Supporting Information

for

Continuous-flow synthesis of highly functionalized imidazo-oxadiazoles facilitated by microfluidic extraction

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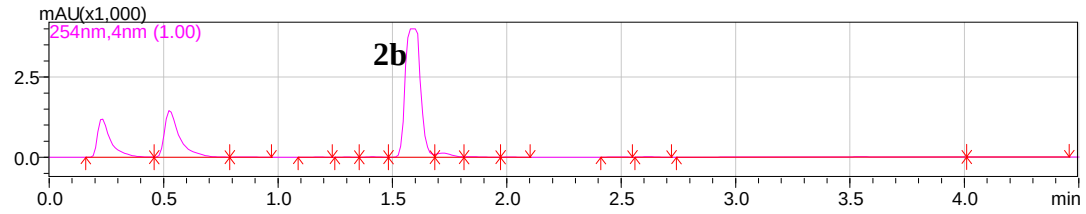
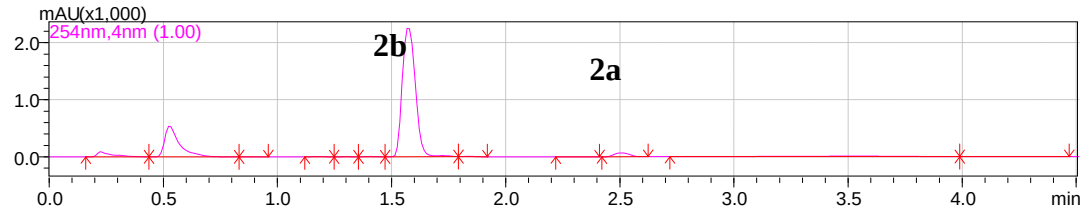
Experimental data

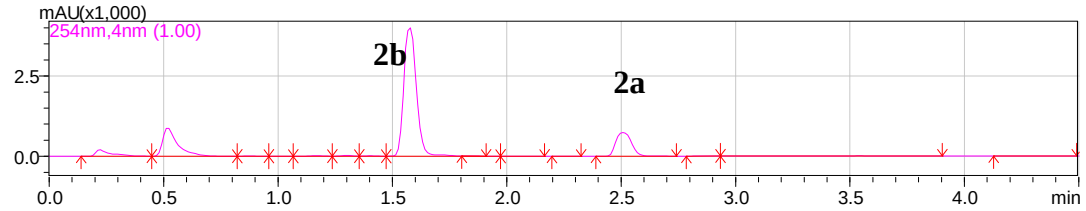
Entry 1, T = 50 °C



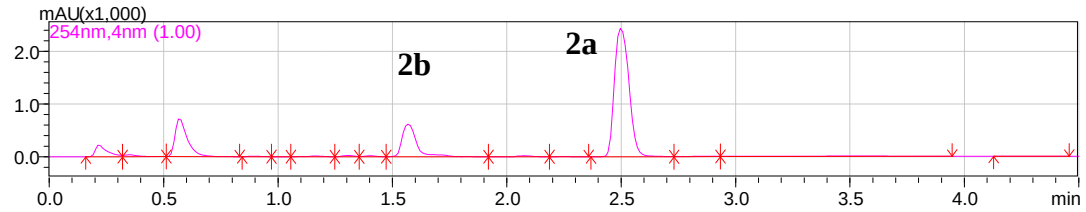
Entry 2, T = 75 °C



Entry 3, T = 100 °C



Entry 4, T = 125 °C



Entry 5, T = 150 °C

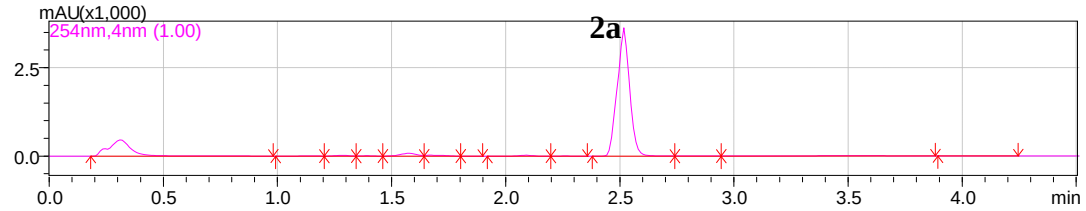


Figure S1: LC–MS traces used to determine compound ratios for experiments in Table 1.

Optimization of liquid–liquid microfluidic extraction

The AFRICA® fluidic liquid-liquid extraction (FLLEX) module consists of a contactor, a separator, two optical sensors to monitor output stream purity and two back pressure regulators to accurately control fluid Pressure (Figure S2). Separation is achieved by passing the slug flow stream from the contactor over a porous poly(tetrafluoroethylene) (PTFE) membrane. This occurs inside the separator chip. The porous PTFE membrane is hydrophobic and repels the aqueous slugs but allows the organic stream to pass through. A pressure differential across this membrane is controlled using back pressure regulators. As the mixture moves through the channel, the differential in pressure drives the organic phase through the membrane while the aqueous phase is retained (Figure S2). We hypothesized that we could use this module to remove high boiling water soluble solvent from the reaction mixture. Initially, we focused our efforts on combining a simple one chip reaction with microfluidic extraction unit (Figure S3). Product exiting from the reactor was mixed with excess water and dichloromethane (introduced by an external pump - AcuFlow Series III pump). Next this stream was introduced in to the liquid–liquid extractor unit. Organic and aqueous layer analyzed by LC–MS and showed that the extraction of the product to dichloromethane (DCM) layer is successful at 165 or 100 (see Figure S3 below) mbar cross membrane pressure. A back pressure of 3.0 bar was maintained on the aqueous outlet of the FLLEX, while the organic outlet's back pressure was maintained at a 165 or 100 mbar deficit (see Figure S3 below) to the aqueous outlet by way of the FLLEX module's internal pressure differential control valve.

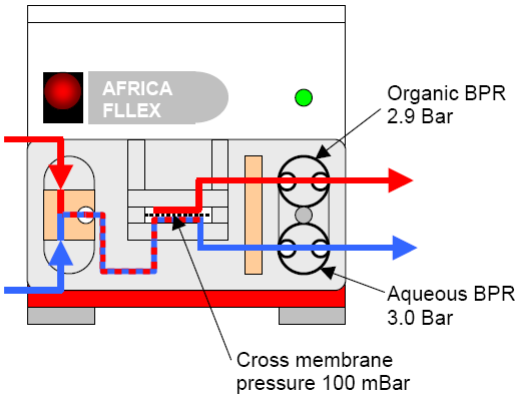


Figure S2: AFRICA® Fluidic Liquid-Liquid Extraction (FLLEX) Module.

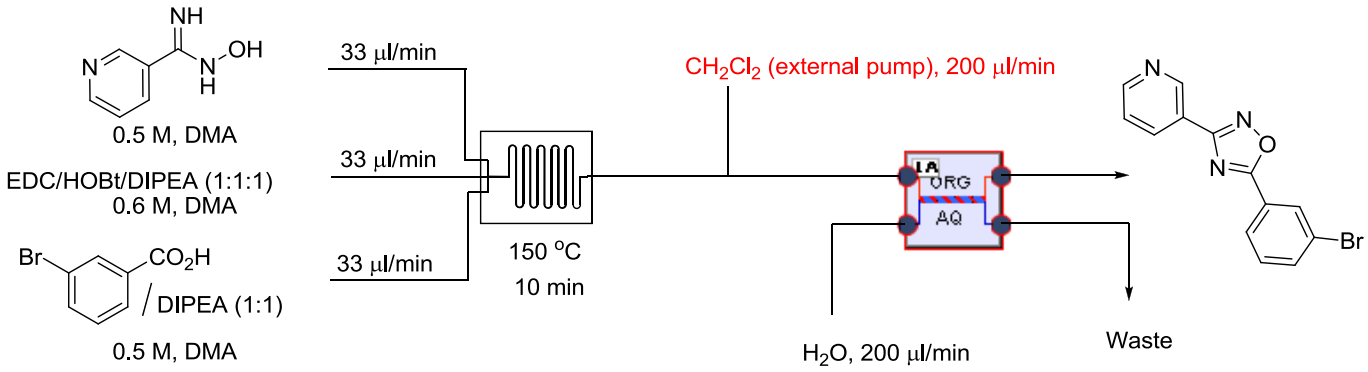
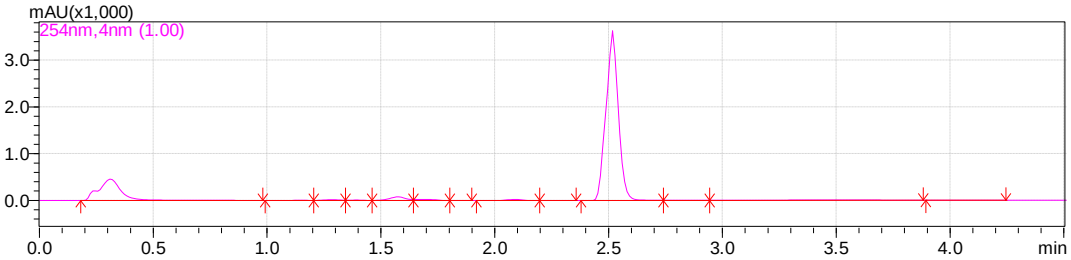
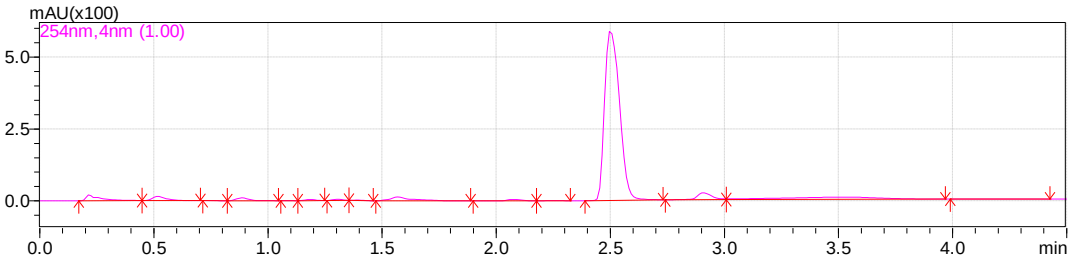


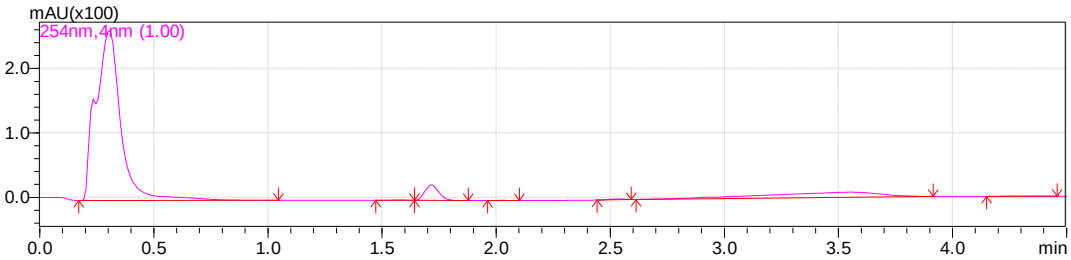
Figure S3: Flow synthesis of oxadiazoles in combination with microfluidic extraction.



Crude



Organic layer

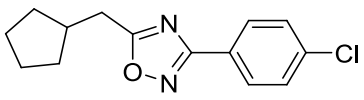


Aqueous layer

The Syrris AFRICA FLLEX module (FLLEX module controlled with a computer) was successfully combined with a Vapourtec system to remove solvent (DMA) and impurities from the reaction medium. Further experimentation showed that toluene is much better than CH_2Cl_2 for the extraction. On a preparative scale using the three reactor flow reaction setup (Schemes 2 and 3 of main article), the desired oxadiazole derivatives were obtained in good yield with a throughput of ≈0.5 g/h.

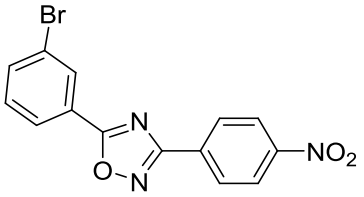
Procedures and data for the flow synthesis of 1,2,4-oxadiazoles in Table 2.

3-(4-Chlorophenyl)-5-(cyclopentylmethyl)-1,2,4-oxadiazole (Table 2, entry 1)



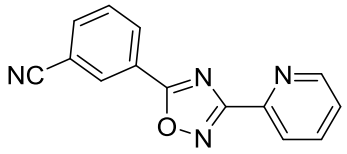
Following the general procedure the reaction mixture (2.5 mL) was collected, and this was purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (70 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 2H), 7.45 (m, 2H), 2.95 (dd, *J* = 2.3, 7.3 Hz, 2H), 2.41 (septet, *J* = 7.8 Hz, 1H), 1.89 (m, 2H), 1.64 (m, 4H), 1.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 167.4, 137.1, 129.1, 128.7, 125.5, 37.9, 32.4, 32.3, 24.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{15}ClN_2O$ $[M+H]^+$ 263.0946, found 263.0947.

5-(3-Bromophenyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole[1] (Table 2, entry 2)



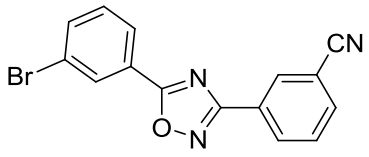
Following the general procedure, the reaction mixture (2.5 mL) was collected, and this was purified using automated SiO_2 chromatography to provide the title compound as a white solid (61 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (m, 5H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 167.5, 149.6, 136.1, 132.5, 131.1, 130.8, 128.5, 126.7, 125.5, 124.1, 123.3; LCMS (ESI) *m/z* calcd for $C_{14}H_8BrN_3O_3$ $[M+H]^+$ 345.9749, found 346.00.

3-(3-(Pyridin-2-yl)-1,2,4-oxadiazol-5-yl)benzonitrile[2] (Table 2, entry 3)



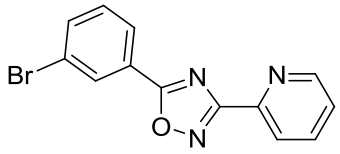
Following the general procedure, the reaction mixture (2.5 mL) was collected, and this was purified using automated SiO_2 chromatography to provide the title compound as a white solid (61 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (m, 1H), 8.54 (m, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.86 (m, 2H), 7.68 (t, *J* = 8.7 Hz, 1H), 7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 169.0, 150.5, 145.8, 138.0, 136.2, 132.4, 132.0, 130.5, 126.3, 125.5, 123.8, 117.6, 114.2; HRMS (ESI) *m/z* calcd for $C_{14}H_8N_4O$ $[M+H]^+$ 249.0698, found 249.0770.

3-(5-(3-Bromophenyl)-1,2,4-oxadiazol-3-yl)benzonitrile (Table 2, entry 4)



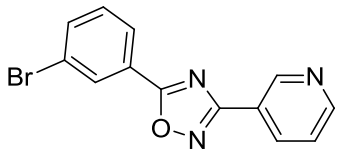
Following the general procedure, the reaction mixture (2.5 mL) was collected, and this was purified using automated SiO_2 chromatography to provide the title compound as a white solid (94 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.40 (m, 2H), 8.16 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.83 (m, 1H), 7.77 (m, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz MHz, $CDCl_3$) δ 175.0, 167.4, 136.1, 134.5, 131.4, 131.11, 130.09, 130.8, 129.9, 128.1, 126.7, 125.6, 123.3, 118.0, 113.4; HRMS (ESI) *m/z* calcd for $C_{15}H_8BrN_3O$ $[M+H]^+$ 324.9924, found 324.9916.

5-(3-Bromophenyl)-3-(pyridin-2-yl)-1,2,4-oxadiazole[3] (Table 2, entry 5)



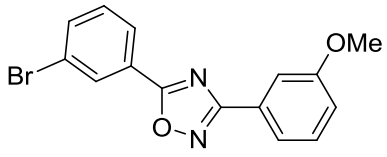
Following the general procedure, the reaction mixture (2.5 mL) was collected, and this was purified using automated SiO_2 chromatography to provide the title compound as a white solid (68 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 5.0 Hz, 1H), 8.45 (s, 1H), 8.19 (m, 2H), 7.86 (dt, *J* = 1.8, 8.0 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.44 (m, 2H); ^{13}C NMR (100 MHz MHz, $CDCl_3$) δ 175.1, 168.9, 150.5, 146.2, 137.1, 135.9, 131.2, 130.6, 126.8, 125.7, 125.6, 123.3, 123.2; HRMS (ESI) *m/z* calcd for $C_{13}H_8BrN_3O$ $[M+H]^+$ 301.9852, found 301.9924.

5-(3-Bromophenyl)-3-(pyridin-3-yl)-1,2,4-oxadiazole[4] (Table 2, entry 6)



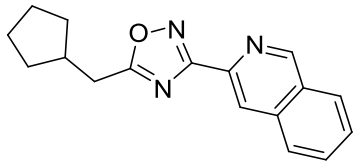
Following the general procedure, the reaction mixture (2.5 mL) was collected, and this was purified using automated SiO_2 chromatography to provide the title compound as a white solid (79 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (m, 1H), 8.75 (d, *J* = 1.4, 4.6 Hz, 1H), 8.41 (dt, *J* = 1.8, 8.2 Hz 1H), 8.36 (m, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.73 (m, 1H), 7.43 (m, 2H); ^{13}C NMR (100 MHz MHz, $CDCl_3$) δ 174.8, 167.1, 152.2, 148.7, 136.0, 134.7, 131.1, 130.7, 126.7, 125.7, 123.7, 123.2, 123.0; HRMS (ESI) *m/z* calcd for $C_{13}H_8BrN_3O$ $[M+H]^+$ 301.9853, found 301.9925.

5-(3-Bromophenyl)-3-(3-methoxyphenyl)-1,2,4-oxadiazole[5] (Table 2, entry 7)



Following the general procedure, the reaction mixture (2.5 mL) was collected, and this was purified using automated SiO_2 chromatography to provide the title compound as a white solid (84 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.73 (m, 2H), 7.67 (s, 1H), 7.40 (m, 2H), 7.05 (dd, *J* = 2.8, 8.2 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz MHz, $CDCl_3$) δ 174.3, 169.0, 159.9, 135.7, 131.0, 130.7, 130.0, 127.8, 126.6, 126.0, 123.1, 120.0, 117.9, 112.0, 55.5; HRMS (ESI) *m/z* calcd for $C_{15}H_{11}BrN_2O_2$ $[M+H]^+$ 331.0608, found 331.0607.

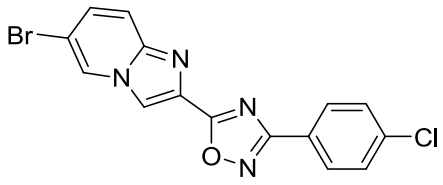
5-(Cyclopentylmethyl)-3-(isoquinolin-3-yl)-1,2,4-oxadiazole[6] (Table 2, entry 8)



Following the general procedure, the reaction mixture (2.5 mL) was collected, and this was purified using automated SiO_2 chromatography to provide the title compound as a white solid (64 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.51 (s, 1H), 8.02 (d, *J* = 7.8 Hz 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.75 (t, *J* = 6.9 Hz, 1H), 7.68 (t, *J* = 6.9 Hz, 1H), 3.00 (m, 2H), 2.46 (septet, , *J* = 7.8 Hz, 1H), 1.89 (m, 2H), 1.62 (m, 4H), 1.32 (m, 2H); ^{13}C NMR (100 MHz MHz, $CDCl_3$) δ 180.2, 168.4, 153.3, 140.1, 135.8, 131.1, 129.3, 128.7, 127.8, 127.4, 120.6, 38.0, 32.5, 32.4, 24.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{17}N_3O$ $[M+H]^+$ 280.1444, found 280.1430.

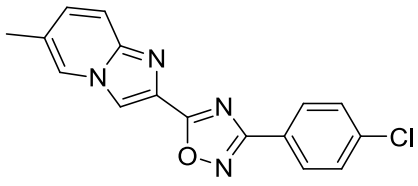
General procedure for the continuous flow synthesis of imidazo[1,2-*a*]pyridine-2-yl-1,2,4-oxadiazoles (Table 3).

5-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (Table 3, entry 1)



Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (51 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.31 (s, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 7.65 (d, *J* = 9.6 Hz, 1H), 7.48 (s, 1H), 7.46 (s, 1H), 7.37 (dd, *J* = 1.8, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 168.2, 144.6, 137.6, 131.7, 130.5, 129.2, 129.0, 126.2, 125.2, 119.4, 114.7, 109.4; HRMS (ESI) *m/z* calcd for $C_{15}H_8BrClN_4O$ $[M+H]^+$ 376.9621, found 376.9622.

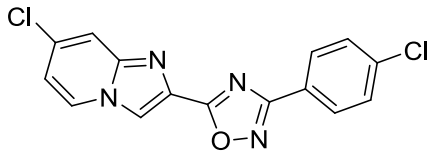
3-(4-Chlorophenyl)-5-(6-methylimidazo[1,2-*a*]pyridin-2-yl)-1,2,4-oxadiazole (Table 3, entry 2)



Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (30 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.16 (m, 2H), 7.97 (s, 1H), 7.63 (d, *J* = 9.6 Hz, 1H), 7.40 (m, 2H), 7.15 (d, *J* = 9.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 168.2, 145.3, 137.5, 130.6, 130.0, 129.1,

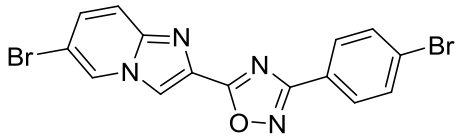
129.0, 125.3, 124.1, 123.6, 118.1, 114.5, 18.0; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}ClN_4O$ $[M+H]^+$ 311.0694, found 311.0678.

5-(7-Chloroimidazo[1,2-*a*]pyridin-2-yl)-3-(4-chlorophenyl)-1,2,4-oxadiazole(Table 3, entry 3)



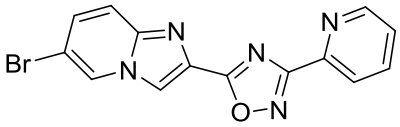
Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (43 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.16 (s, 1H), 8.14 (s, 1H), 8.12 (s, 1H), 7.74 (s, 1H), 7.48 (s, 1H), 7.46 (s, 1H), 6.93 (dd, *J* = 1.8, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 138.4, 137.4, 134.6, 132.4, 129.1, 128.9, 128.5, 127.6, 127.4, 125.5, 111.6, 110.4; HRMS (ESI) *m/z* calcd for $C_{15}H_8Br_2N_4O$ $[M+H]^+$ 420.9118, found 420.9120.

5-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-3-(4-bromophenyl)-1,2,4-oxadiazole(Table 3, entry 4)



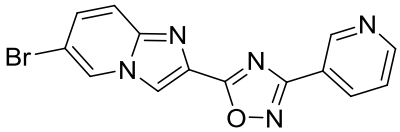
Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (52 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.31 (s, 1H), 8.09 (s, 1H), 8.07 (s, 1H), 7.64 (m, 3H), 7.37 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 168.4, 144.8, 132.1, 131.7, 130.5, 129.2, 126.1, 125.91, 125.89, 119.5, 114.9, 109.3; HRMS (ESI) *m/z* calcd for $C_{15}H_8Br_2N_4O$ $[M+H]^+$ 418.9066, found 418. 9127.

5-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-3-(pyridin-2-yl)-1,2,4-oxadiazole (Table 3, entry 5)



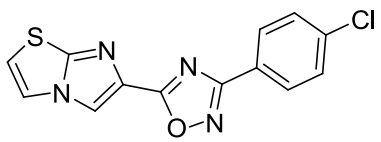
Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (56 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4.6 Hz, 1H), 8.43 (s, 1H), 8.40 (s, 1H), 8.30 (d, *J* = 7.8 Hz, 1H), 7.89 (dt, *J* = 1.8, 7.8 Hz, 1H), 7.67 (d, *J* = 9.6 Hz, 1H), 7.47 (m, 1H), 7.39 (dd, *J* = 1.8, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.7, 150.4, 146.3, 144.6, 137.1, 130.5, 126.2, 125.6, 123.5, 119.5, 115.2, 109.2; HRMS (ESI) *m/z* calcd for $C_{14}H_8BrN_5O$ $[M+H]^+$ 341.9985, found 341.9980.

5-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-3-(pyridin-3-yl)-1,2,4-oxadiazole (Table 3, entry 6)



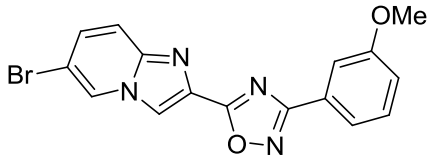
Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (60 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.78 (m, 1H), 8.50 (d, *J* = 8.2 Hz, 1H), 8.40 (s, 1H), 8.36 (s, 1H), 7.68 (d, *J* = 9.6 Hz, 1H), 7.47 (m, 1H), 7.41 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 167.1, 152.1, 148.8, 144.6, 135.0, 131.5, 130.6, 126.1, 123.7, 123.0,119.5, 115.0, 109.3; HRMS (ESI) *m/z* calcd for $C_{14}H_8BrN_5O$ $[M+H]^+$ 341.9985, found 341.9976.

3-(4-Chlorophenyl)-5-(imidazo[2,1-*b*]thiazol-6-yl)-1,2,4-oxadiazole (Table 3, entry 7)



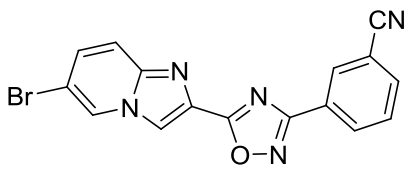
Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (60 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, *J* = 3.2 Hz, 1H), 8.08 (m, 2H), 8.03 (dd, *J* = 2.8, 4.6 Hz, 1H), 7.68 (m, 2H), 7.50 (dd, *J* = 2.8, 4.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.7, 167.1, 151.3, 136.4, 131.2, 129.4, 128.9, 125.1, 120.1, 117.6; HRMS (ESI) *m/z* calcd for $C_{13}H_7ClN_4OS$ $[M+H]^+$ 303.0102, found 303.0099.

5-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-3-(3-methoxyphenyl)-1,2,4-oxadiazole (Table 3, entry 8)



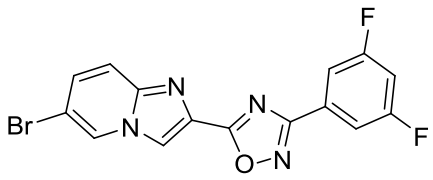
Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a yellow solid (39 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.31 (s, 1H), 7.80 (d, *J* = 7.3 Hz, 1H), 7.73 (m, 1H), 7.65 (d, *J* = 9.6 Hz, 1H), 7.38 (m, 2H), 7.06 (dd, *J* = 2.3, 8.2 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 169.0, 159.9, 144.6, 131.8, 130.4, 129.9, 127.8, 126.1, 120.1, 119.4, 118.1, 114.8, 112.0, 109.2, 55.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{11}BrN_4O_2$ $[M+H]^+$ 371.0138, found 371.0119.

3-(5-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-1,2,4-oxadiazol-3-yl)benzonitrile (Table 3, entry 9)



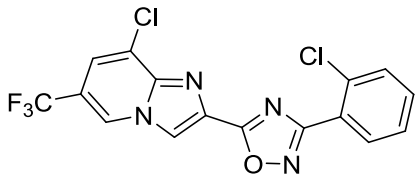
Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a white solid (38 mg, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.85 (s, 1H), 8.46 (s, 1H), 8.41 (d, *J* = 8.7 Hz 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 9.6 Hz, 1H), 7.58 (d, *J* = 9.6 Hz, 1H); HRMS (ESI) *m/z* calcd for $C_{16}H_8BrN_5O$ $[M+H]^+$ 365.9985, found 365.9983.

5-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)-3-(3,5-difluorophenyl)-1,2,4-oxadiazole (Table 3, entry 10)



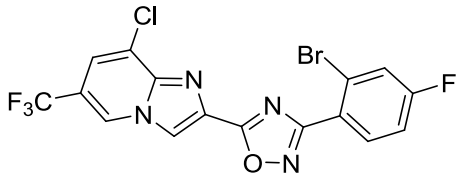
Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a white solid (33 mg, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.32 (s, 1H), 7.76 (d, *J* = 6.9 Hz, 2H), 7.65 (d, *J* = 10.0 Hz, 1H), 7.39 (d, *J* = 9.6 Hz, 1H), 6.96 (t, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 167.5, 164.5, 161.8, 144.7, 130.6, 126.2, 119.3, 115.1, 110.9, 110.7, 109.4, 106.7; HRMS (ESI) *m/z* calcd for $C_{15}H_7BrF_2N_4O$ $[M+H]^+$ 376.9844, found 376.9846.

5-(8-Chloro-6-(trifluoromethyl)imidazo[1,2-*a*]pyridin-2-yl)-3-(2-chlorophenyl)-1,2,4-oxadiazole[7] (Table 3, entry 11)



Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a white solid (24 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.53 (s, 1H), 8.05 (d, *J* = 7.3 Hz, 1H), 7.55 (m, 2H), 7.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 167.9, 143.5, 133.6, 133.2, 132.0, 131.9, 130.9, 126.9, 126.1, 125.7, 123.8, 121.4, 121.0, 119.0,118.6, 117.7; HRMS (ESI) *m/z* calcd for $C_{16}H_7Cl_2F_3N_4O$ $[M+H]^+$ 398.9950, found 399.0024.

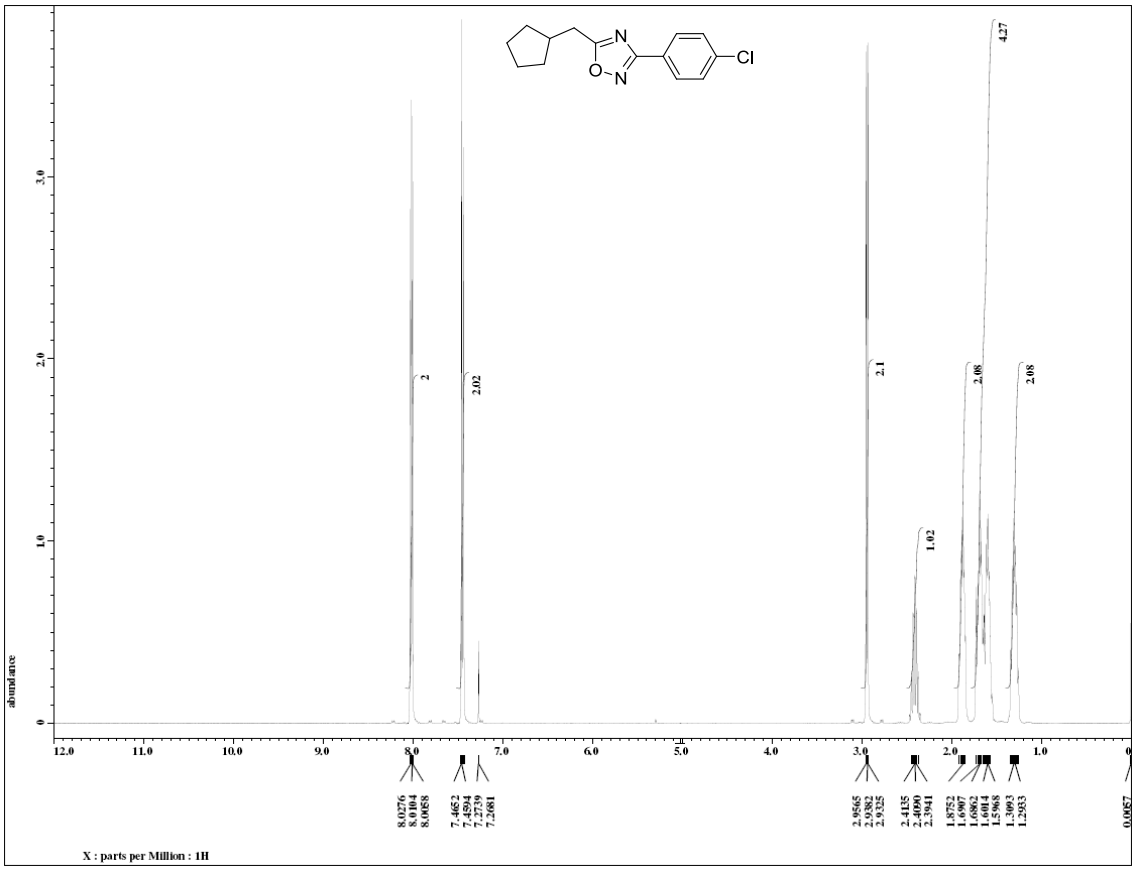
3-(2-Bromo-4-fluorophenyl)-5-(8-chloro-6-(trifluoromethyl)imidazo[1,2-*a*]pyridin-2-yl)-1,2,4-oxadiazole[7] (Table 3, entry 12)



Following the general procedure, the reaction mixture (3.0 mL) was collected, purified using automated SiO_2 chromatography to provide the title compound as a white solid (34 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.55 (s, 1H), 8.01 (dd, *J* = 5.9, 8.7 Hz, 1H), 7.57 (s, 1H), 7.52 (dd, *J* = 2.8, 7.8 Hz, 1H), 7.19 (dt, *J* = 2.8, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 168.0, 164.7, 162.2, 143.6, 133.7, 133.6, 133.0, 126.1, 124.2, 123.9, 123.0, 122.9, 121.8, 121.6, 121.0, 119.0, 118.7, 117.8, 115.0, 114.8; HRMS (ESI) *m/z* calcd for $C_{16}H_6BrClF_4N_4O$ $[M+H]^+$ 460.9351, found 460.9424.

References

1. Compound is commercially available.
2. Grant, D.; Dahl, R.; Cosford, N. D. P. *J. Org. Chem*. **2008**, *73(18)*, 7219-7223.
3. Raboisson, P.; Breitholtz-Emanuelsson, A.; Dahlloef, H.; Edwards, L.; Heaton, W. L.; Isaac, M.; Jarvie, K.; Kers, A.; Minidis, A.r B. E.; Nordmark, A.; et al. *Bioorg. Med. Chem. Lett.* **2012**, *22(22),* 6974-6979.
4. Gopalakrishnan, M.; Honore, M. P.; Lee, C.-H.; Malysz, J.n; Ji, J.; Li, T.; Schrimpf, M.l R.; Sippy, K. B.; Anderson, D. J. Oxadiazole derivatives as neuronal nicotinic acetylcholine receptor ligands and α4β2 pos. allosteric modulators and their preparation, pharmaceutical compositions and use in the treatment of diseases. WO 2008073942 A2 Jun 19, 2008 WO 2007-US87090 Dec 12, 2007.
5. Compound is commercially available.
6. Compound is commercially available.
7. Bannen, L.; Chan, D. S.-M.; Gu, X.-H.; Mac, M. B.; Ng, S.; Wang, T.-L.; Wang, Y.; Xu, W. Imidazo[1,2-*a*]pyridine derivatives, their use as S1P1 agonists and methods for their production. WO 2010065760 A1 Jun 10, 2010 WO 2009-US66620 Dec 3, 2009.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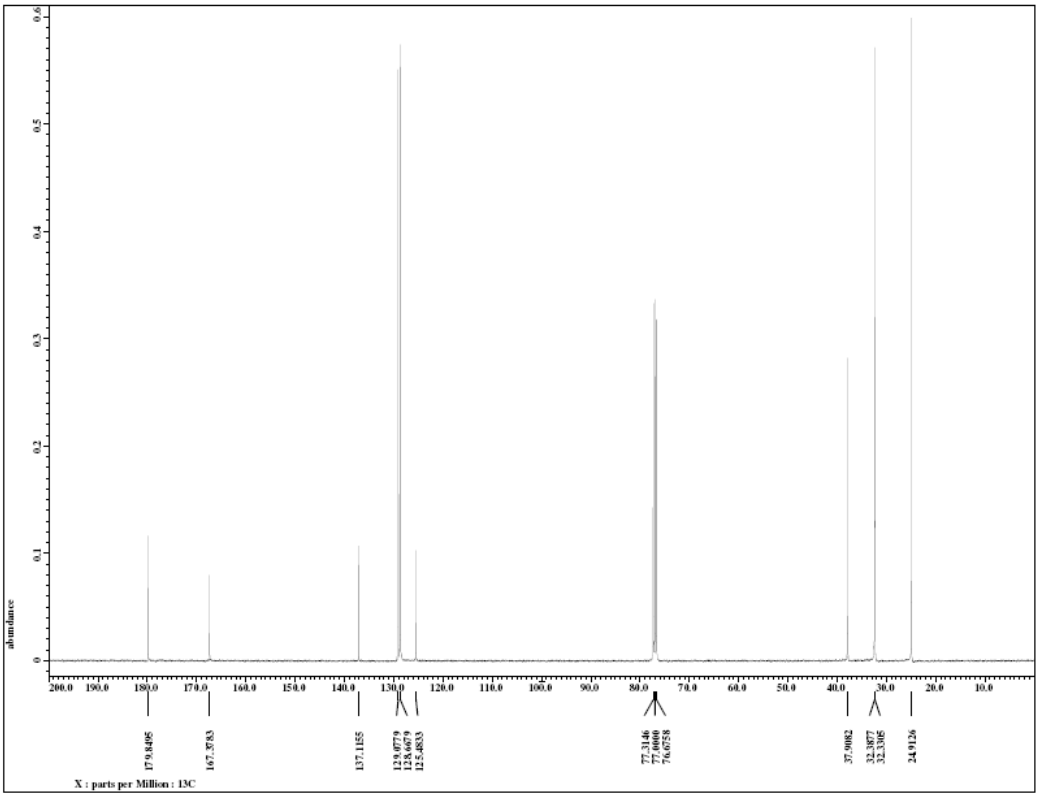
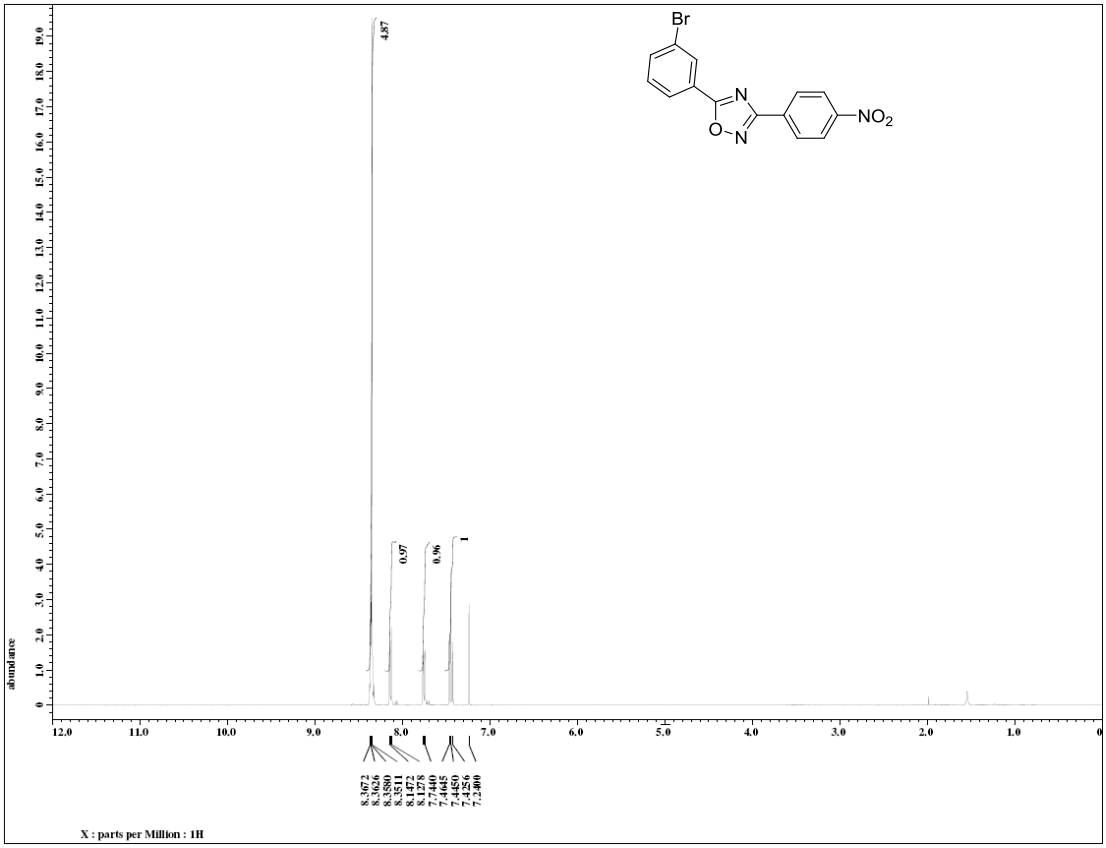

abundance
X : parts per Million : 13C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O
N
NO2
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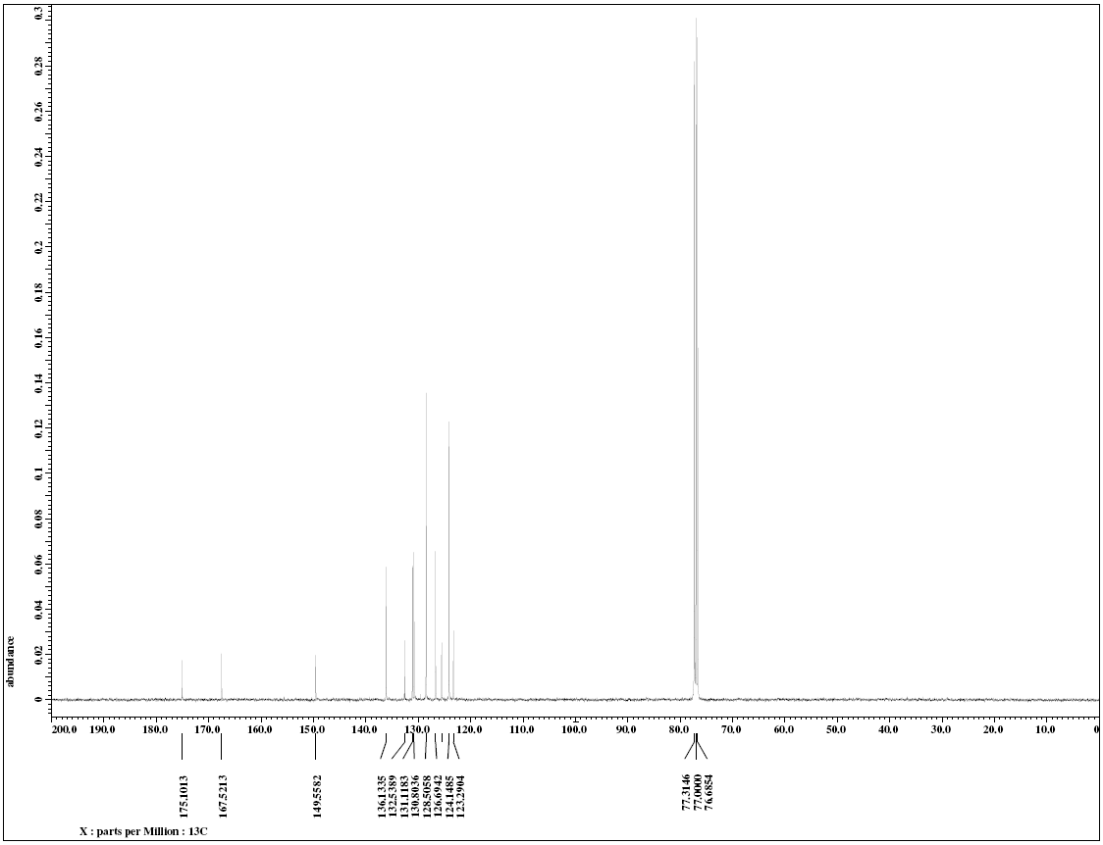
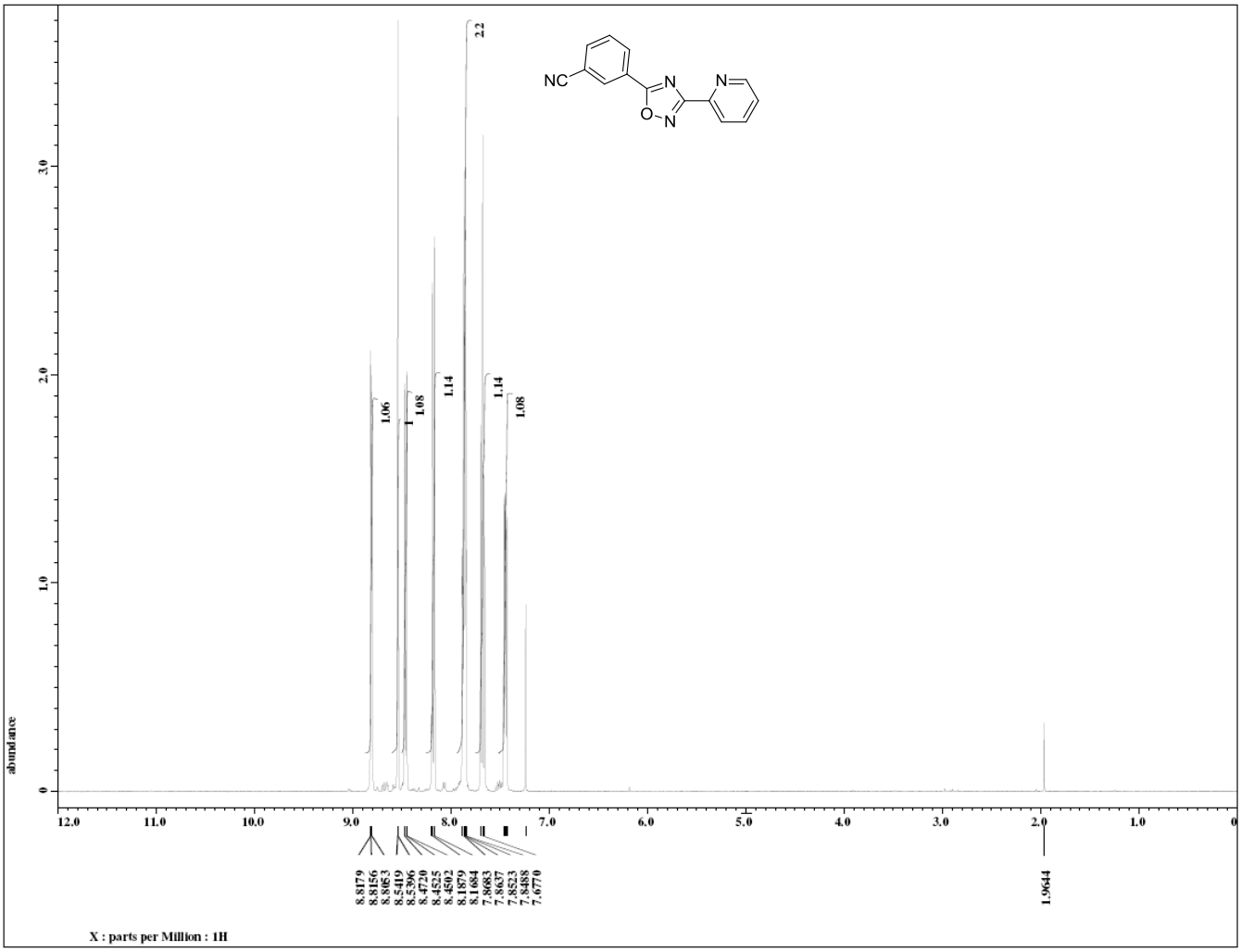
0.97
0.96
1
abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C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N
O
N
abundance
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0
2.2
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1.08
1.14
1.14
1.08
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
8.8179
8.8156
8.8053
8.5419
8.5396
8.4720
8.4525
8.4502
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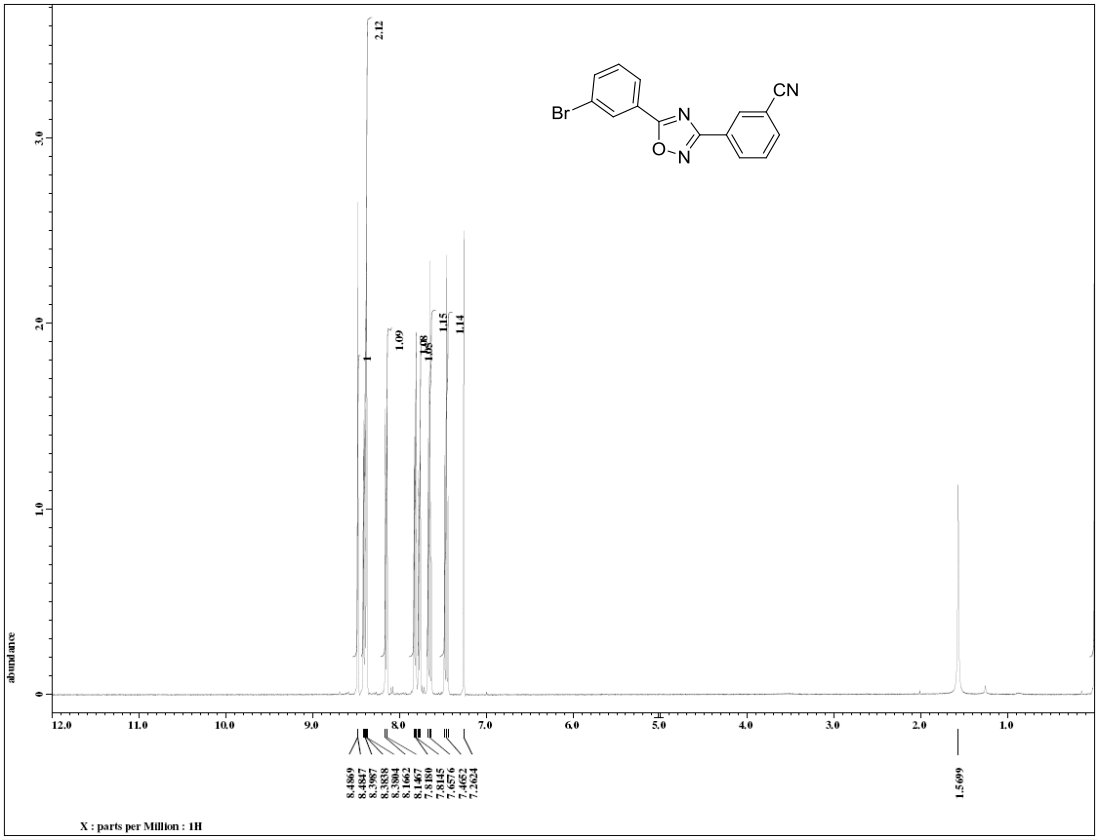
7.6770
1.9644
X : parts per Million : 1H


Br
N
O
N
CN
2.12
1.09
1.08
1.15
1.14
1.00
abundance
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
8.4869
8.4847
8.3987
8.3838
8.3804
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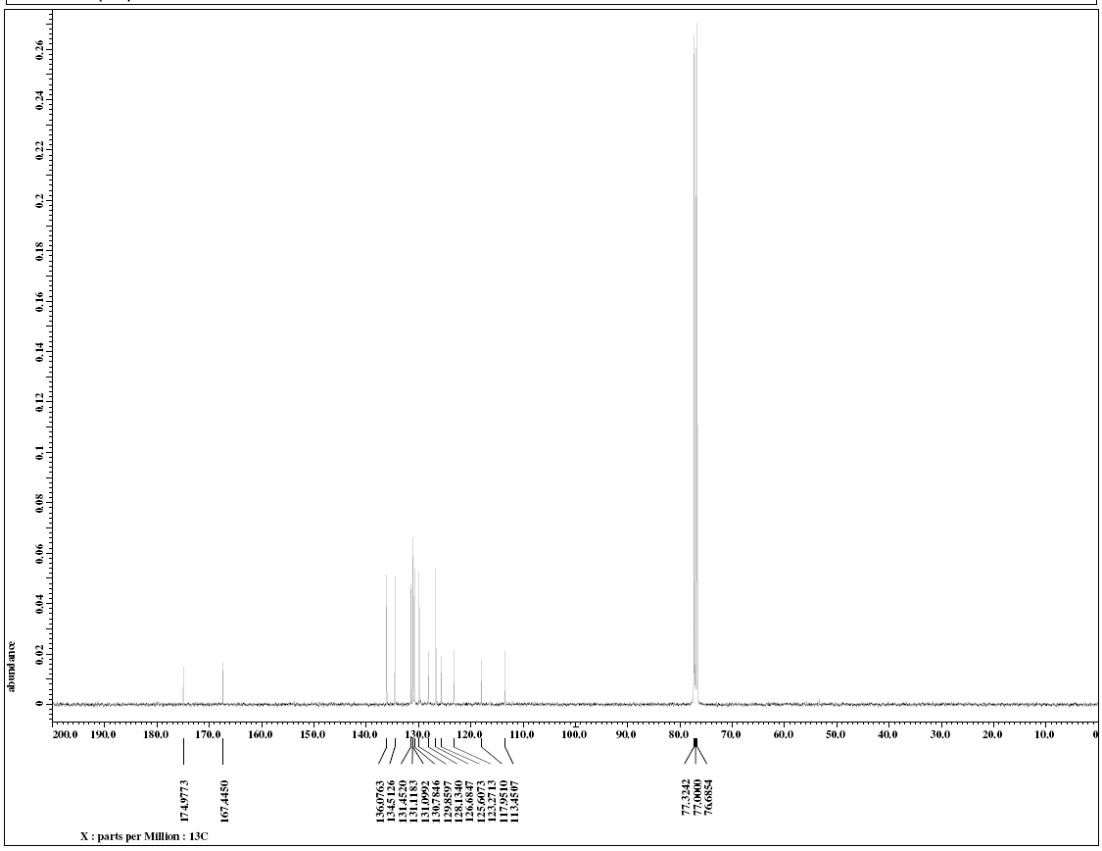
1.5699
X : parts per Million : 1H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110.0
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80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
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134.5126
131.4520
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131.0992
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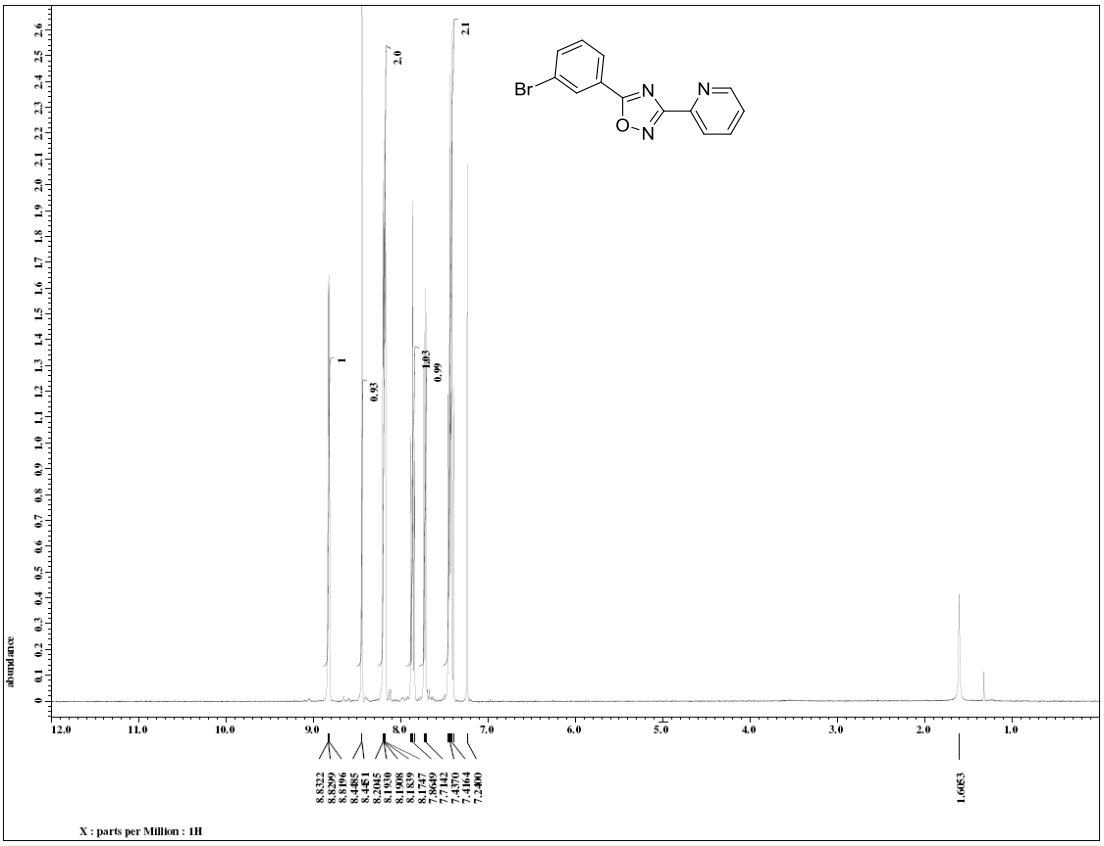
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O
N
N
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8.8299
8.8196
8.4485
8.4453
8.2045
8.1930
8.1908
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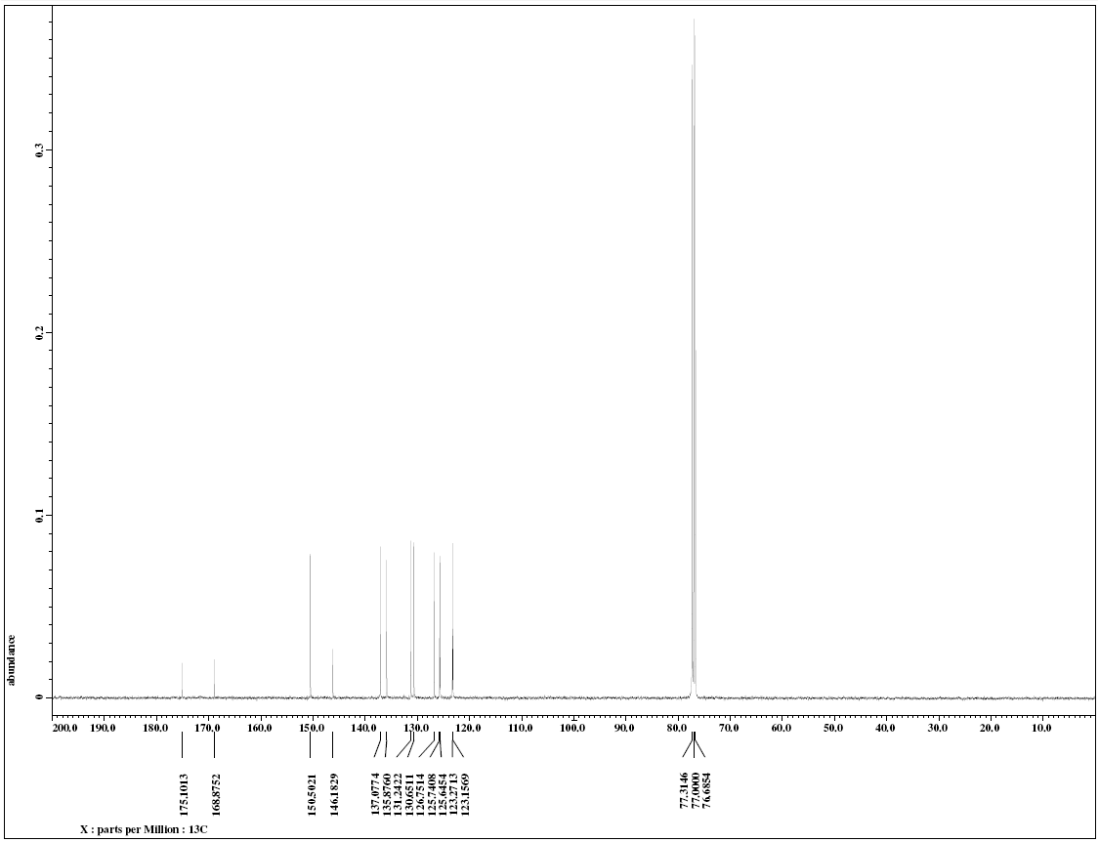
X : parts per Million : 1H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135.8760
131.2422
130.6511
126.3514
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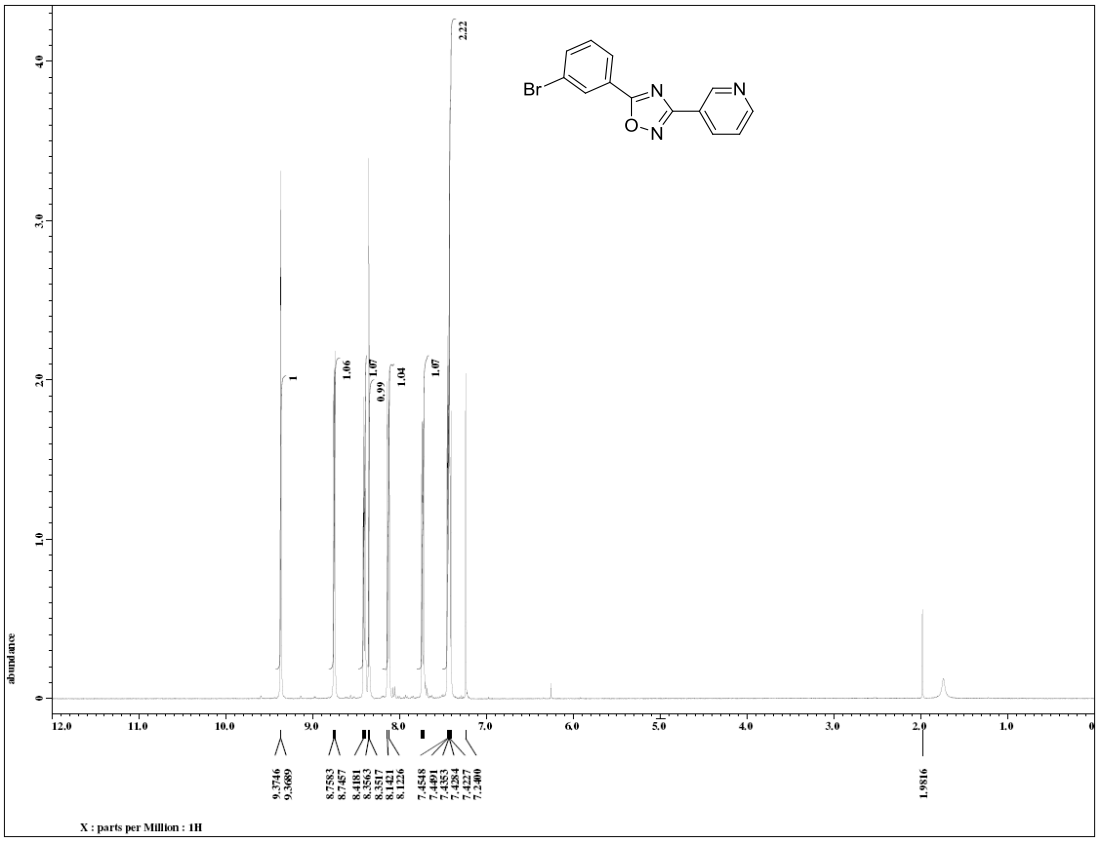
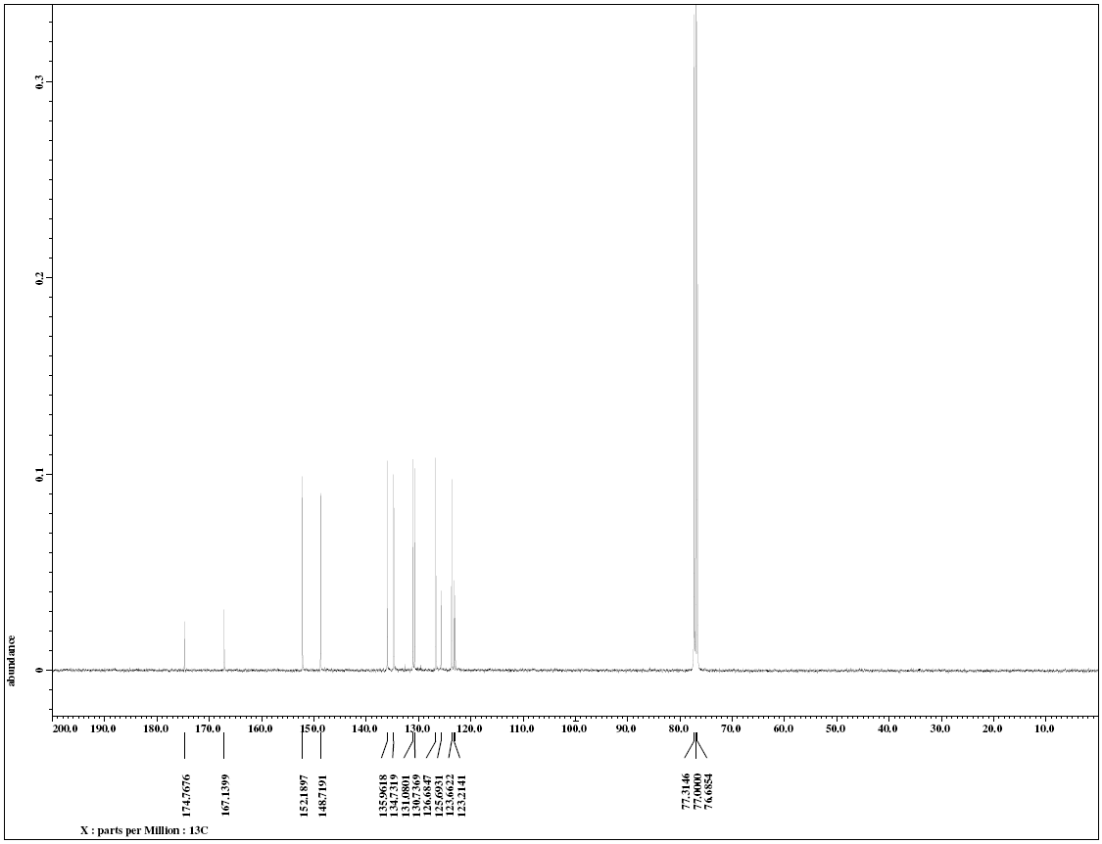
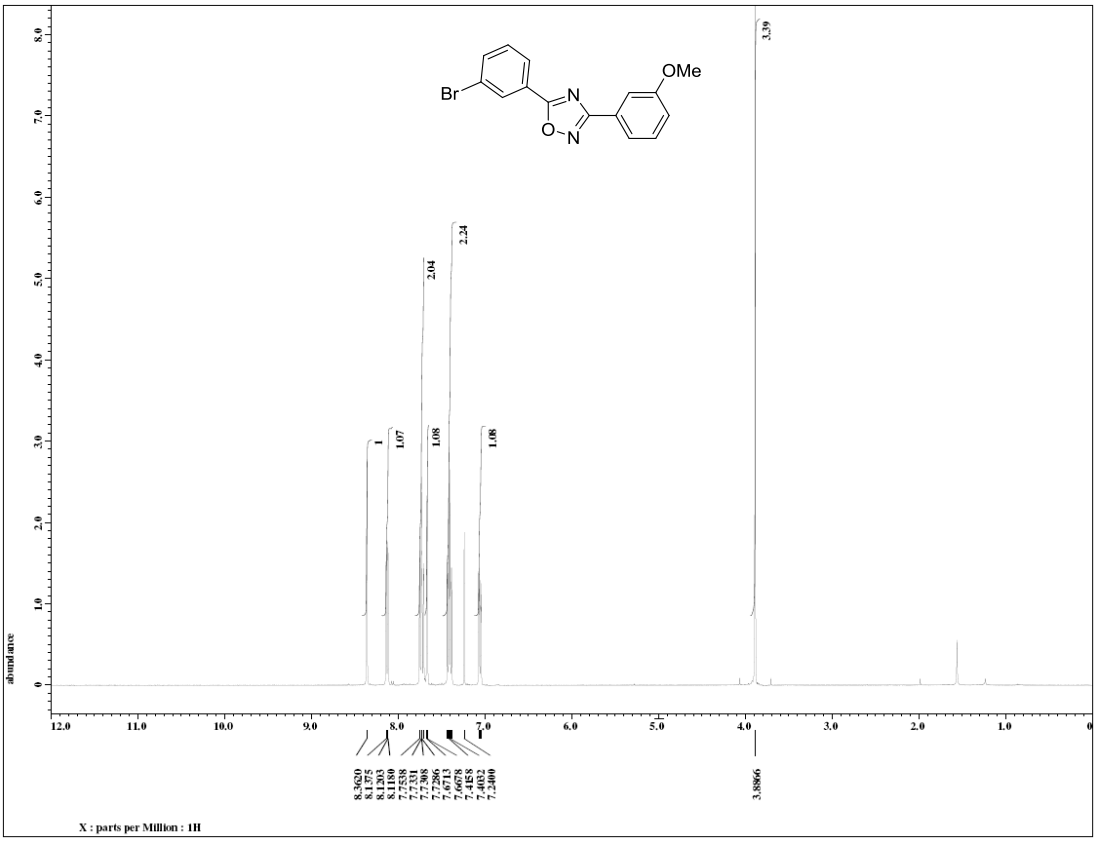
125.6454
123.2713
123.1569
77.3146
77.0000
76.6854
X : parts per Million : 13C


Br
N
N
O
N
abundance
X : parts per Million : 1H


abundance
X : parts per Million : 13C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O
N
OMe
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1.08
1.08
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8.1375
8.1203
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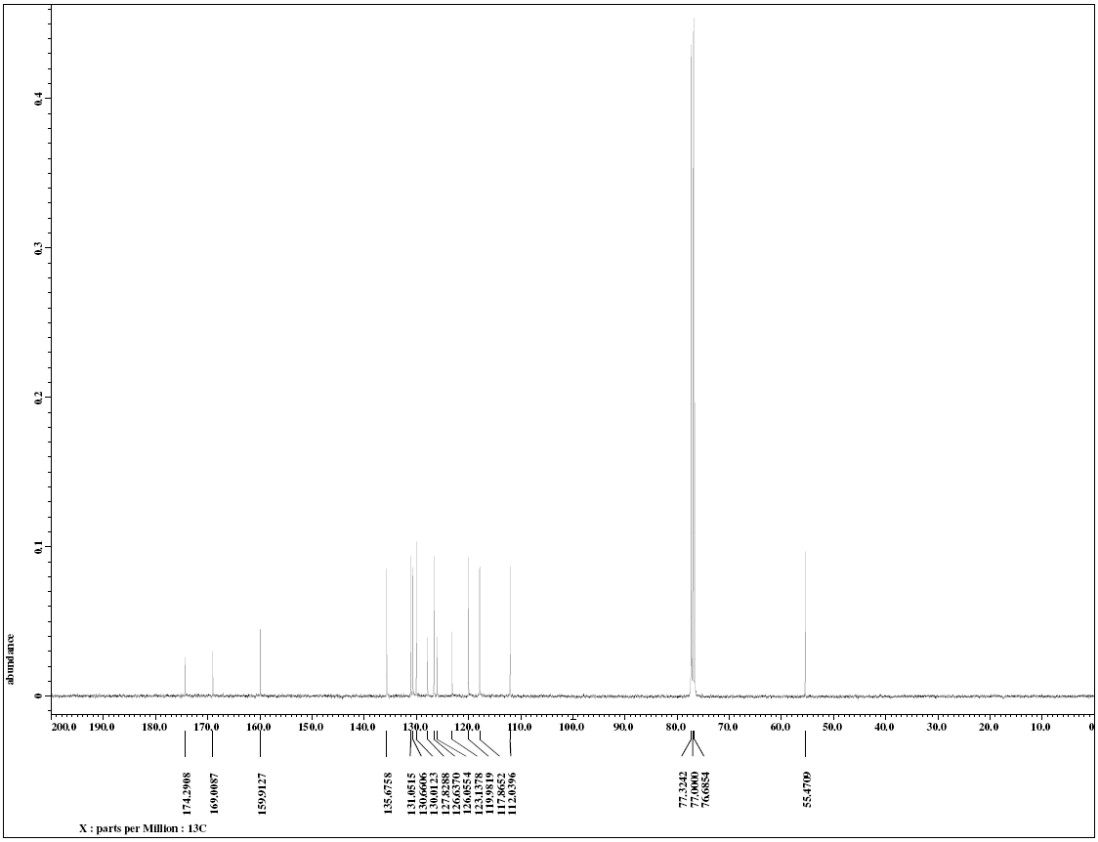
X : parts per Million : 1H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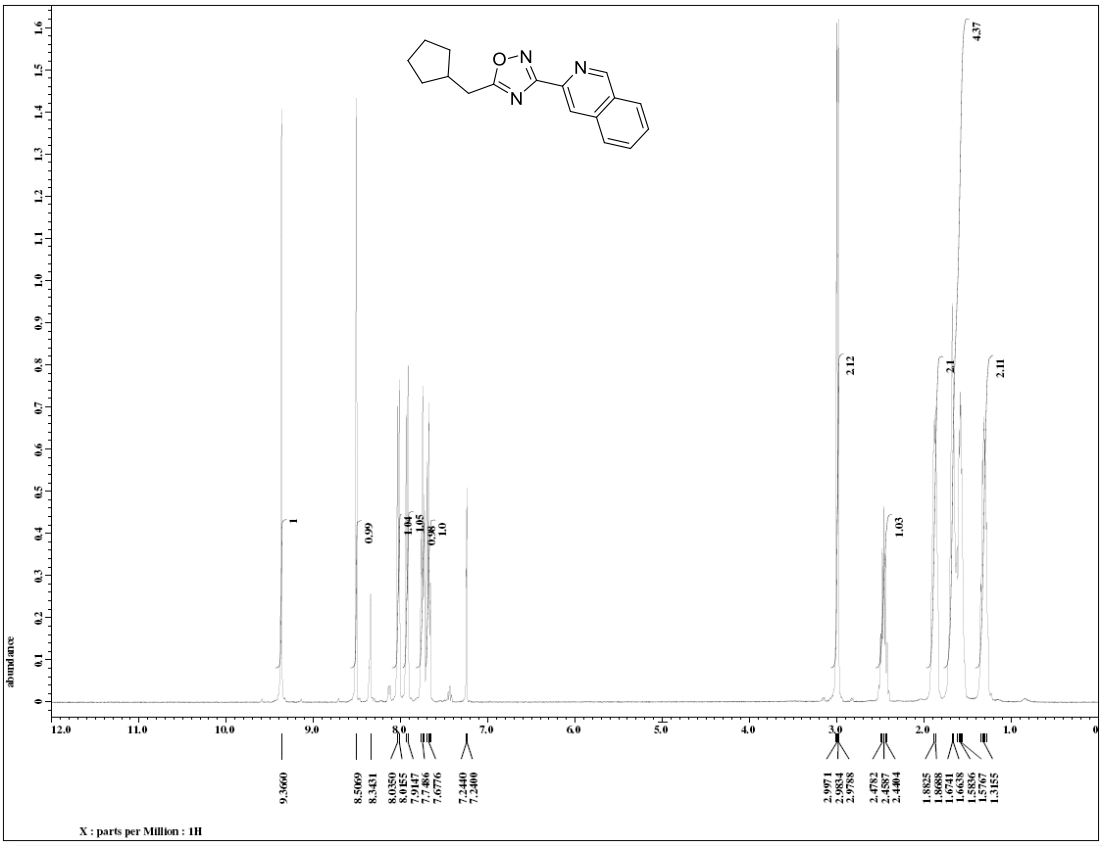
X : parts per Million : 13C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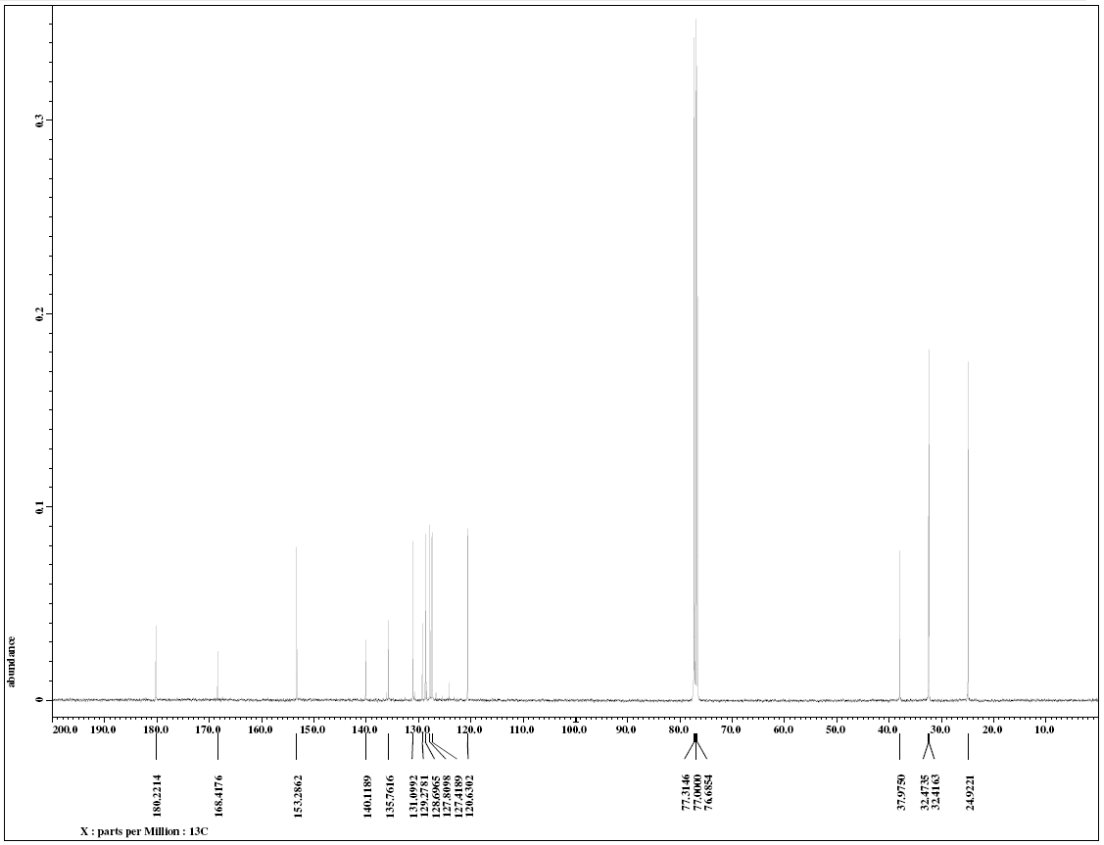
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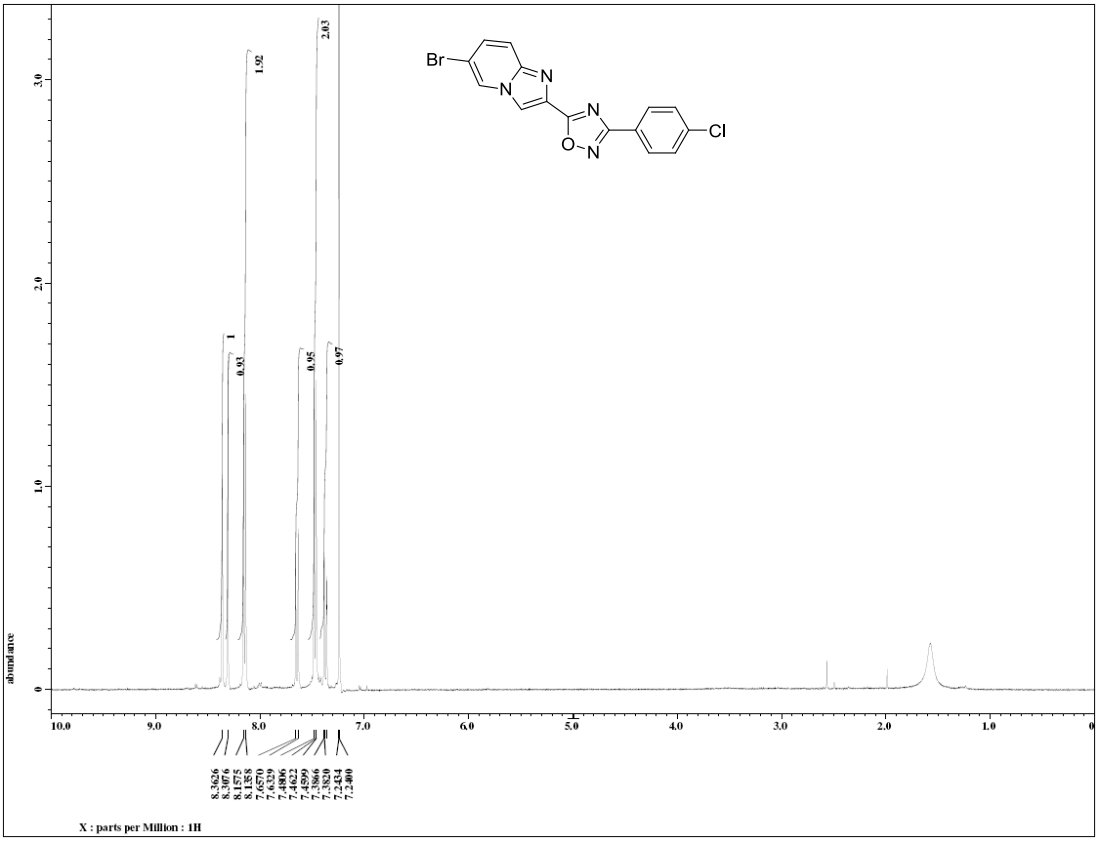
X : parts per Million : 13C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O
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Cl
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8.1575
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7.6570
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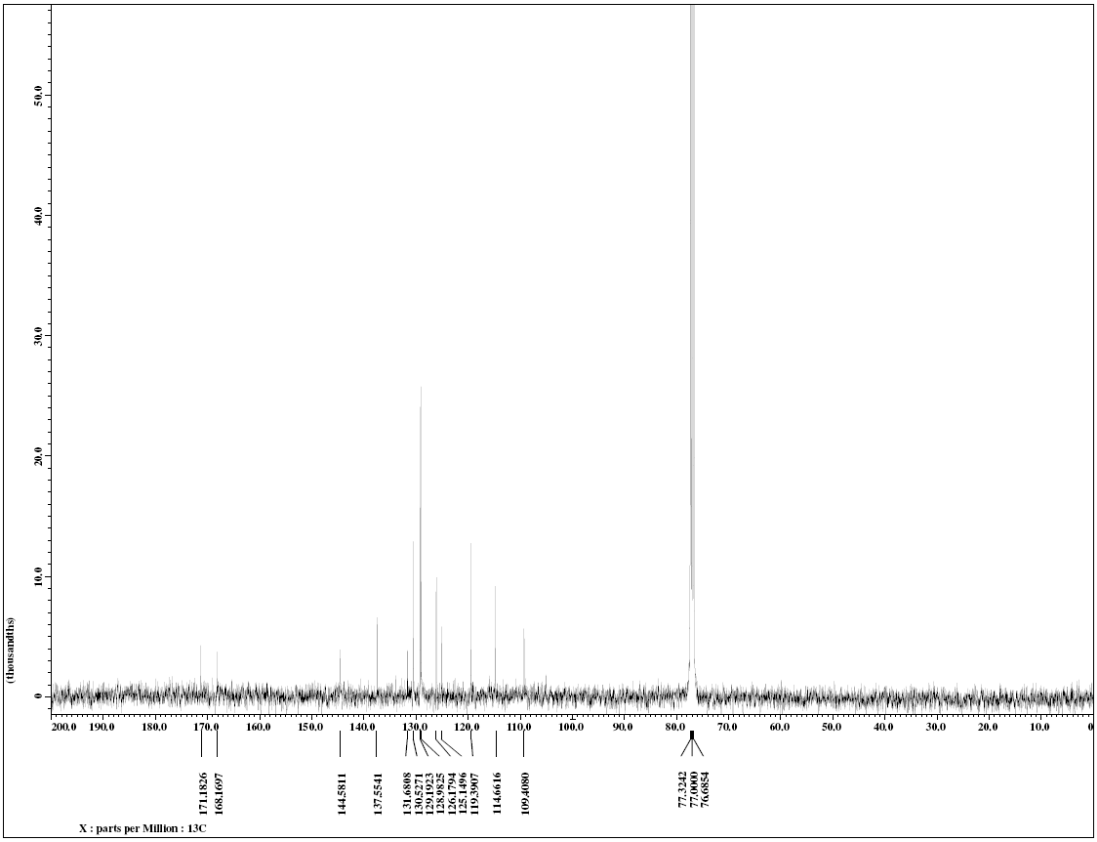
X : parts per Million : 1H


(Thousandths)
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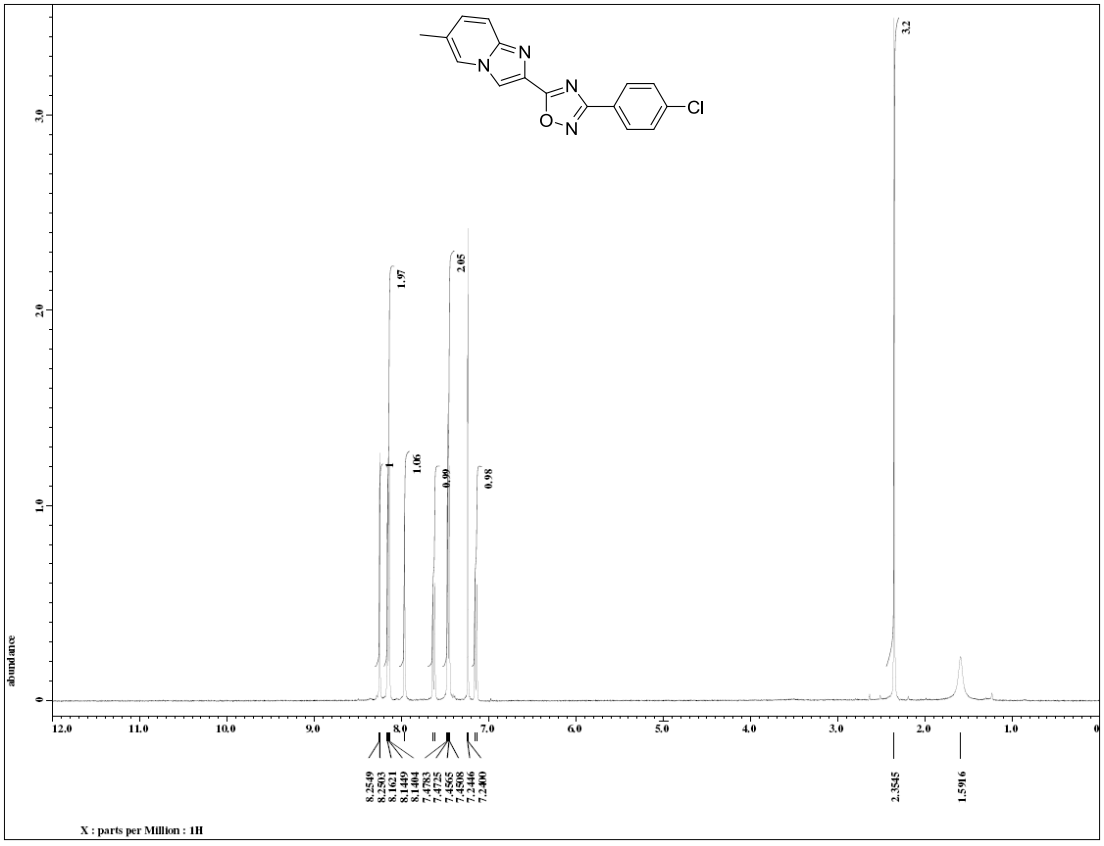
X : parts per Million : 13C


abundance
X : parts per Million : 1H
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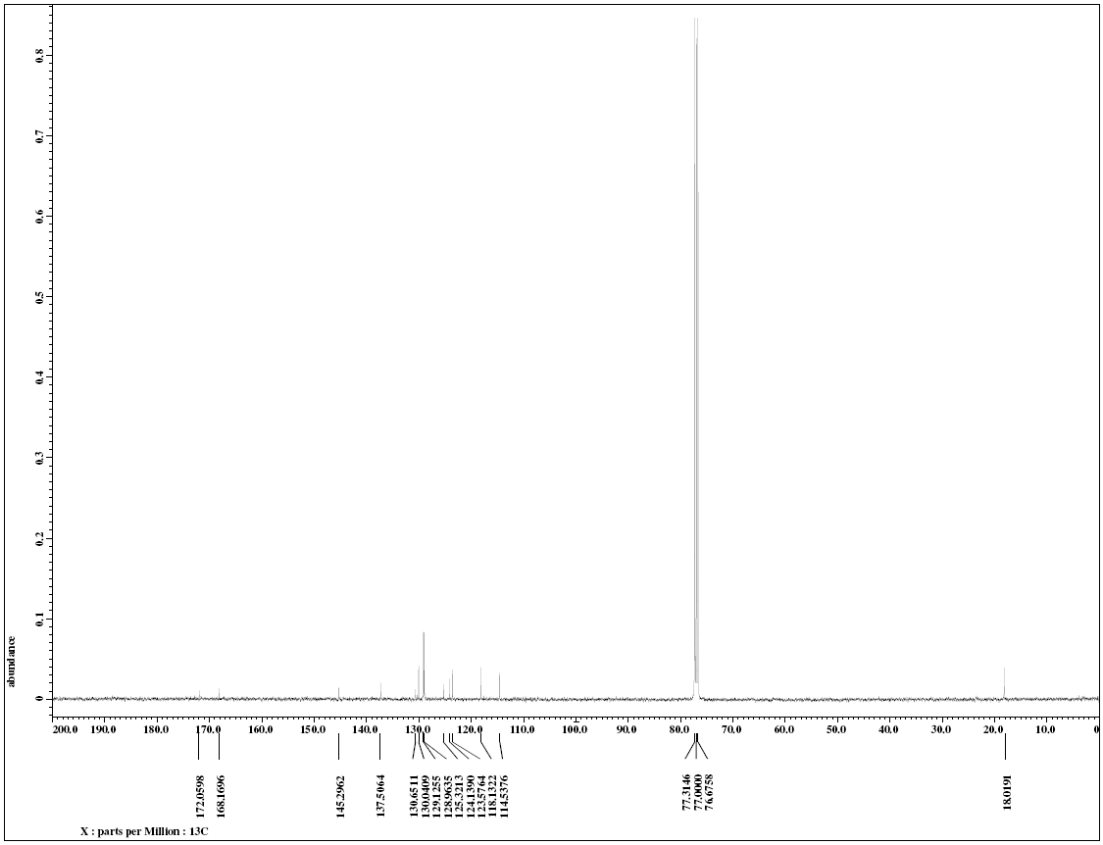
abundance
X : parts per Million : 13C
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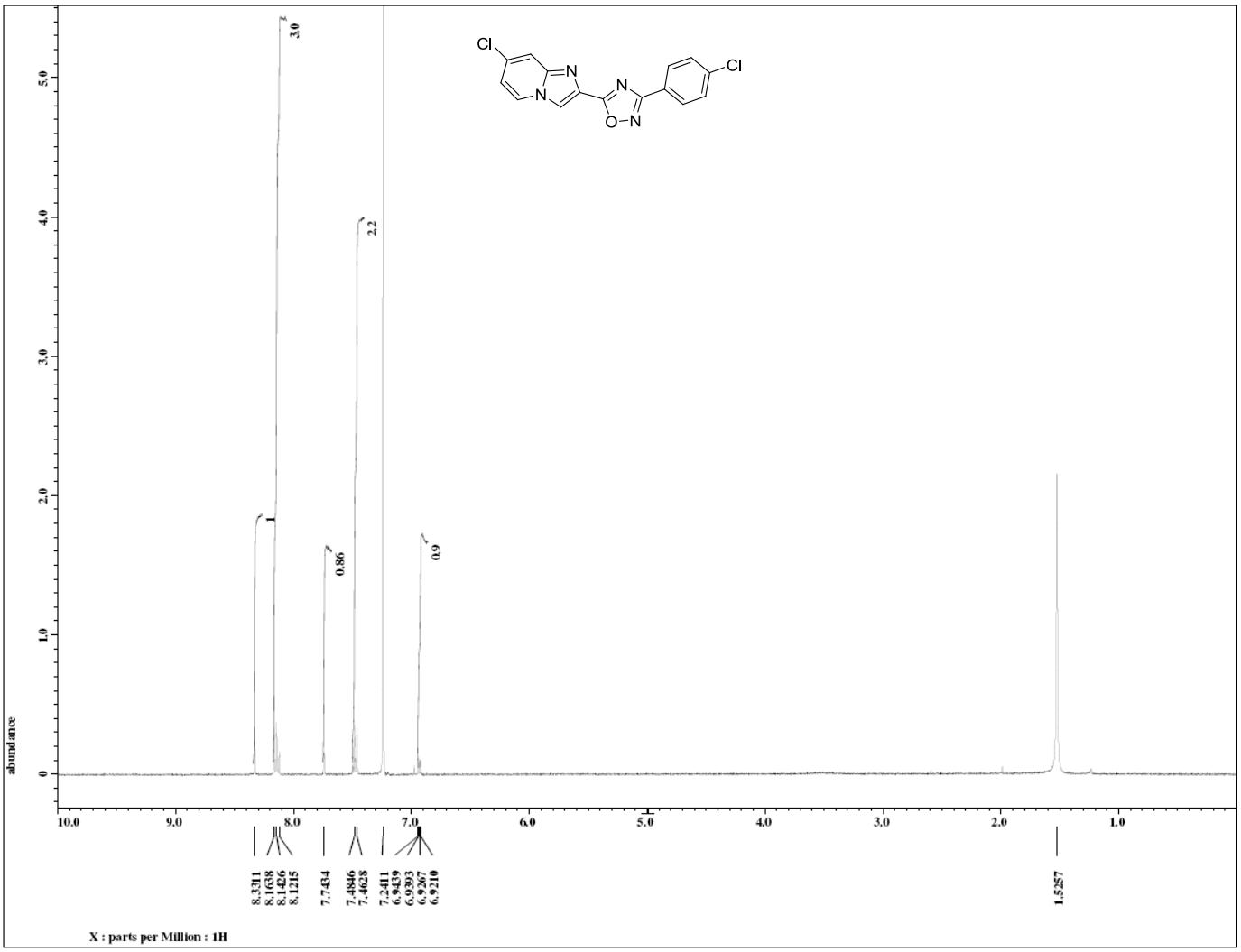
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O–N
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2.2
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0.9
abundance
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8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
8.3311
8.1638
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7.7434
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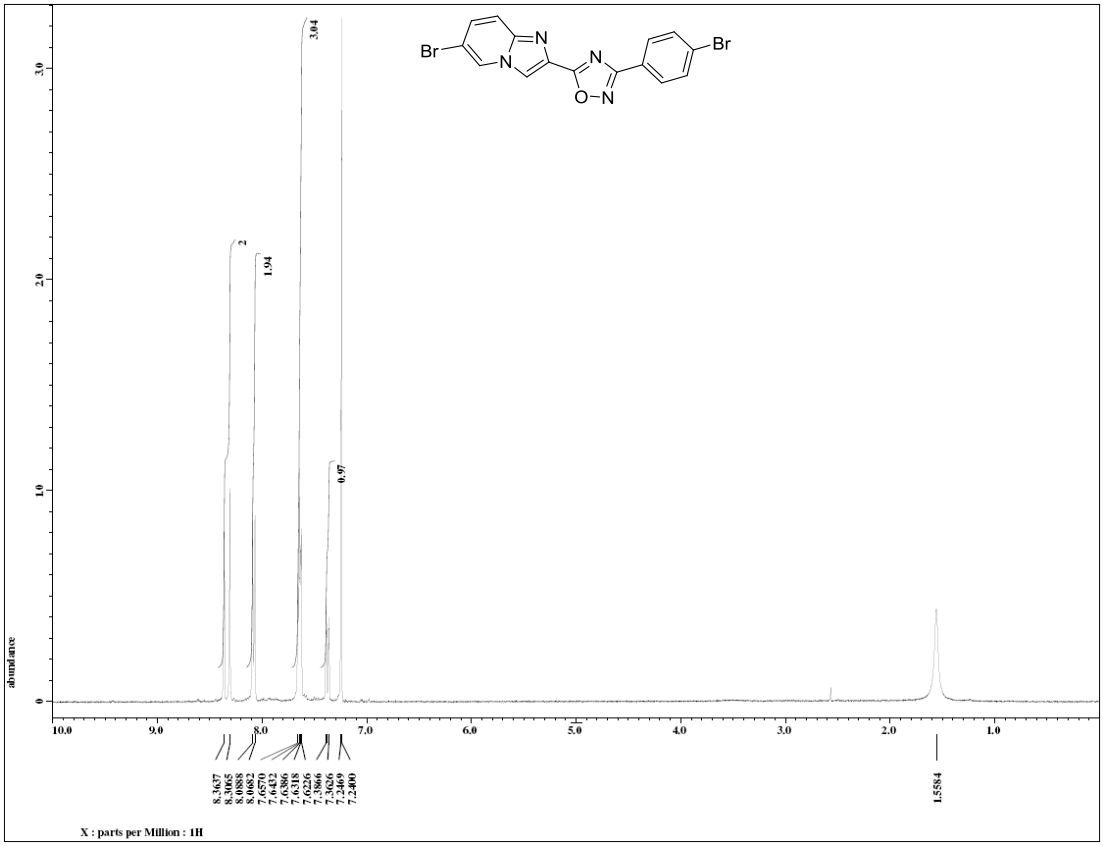
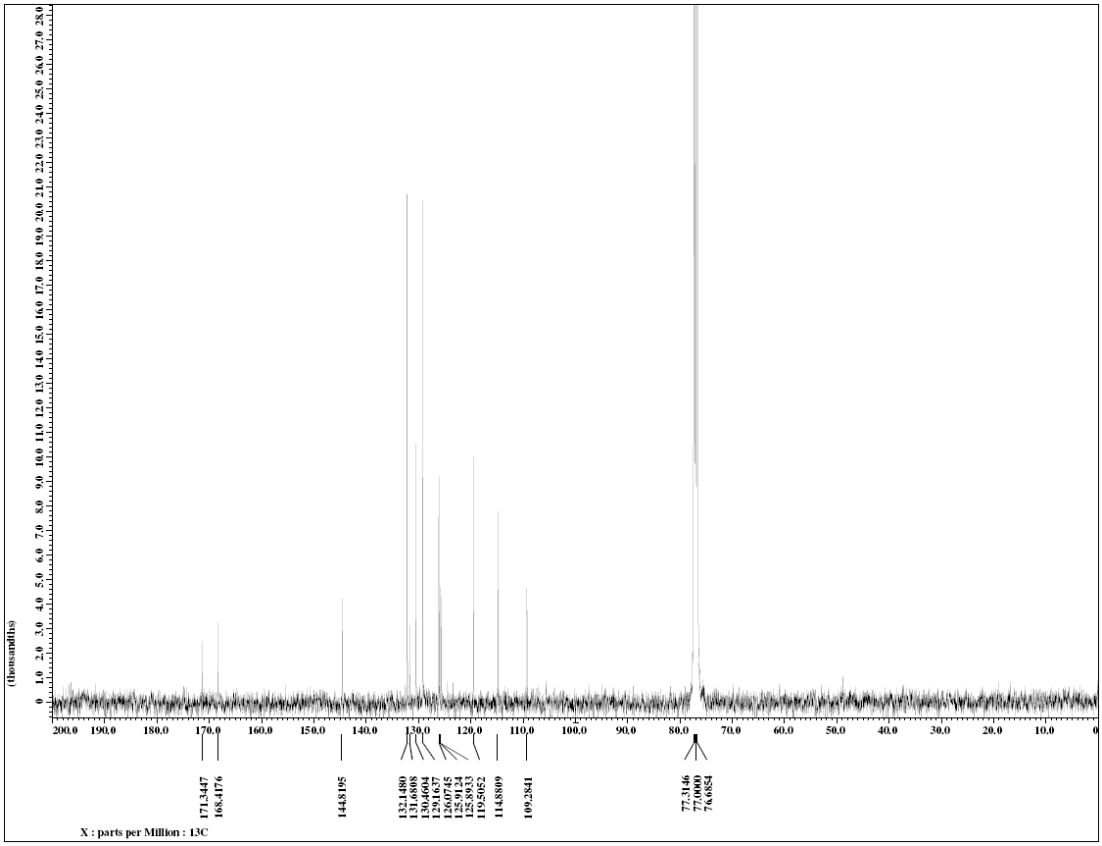
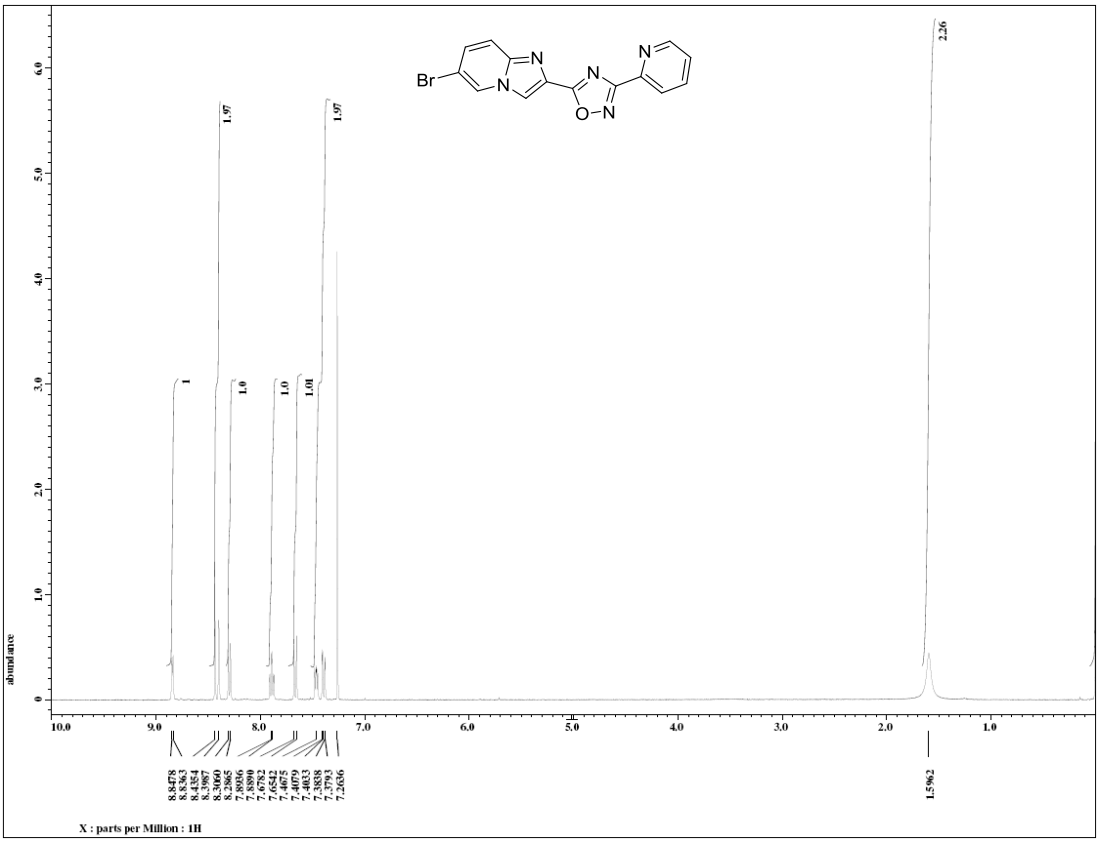
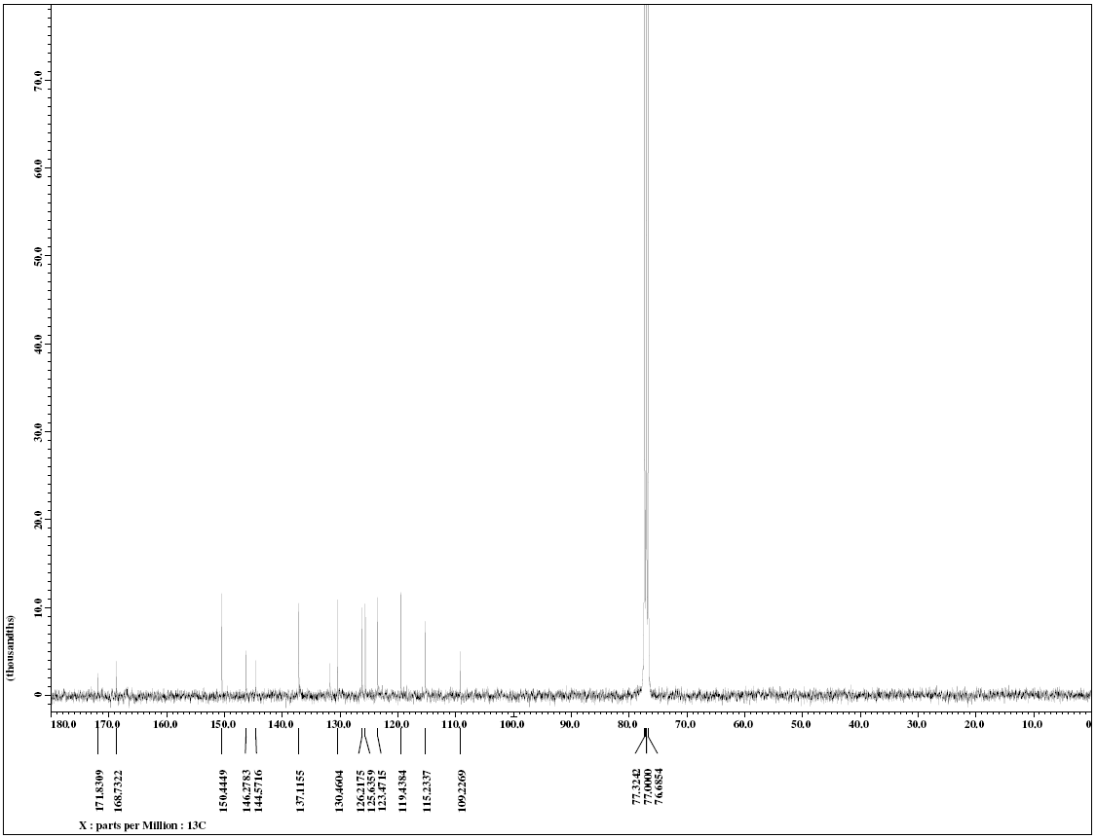
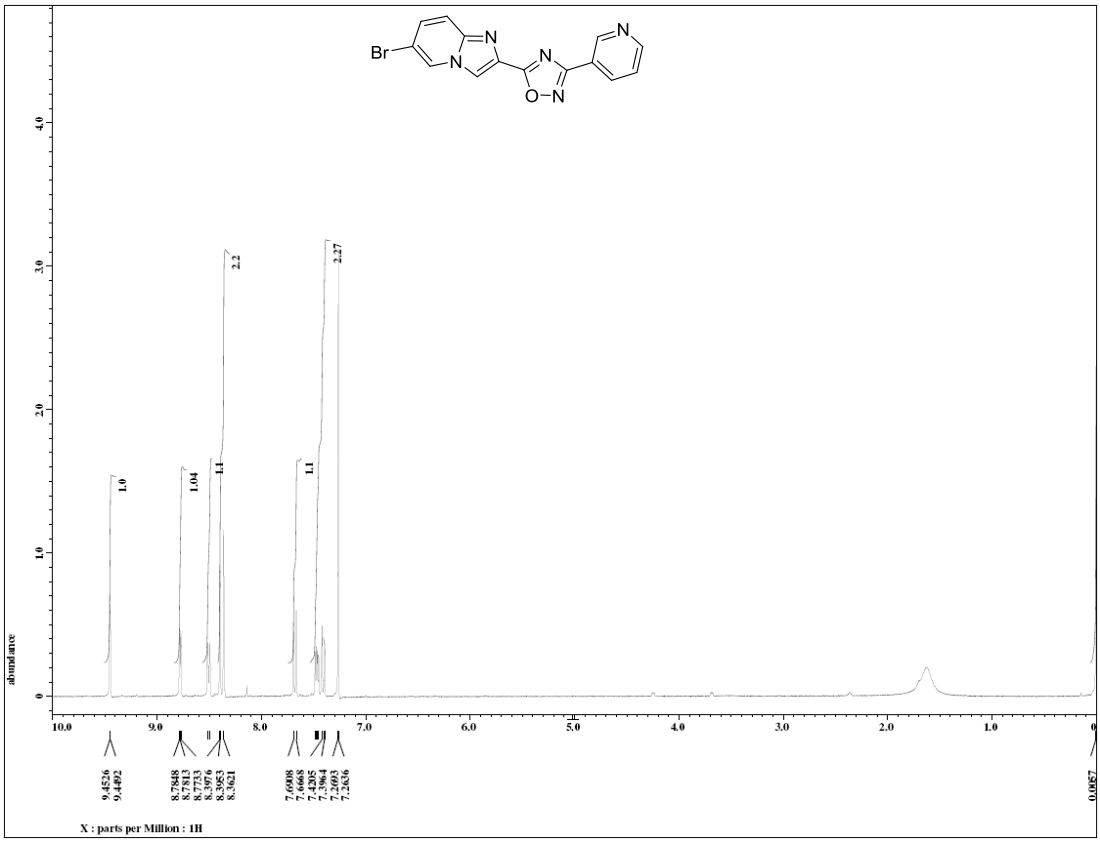
7.4628
7.2411
6.9439
6.9303
6.9267
6.9210
1.5257
X : parts per Million : 1H

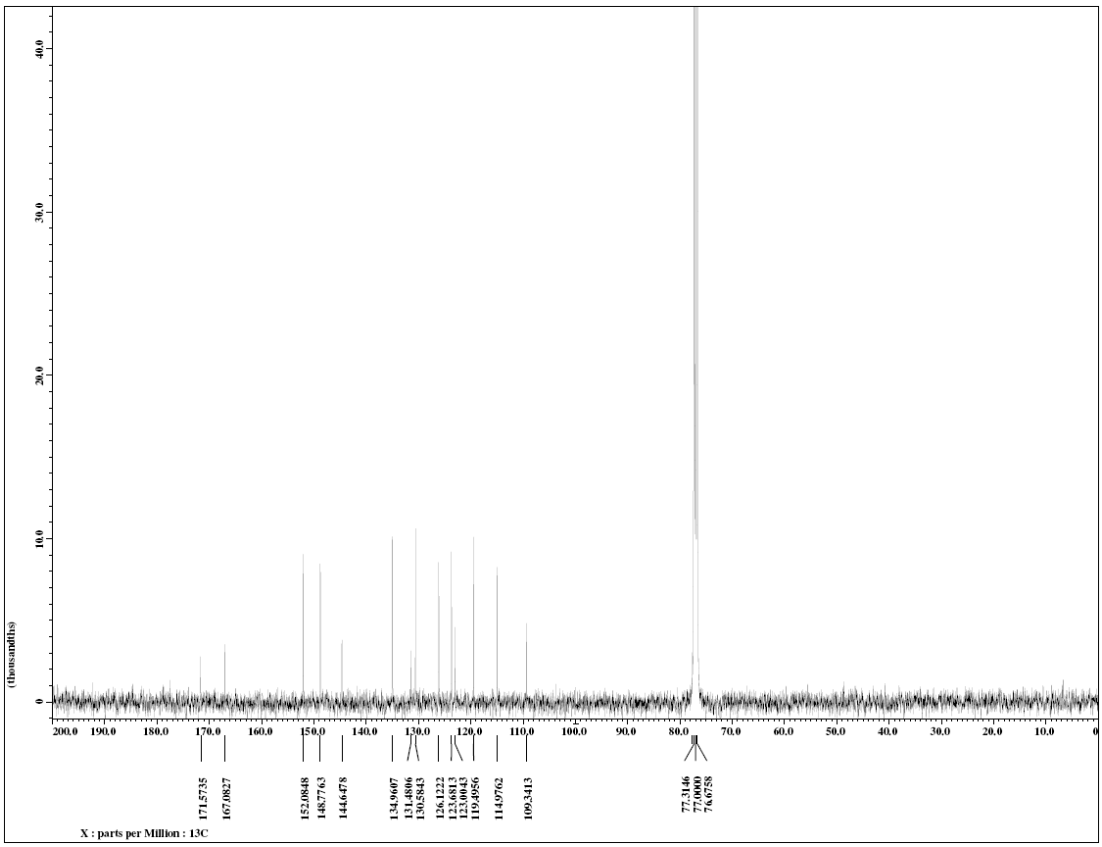

Br
N
N
N
O
N
Br
abundance
3.04
2
1.94
0.97
1.5884
X : parts per Million : 1H

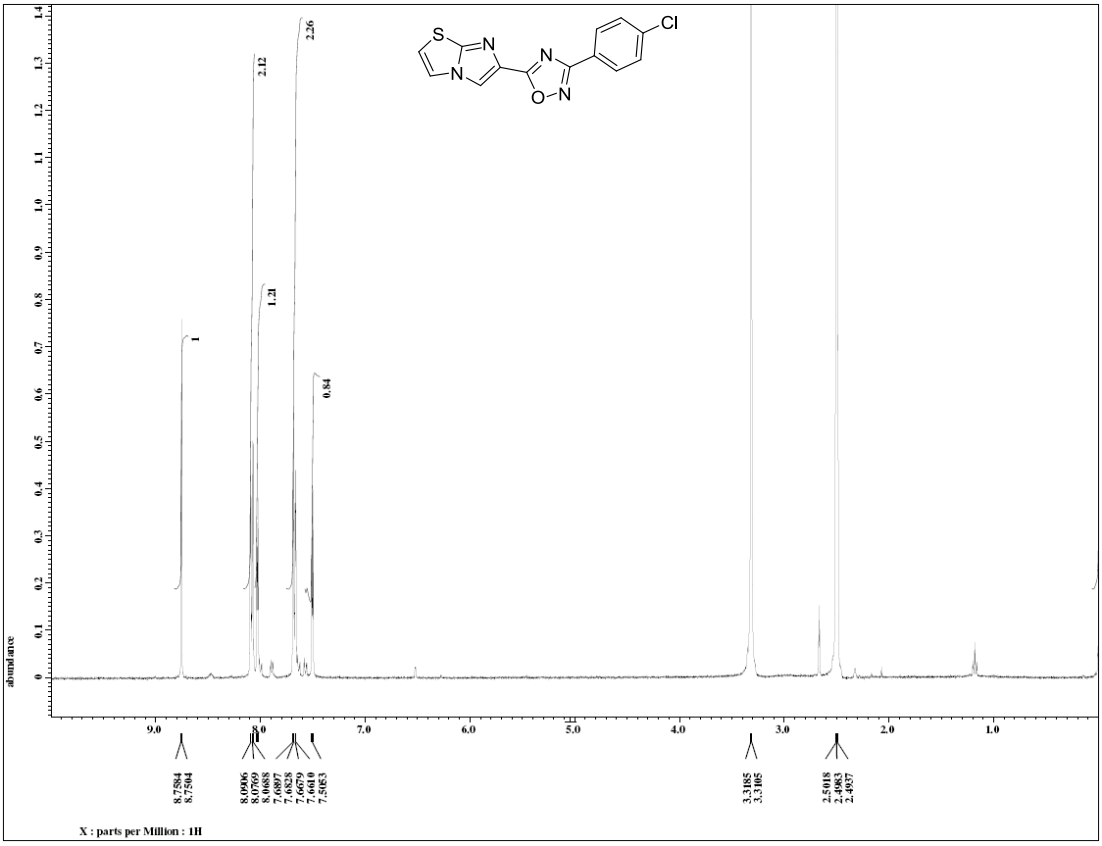

(benzandthx)
171.3447
168.4176
144.8195
132.1480
131.6808
130.4604
129.1637
126.0745
125.9134
125.8933
119.5052
114.8809
109.2841
77.3146
77.0000
76.6854
X : parts per Million : 13C

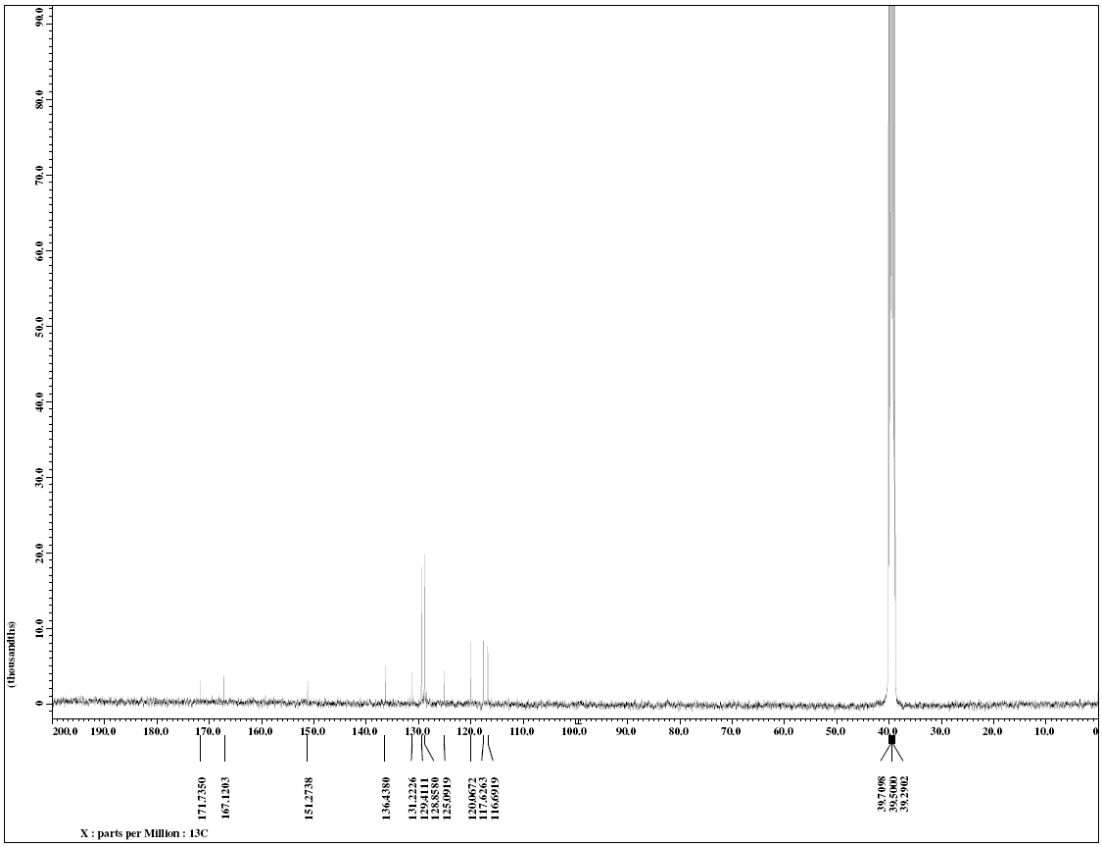

Br
N
N
N
O
N
abundance
1
1.97
1.0
1.0
1.01
1.97
2.26
8.8478
8.5363
8.4354
8.3987
8.3060
8.2885
7.8896
7.6782
7.6542
7.4675
7.4070
7.4033
7.3838
7.3793
7.2656
1.5962
X : parts per Million : 1H

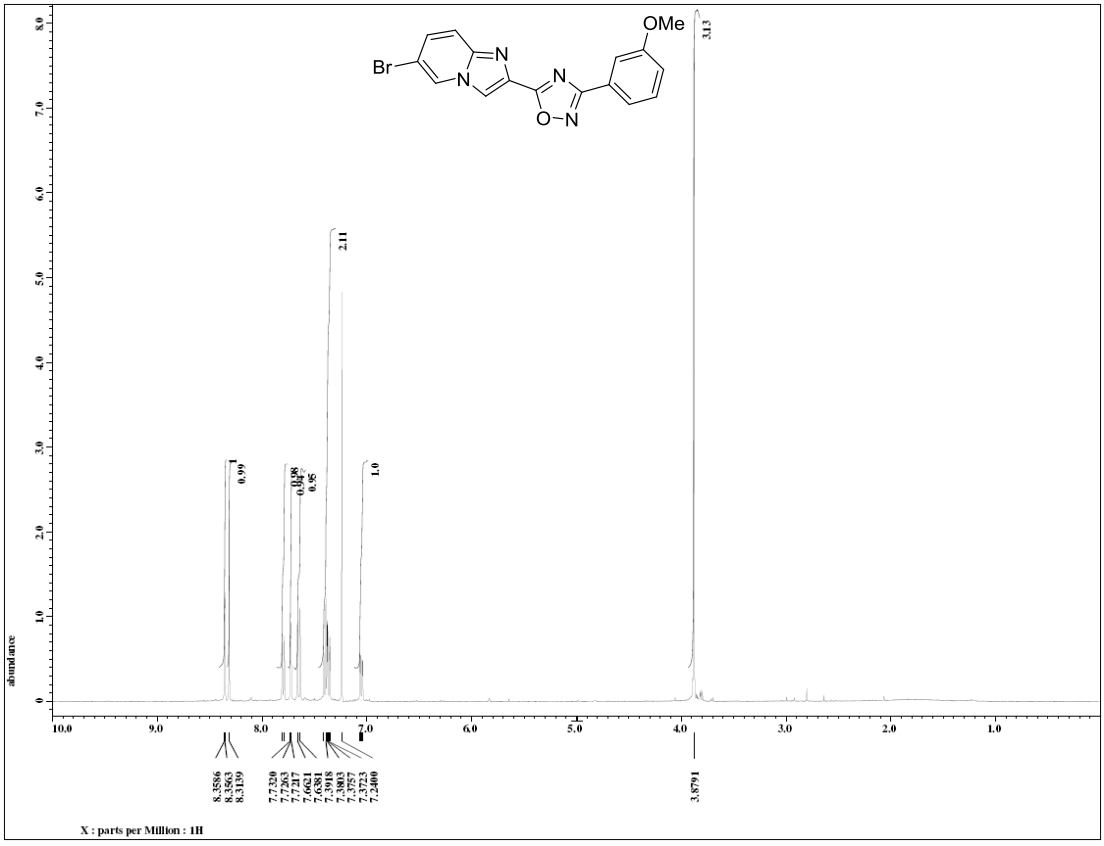

(Thousandths)
17.8309
168.7322
150.4449
146.2783
144.5716
137.1155
130.4604
126.2175
125.6359
123.4715
119.4384
115.2337
109.2269
77.3242
77.0000
76.6854
X : parts per Million : 13C

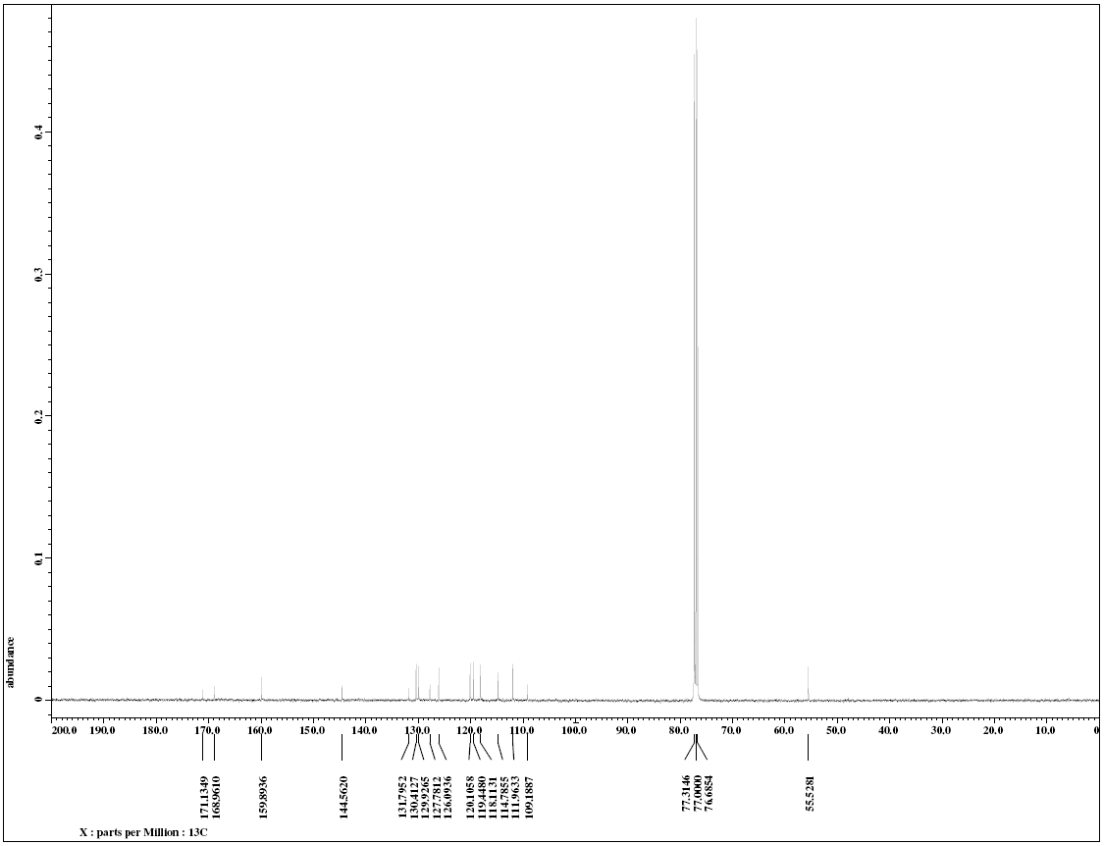

Br
N
N
N
O–N
N
abundance
1.0
1.04
1.1
2.2
1.1
2.27
9.4526
9.4492
8.7848
8.7813
8.7773
8.3976
8.3953
8.3621
7.6908
7.6668
7.4305
7.3964
7.2693
7.2636
0.0057
X : parts per Million : 1H

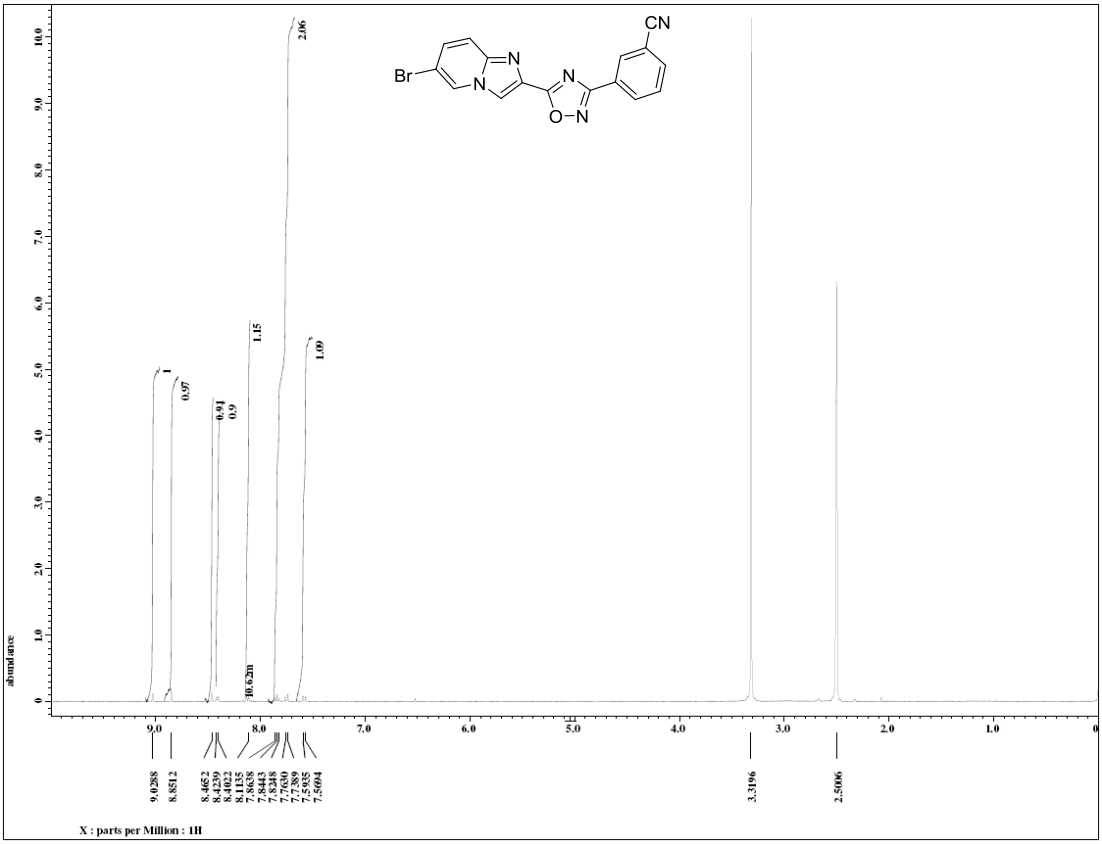

(Thousandths)
171.5735
167.0827
152.0848
148.7763
144.6478
134.9607
131.4806
130.5843
126.1222
123.6013
121.0645
119.4956
114.9762
109.3413
77.3146
77.0000
76.6758
X : parts per Million : 13C

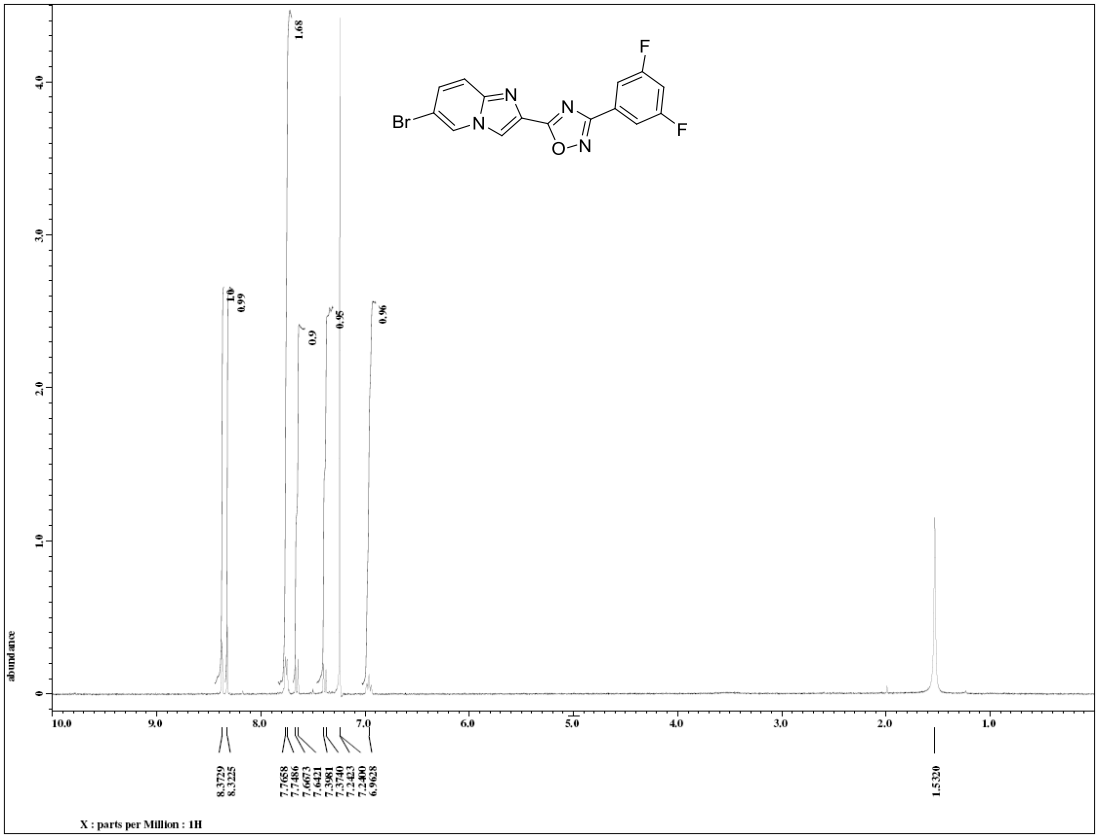

abundance
2.26
2.12
1.21
1
0.84
8.7584
8.7584
8.0906
8.0799
8.0688
7.6897
7.6828
7.6679
7.6540
7.5083
3.3185
3.3185
2.5018
2.4983
2.4937
X : parts per Million : 1H

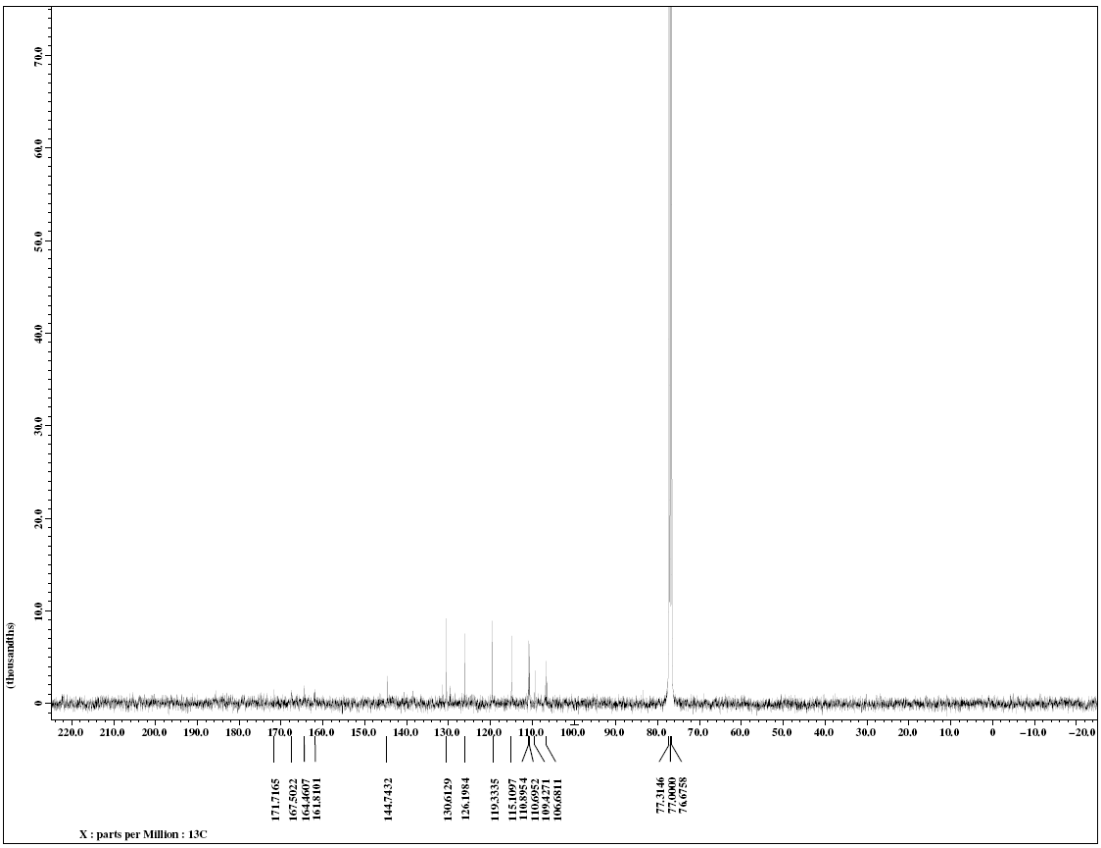

(thousandths)
171.7350
167.1203
151.2738
136.4380
131.2226
129.4141
128.3538
125.0919
120.0672
117.6263
116.6919
39.7098
39.5000
39.2902
X : parts per Million : 13C

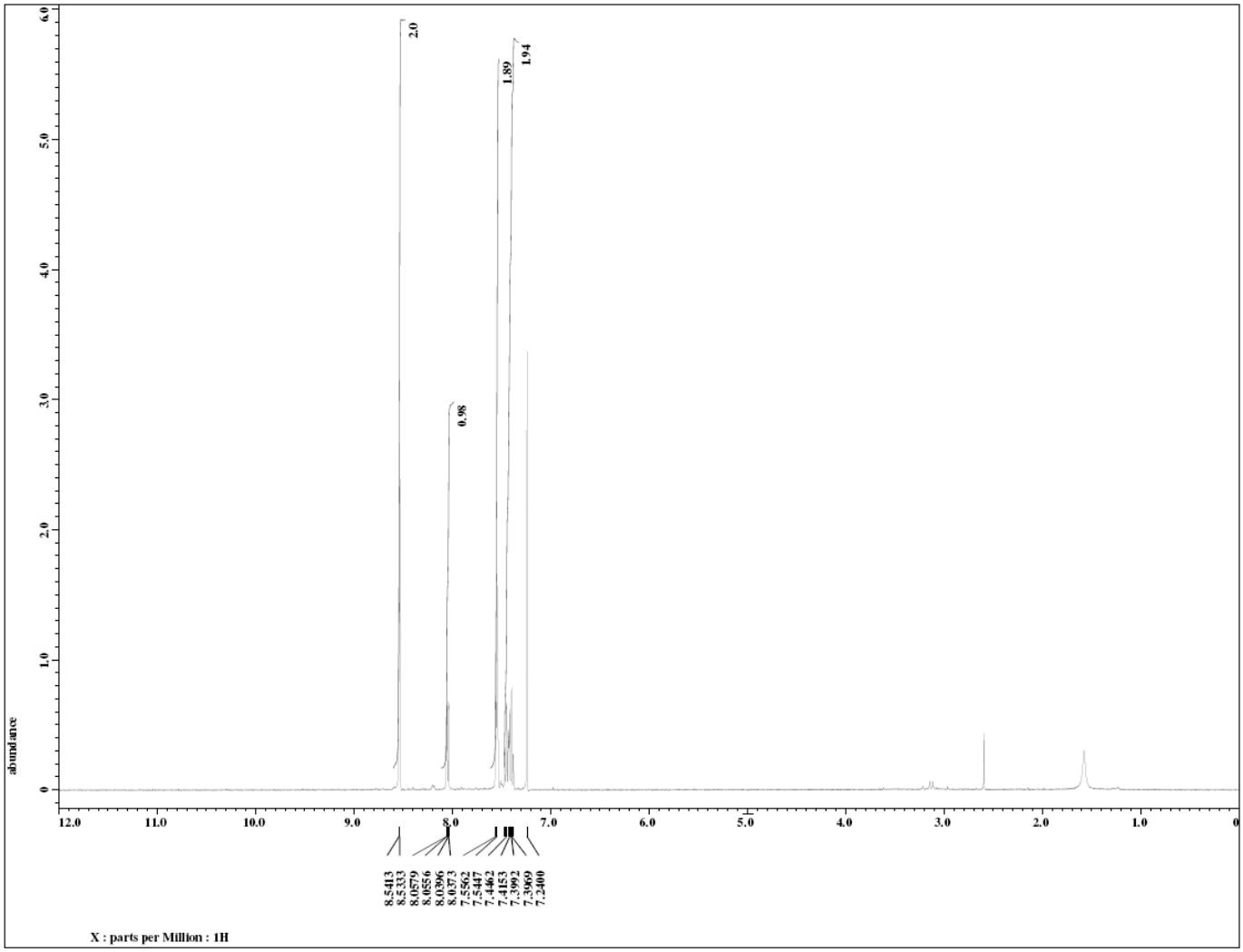

OMe
Br
N
N
O
N
abundance
X : parts per Million : 1H

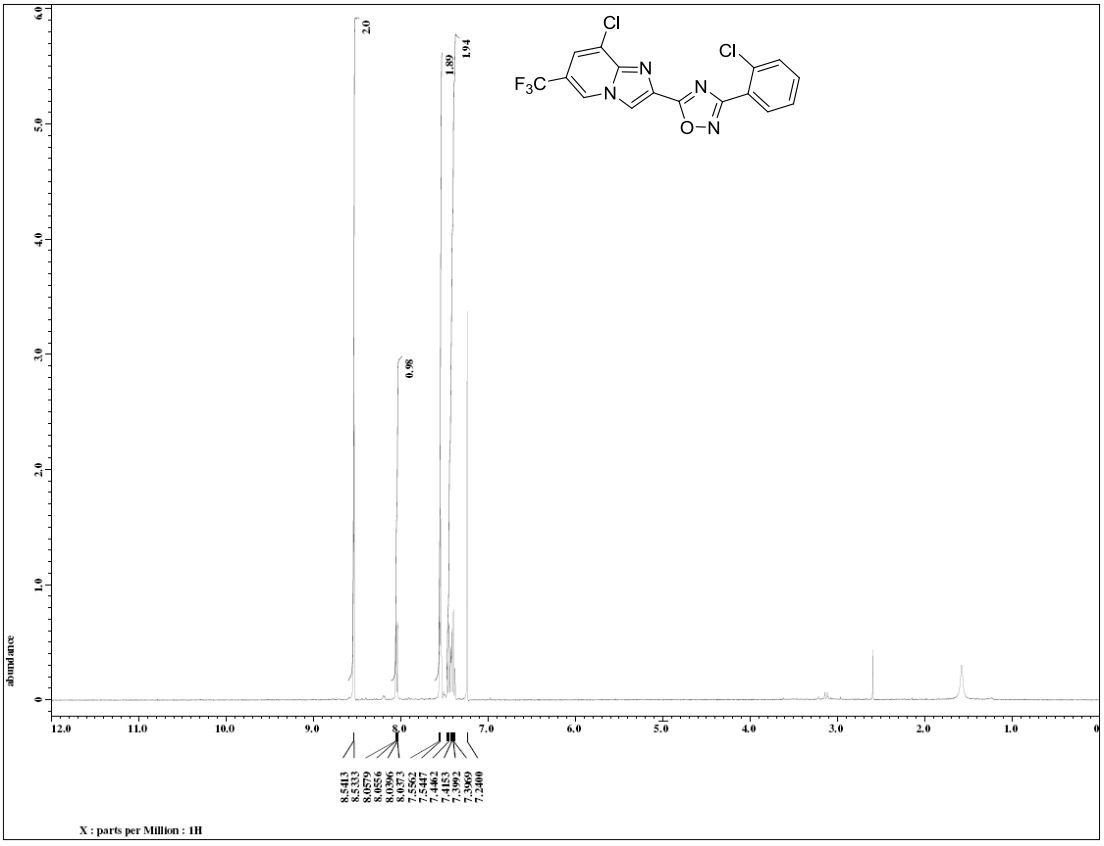

abundance
X : parts per Million : 13C

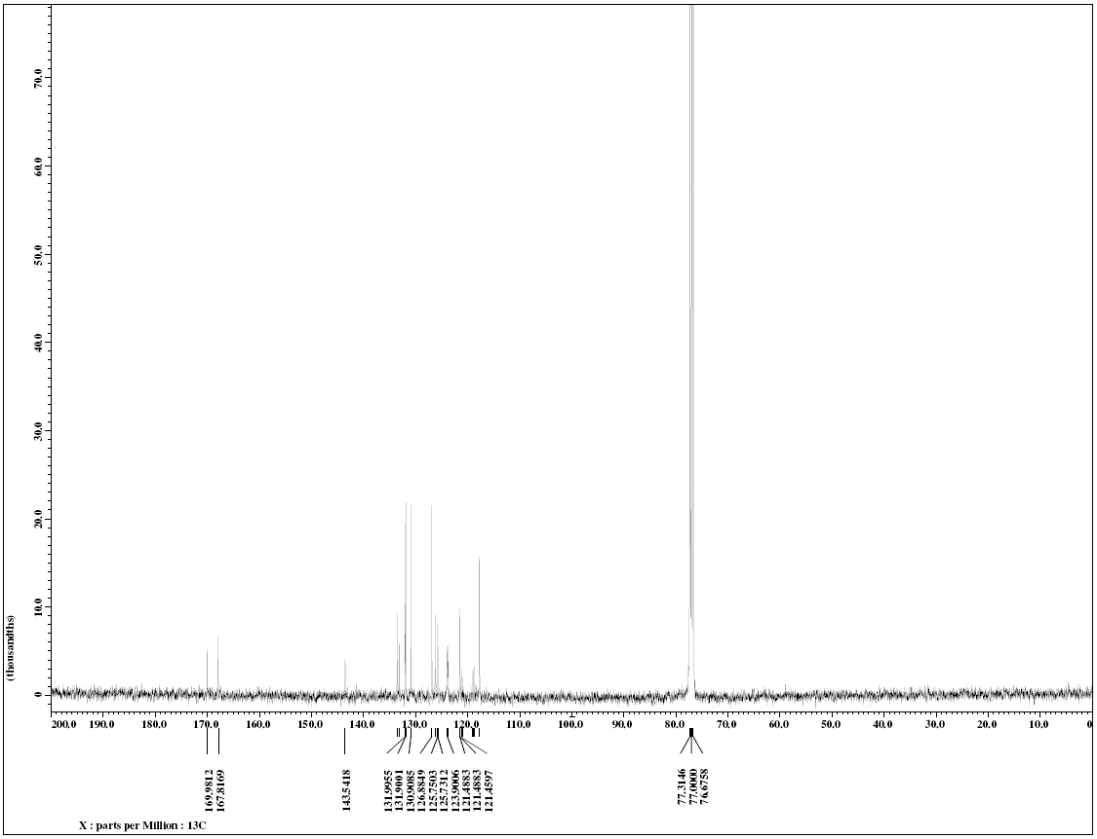

Br
N
N
N
O–N
CN
abundance
2.06
1.15
1.09
1
0.97
0.91
0.9
10.62m
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
9.0288
8.8512
8.4662
8.4239
8.4032
8.1135
7.8638
7.8443
7.8248
7.7930
7.7788
7.5935
7.5694
3.3196
2.5006
X : parts per Million : 1H

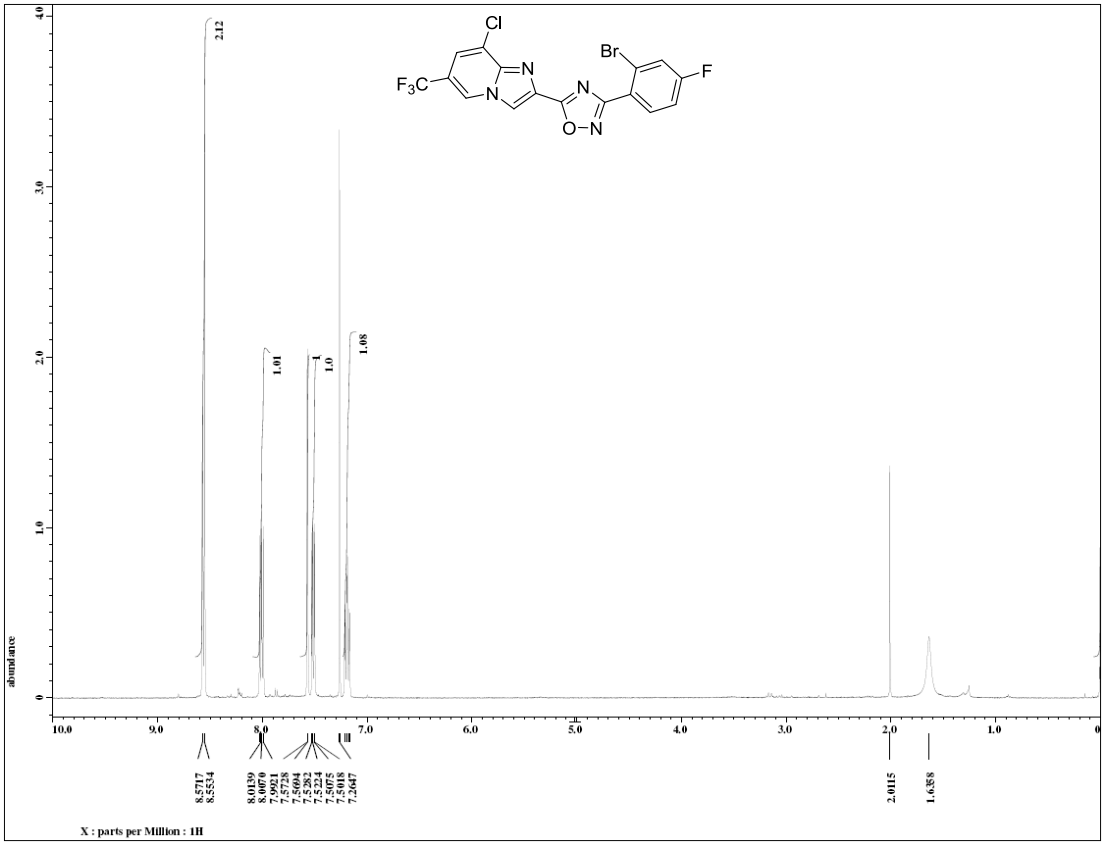

F
Br
N
N
N
O
N
F
abundance
1.68
1.0
0.99
0.9
0.95
0.96
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
8.3729
8.3225
7.7688
7.7486
7.6673
7.6421
7.3981
7.3740
7.3543
7.2340
6.9628
1.5320
X : parts per Million : 1H

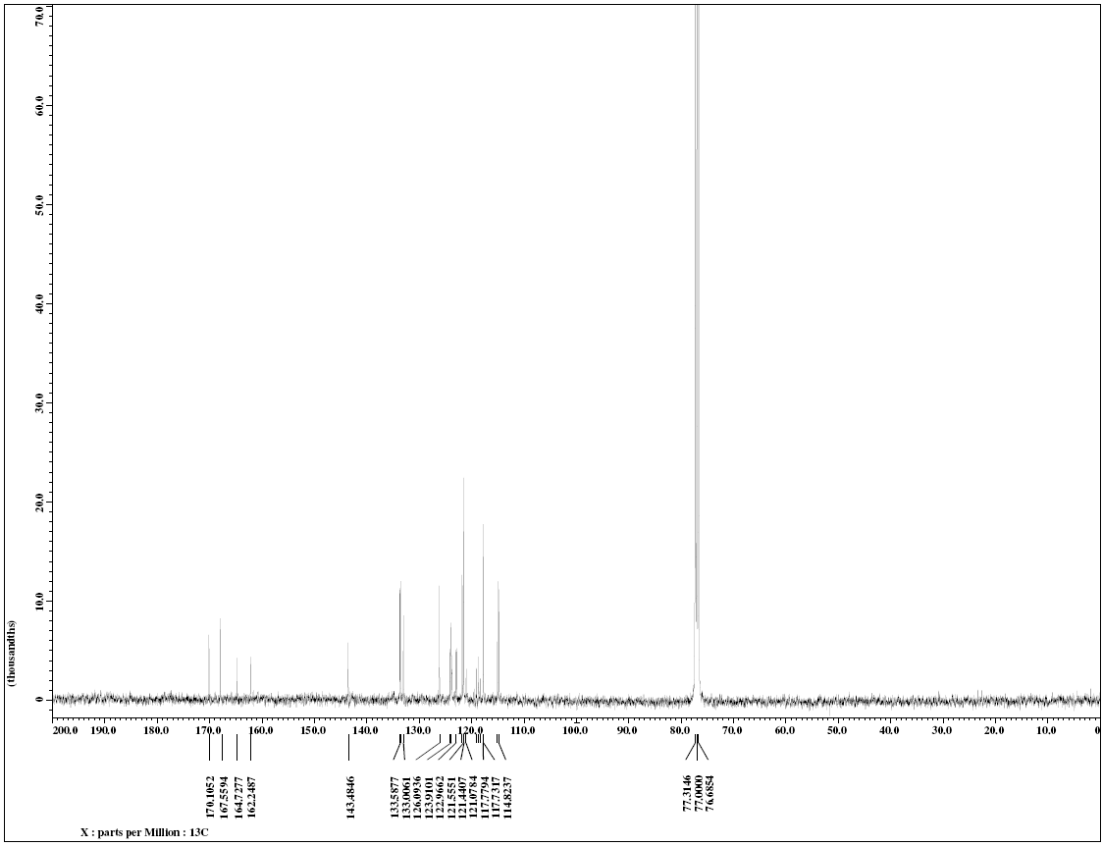

(thousandths)
220.0
210.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
−10.0
−20.0
171.7165
167.5022
164.4607
161.8101
144.7432
130.6129
126.1984
119.3335
115.1097
110.9954
110.6952
109.4271
106.6811
77.3146
77.0000
76.6758
X : parts per Million : 13C


abundance
2.0
0.98
1.89
1.94
8.543
8.533
8.059
8.056
8.036
8.033
7.566
7.547
7.462
7.415
7.399
7.397
7.240
X : parts per Million : 1H


Cl
Cl
F3C
N
N
N
O
2.0
1.89
1.94
0.98
abundance
X : parts per Million : 1H


(Thousandths)
169.9812
167.8169
143.5418
131.9955
131.9001
130.9085
126.8949
125.7595
125.7312
123.9006
121.4883
121.4853
121.4697
77.3146
77.0000
76.6758
X : parts per Million : 13C


Cl
Br
F
F3C
N
N
N
O–N
2.12
1.01
1.0
1.08
abundance
X : parts per Million : 1H


(Intensities)
X : parts per Million : 13C