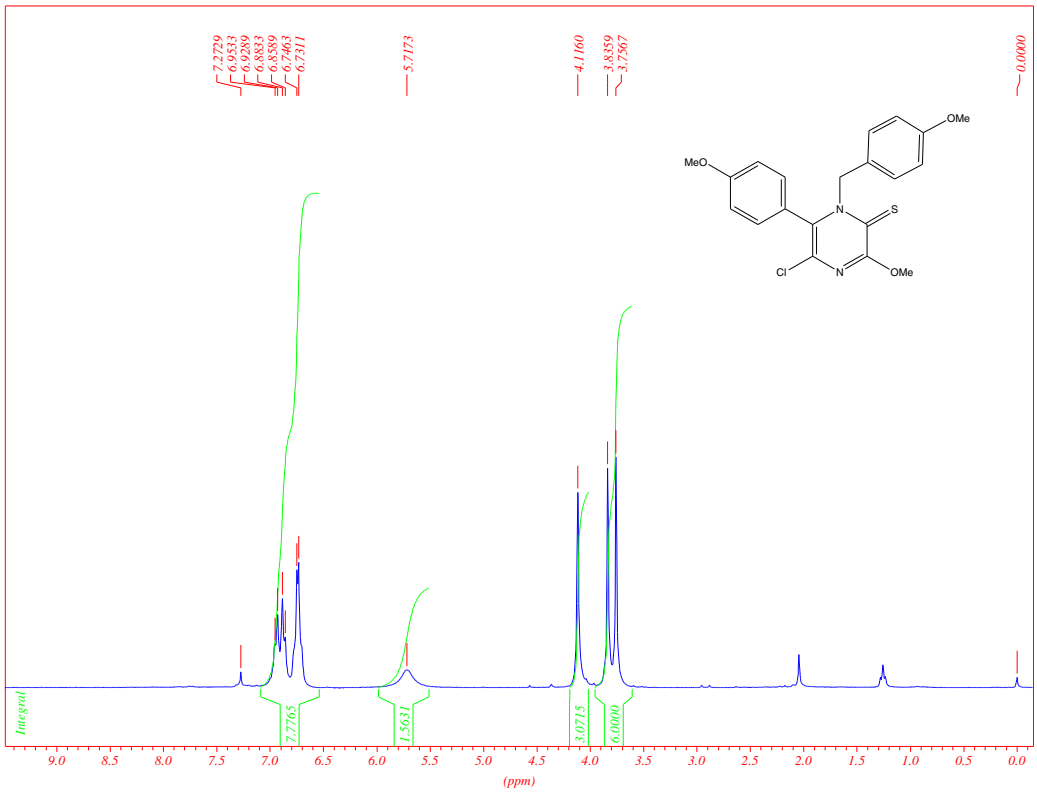
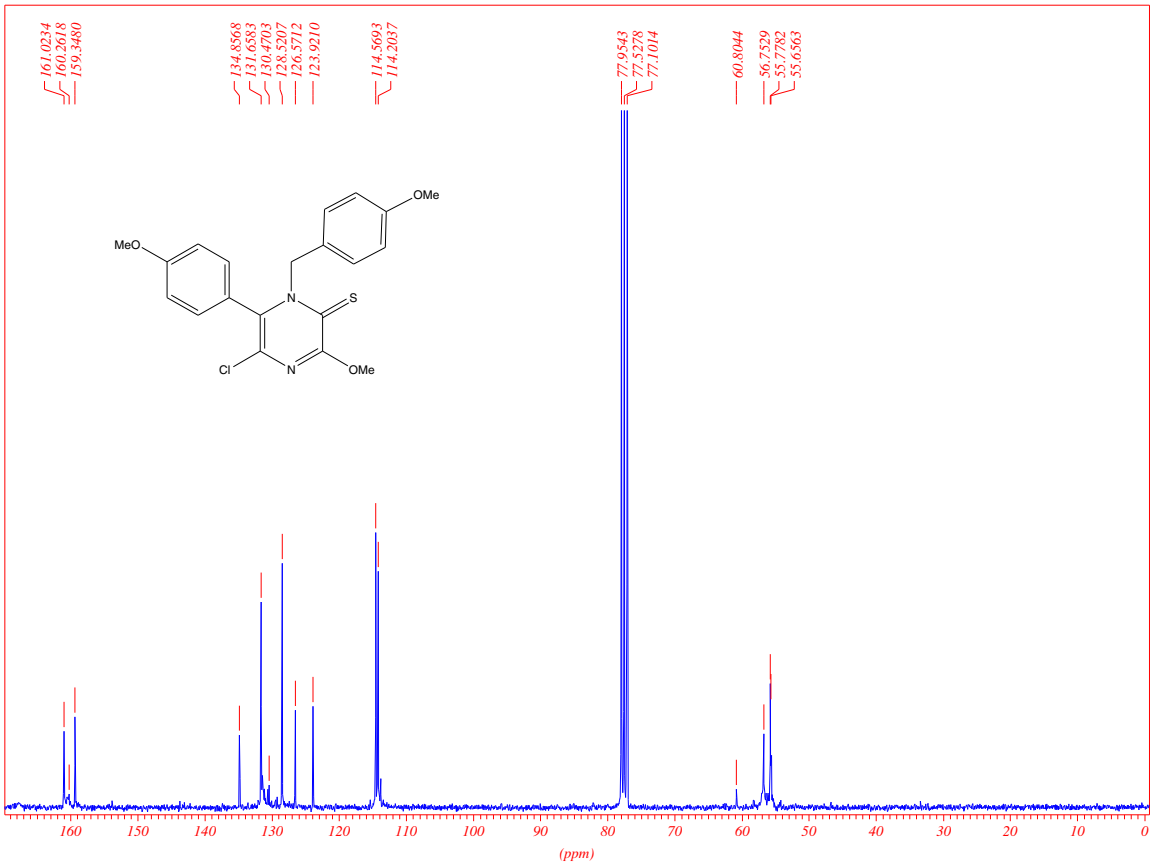
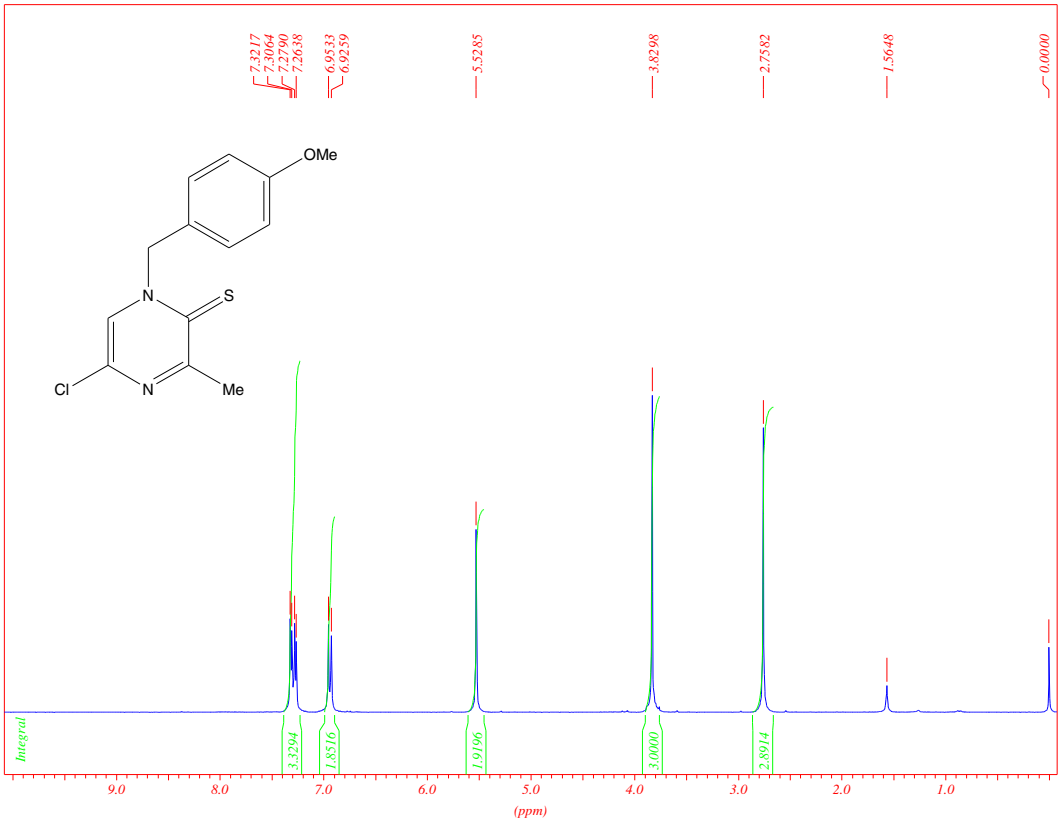
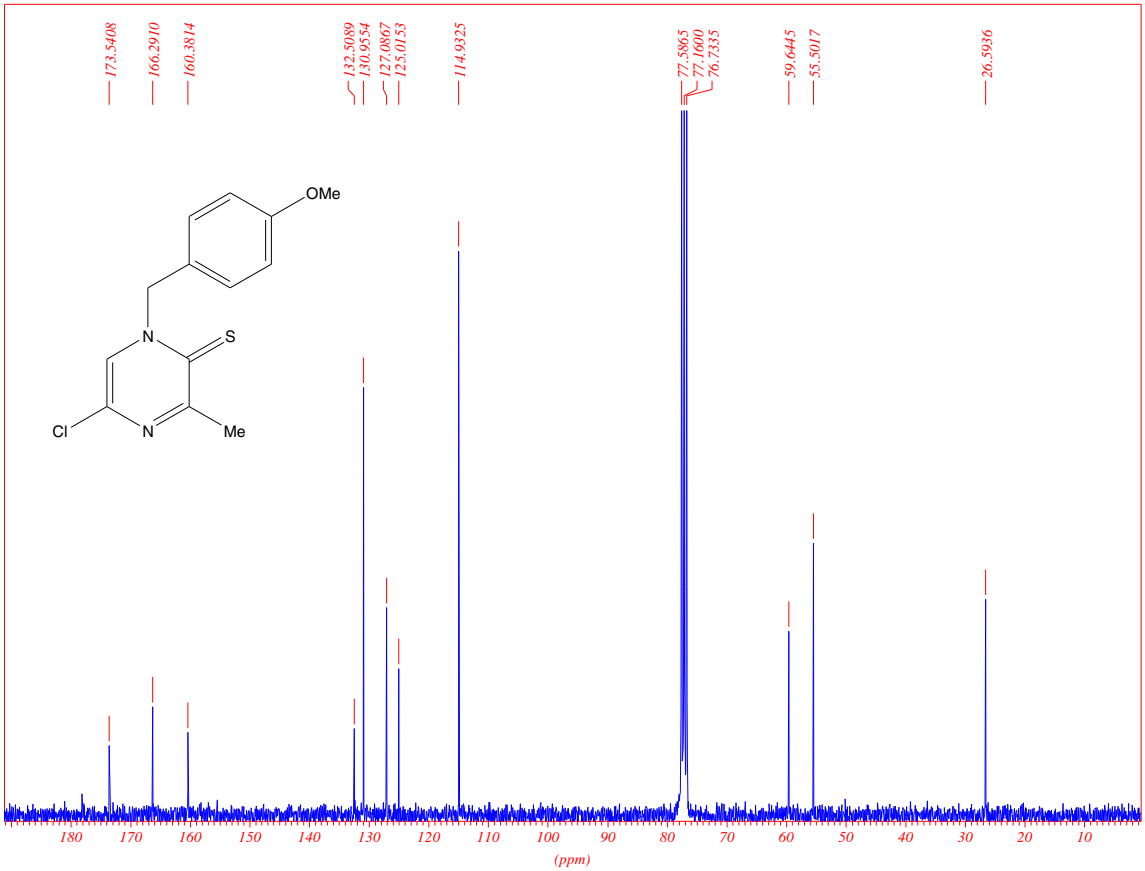


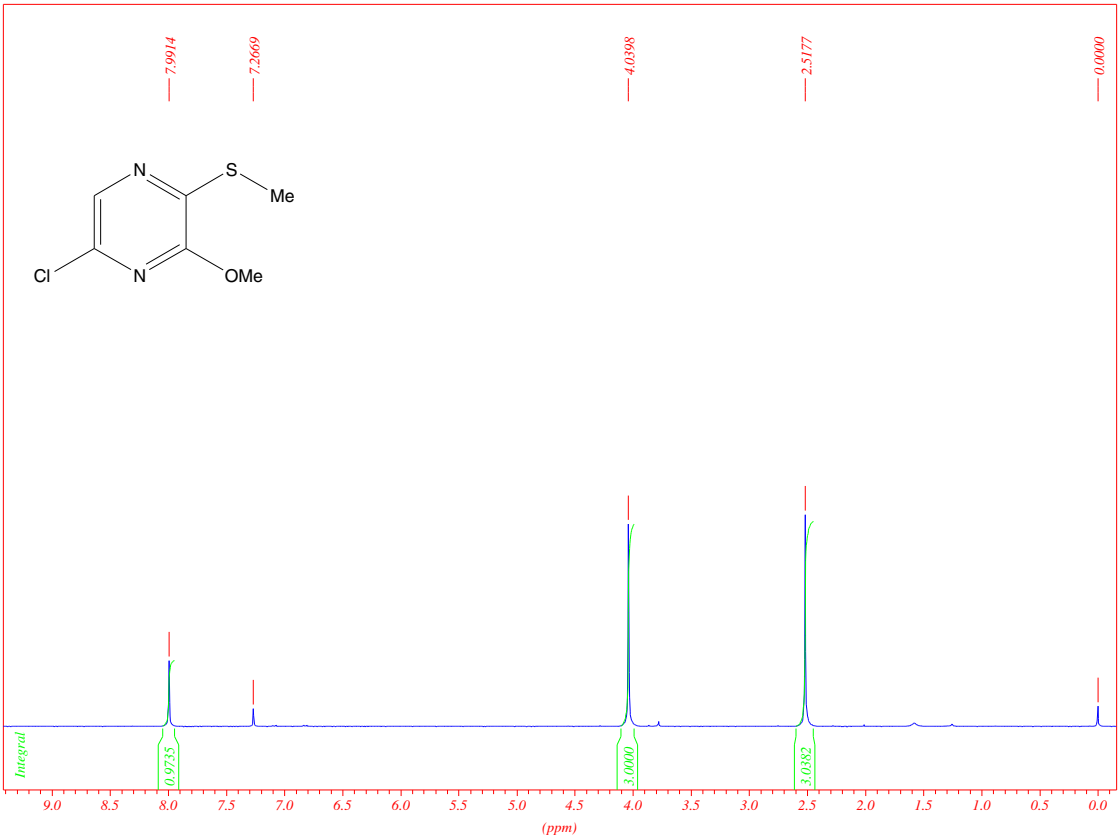


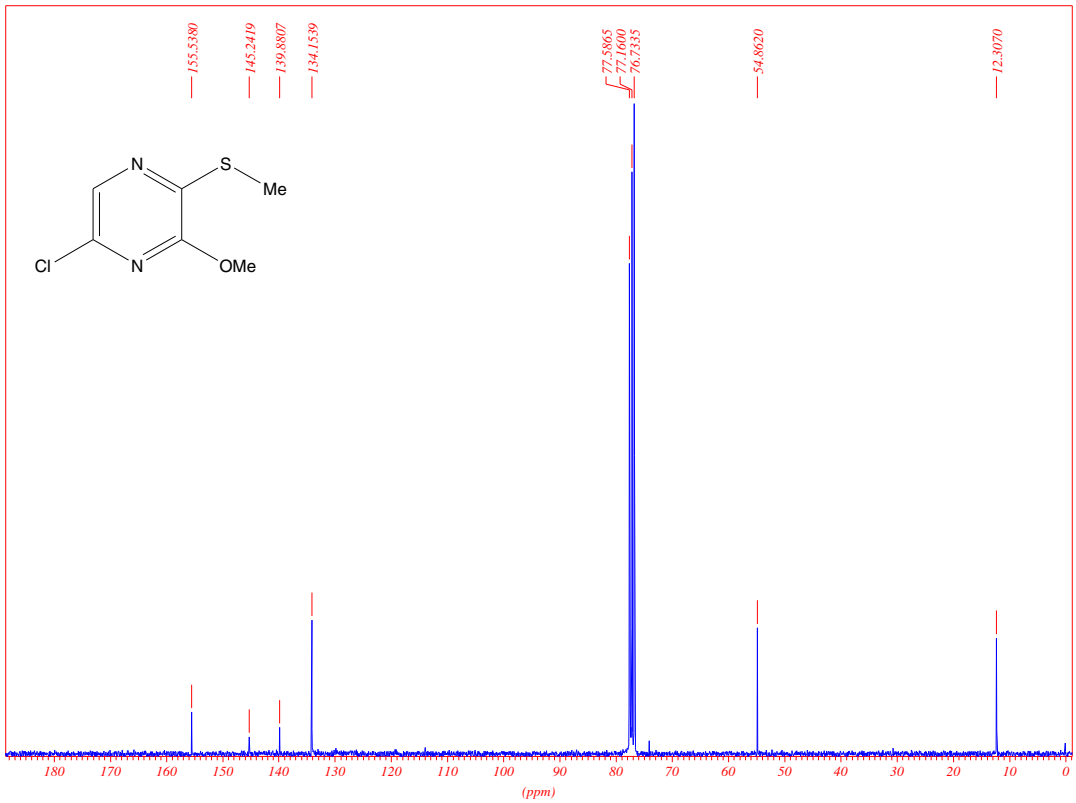
^{1}H and ^{13}C Spectra of compound 3c (300 MHz, $CDCl_3$).



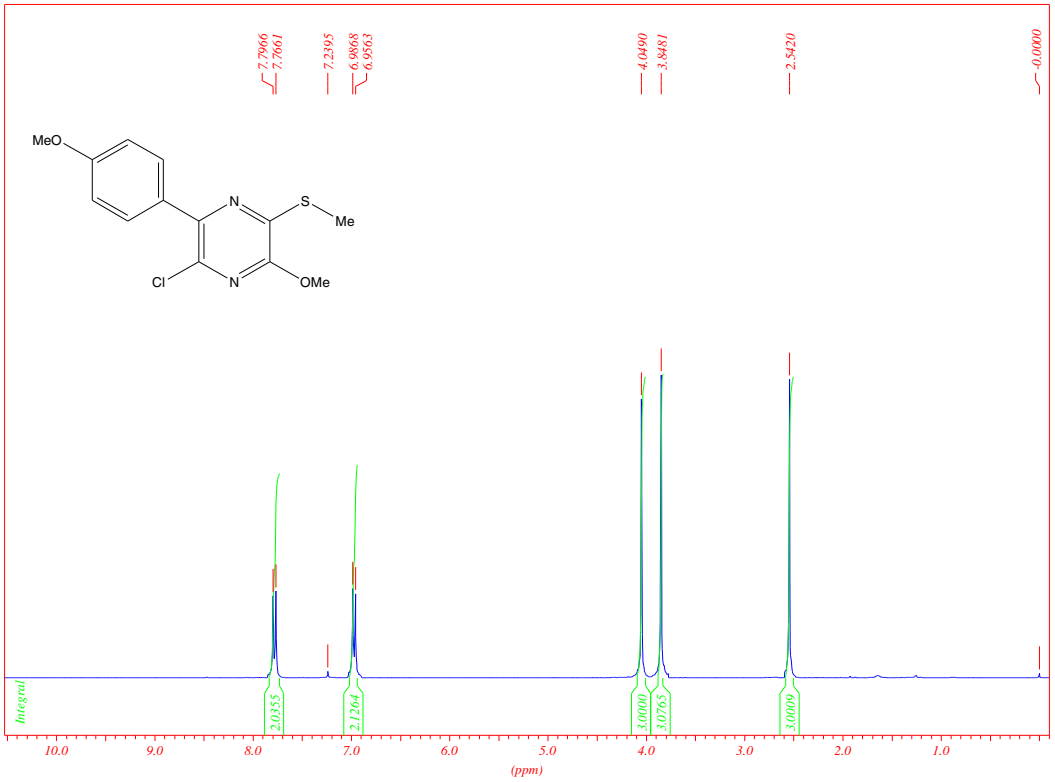


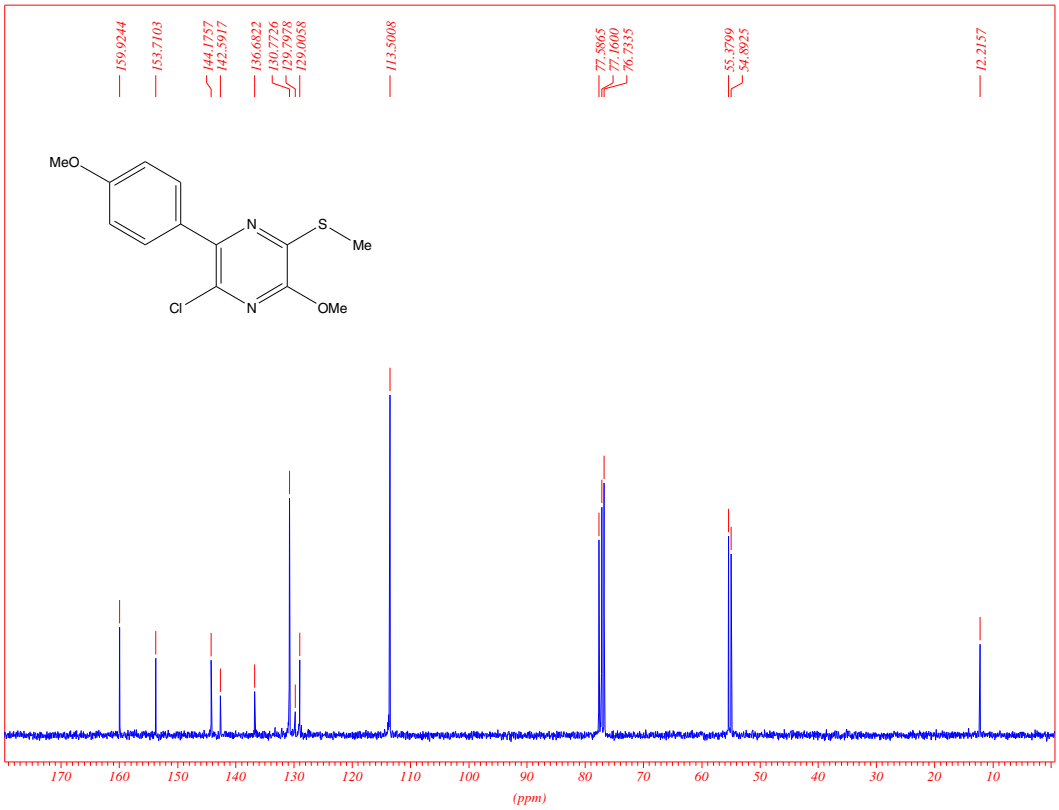
^{1}H and ^{13}C Spectra of compound 4a (300 MHz, $CDCl_3$).



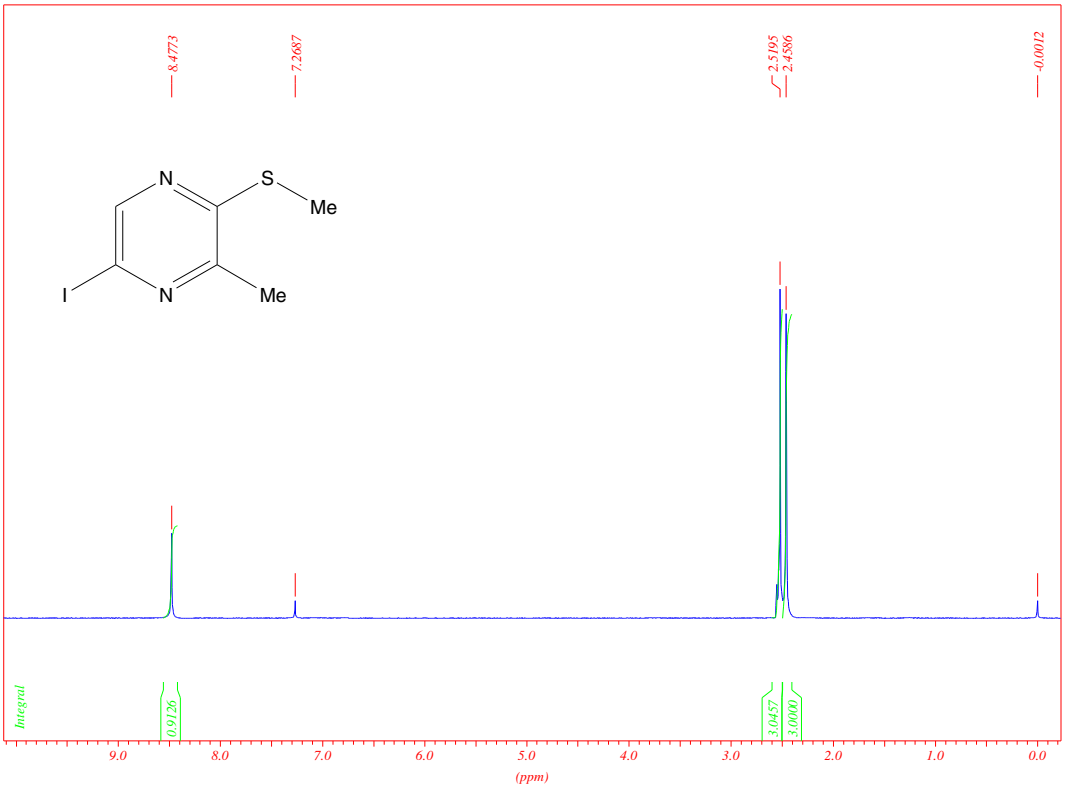


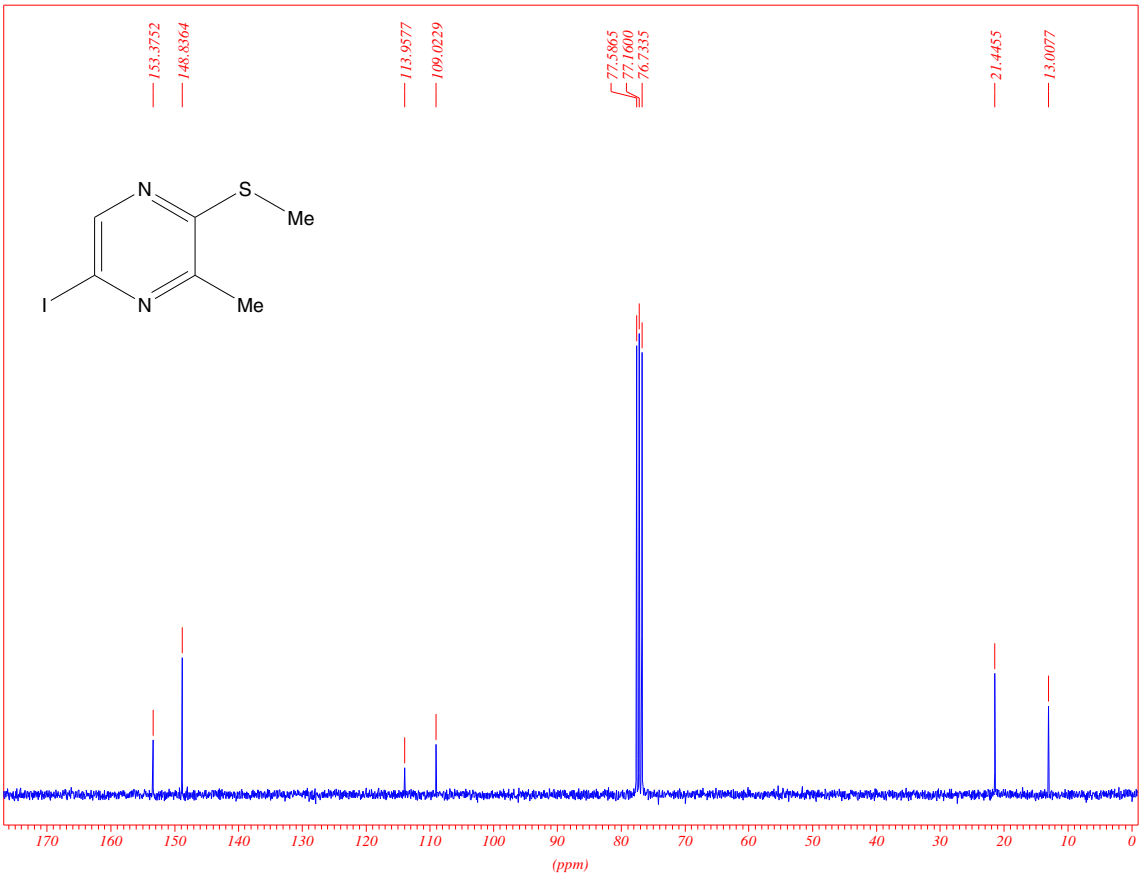
^{1}H and ^{13}C Spectra of compound 4b (300 MHz, $CDCl_3$).



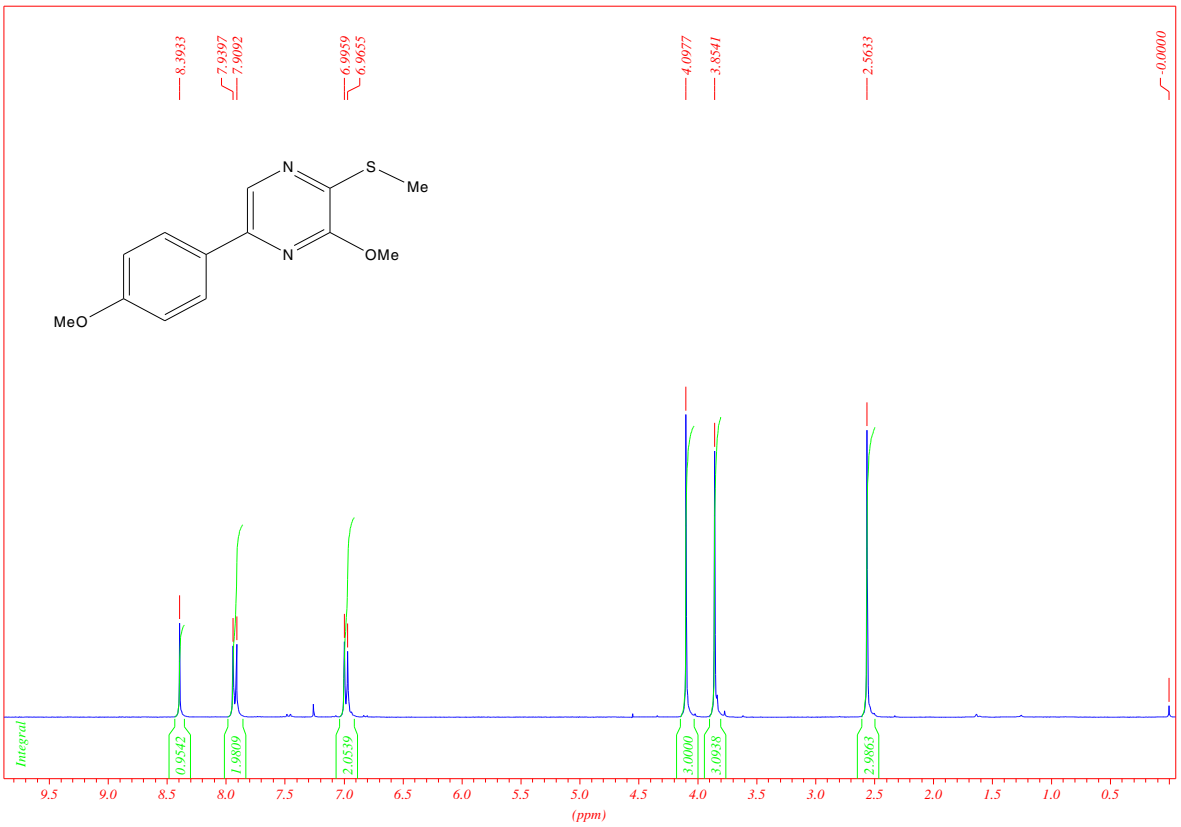


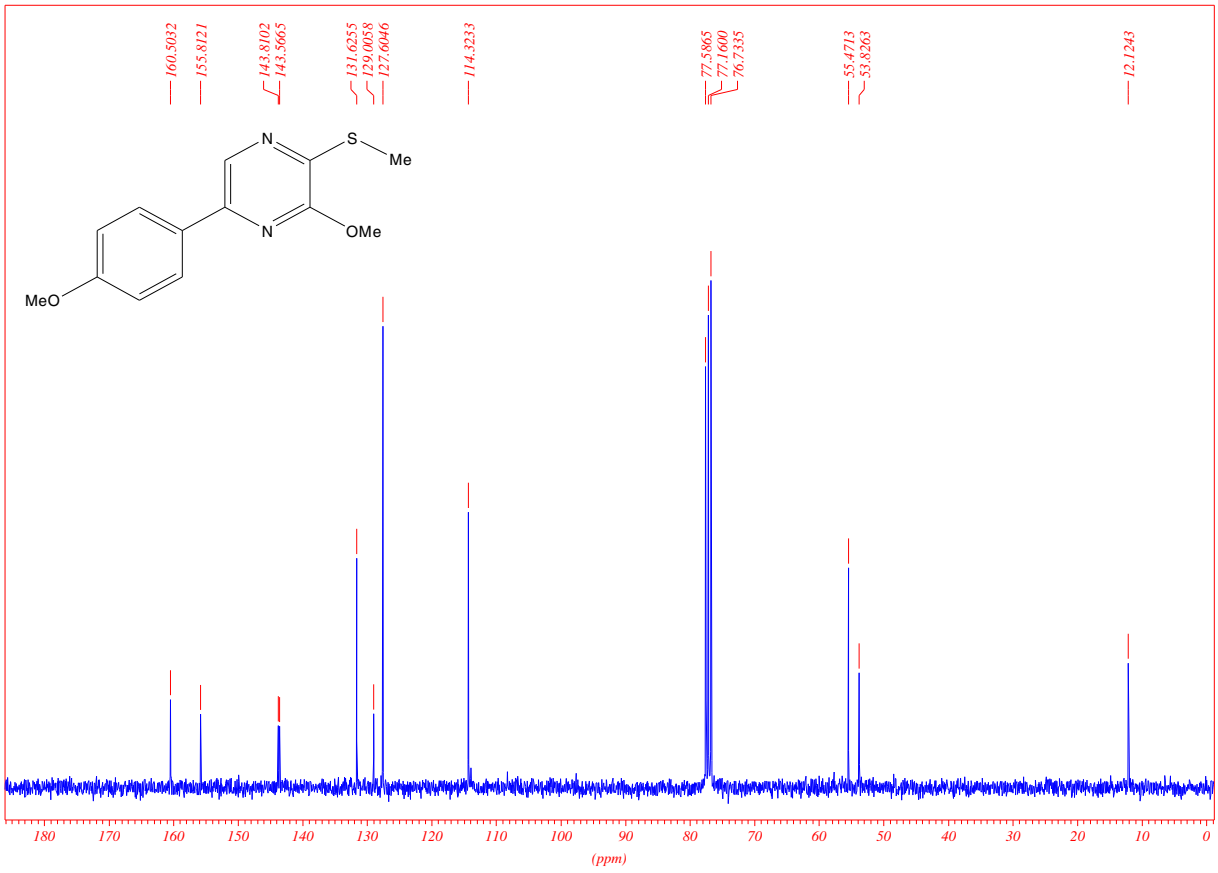
^{1}H and ^{13}C Spectra of compound 4c (300 MHz, $CDCl_3$).



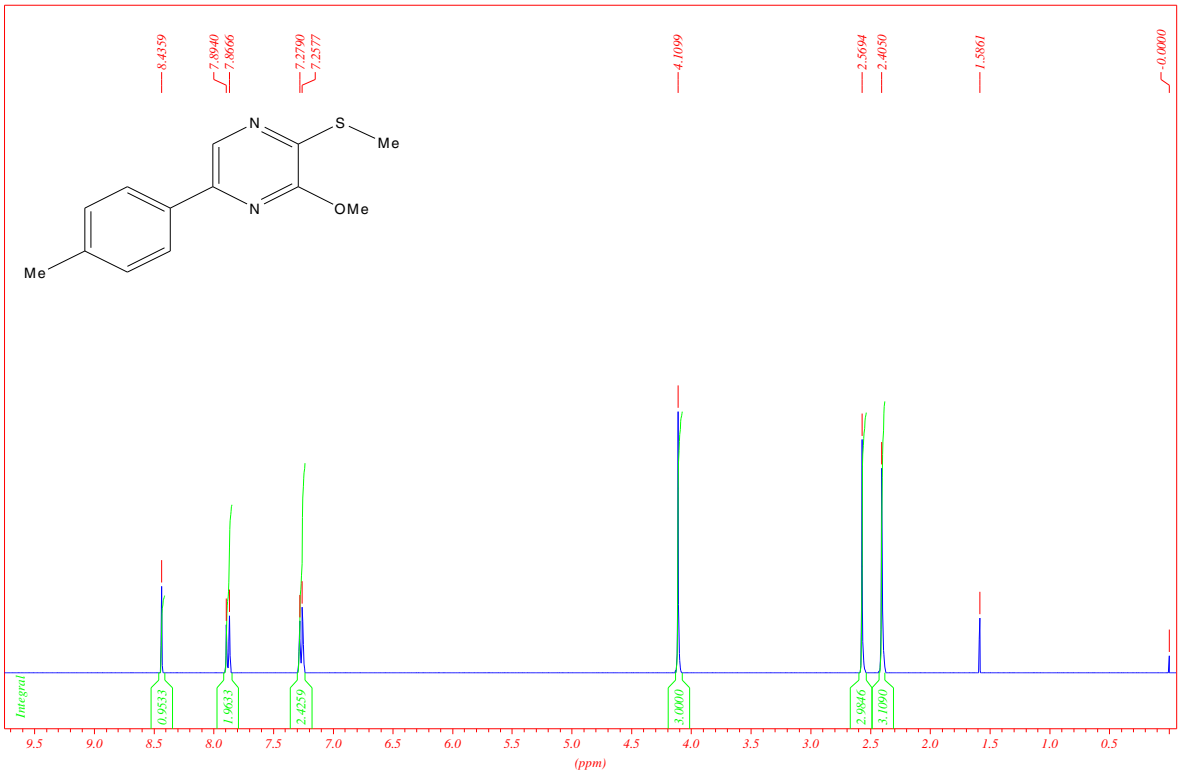


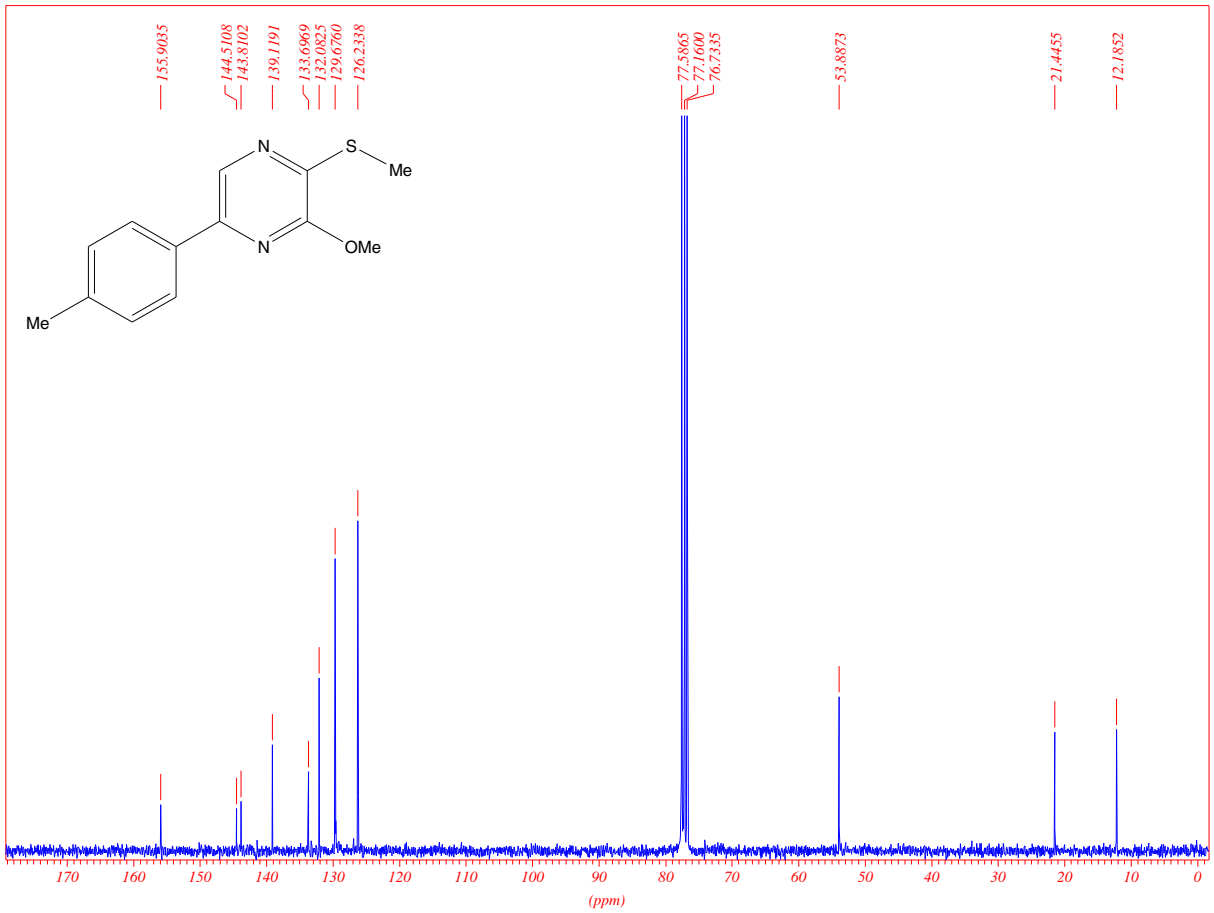
^{1}H and ^{13}C Spectra of compound 5a (300 MHz, $CDCl_3$).



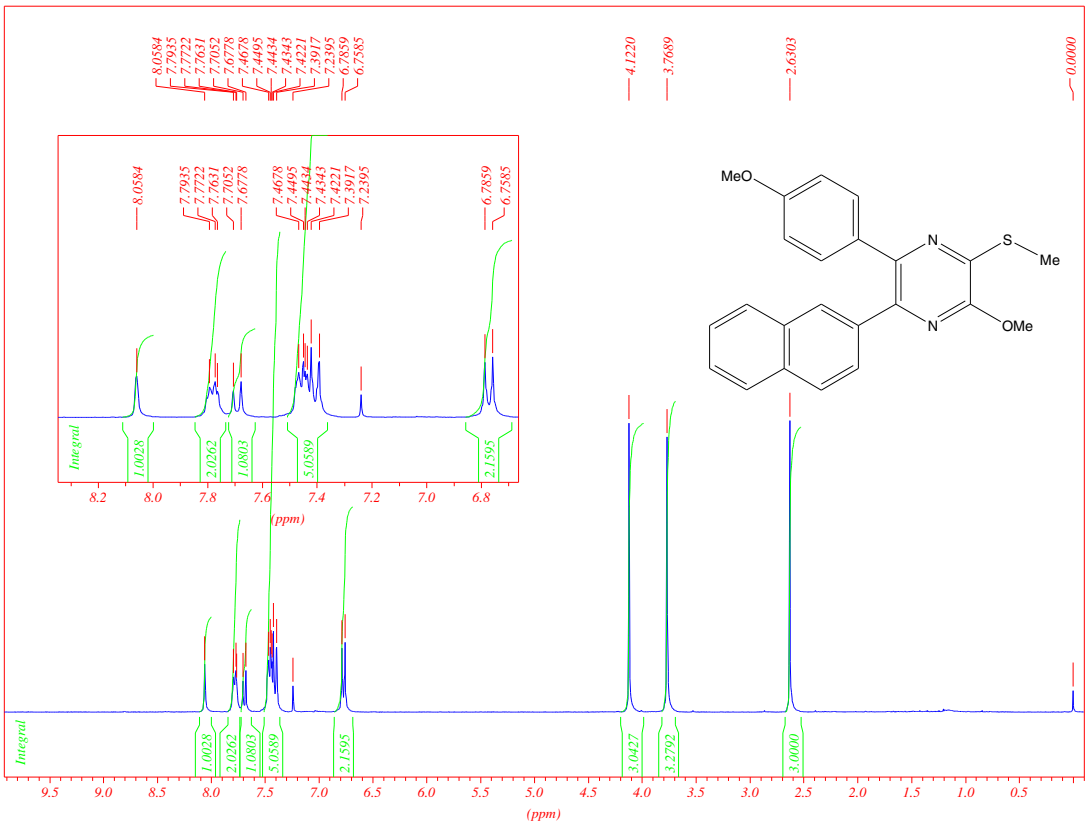


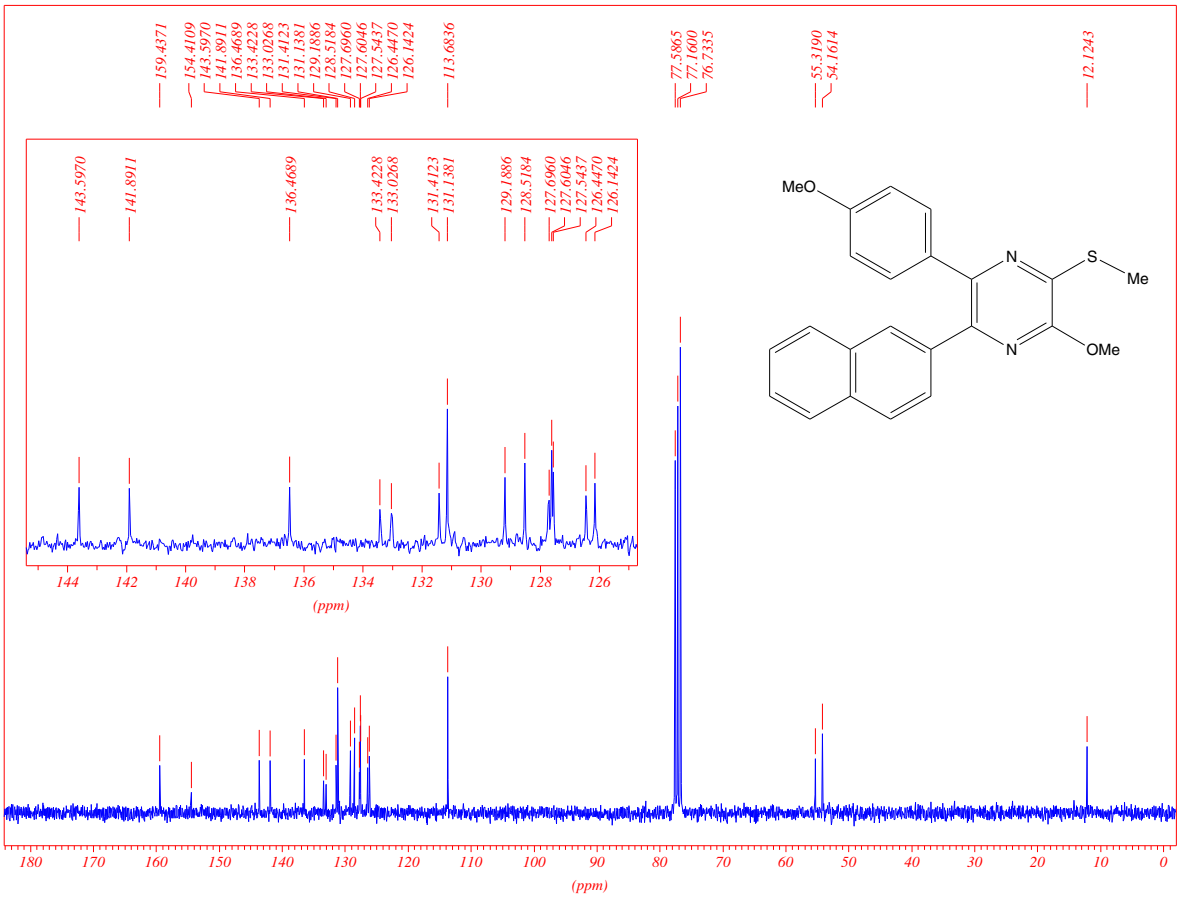
^{1}H and ^{13}C Spectra of compound 5b (300 MHz, $CDCl_3$).



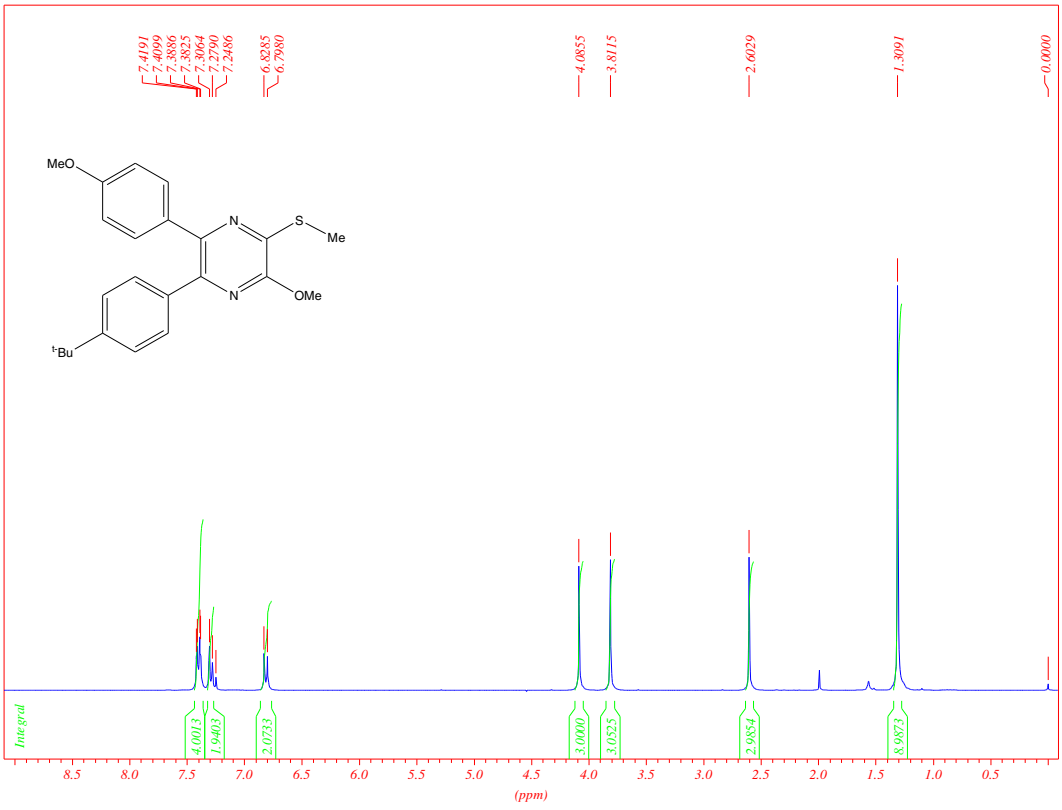


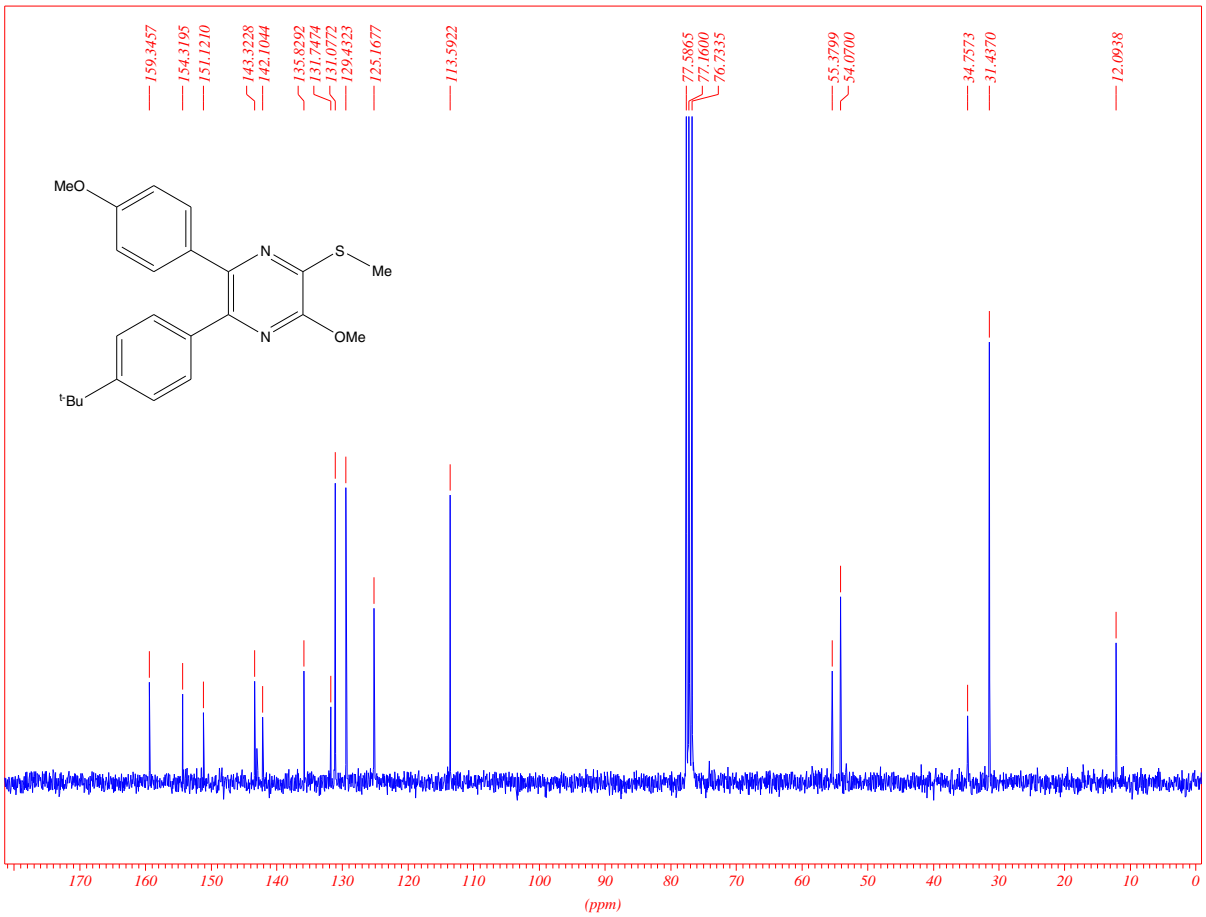
^{1}H and ^{13}C Spectra of compound 5c (300 MHz, $CDCl_3$).



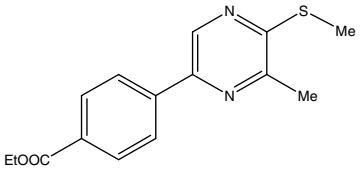


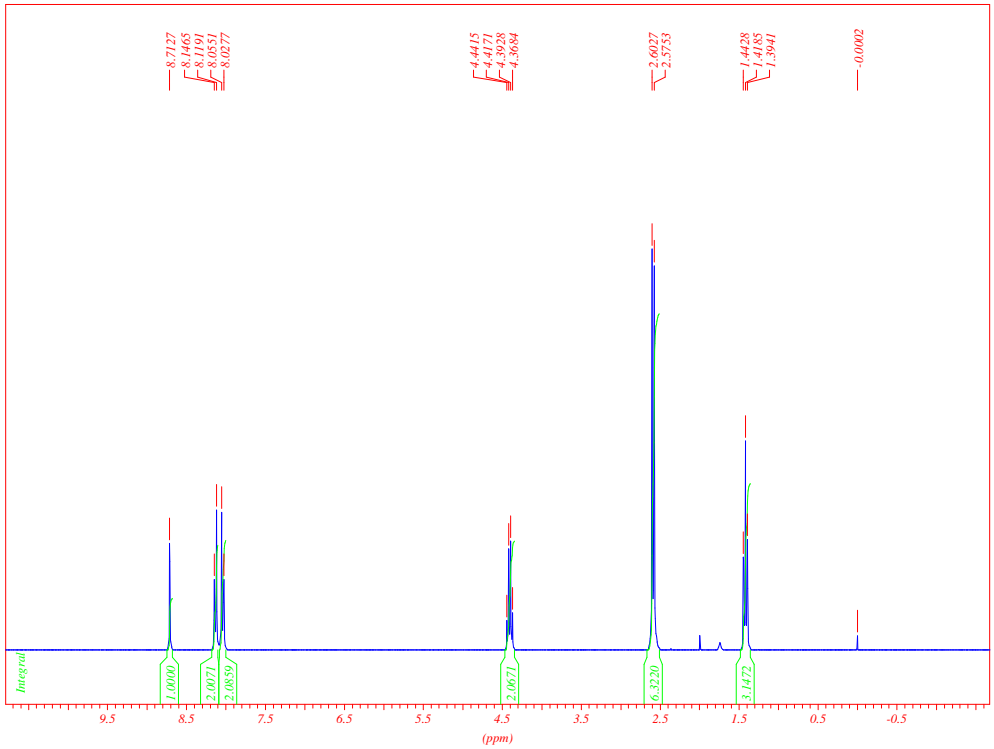
^{1}H and ^{13}C Spectra of compound 5d (300 MHz, $CDCl_3$).

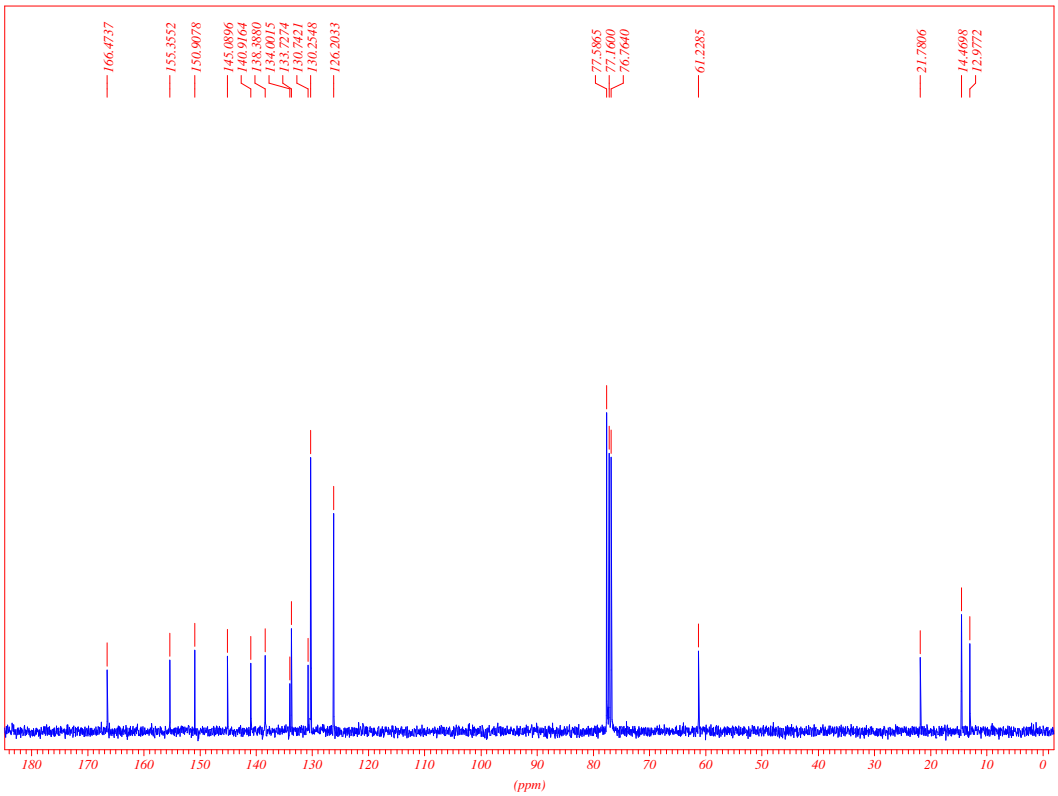




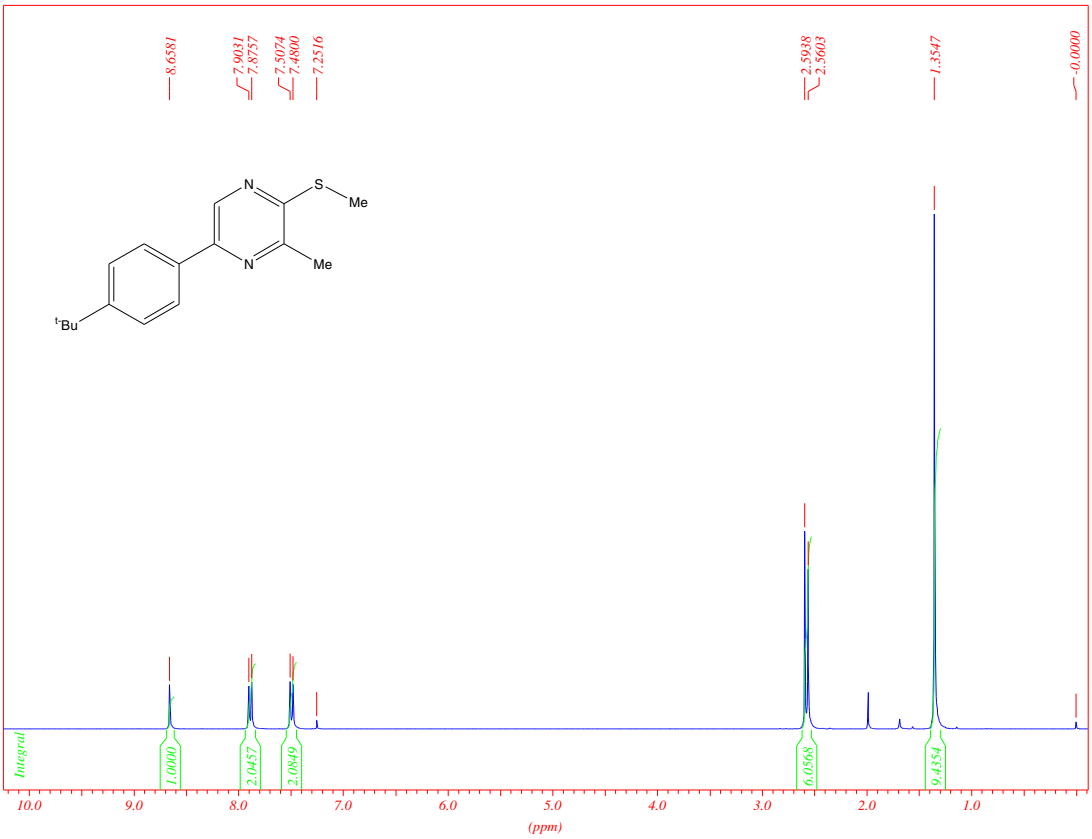
^{1}H and ^{13}C Spectra of compound 5g (300 MHz, $CDCl_3$).

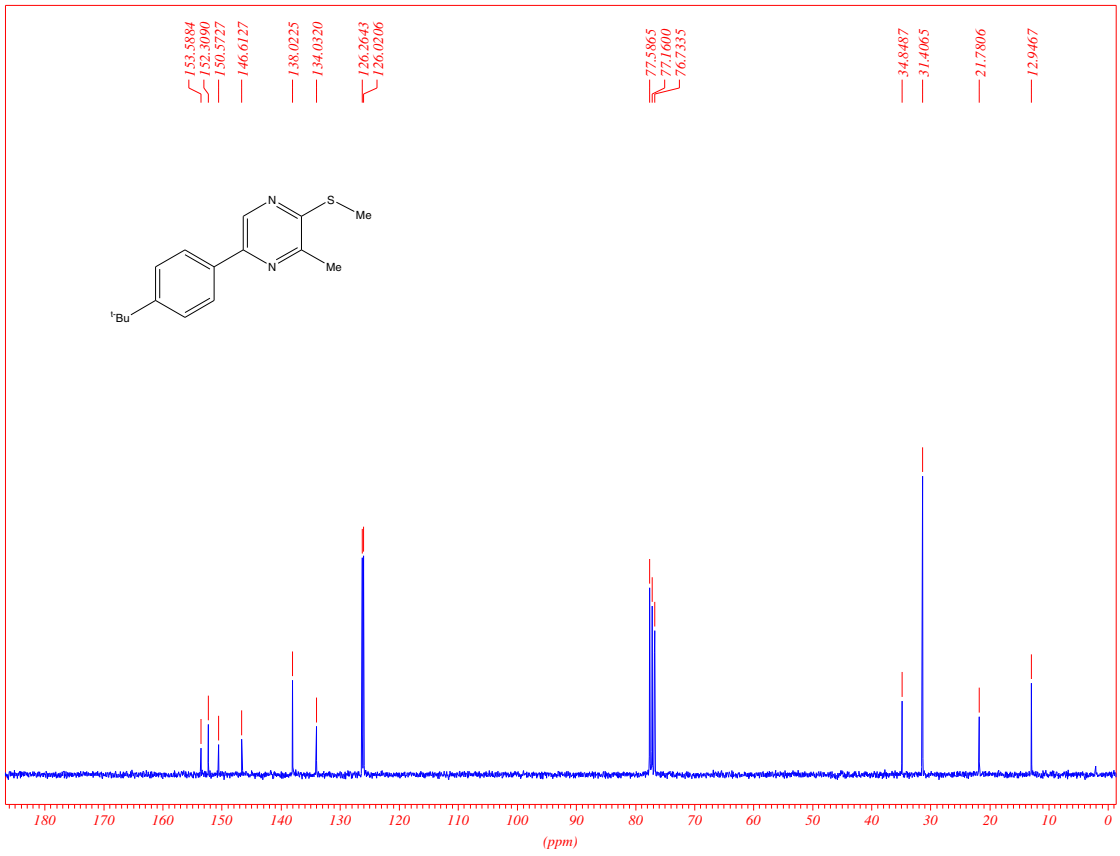




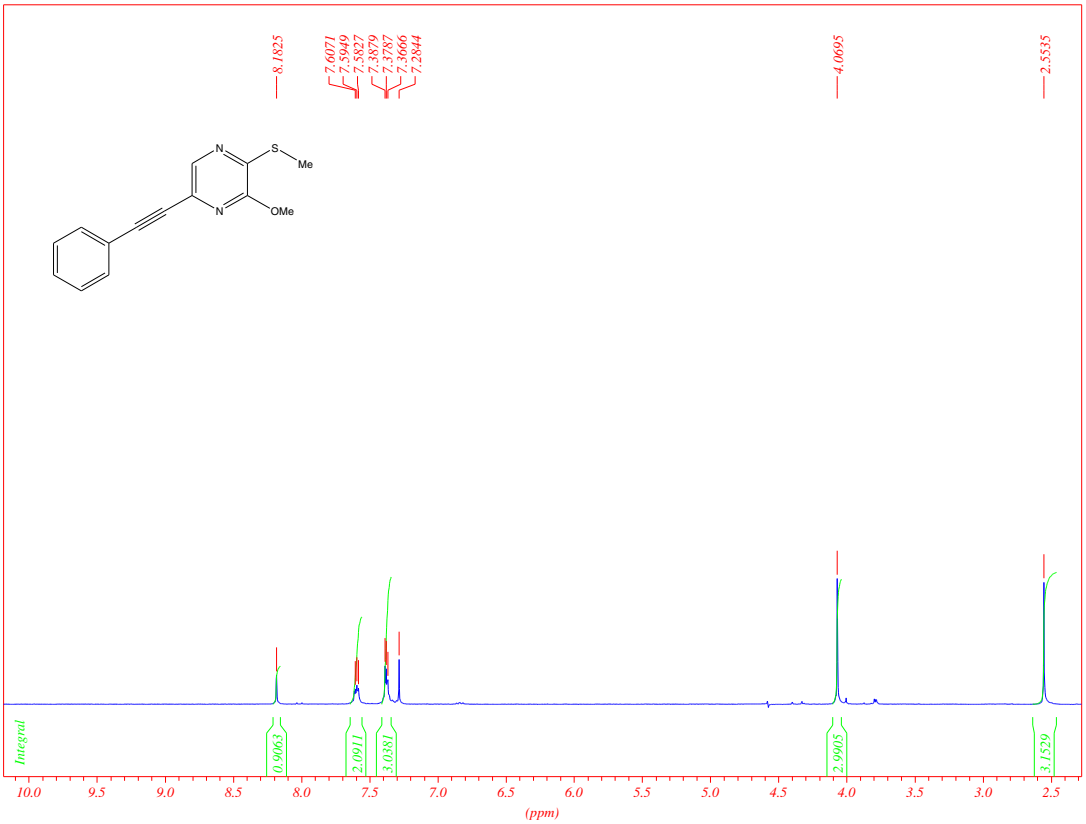


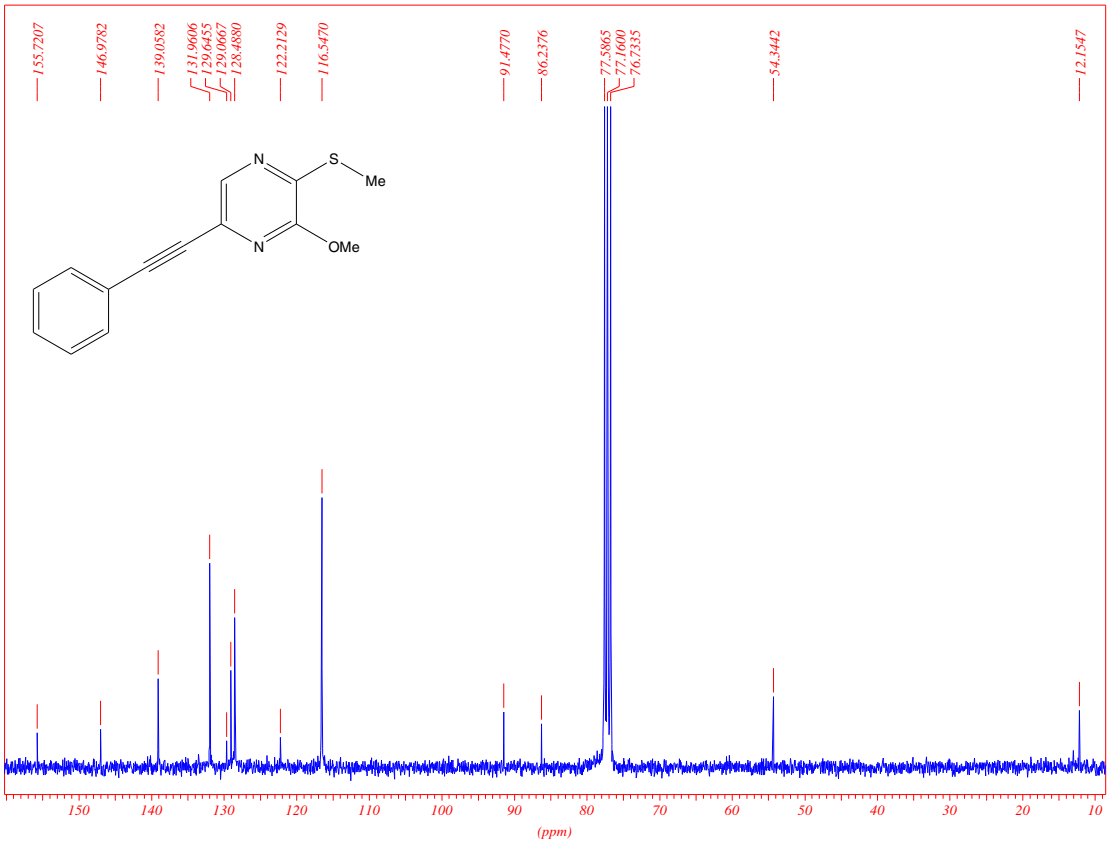
^{1}H and ^{13}C Spectra of compound 5h (300 MHz, $CDCl_3$).



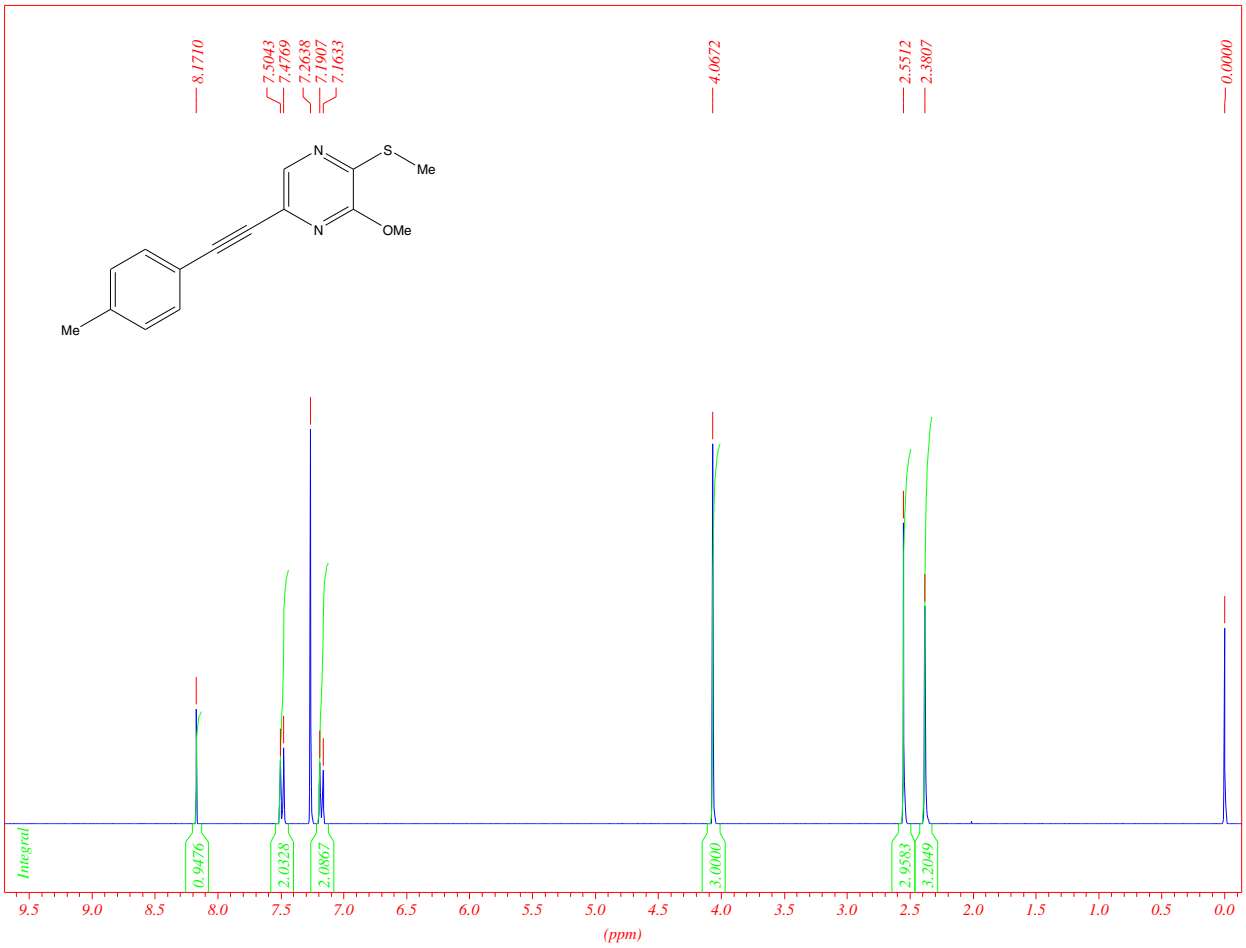


^{1}H and ^{13}C Spectra of compound 7a (300 MHz, $CDCl_3$).

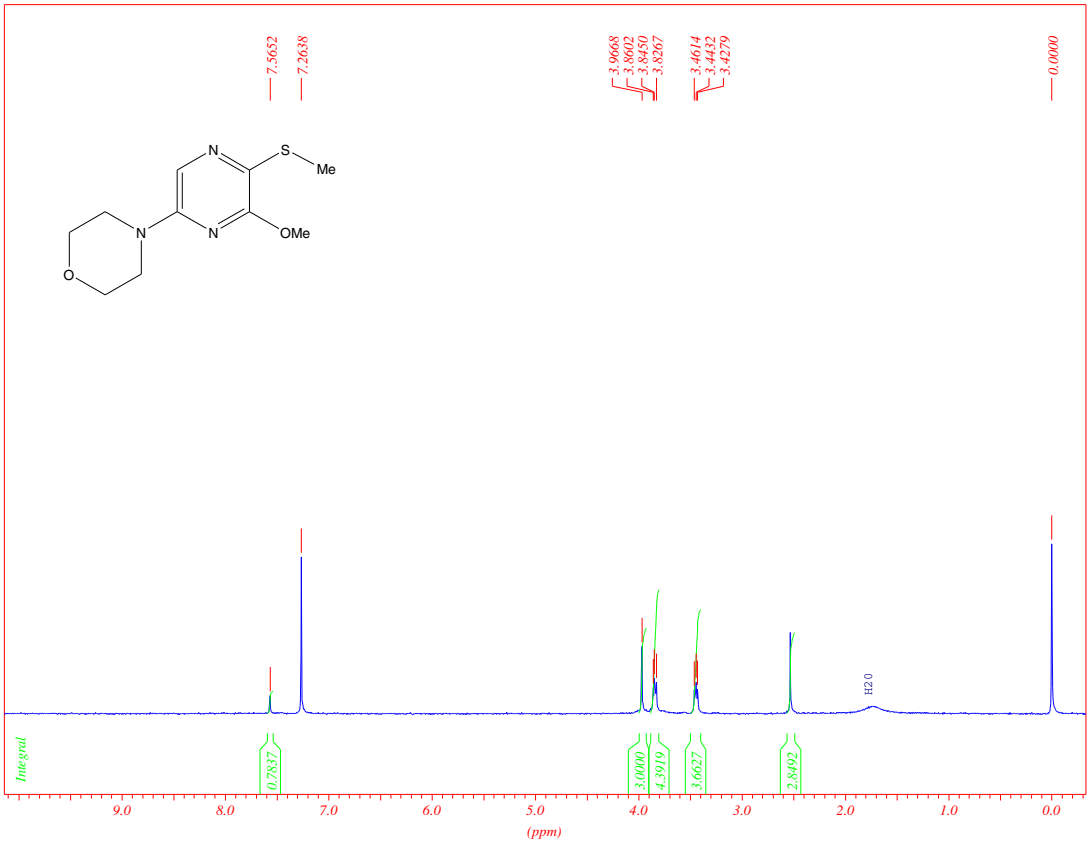


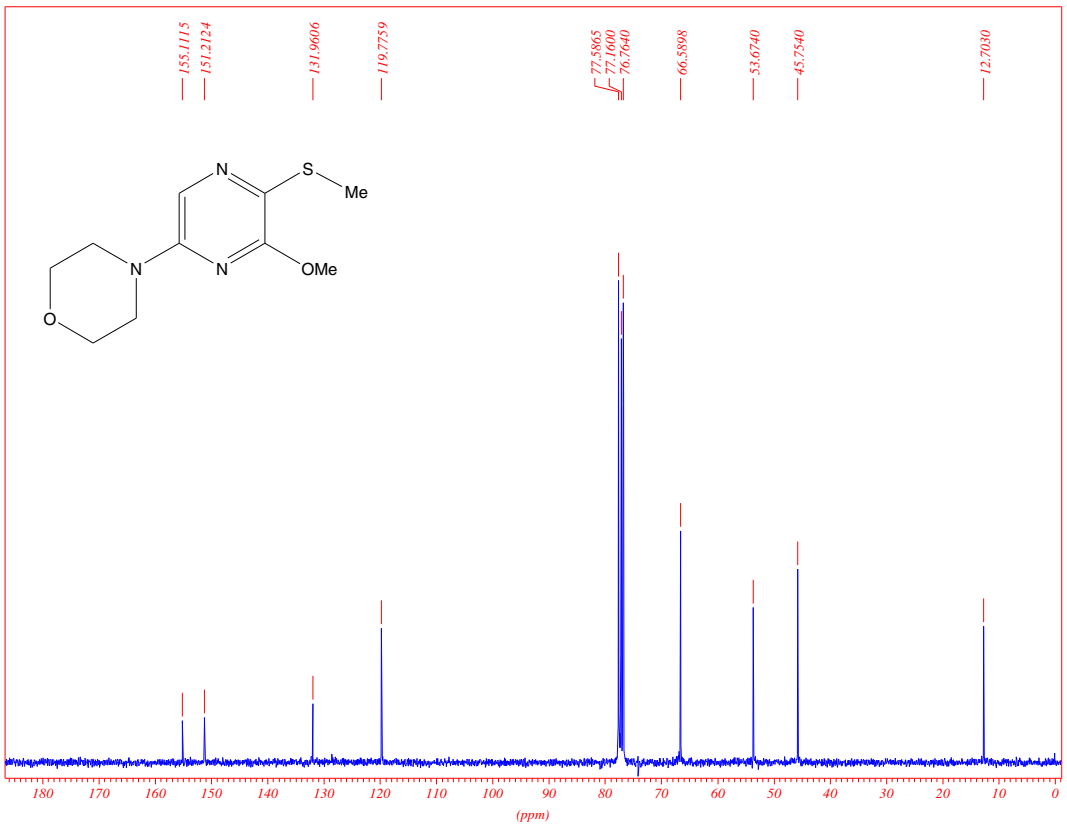


^{1}H and ^{13}C Spectra of compound 7b (300 MHz, $CDCl_3$).

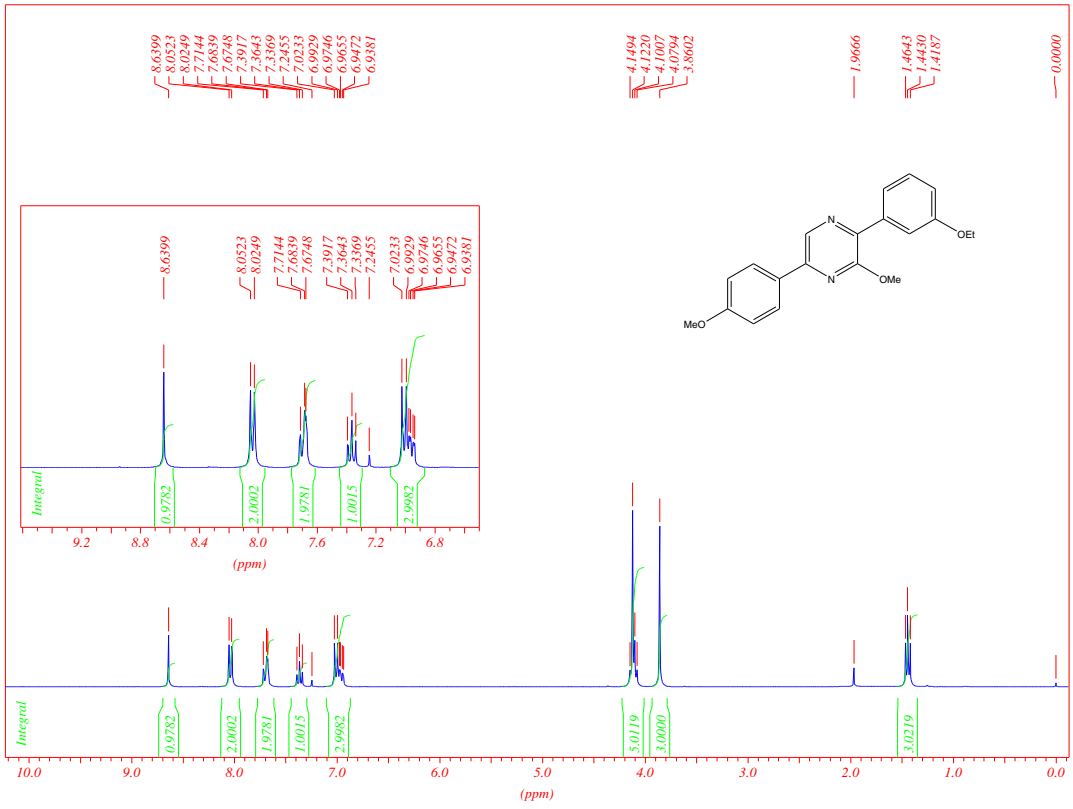


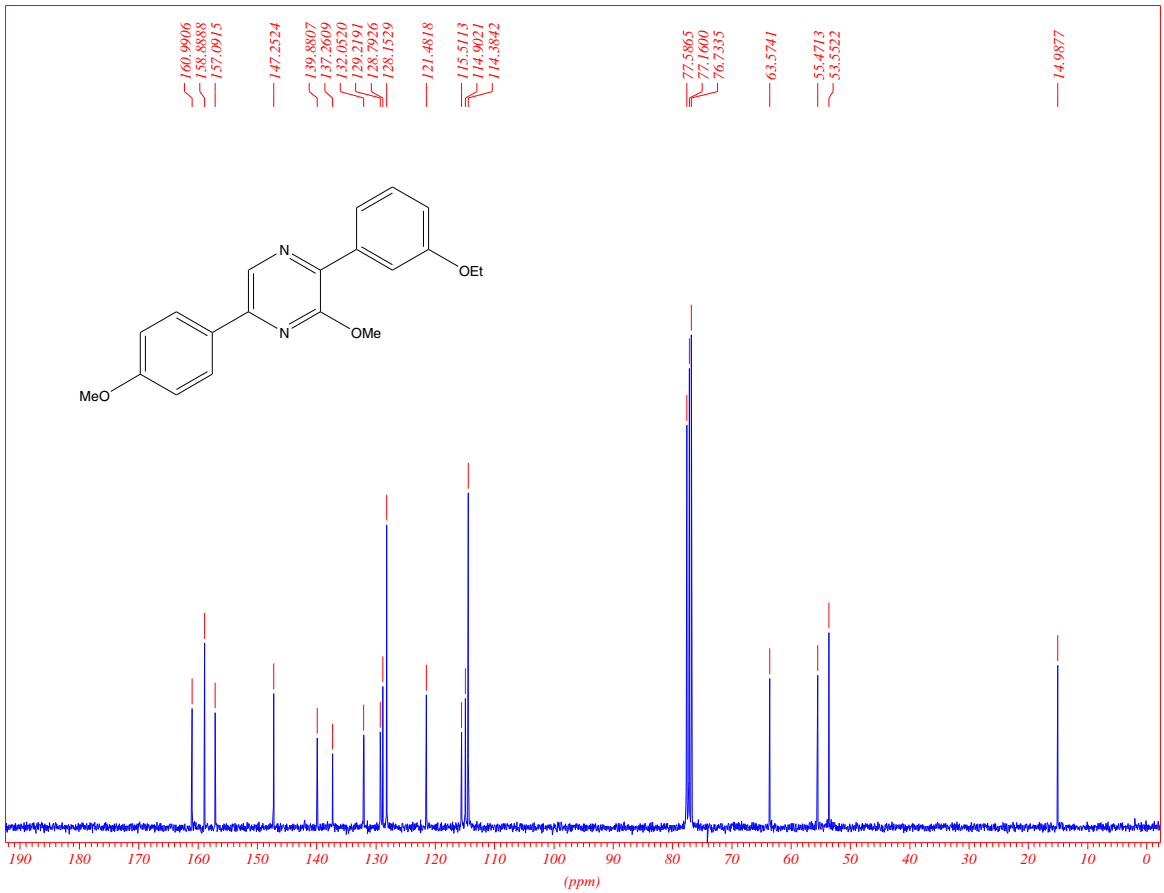
^{1}H and ^{13}C Spectra of compound 7d (300 MHz, $CDCl_3$).



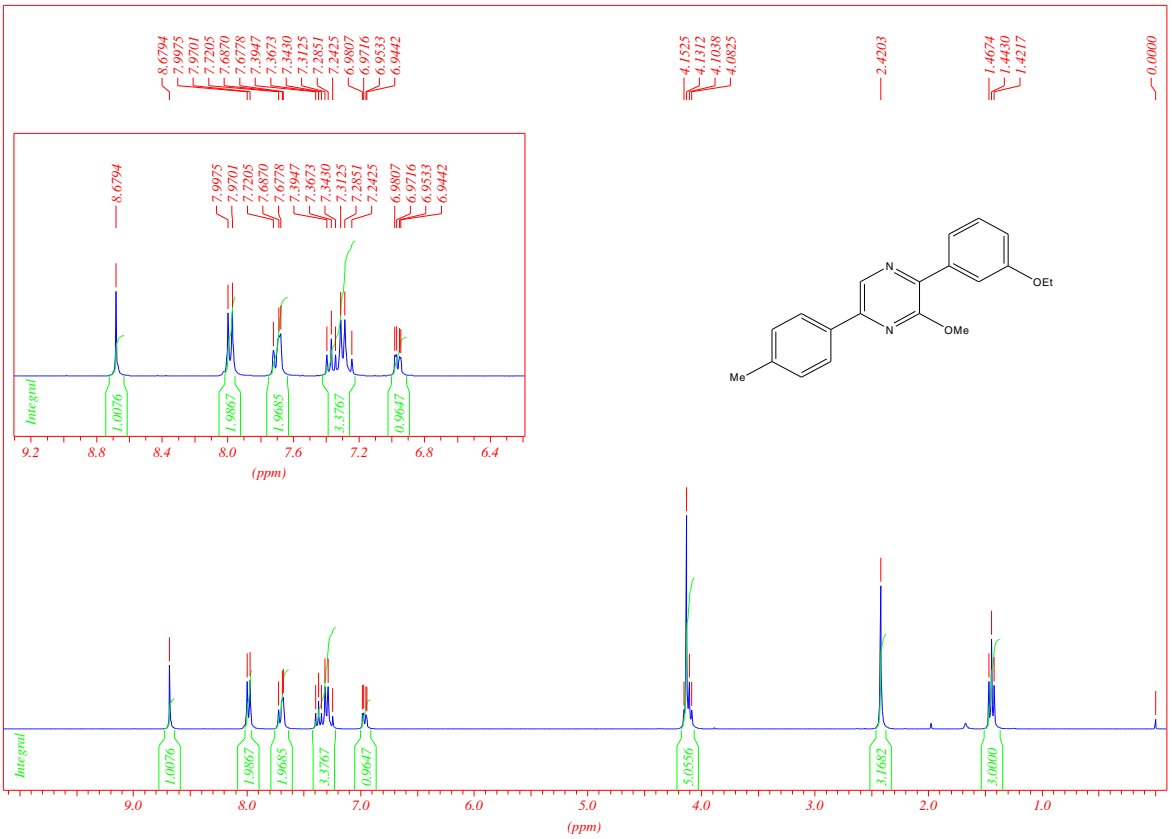


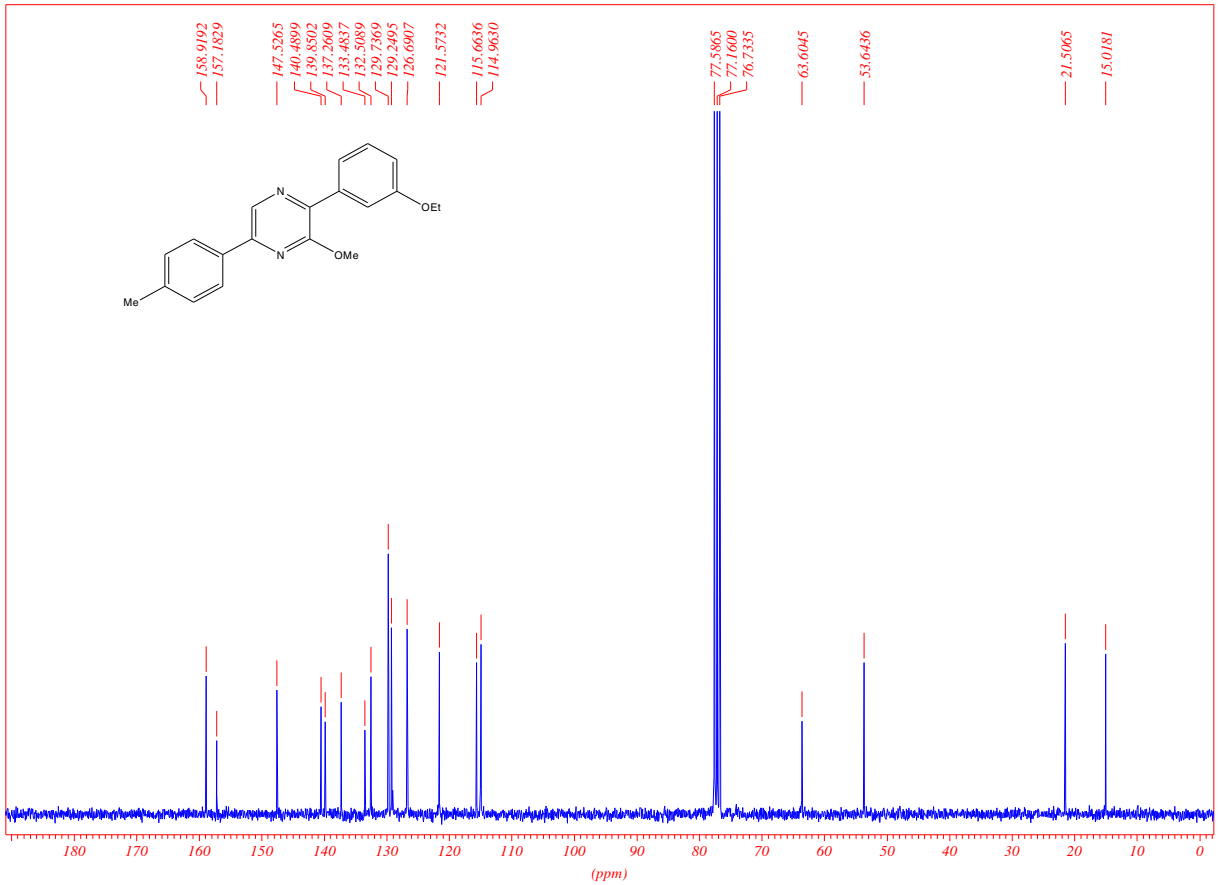
^{1}H and ^{13}C Spectra of compound 8a (300 MHz, $CDCl_3$).



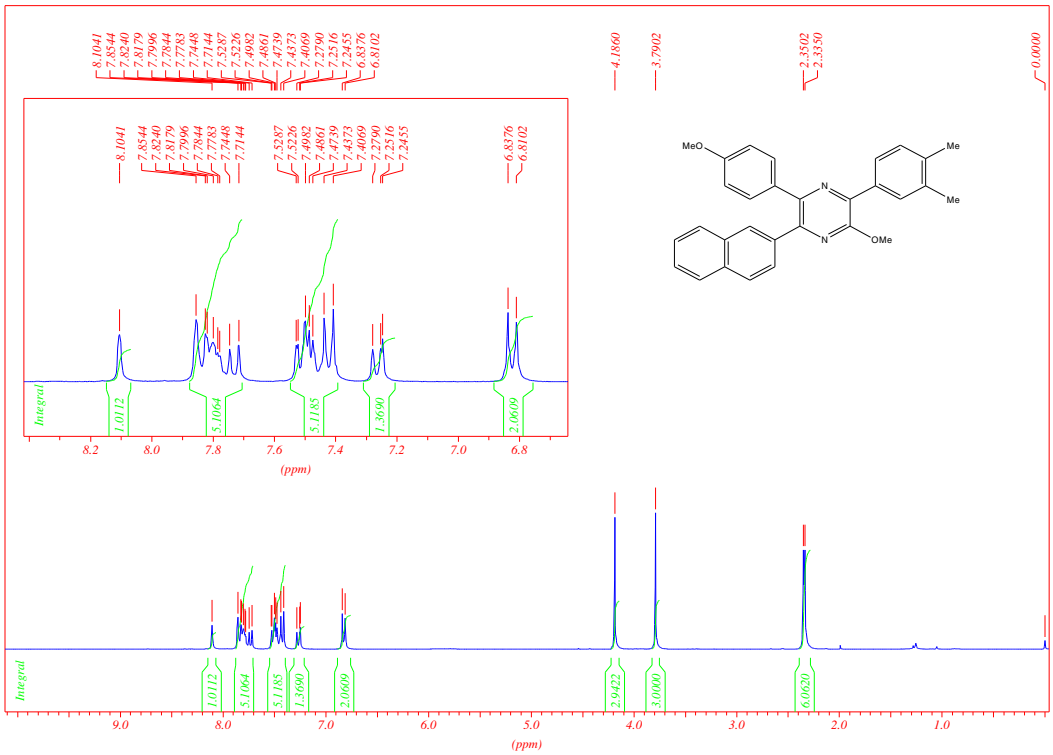


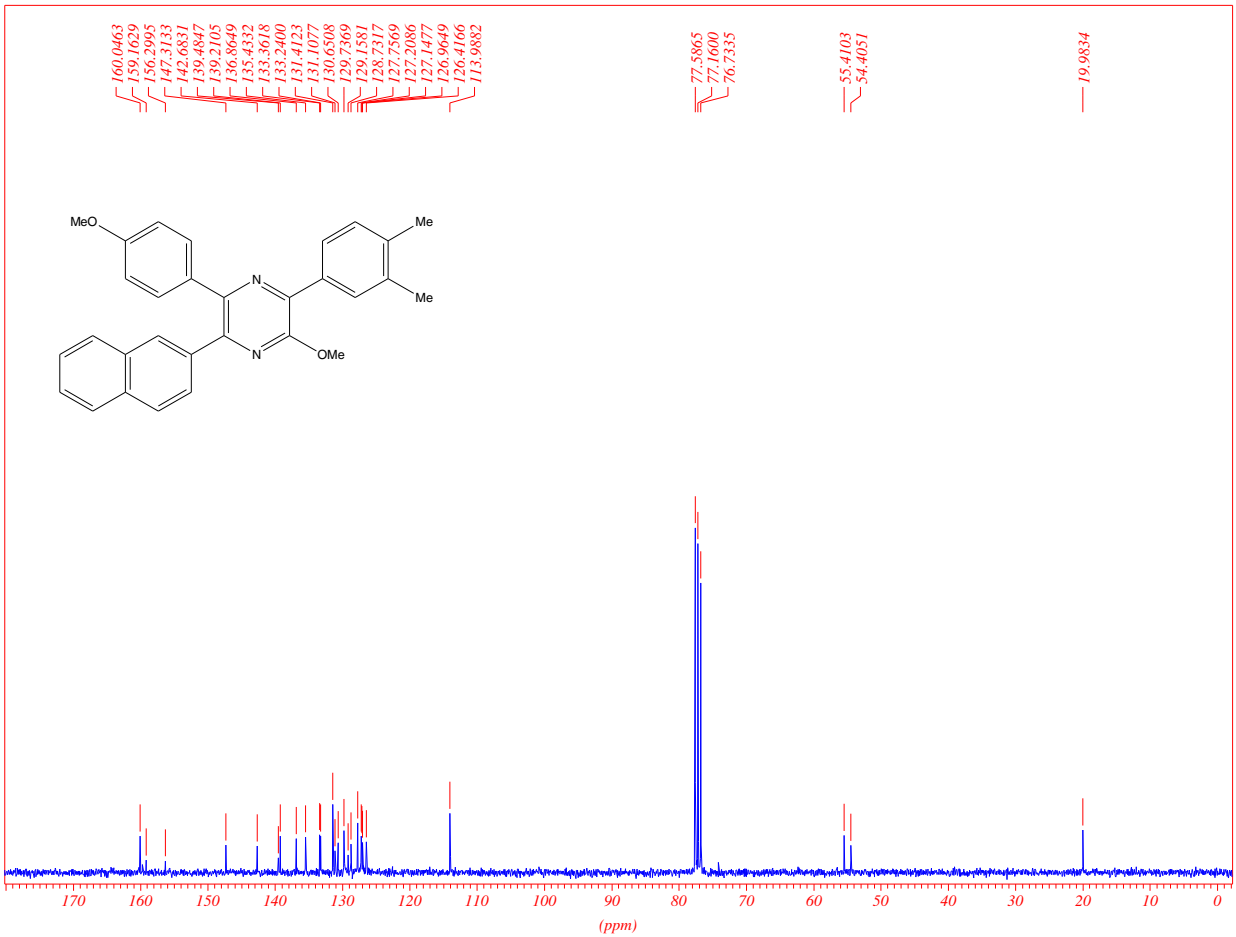
^{1}H and ^{13}C Spectra of compound 8b (300 MHz, $CDCl_3$).



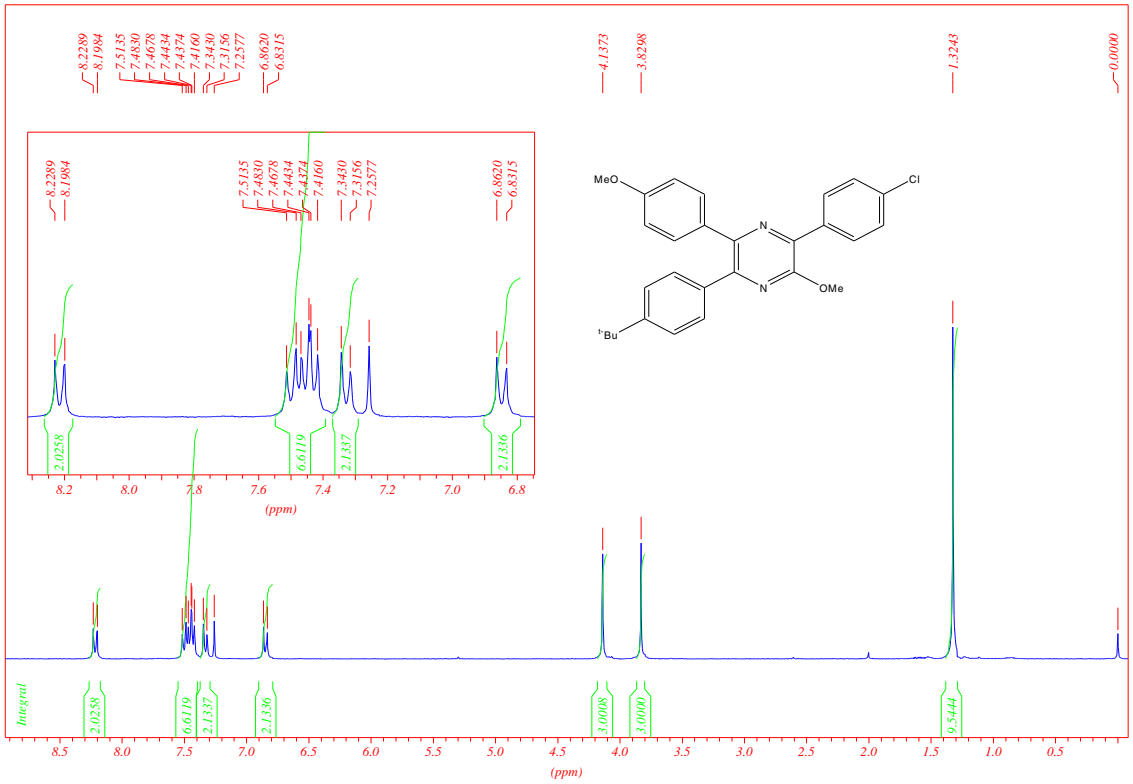


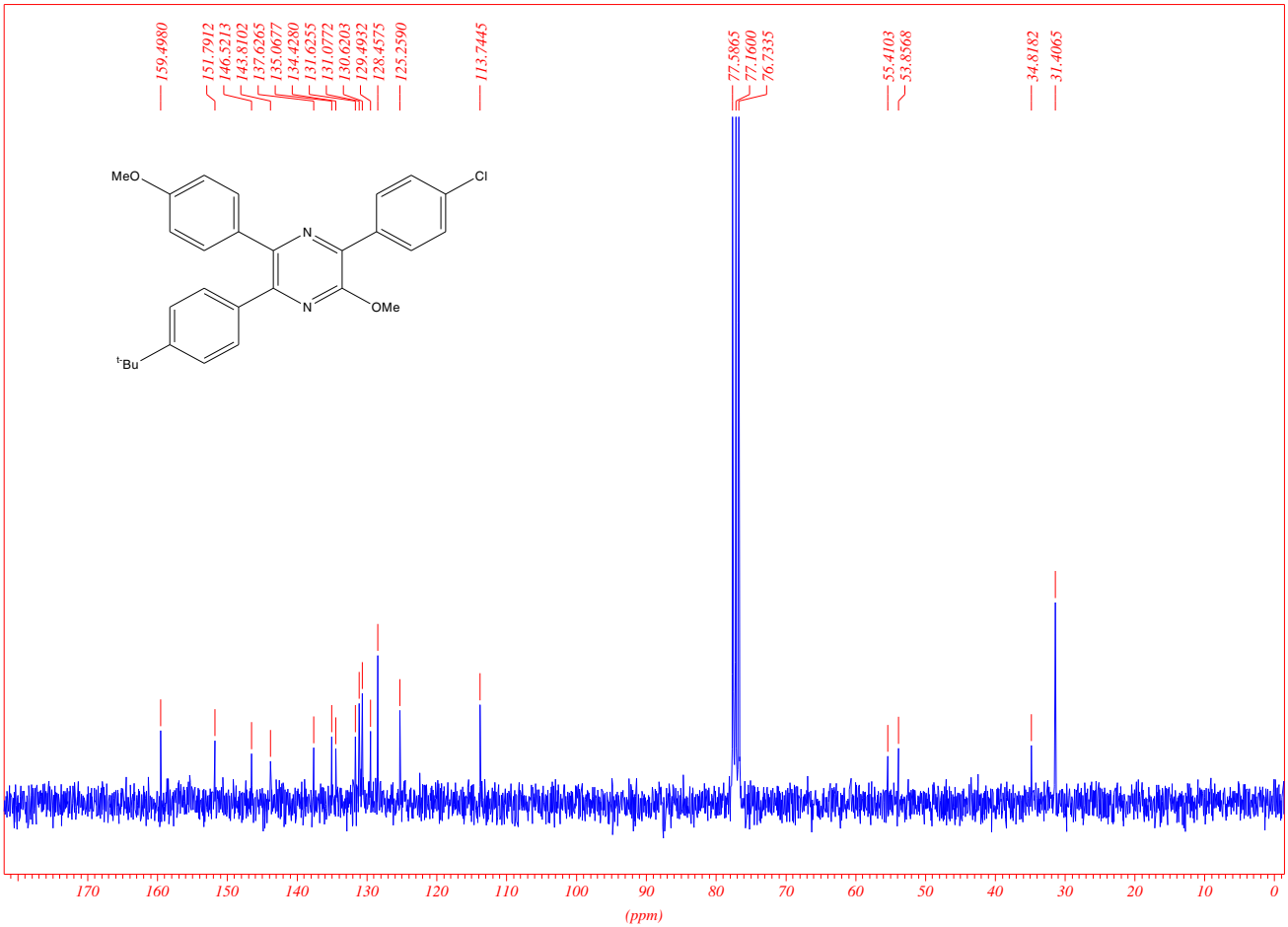
^{1}H and ^{13}C Spectra of compound 8c (300 MHz, $CDCl_3$).





^{1}H and ^{13}C Spectra of compound 8d (300 MHz, $CDCl_3$).





^{1}H and ^{13}C Spectra of compound 8e (300 MHz, $CDCl_3$).