Electronic Supplementary Material (ESI) for RSC Advances.

Crafting mono- and novel bis-methylated pyrroloquinoxaline derivatives from a shared precursor and its application in the total synthesis of marinoquinoline A

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Electronic Supplementary Information

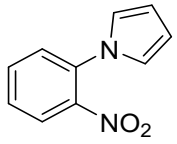
Contents

Experimental procedures and analytical data

General experimental

All reactions requiring the use of dry conditions were carried out under an atmosphere of nitrogen. Stirring was by internal magnetic follower unless otherwise stated. All reactions were followed by TLC and the products were purified by flash column chromatography. The silica gel used was Merck 60 (230-400 mesh). Analytical TLC was carried out on Merck 60 F_{245} aluminium-backed silica gel plates. Short wave UV (245 nm) was used to visualise components. Reagents and solvents were purchased and used as received from commercial sources. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AV500 spectrometer operating at 500 MHz for proton and 126 MHz for carbon. Spectra were recorded in deuterochloroform and referenced to residual $CHCl_3$ (^{1}H, 7.27 ppm; ^{13}C, 77.0 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) are reported in Hz. The following abbreviations are used to describe multiplicity; s-singlet, d-doublet, t-triplet, q-quartet and m-multiplet. High resolution mass spectra were recorded on a LTQ Orbitrap XL utilising nanospray ionisation (NSI) with MeOH mobile phase or atmospheric pressure chemical ionisation (APCI) with a 1:1 H_2O:MeOH mobile phase, recorded in the positive mode. Melting points were determined using open glass capillaries on a Stuart Scientific SMP3 apparatus and are uncorrected. Infrared spectra were recorded on an Agilent Technologies Cary 630 FT-IR spectrometer. GC–MS analysis was performed using a Agilent 7890A GC system with Agilent 5977B Series MSD. Helium was used as the carrier gas with a flow rate of 1.2 mL/min and a spitless injection was used. A HP 5MS ultra-inert capillary column (30 m × 250 μm × 0.25 μm) was used for separation with the following temperature gradient: an initial temperature of 120 °C for 2 min and ramping to 320 °C at 10 °C/min and hold for 3 min. Eluted compounds are ionized by electron ionization with an electron energy of 70 eV and an ion source temperature of 280 °C. Full MS scans were performed at the mass range of 30–210 m/z.

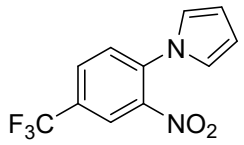
1-(2-Nitrophenyl)-1*H*-pyrrole (1a)[1]



Pyrrole (1.32 mL, 19.0 mmol) in DMSO (19 mL) was slowly treated with sodium hydroxide (0.76 g, 19.0 mmol) followed by 1-fluoro-2-nitrobenzene (2.0 mL, 19.0 mmol). The reaction mixture was stirred for 1.5 hr at room temperature, extracted with ethyl acetate (3 × 20 mL), washed water (3 × 100 mL) and dried over Na_2SO_4. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (4:1 Hex/EtOAc) to give 1-(2-nitrophenyl)-1*H*-pyrrole (3.29 g, 92%) as a brown oil; ν_{max} (neat) 1525 (NO_2), 1351 (NO_2); δ_H (500 MHz, $CDCl_3$) 7.83-7.89 (1H, m,

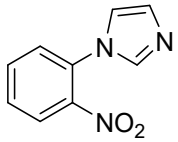
ArH), 7.63-7.70 (1H, m, ArH), 7.45-7.52 (2H, m, 2 × ArH), 6.78-6.84 (2H, m, 2 × ArH), 6.35-6.40 (2H, m, 2 × ArH), δ_C (126 MHz, $CDCl_3$) 145.3 (C), 134.2 (C), 133.1 (CH), 127.8 (CH), 127.6 (CH), 124.9 (CH), 121.3 (2 × CH), 111.0 (2 × CH); *m/z* (NSI) 189.0658 ($[M+H]^+$, $C_{10}H_9N_2O_2$ requires 189.0659).

1-(2-Nitro-4-(trifluoromethyl)phenyl)-1*H*-pyrrole (1b)[1]



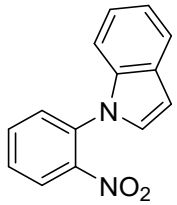
Pyrrole (0.99 mL, 14.3 mmol) in DMSO (14 mL) was slowly treated with sodium hydroxide (0.57 g, 14.3 mmol) and 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (2.0 mL, 14.3 mmol). The reaction mixture was stirred for 1.5 hr at room temperature, extracted with ethyl acetate (3 × 20 mL), washed water (3 × 100 mL) and dried over Na_2SO_4. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (2.18 g, 73%) as a brown oil; ν_{max} (neat) 1540 (NO_2), 1319 (NO_2), 1128 (C-F), δ_H (500 MHz, $CDCl_3$) 8.12 (1H, d, *J* 1.8, ArH), 7.92 (1H, dd, *J* 8.6, 6.0, ArH), 7.64 (1H, d, *J* 8.6, ArH) 6.83 (2H, dd, *J* 2.0, 2.0, 2 × ArH), 6.42 (2H, dd, *J* 2.0, 2.0, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 144.5 (C), 136.8 (C), 129.9 (q, *J* 3.7, CH), 129.6 (q, *J* 34.8, C), 128.1 (CH), 122.6 (q, *J* 3.7, CH), 121.0 (2 × CH), 122.6 (q, *J* 272.2, C), 112.2 (2 × CH); *m/z* (APCI) 257.0528 ($[M+H]^+$, $C_{11}H_8F_3N_2O_2$ requires 257.0532).

1-(2-Nitrophenyl)-1*H*-imidazole (1c)[2]



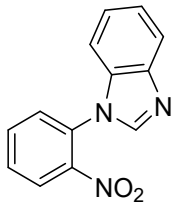
A mixture of 1-fluoro-2-nitrobenzene (3.00 mL, 28.5 mmol), imidazole (1.76 g, 25.0 mmol) and K_2CO_3 (8.08 g, 58.0 mmol) in CH_3CN (40 mL) was heated at reflux overnight. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (30 mL). The solution was washed with water (2 × 30 mL), dried over $MgSO_4$ and the mixture was concentrated under reduced pressure to give the title compound (3.46 g, 98%) as a brown oil. νmax (neat) 3121 (CH), 1513 (NO_2), 1342 (NO_2); δ_H (500 MHz, $CDCl_3$) 8.02 (1H, dd, *J* 8.2, 1.6, ArH), 7.75 (1H, td, *J* 7.7, 1.3, ArH), 7.66 (1H, s, ArH), 7.61-7.64 (1H, m, ArH), 7.49 (1H, dd, *J* 7.9, 1.3, ArH), 7.24 (1H, s, ArH), 7.09 (1H, dd, *J* 1.3, 1.3, ArH); δ_C (126 MHz, $CDCl_3$) 145.3 (C), 137.2 (CH), 133.7 (CH), 130.6 (C), 130.5 (CH), 129.6 (CH), 128.6 (CH), 125.4 (CH), 120.2 (CH); *m/z* (APCI) 190.0609 ($[M+H]^+$, $C_9H_7N_3O_2$ requires 190.0611).

1-(2-Nitrophenyl)-1*H*-indole (1d)[3]



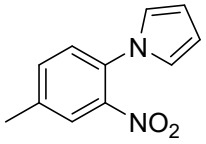
Indole (2.22 mL, 19.0 mmol) in DMSO (30 mL) was slowly treated with sodium hydroxide (1.14 g, 28.5 mmol) and 1-fluoro-2-nitrobenzene (2.0 mL, 19.0 mmol). The reaction mixture was stirred for 1.5 hr at room temperature, extracted with ethyl acetate (3 × 20 mL), washed water (3 × 100 mL) and dried over Na_2SO_4. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (3.32 g, 74%) as a yellow solid; m.p. 77-78 °C; ν_{max} (neat) 3106 (CH), 3051 (CH), 1511 (NO_2), 1345 (NO_2); δ_H (500 MHz, $CDCl_3$) 8.04 (1 H, dd, *J* 8.1, 1.5, ArH), 7.77-7.72 (1 H, m, ArH), 7.71-7.68 (1 H, m, ArH), 7.62-7.55 (2 H, m, 2 × ArH), 7.22-7.18 (2 H, m, 2 × ArH), 7.18-7.13 (2 H, m, 2 × ArH), 6.75-6.74 (1H, m, ArH); δ_C (126 MHz, $CDCl_3$) 146.4 (C), 136.8 (C), 133.8 (CH), 133.0 (C), 129.9 (CH), 129.1 (C), 128.5 (CH), 128.1 (CH), 125.7 (CH), 123.1 (CH), 121.5 (CH), 121.1 (CH), 109.6 (CH), 105.2 (CH); *m/z* (NSI) 239.0815 ($[M+H]^+$, $C_{14}H_{11}N_2O_2$ requires 239.0815.

1-(2-Nitrophenyl)-1*H*-benzo[*d*]imidazole (1e)[4]



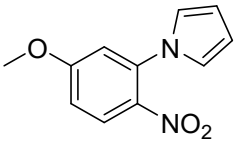
A mixture of 1-fluoro-2-nitrobenzene (3.00 mL, 28.5 mmol), benzimidazole (3.36 g, 28.5 mmol) and K_2CO_3 (4.01 g, 29.0 mmol) in DMF (85 mL) was heated at 125 °C overnight. The resulting solution was allowed to cool to room temperature and water (100 mL) was added and extracted with diethyl ether (3 × 100 mL). The combined layers were washed with water (3 × 100 mL), dried over $MgSO_4$ and the mixture was concentrated under reduced pressure to give the *title compound* (3.20 g, 47%) as a yellow oil. ν_{max} (neat) 3056 (CH), 1521 (NO_2), 1347 (NO_2); δ_H (500 MHz, $CDCl_3$) 8.09 (1H, dd, *J* 8.2, 1.6, ArH), 7.82 (1H, d, *J* 8.2, ArH), 7.75 (1H, td, *J* 7.7, 1.6, ArH), 7.61-7.66 (1H, m, ArH), 7.51 (1H, dd, *J* 7.9, 1.3, ArH), 7.29 (1H, td, *J* 7.3, 1.3, ArH), 7.24 (1H, td, *J* 7.6, 1.3, ArH), 7.08-7.12 (1H, m, ArH); δ_C (126 MHz, $CDCl_3$) 145.5 (C), 143.0 (C), 142.3 (CH), 134.3 (CH), 134.2 (C), 129.9 (CH), 129.6 (CH), 129.0 (C), 125.8 (CH), 124.0 (CH), 123.0 (CH), 120.4 (CH), 109.3 (CH); *m/z* (APCI) 240.0765 ($[M+H]^+$, $C_{13}H_{10}N_3O_2$ requires 240.0768).

1-(4-Methyl-2-nitrophenyl)-1*H*-pyrrole (1f)[5]



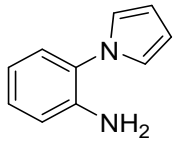
4-Methyl-2-nitroaniline (5.00 g, 32.9 mmol) and 2,5-dimethoxytetrahydrofuran (4.26 mL, 32.9 mmol) in acetic acid (46 mL) was heated at reflux for 1 hr with vigorous stirring. After cooling the mixture was poured into water (125 mL). The precipitate was filtered, dissolved in diethyl ether (100 mL). The layers were partitioned, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give an orange solid. The solid was recrystallised from Hexane (75 mL) to give the *title compound* (6.35 g, 96%) as orange crystals. m.p. 55-56 °C; ν_{max} (neat) 1510 (NO_2), 1334 (NO_2); δ_H (500 MHz, $CDCl_3$) 7.67 (1H, d, *J* 1.3, ArH), 7.46 (1H, ddd, *J* 8.1, 1.8, 0.5, ArH), 7.36 (1H, d, *J* 8.1, ArH), 6.79 (2H, dd, *J* 2.1, 2.1, 2 × ArH), 6.36 (2H, dd, *J* 2.1, 2.1, 2 × ArH), 2.49 (3H, s, CH_3); δC (126 MHz, $CDCl_3$) 145.0 (C), 138.4 (C), 133.7 (CH), 131.7 (C), 127.7 (CH), 125.0 (CH), 121.3 (2 × CH), 110.6 (2 × CH), 20.7 (CH_3); *m/z* (APCI) 203.0815 ($[M+H]^+$, $C_{11}H_{11}N_2O_2$ requires 203.0815).

1-(5-Methoxy-2-nitrophenyl)-1*H*-pyrrole (1g)[1]



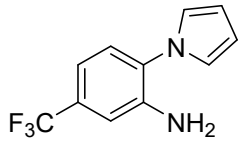
5-Methoxy-2-nitroaniline (3.00 g, 17.8 mmol) and 2,5-dimethoxytetrahydrofuran (2.31 mL, 17.8 mmol) in acetic acid (25 mL) was heated at reflux for 1 hr with vigorous stirring. After cooling the mixture was poured into water (75 mL). The precipitate was filtered, dissolved in diethyl ether (50 mL), washed with water (10 mL) and dried over $MgSO_4$. The solution was concentrated under reduced pressure to give an orange solid which was recrystallised from hexane (35 mL) to give the *title compound* (1.54 g, 40%) as orange crystals; m.p. 47-48 °C; ν_{max} (neat) 2943 (C-H), 1514 (NO_2), 1334 (NO_2); δ_H (500 MHz, $CDCl_3$) 7.97 (1H, d, *J* 9.1, ArH), 6.94 (1H, dd, *J* 8.5, 2.8, ArH), 6.91 (1H, d, *J* 2.5, ArH), 6.80 (2H, dd, *J* 2.2, 2.2, 2 × ArH), 6.38 (2H, dd, *J* 2.2, 2 × ArH), 3.92 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 163.2 (C), 138.1 (C), 136.7 (C), 127.6 (CH), 121.3 (2 × CH), 113.0 (CH), 112.8 (CH), 110.8 (2 × CH), 56.2 (CH_3); *m/z* (APCI) 219.0762 ($[M+H]^+$, $C_{11}H_{11}N_2O_3$ requires 219.0764).

2-(1*H*-Pyrrol-1-yl)aniline (2a)[6]



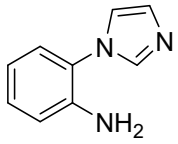
To a solution of 1-(2-nitrophenyl)-1H-pyrrole (4.19 g, 22.2 mmol) in ethanol (140 mL) was added hydrazine hydrate (13.84 mL, 222.9 mmol). Palladium on carbon (0.42 g) was added to the reaction mixture and heated at reflux overnight. The reaction mixture was allowed to cool, the ethanolic solution was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hex:EtOAc) to give the *title compound* (2.70 g, 76%) as a colourless solid; m.p. 95-97 °C; ν_{max} (neat) 3373 (NH_2), 3301 (NH_2); δ_H (500 MHz, $CDCl_3$) 7.15-7.23 (2H, m, 2 × ArH), 6.85-6.89 (2H, m, 2 × ArH), 6.79-6.85 (2H, m, 2 × ArH), 6.35-6.41 (2H, m, 2 × ArH), 3.73 (2H, br. s, NH_2); δ_C (126 MHz, $CDCl_3$) 142.0 (C), 128.5 (CH), 127.5 (C), 127.1 (CH), 121.6 (2 × CH), 118.3 (CH), 116.0 (CH), 109.3 (2 × CH); *m/z* (APCI) 159.0915 ($[M+H]^+$, $C_{10}H_{11}N_2$ requires 159.0917).

2-(1*H*-Pyrrol-1-yl)-5-(trifluoromethyl)aniline (2b)[7]



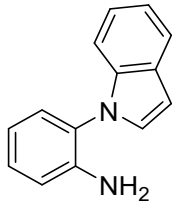
To a solution of 1-(2-nitro-4-(trifluoromethyl)phenyl)-1*H*-pyrrole (0.80 g, 3.12 mmol) in ethanol (20 mL) was added hydrazine hydrate (2.77 mL, 31.2 mmol). Palladium on carbon (0.08 g) was added to the reaction mixture and heated at reflux for 3 hr. The reaction mixture was allowed to cool, the ethanolic solution was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (0.57 g, 81%) as a colourless solid; m.p. 99-101 °C, ν_{max} (neat) 3379 (N-H), 3313 (N-H), 1131 (C-F); δ_H (500 MHz, $CDCl_3$) 7.23-7.30 (1H, m, ArH), 7.04-7.11 (2H, m, 2 × ArH), 6.89 (2H, dd, *J* 2.1, 2.1, 2 × ArH), 6.43 (2H, dd, *J* 2.1, 2.1, 2 × ArH), 3.97 (2H, br. s, NH_2); δ_C (126 MHz, $CDCl_3$) 142.2 (C), 130.5 (q, *J* 32.1, C), 129.8 (C), 127.3 (CH), 123.9 (q, *J* 272.2, C), 121.3 (2 × CH), 114.9 (q, *J* 3.7, CH), 112.7 (q, *J* 3.7, CH), 110.1 (2 × CH); *m/z* (NSI) 227.0791 ($[M+H]^+$, $C_{11}H_{10}F_3N_2$ requires 227.0791).

2-(1*H*-Imidazol-1-yl)aniline (2c)[7]



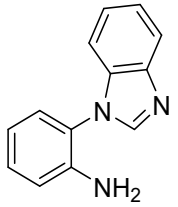
To a solution of 1-(2-nitrophenyl)-1*H*-imidazole (3.46 g, 18.0 mmol) in ethanol (42 mL) was added hydrazine hydrate (17.5 mL, 180 mmol). Palladium on carbon (0.35 g) was added to the reaction mixture and heated at reflux overnight. The reaction mixture was allowed to cool, the ethanolic solution was filtered and concentrated under reduced pressure to give the *title compound* (2.57 g, 91%) light yellow solid; m.p. 103-105 °C; ν_{max} (neat) 3365 (NH_2), 3323 (NH_2); δ_H (500 MHz, $CDCl_3$) 7.63 (1H, s, ArH), 7.19-7.25 (2H, m, 2 × ArH), 7.07-7.13 (2H, m, 2 × ArH), 6.77-6.85 (2H, m, 2 × ArH), 3.75 (2H, br. s, NH_2); δ_C (126 MHz, $CDCl_3$) 141.9 (C), 137.6 (CH), 129.9 (CH), 129.8 (CH), 127.1 (CH), 123.2 (C), 120.1 (CH), 118.5 (CH), 116.3 (CH); *m/z* (APCI) 160.0865 ($[M+H]^+$, $C_9H_{10}N_3$ requires 160.0869).

2-(1*H*-Indol-1-yl)aniline (2d)[6]



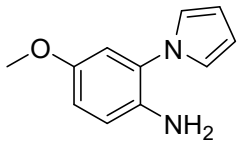
To a solution of 1-(2-nitrophenyl)-1*H*-indole (1.00 g, 4.20 mmol) in ethanol (26 mL) was added hydrazine hydrate (2.60 mL, 42.0 mmol). Palladium on carbon (0.10 g) was added to the reaction mixture and heated at reflux for 3 hr. The reaction mixture was allowed to cool, the ethanolic solution was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hex:EtOAc) to give the *title compound* (0.57 g, 65%) as an colourless oil; ν_{max} (neat) 3464 (NH_2), 3370 (NH_2), 3050 (CH); δ_H (500 MHz, $CDCl_3$) 7.76 (1H, d, *J* 8.2, ArH), 7.18-7.34 (6H, m, 6 × ArH), 6.87-6.95 (2H, m, 2 × ArH), 6.75 (1H, d, *J* 3.2, ArH), 3.61 (2H, br. s, NH_2); δ_H (126 MHz, $CDCl_3$) 143.1 (C), 136.3 (C), 129.1 (CH), 128.6 (CH), 128.6 (CH), 128.5 (C), 124.8 (C), 122.2 (CH), 120.9 (CH), 120.1 (CH), 118.5 (CH), 116.2 (CH), 110.7 (CH), 103.2 (CH); *m/z* (NSI) 209.1074 ($[M + H]^+$, $C_{14}H_{13}N_2$ requires 209.1074).

2-(1*H*-Benzo[*d*]imidazol-1-yl)aniline (2e)[7]



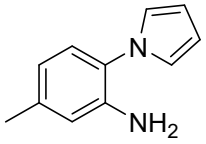
To a solution of 1-(2-nitrophenyl)-1*H*-benzo[*d*]imidazole (2.00 g, 9.56 mmol) in ethanol (22 mL) was added hydrazine hydrate (5.95 mL, 95.6 mmol). Palladium on carbon (0.20 g) was added to the reaction mixture and heated at reflux overnight. The reaction mixture was allowed to cool, the ethanolic solution was filtered and concentrated under reduced pressure to give the *title compound* (1.58 g, 79%) as an colourless oil; ν_{max} (neat) 3219 (NH), 3208 (NH), 3001 (CH); δ_H (500 MHz, $CDCl_3$) 8.01 (1H, s, ArH), 7.87-7.90 (1H, m, ArH), 7.29-7.36 (3H, m, 3 × ArH), 7.24-7.28 (1H, m, ArH), 7.19 (1H, dd, *J* 7.9, 1.6, ArH), 6.92 (1H, dd, *J* 8.0, 1.1, ArH), 6.88 (1H, td, *J* 7.6, 1.3, ArH), 3.68 (2H, br. s, NH_2); δ_C (126 MHz, $CDCl_3$) 143.0 (CH), 142.9 (C), 142.5 (C), 133.5 (C), 130.1 (CH), 127.8 (CH), 123.5 (CH), 122.6 (CH), 120.4 (C), 119.6 (CH), 118.1 (CH), 116.4 (CH), 110.7 (CH); *m/z* (APCI) 210.1024 ($[M+H]^+$, $C_{13}H_{12}N_3$ requires 210.1026).

4-Methoxy-2-(1*H*-pyrrol-1-yl)aniline (2f)[7]



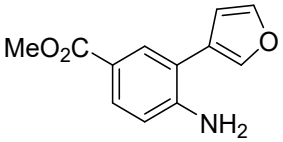
To a solution of 1-(5-methoxy-2-nitrophenyl)-1*H*-pyrrole (1.52 g, 6.97 mmol) in ethanol (45 mL) was added bismuth chloride (3.29 g, 10.5 mmol). Sodium borohydride (2.11 g, 55.7 mmol) was added portion-wise at 0 °C to the reaction mixture and stirred at room temperature for 2 hr. The solution was poured into an aqueous hydrochloric acid solution (1 N, 35 mL) and stirred for another hour. The ethanol was evaporated under reduced pressure. The residue was made alkaline with concentrated aqueous ammonium hydroxide solution (8 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (0.53 g, 40% yield) as a colourless solid; mp: 42-43 °C; ν_{max} (neat) 3433 (NH_2), 3350 (NH_2), 2935 (C-H); δ_H (500 MHz, $CDCl_3$) 6.87 (2H, dd, *J* 2.0, 2.0, 2 × ArH), 6.75-6.82 (3H, m, 3 × ArH), 6.36 (2H, dd, *J* 2.0, 2.0, 2 × ArH), 3.77 (3H, s, CH_3), 3.45 (2H, br. s, NH_2); δ_C (126 MHz, $CDCl_3$) 152.4 (C), 135.4 (C), 128.0 (C), 121.6 (2 × CH), 117.2 (CH), 114.7 (CH), 112.4 (CH), 109.4 (2 × CH), 55.8 (CH_3); *m/z* (APCI) 189.1020 ($[M+H]^+$, $C_{11}H_{13}N_2O_2$ requires 189.1022).

5-Methyl-2-(1*H*-pyrrol-1-yl)aniline (2g)[6]



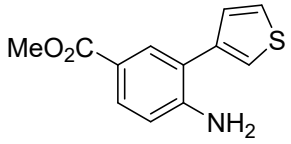
To a solution of 1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole (6.35 g, 31.4 mmol) in ethanol (204 mL) was added bismuth chloride (9.90 g, 31.4 mmol). Sodium borohydride (9.50 g, 251 mmol) was added portion-wise at 0 °C to the reaction mixture and stirred at room temperature for 2 hr. The solution was poured into an aqueous hydrochloric acid solution (1 N, 35 mL) and stirred for another hour. The ethanol was evaporated under reduced pressure. The residue was made alkaline with concentrated aqueous ammonium hydroxide solution (8 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the *title compound* (4.21 g, 78% yield) as a light brown solid; mp: 88-89 °C; ν_{max} (neat) 3383 (NH_2), 3304 (NH_2); δ_H (500 MHz, $CDCl_3$) 7.05 (1H, d, *J* 7.9, ArH), 6.83 (2H, dd, *J* 2.3, 2 × ArH), 6.60-6.66 (2H, m, 2 × ArH), 6.35 (2H, dd, *J* 2.3, 2 × ArH), 3.65 (2H, br. s, NH_2), 2.33 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 141.8 (C), 138.6 (C), 126.9 (CH), 125.2 (C), 121.8 (2 × CH), 119.2 (CH), 116.5 (CH), 109.2 (2 × CH), 21.2 (CH_3); *m/z* (NSI) 173.1072 ($[M+H]^+$, $C_{11}H_{13}N_2$ requires 173.1073).

Methyl 4-amino-3-(furan-3-yl)benzoate (2h)



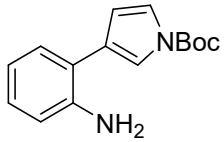
$Pd(PPh_3)_4$ (0.042 g, 0.036 mmol) was added to a solution of methyl 4-amino-3-iodobenzoate (0.20 g, 0.72 mmol) and furan-3-ylboronic acid (0.081 g, 0.72 mmol) in toluene (8 mL), ethanol (4 mL) and Na_2CO_3 aq. (3.73 mL, 7.46 mmol). The mixture was heated at 80 °C for 3 hr. The mixture was allowed to cool to room temperature. EtOAc (50 mL) and sat. aq. $NaHCO_3$ (25 mL) were added and the layers were separated. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hex:EtOAc) to give methyl 4-amino-3-(furan-3-yl)benzoate (0.45 g, 62%) as an orange oil; ν_{max} (neat) 3476 (NH), 3367 (NH), 2951 (CH), 1701 (C=O), 1252 (C-O); δ_H (500 MHz, $CDCl_3$) 7.89 (1H, d, *J* 2.0, ArH), 7.81 (1H, dd, *J* 8.6, 2.0, ArH), 7.65 (1H, dd, *J* 1.5, 1.0, ArH), 7.54 (1H, dd, *J* 1.5, 1.5, ArH), 6.72 (1H, d, *J* 8.6, ArH), 6.63 (1H, dd, *J* 2.0, 1.0, ArH), 4.31 (2H, br. s, NH_2), 3.87 (3H, s, OCH_3); δ_C (126 MHz, $CDCl_3$) 167.1 (C), 148.4 (C), 143.5 (CH), 139.9 (CH), 131.8 (CH), 130.3 (CH), 122.5 (C), 119.8 (C), 117.3 (C), 114.5 (CH), 110.6 (CH), 51.6 (CH_3); *m/z* (NSI) 240.0640 ($[M + Na]^+$, $C_{12}H_{11}NO_3Na$ requires 240.0637).

Methyl 4-amino-3-(thiophen-3-yl)benzoate (2i)



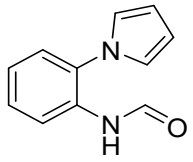
$Pd(PPh_3)_4$ (0.031 g, 0.027 mmol) was added to a solution of methyl 4-amino-3-iodobenzoate (0.15 g, 0.54 mmol) and thiophen-3-ylboronic acid (0.069 g, 0.54 mmol) in toluene (6 mL), ethanol (3 mL) and Na_2CO_3 aq. (2.80 mL, 5.60 mmol). The mixture was heated at 80 °C for 3 hr. The mixture was allowed to cool to room temperature. EtOAc (50 mL) and sat. aq. $NaHCO_3$ (25 mL) were added and the layers were separated. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hex:EtOAc) to give methyl 4-amino-3-(thiophen-3-yl)benzoate (0.099 g, 79%) as a colourless solid; m.p. 135-136 °C; ν_{max} (neat) 3474 (NH), 3364 (NH), 1699 (C=O); δ_H (500 MHz, $CDCl_3$) 7.91 (1H, d, *J* 2.0, ArH), 7.83 (1H, dd, *J* 8.3, 2.0, ArH), 7.45 (1H, dd, *J* 4.8, 3.0, ArH), 7.39 (1H, dd, *J* 3.0, 1.5, ArH), 7.25 (1H, dd, *J* 4.8, 1.5, ArH), 6.73 (1H, d, *J* 8.3, ArH), 4.29 (2H, br. s, NH_2), 3.87 (3H, s, OCH_3); δ_C (126 MHz, $CDCl_3$) 167.1 (C), 148.3 (C), 138.6 (C), 132.2 (CH), 130.4 (CH), 128.1 (CH), 126.5 (CH), 123.0 (CH), 121.4 (C), 119.7 (C), 114.5 (CH), 51.6 (CH_3); *m/z* (NSI) 234.0598 ($[M + H]^+$, $C_{12}H_{12}NO_2S$ requires 234.0583).

***tert*-Butyl 3-(2-aminophenyl)-1*H*-pyrrole-1-carboxylate (2j)**[8]



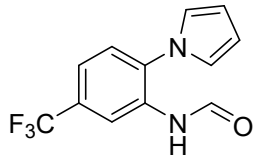
$Pd(PPh_3)_4$ (0.50 g, 0.43 mmol) was added to a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (2.07 g, 9.43 mmol) and *tert*-butyl 3-bromo-1*H*-pyrrole-1-carboxylate (2.11 g, 8.57 mmol) in toluene (40.0 mL) and ethanol (20 mL) followed by the addition of 2 M aqueous solution of sodium carbonate (42.9 mL, 86.0 mmol). The mixture was heated at 80 °C overnight. The mixture was allowed to cool to room temperature. Ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate (25 mL) were added and the layers were separated. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hex:EtOAc) to give the *title compound* (1.16 g, 52%) as a pale yellow oil; ν_{max} (neat) 2979 (NH_2), 2934 (NH_2), 1735 (C=O); δ_H (500 MHz, $CDCl_3$) 7.41-7.44 (1H, m, ArH), 7.32-7.34 (1H, m, ArH), 7.20-7.23 (1H, m, ArH), 7.07-7.12 (1H, m, ArH), 6.76-6.81 (1H, m, ArH), 6.73-6.76 (1H, m, ArH), 6.44-6.46 (1H, m, ArH), 3.91 (2H, br. s, NH_2), 1.62 (9H, s, 3 × CH_3); δ_C (101 MHz, $CDCl_3$) 171.2 (C), 148.9 (C), 144.1 (C), 129.8 (CH), 128.1 (CH), 125.3 (C), 120.7 (CH), 118.7 (CH), 117.6 (CH), 115.7 (CH), 112.8 (CH), 83.9 (C), 28.1 (CH_3); *m/z* (NSI) 259.1443 ($[M+H]^+$, $C_{15}H_{19}N_2O_2$ requires 259.1441).

***N*-(2-(1*H*-Pyrrol-1-yl)phenyl)formamide (3a)**[9]



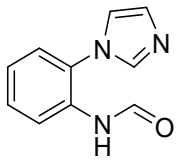
A solution of methyl 2-(1*H*-pyrrol-1-yl)aniline (0.63 g, 3.96 mmol) in ethyl formate (25 mL, 309 mmol) and formic acid (3.34 mL, 87.0 mmol) was heated at reflux overnight. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by column chromatography (8:2 Hex:EtOAc) to give the *title compound* (0.54 g, 73%) as a 70:30 mixture of rotamers colourless solid; m.p. 110-112 °C; ν_{max} (neat) 3267 (NH), 1657 (C=O); δ_H (500 MHz, $CDCl_3$) 8.61 (0.3H, d, *J* 11.4, CHO), 8.45 (0.7H, d, *J* 8.6, CHO), 8.30 (0.7H, d, *J* 1.3, NH), 7.10-7.46 (4.3H, m, 4 × ArH, 0.3 × NH), 6.77-6.82 (2H, m, 2 × ArH), 6.35-6.44 (2H, m, , 2 × ArH); δ_C (126 MHz, $CDCl_3$) 161.5 (CH), 159.0 (CH), 132.8 (C), 132.4 (C), 131.5 (C), 130.4 (C), 128.8 (2 × CH), 127.9 (CH), 127.1 (CH), 125.4 (CH), 124.6 (CH), 122.0 (3 × CH), 121.7 (CH), 121.7 (2 × CH), 118.4 (CH), 110.7 (CH), 110.5 (2 × CH); m/z (NSI) 187.0864 ($[M+H]^+$, $C_{11}H_{11}N_2O$ requires 187.0866).

***N*-(2-(1*H*-Pyrrol-1-yl)-5-(trifluoromethyl)phenyl)formamide (3b)**



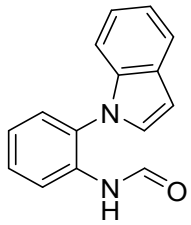
A solution of 2-(1*H*-pyrrol-1-yl)-5-(trifluoromethyl)aniline (0.48 g, 2.12 mmol) in ethyl formate (14 mL, 166 mmol) and formic acid (1.79 mL, 46.7 mmol) was heated at reflux overnight. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (0.45 g, 83%) as an 80:20 mixture of rotamers colourless solid; mp 123-124 °C; ν_{max} (neat) 3259 (N-H), 1669 (C=O), 1120 (C-F); δ_H (500 MHz, $CDCl_3$) 8.85 (0.8H, s, CHO), 8.73 (0.2H, d, *J* 10.9, CHO), 8.34-8.41 (0.8H, m, ArH), 7.60 (0.2H, s, ArH), 7.51-7.55 (0.2H, m, ArH), 7.45-7.50 (1H, m, ArH), 7.39-7.43 (0.8H, m, ArH), 7.33 (0.2H, br. s, NH), 7.22 (0.8H, br. s, NH), 6.78-6.84 (2H, m, 2 × ArH), 6.42-6.48 (2H, m, 2 × ArH); δC (126 MHz, $CDCl_3$) peaks assignable to major rotamer: 158.9 (CH), 133.3 (C), 132.8 (C), 131.0 (q, *J* 32.1, C), 127.5 (CH), 123.5 (q, *J* 273.1, C) 121.7 (2 × CH), 121.4 (q, *J* 3.7, CH), 118.7 (q, *J* 3.7, CH), 111.5 (2 × CH); *m/z* (NSI) 255.0742 ($[M+H]^+$, $C_{12}H_{10}F_3N_2O$ requires 255.0740).

N-(2-(1*H*-Imidazol-1-yl)phenyl)formamide (3c)



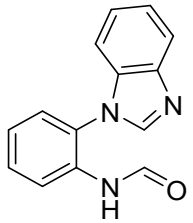
A solution of 2-(1*H*-imidazol-1-yl)aniline (2.00 g, 13.0 mmol) in ethyl formate (79 mL, 980 mmol) and formic acid (10.8 mL, 290 mmol) was heated at reflux overnight. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by column chromatography (8:2 Hex:EtOAc) to give the *title compound* (1.83 g, 75%) as a 76:24 mixture of rotamers colourless solid; m.p. 200-202 ˚C; ν_{max} (neat) 3301 (NH), 1689 (C=O); δ_H (500 MHz, DMSO-d_6) 9.61 (1H, br. s, NH), 8.15-8.20 (1H, m, ArH), 7.92-8.02 (1H, m, ArH), 7.81-7.87 (1H, m, ArH), 7.29-7.49 (4H, m, 4 × ArH), 7.11 (1H, s, ArH); δ_C (126 MHz, DMSO-d_6) 163.5 (CH), 160.6 (CH), 159.0 (CH), 137.7 (CH), 137.6 (CH), 132.4 (C), 131.8 (C), 130.8 (C), 129.7 (C), 129.2 (CH), 129.1 (CH), 129.1 (CH), 128.8 (CH), 127.2 (CH), 127.1 (CH), 126.6 (CH), 125.8 (CH), 125.0 (CH), 124.8 (CH), 120.7 (CH); *m/z* (APCI) 188.0815 ([M + H]$^+$, $C_{10}H_{10}N_3O$ requires 188.0818).

N-(2-(1*H*-Indol-1-yl)phenyl)formamide (3d)



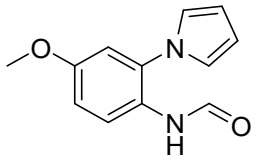
A solution of 2-(1*H*-indol-1-yl)aniline (0.24 g, 1.14 mmol) in ethyl formate (8 mL, 89.0 mmol) and formic acid (0.96 mL, 25.1 mmol) was heated at reflux overnight. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by column chromatography (8:2 Hex:EtOAc) to give the *title compound* (0.19 g, 72%) as a 75:25 mixture of rotamers colourless solid; m.p. 92-93 °C; ν_{max} (neat) 3287 (NH), 2934 (CH), 1700 (C=O); δ_H (500 MHz, $CDCl_3$) 8.66 (0.25H, d, *J* 11.3, CHO), 8.55 (0.75H, d, *J* 8.5, CHO), 8.17 (0.75H, s, ArH), 7.69-7.76 (1H, m, ArH), 7.47-7.53 (1H, m, ArH), 7.38-7.45 (0.5H, m, ArH), 7.31-7.37 (1H, m, ArH), 7.19-7.29 (3.25H, m, ArH), 7.02-7.17 (1.75H, m, NH, ArH), (0.75H, s, ArH), 6.74-6.80 (1H, m, ArH); δH (126 MHz, $CDCl_3$) 161.2 (CH), 159.0 (CH), 136.6 (C), 136.6 (C), 133.8 (2 × C), 129.5 (CH), 129.4 (CH), 129.4 (2 × CH), 129.1 (C), 128.7 (2 × C), 128.5 (CH), 128.4 (CH), 128.1 (C), 128.0 (CH), 125.6 (CH), 125.0 (CH), 123.1 (CH), 123.0 (CH), 121.9 (CH), 121.4 (CH), 121.3 (CH), 120.8 (CH), 118.2 (CH), 110.3 (CH), 109.8 (CH), 104.7 (CH), 104.5 (CH); *m/z* (APCI) 237.1021 ([M + H]$^+$, $C_{15}H_{13}N_2O$ requires 237.1022).

***N*-(2-(1*H*-Benzo[*d*]imidazol-1-yl)phenyl)formamide (3e)**



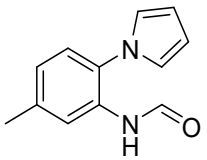
A solution of 2-(1*H*-benzo[*d*]imidazol-1-yl)aniline (1.29 g, 2.39 mmol) in ethyl formate (15 mL, 186 mmol) and formic acid (1.98 mL, 52.6 mmol) was heated at reflux overnight. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by column chromatography (8:2 EtOAc:Hex) to give the *title compound* (0.35 g, 62%) as a 87:13 mixture of rotamers colourless solid; m.p. 223-225 ˚C; ν_{max} (neat) 3308 (NH), 1669 (C=O); δ_H (500 MHz, $CDCl_3$) 10.10 (0.87H, s, CHO), 9.90 (0.13H, d, *J* 10.4, CHO), 8.54 (0.13H, d, *J* 10.4, ArH), 8.49 (0.87H, dd, *J* 8.4, 1.1, ArH), 8.34 (0.87H, d, *J* 1.9, ArH), 7.52-7.61 (1.13H, m, ArH), 7.48 (0.13H, d, *J* 7.6, ArH), 7.41 (0.87H, s, ArH), 7.16-7.37 (4H, m, ArH), 7.06-7.11 (1.87H, m, ArH); δ_C (126 MHz, $CDCl_3$) 162.6 (CH), 160.3 (CH), 142.4 (CH), 142.3 (CH), 142.4 (CH), 142.2 (C), 133.9 (C), 133.6 (C), 133.3 (C), 130.3 (CH), 130.2 (CH), 128.5 (CH), 127.9 (CH), 126.7 (C), 126.1 (CH), 125.0 (CH), 124.9 (C), 123.9 (CH), 123.9 (CH), 123.3 (CH), 123.0 (CH), 121.3 (CH), 119.3 (CH), 118.9 (CH), 110.5 (CH), 110.2 (CH); *m/z* (APCI) 238.0972 ($[M + H]^+$, $C_{14}H_{12}N_3O$ requires 238.0975).

***N*-(4-Methoxy-2-(1*H*-pyrrol-1-yl)phenyl)formamide (3f)**



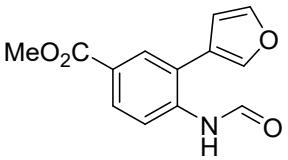
A solution of 4-methoxy-2-(1*H*-pyrrol-1-yl)aniline (0.23 g, 1.24 mmol) in ethyl formate (8 mL, 97.0 mmol) and formic acid (1.05 mL, 27.3 mmol) was heated at reflux overnight. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (0.19 g, 72%) as a 70:30 mixture of rotamers colourless solid; m.p. 132-133 °C; ν_{max} (neat) 3296 (N-H), 1655 (C=O); δ_H (500 MHz, $CDCl_3$) 8.33 (0.3H, d, *J* 11.3, CHO), 8.18-8.24 (1.4H, m, CHO, ArH), 7.34 (0.3H, d, *J* 11.3, NH), 7.14-7.23 (1H, m, NH, ArH), 6.87-6.95 (1.3H, m, ArH), 6.77-6.84 (2.7H, m, ArH), 6.32-6.39 (2H, m, ArH), 3.82 (0.9H, s, CH_3), 3.80 (2.1H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 162.2 (CH), 159.0 (CH), 157.7 (C), 156.5 (C), 133.7 (C), 132.1 (C), 125.3 (C), 124.6 (C), 123.6 (2 × CH), 122.1 (CH), 121.8 (2 × CH), 121.6 (CH), 113.9 (CH), 113.7 (CH), 112.8 (CH), 112.4 (CH), 110.5 (2 × CH), 110.3 (2 × CH), 55.7 (CH_3), 55.6 (CH_3); *m/z* (NSI) 217.0972 ($[M+H]^+$, $C_{12}H_{13}N_2O_2$ requires 217.0972).

_N_-(5-Methyl-2-(1_H_-pyrrol-1-yl)phenyl)formamide (3g)[9]



A solution of methyl 2-(1*H*-pyrrol-1-yl)aniline (4.20 g, 24.4 mmol) in ethyl formate (155 mL, 1902 mmol) and formic acid (20.6 mL, 537 mmol) was heated at reflux overnight. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was purified by column chromatography (8:2 Hex:EtOAc) to give the *title compound* (3.69 g, 75%) as a 70:30 mixture of rotamers colourless solid; m.p. 73-75 ˚C; ν_{max} (neat) 3292 (NH), 1682 (C=O); δ_H (500 MHz, $CDCl_3$) 8.53 (0.3H, d, *J* 11.3, CHO), 8.22-8.28 (1.3H, m, CHO, 2 × 0.3H), 7.47 (0.3H, br. s, NH), 7.12-7.24 (2.1H, m, 0.7 × NH, 2 × 0.7ArH), 7.07 (0.3H, d, *J* 7.6, ArH), 7.00 (0.7H, dd, *J* 7.6, 1.6, ArH), 6.76 (2H, ddd, *J* 6.9, 2.2, 2.2, 2 × ArH), 6.37 (2H, ddd, *J* 8.2, 2.2, 2.2, 2 × ArH), 2.43 (0.9H, s, CH_3), 2.42 (2.1H, s, CH_3); δ_C (126 MHz, $CDCl_3$) peaks assignable to major rotamer: 159.2 (CH), 139.0 (C), 132.3 (C), 128.0 (C), 126.7 (CH), 125.3 (CH), 122.1 (2 × CH), 122.1 (CH), 110.2 (2 × CH), 21.4 (CH_3); *m/z* (NSI) 201.1019 ($[M+H]^+$, $C_{12}H_{10}F_3N_2O$ requires 201.1022).

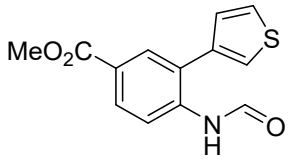
Methyl 4-formamido-3-(furan-3-yl)benzoate (3h)



To a stirred solution of acetic anhydride (0.039 mL, 0.41 mmol) in THF (1.5 mL) at 0 °C was added formic acid (0.016 mL, 0.41 mmol). The resulting mixture was heated at reflux for 2 hr. The mixture was cooled to 0 °C and a solution of methyl 4-amino-3-(furan-3-yl)benzoate (0.09 g, 0.41 mmol) in THF (1.5 mL) was added and stirred at room temperature overnight. EtOAc (10 mL) was and the mixture was washed with a saturated aqueous solution of Na_2CO_3 (3 x 5 mL). The organic layer was separated and dried over $MgSO_4$. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (6:4 Hex:EtOAc) to give the *title compound* (0.085 g, 83%) as a 63:37 mixture of rotamers as an orange solid; m.p. 122-123 °C; ν_{max} (neat) 3320 (NH), 3144 (CH), 2951 (CH), 1698 (C=O), 1257 (C-O); δ_H (500 MHz, $CDCl_3$) 8.78 (0.37H, d, *J* 11.3, CHO), 8.46 (0.67H, d, *J* 8.5, CHO), 8.41 (0.67H, d, *J* 1.9, ArH), 8.02 (0.37H, d, *J* 2.2, ArH), 7.98 (1H, dd, *J* 8.5, 2.2, ArH), 7.94 (0.67H, d, *J* 2.2, ArH), 7.75-7.66 (1H, m, NH), 7.63-7.60 (1H, m, ArH), 7.59-7.55 (1H, m, ArH), 7.33 (0.37H, d, *J* 8.5, ArH), 6.57-6.54 (1H, m, ArH), 3.91 (1.11H, s, OCH_3), 3.89 (1.89H, s, OCH_3); δ_C (126 MHz, $CDCl_3$) 166.3 (C), 166.1 (C), 161.4 (CH), 159.0 (CH), 144.3 (2 × CH), 140.6 (2 × CH), 138.5 (C), 138.1 (C), 132.1 (CH), 131.4 (CH), 130.1 (2 × CH), 126.7 (C), 125.8 (C), 123.3 (C), 122.2 (C), 121.0 (C), 120.8

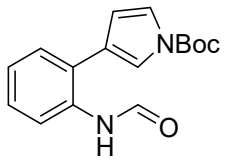
(C), 120.5 (CH), 117.3 (CH), 111.0 (CH), 110.6 (CH), 52.2 (CH_3), 52.1 (CH_3); *m/z* (NSI) 268.0598 ([M + Na]$^+$, $C_{13}H_{11}NO_4Na$ requires 268.0586).

Methyl 4-formamido-3-(thiophen-3-yl)benzoate (3i)



To a stirred solution of acetic anhydride (0.040 mL, 0.42 mmol) in THF (1.5 mL) at 0 °C was added formic acid (0.016 mL, 0.42 mmol). The resulting mixture was heated at reflux for 2 hr. The mixture was cooled to 0 °C and a solution of methyl 4-amino-3-(thiophen-3-yl)benzoate (0.10 g, 0.42 mmol) in THF (1.5 mL) was added and stirred at room temperature overnight. EtOAc (10 mL) was and the mixture was washed with a saturated aqueous solution of Na_2CO_3 (3 x 5 mL). The organic layer was separated and dried over $MgSO_4$. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (6:4 Hex:EtOAc) to give the *title compound* (0.088 g, 79%) as a 65:35 mixture of rotamers as a colourless oil; ν_{max} (neat) 3332 (NH), 3103 (CH), 2950 (CH), 1713 (C=O), 1696 (C=O), 1243 (C-O); δ_H (500 MHz, $CDCl_3$) 8.81 (0.35H, d, *J* 11.4, CHO), 8.51 (0.65H, d, *J* 8.8, CHO), 8.38 (0.65H, d, *J* 1.8, ArH), 8.05-7.98 (1.35H, m, ArH), 7.96 (0.65H, d, *J* 2.3, ArH), 7.68-7.58 (1H, m, NH), 7.53-7.48 (1H, m, ArH), 7.59-7.55 (1H, m, ArH), 7.39-7.32 (1H, m, ArH), 7.18-7.12 (1H, m, ArH), 3.91 (1.05H, s, OCH_3), 3.90 (1.95H, s, OCH_3); δ_C (126 MHz, $CDCl_3$) 166.3 (C), 166.1 (C), 161.2 (CH), 159.0 (CH), 138.3 (C), 138.1 (C), 136.9 (C), 136.4 (C), 132.5 (CH), 131.5 (CH), 130.2 (CH), 130.1 (CH), 128.1 (CH), 127.9 (CH), 127.6 (2 × CH), 126.9 (C), 126.5 (C), 126.1 (C), 125.7 (C), 124.5 (CH), 124.4 (CH), 120.4 (CH), 116.5 (CH), 52.2 (CH_3), 52.1 (CH_3).; *m/z* (NSI) 268.0598 284.0363 ([M + Na]$^+$, $C_{13}H_{11}NO_3SNa$ requires 284.0352).

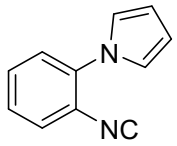
***tert*-Butyl 3-(2-formamidophenyl)-1*H*-pyrrole-1-carboxylate (3j)**[8]



Formic acid (0.16 mL, 4.18 mmol) was added to a stirred solution of acetic anhydride (0.39 mL, 4.18 mmol) in THF (10.0 mL) at 0 °C. The resulting mixture was heated at reflux for 2 hours. The reaction was cooled to 0 °C and a solution of *tert*-butyl 3-(2-formamidophenyl)-1*H*-pyrrole-1-carboxylate (1.08 g, 4.18 mmol) in THF (10.0 mL) was added and stirred at room temperature overnight. EtOAc (20 mL) was and the mixture was washed with a saturated aqueous solution of Na_2CO_3 (3 x 10 mL). The organic layer was separated and dried over $MgSO_4$. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (3:1 Hex:EtOAc) to

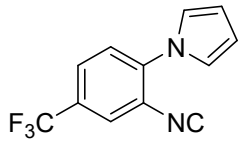
give the *title compound* (1.10 g, 92%) as a yellow oil; ν_{max} (neat) 3265 (CH), 1742 (C=O), 1669 (C=O); δ_H (500 MHz, $CDCl_3$) 8.21 (1H, d, *J* 8.1 Hz, CHO), 7.45 (1H, br. s, NH), 7.31-7.37 (3H, m, ArH), 7.29 (2H, d, *J* 8.1, ArH), 7.09-7.14 (1H, m, ArH), 6.34-6.37 (1H, m, ArH), 1.62 (9H, s, 3 × CH_3); δ_C (126 MHz, $CDCl_3$) 168.3 (C), 148.6 (C), 135.2 (C), 129.7 (CH), 128.2, 125.3 (C), 124.4, 124.0 (CH), 121.6 (CH), 121.3 (CH), 118.3 (CH), 112.6 (CH), 84.5 (C), 28.1 (CH_3); *m/z* (NSI) 287.0923 ($[M+H]^+$, $C_{16}H_{19}N_2O_3$ requires 287.0921).

1-(2-Isocyanophenyl)-1*H*-pyrrole (4a)[10]



To a solution of *N*-(2-(1*H*-pyrrol-1-yl)phenyl)formamide (0.53 g, 2.85 mmol) in CH_2Cl_2 (21.1 mL) at 0 °C was added diisopropylamine (2.4 mL, 17.1 mmol) followed by dropwise addition of phosphoryl trichloride (0.56 mL, 5.98 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (0.42 g, 88%) as a colourless solid; m.p. 42-43 °C; ν_{max} (neat) 2973 (C-H), 2120 (C=N); δ_H (500 MHz, $CDCl_3$) 7.45-7.55 (2H, m, 2 × ArH), 7.32-7.42 (2H, m, 2 × ArH), 7.03 (2H, dd, *J* 2.1, 2 × ArH), 6.40 (2H, dd, *J* 2.1, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 169.6 (C), 137.1 (C), 130.3 (CH), 128.7 (CH), 127.2 (CH), 126.2 (CH), 121.3 (2 × CH), 120.9 (C), 110.5 (2 × CH); *m/z* (APCI) 169.0757 ($[M+H]^+$, $C_{11}H_9N_2$ requires 169.0760).

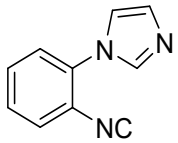
1-(2-Isocyano-4-(trifluoromethyl)phenyl)-1*H*-pyrrole (4b)



To a solution of *N*-(2-(1*H*-pyrrol-1-yl)-5-(trifluoromethyl)phenyl)formamide (0.42 g, 1.65 mmol) in CH_2Cl_2 (12.2 mL) at 0 °C was added diisopropylamine (1.4 mL, 9.91 mmol) followed by dropwise addition of phosphoryl trichloride (0.32 mL, 3.47 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (0.37 g, 96%) as an brown oil; ν_{max} (neat) 2978 (C-H), 2123 (C≡N), 1135 (C-F); δ_H (500 MHz, $CDCl_3$) 7.80 (1H, d, *J* 2.2, ArH), 7.74 (1H, dd,

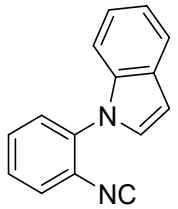
J 8.5, 2.2, ArH), 7.52 (1H, d, *J* 8.5 Hz, ArH), 7.09 (2H, dd, *J* 2.2, 2 × ArH), 6.45 (2H, dd, *J* 2.2, 2 × ArH); δ_C (126 MHz, $CDCl_3$) 172.2 (C), 139.6 (C), 129.3 (q, *J* 34.8, C), 127.2 (q, *J* 3.7, CH), 126.4 (CH), 126.3 (q, *J* 3.7, CH), 121.2 (2 × CH), 120.6 (C), 122.7 (q, *J* 272.2, C), 111.6 (2 × CH); *m/z* (ESI) 237.0642 ($[M+H]^+$, $C_{12}H_7F_3N_2$ requires 237.0640).

1-(2-Isocyanophenyl)-1*H*-imidazole (4c)[10]



To a solution of *N*-(2-(1*H*-imidazol-1-yl)phenyl)formamide (0.24 g, 1.26 mmol) in CH_2Cl_2 (9.4 mL) at 0 °C was added diisopropylamine (1.1 mL, 7.56 mmol) followed by dropwise addition of phosphoryl trichloride (0.25 mL, 2.65 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 EtOAc:MeOH) to give the *title compound* (0.17 g, 80%) as a brown oil; ν_{max} (neat) 3021 (C-H), 2113 (C≡N); δ_H (500 MHz, $CDCl_3$) 9.15 (1H, s, Ar*H*), 8.13-8.18 (2H, m, 2 × Ar*H*), 7.95 (1H, dd, *J* 8.2, 0.9, Ar*H*), 7.84 (1H, d, *J* 0.9, Ar*H*), 7.70 (1H, ddd, *J* 8.4, 7.1, 1.6, Ar*H*), 7.63 (1H, ddd, *J* 8.4, 7.1, 1.6, Ar*H*); δ_C (126 MHz, $CDCl_3$) 144.4 (CH), 138.9 (C), 135.9 (C), 134.5 (CH), 130.8 (CH), 129.0 (CH), 127.3 (C), 126.5 (CH), 114.8 (CH), 112.2 (CH); *m/z* (NSI) 169.0635 ($[M + H]^+$, $C_{10}H_7N_3$ requires 169.0640).

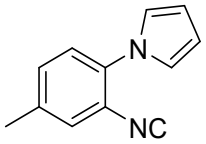
1-(2-Isocyanophenyl)-1*H*-indole (4d)[10]



To a solution of *N*-(2-(1*H*-indol-1-yl)phenyl)formamide (0.27 g, 1.13 mmol) in CH_2Cl_2 (3.2 mL) at 0 °C was added diisopropylamine (0.95 mL, 6.75 mmol) followed by dropwise addition of phosphoryl trichloride (0.22 mL, 2.36 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (9:1 Hex:EtOAc) to give the *title compound* (0.22 g, 91%) as an orange solid; m.p. 64-65 °C; ν_{max} (neat) 3050 (CH),

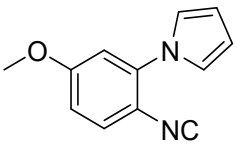
2126 (N≡C); δ_H (500 MHz, $CDCl_3$) 7.71-7.75 (1H, m, ArH), 7.62 (1H, ddd, *J* 7.9, 1.0, 1.0, ArH), 7.54-7.58 (2H, m, 2 × ArH), 7.43-7.50 (1H, m, ArH), 7.36 (1H, d, *J* 3.3, ArH), 7.20-7.30 (3H, m, 3 × ArH), 6.78 (1H, d, *J* 3.3, ArH); δ_C (126 MHz, $CDCl_3$) 169.6 (C), 136.2 (C), 135.9 (C), 130.3 (CH), 128.9 (C), 128.6 (CH), 128.1 (CH), 128.1 (CH), 128.0 (CH), 123.1 (C), 122.7 (CH), 121.3 (CH), 120.8 (CH), 110.3 (CH), 104.6 (CH); *m/z* (NSI) 219.0916 ($[M + H]^+$, $C_{15}H_{11}N_2$ requires 219.0917).

1-(2-Isocyano-4-methylphenyl)-1*H*-pyrrole (4f)[9]



To a solution of *N*-(5-methyl-2-(1*H*-pyrrol-1-yl)phenyl)formamide (3.78 g, 18.9 mmol) in CH_2Cl_2 (140 mL) at 0 °C was added diisopropylamine (16 mL, 113 mmol) followed by dropwise addition of phosphoryl trichloride (3.70 mL, 39.6 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (1.24 g, 36%) as a colourless solid; m.p. 95-96 °C; ν_{max} (neat) 3036 (C-H), 2121 (C≡N); δ_H (500 MHz, $CDCl_3$) 7.33 (1H, s, ArH), 7.26-7.30 (2H, m, 2 × ArH), 7.00 (2H, dd, *J* 2.2, 2 × ArH), 6.40 (2H, dd, *J* 2.2, 2 × ArH), 2.42 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 169.1 (C), 137.6 (C), 134.7 (C), 131.0 (CH), 128.7 (CH), 125.9 (CH), 121.3 (2 × CH), 120.6 (C), 110.2 (2 × CH), 20.6 (CH_3); *m/z* (NSI) 183.0916 ($[M+H]^+$, $C_{12}H_{11}N_2$ requires 183.0916).

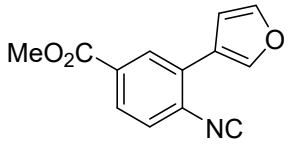
1-(2-Isocyano-5-methoxyphenyl)-1*H*-pyrrole (4g)



To a solution of *N*-(4-methoxy-2-(1*H*-pyrrol-1-yl)phenyl)formamide (0.89 g, 4.13 mmol) in CH_2Cl_2 (31 mL) at 0 °C was added diisopropylamine (3.5 mL, 24.7 mmol) followed by dropwise addition of phosphoryl trichloride (0.81 mL, 8.67 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (95:5 Hex:EtOAc) to give the *title compound* (0.73 g, 89%) as a yellow oil; ν_{max} (neat) 2935 (C-H), 2120 (C≡N);

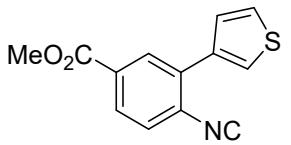
δ_H (500 MHz, $CDCl_3$) 7.43 (1H, d, *J* 8.5, ArH), 7.03 (2H, dd, *J* 1.9, 1.9, 2 × ArH), 6.85-6.87 (2H, m, 2 × ArH), 6.82-6.85 (1H, m, ArH), 6.39 (2H, dd, *J* 1.9, 1.9, ArH), 3.86 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 168.1 (C), 160.4 (C), 138.3 (C), 129.7 (CH), 121.3 (2 × CH), 113.8 (C), 112.8 (CH), 111.3 (CH), 110.6 (2 × CH), 55.8 (CH_3); *m/z* (APCI) 199.0863 ($[M+H]^+$, $C_{12}H_{11}N_2O$ requires 199.0866).

Methyl 3-(furan-3-yl)-4-isocyanobenzoate (4h)



To a solution of methyl 4-formamido-3-(furan-3-yl)benzoate (0.08 g, 0.33 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C was added diisopropylamine (0.27 mL, 1.96 mmol) followed by dropwise addition of phosphoryl trichloride (0.064 mL, 0.69 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 Hex:EtOAc) to give the *title compound* (0.047 g, 63%) as an orange solid; m.p. 78-79 °C; ν_{max} (neat) 3116 (CH), 2952 (CH), 2126 (C≡N), 1726 (C=O); δ_H (500 MHz, $CDCl_3$) 8.18 (1H, d, *J* 1.9, ArH), 8.04 (1H, dd, *J* 1.3, 1.3, ArH), 7.96 (1H, dd, *J* 8.3, 1.9, ArH), 7.57 (1H, dd, *J* 1.9, 1.9, ArH), 7.53 (1H, d, *J* 8.3, ArH), 6.85 (1H, dd, *J* 1.9, 0.9, ArH), 3.96 (3H, s, OCH_3); δ_C (126 MHz, $CDCl_3$) 170.7 (C), 165.5 (C), 143.5 (CH), 141.7 (CH), 131.1 (C), 130.2 (CH), 129.8 (C), 128.5 (CH), 128.4 (CH), 126.7 (C), 120.9 (C), 109.8 (CH), 52.6 (CH_3); *m/z* (APCI) 228.0652 ($[M + H]^+$, $C_{13}H_{10}NO_3$ requires 228.0655).

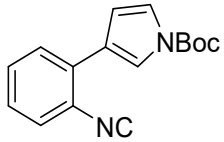
Methyl 4-isocyano-3-(thiophen-3-yl)benzoate (4i)



To a solution of methyl 4-formamido-3-(thiophen-3-yl)benzoate (0.09 g, 0.33 mmol) in CH_2Cl_2 (2.4 mL) at 0 °C was added diisopropylamine (0.27 mL, 1.95 mmol) followed by dropwise addition of phosphoryl trichloride (0.064 mL, 0.68 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 Hex:EtOAc) to give the *title compound* (0.075 g, 95%) as a colourless solid; m.p. 104-106 °C; ν_{max}

(neat) 3100 (CH), 2952 (CH), 2120 (C≡N), 1725 (C=O); δ_H (500 MHz, $CDCl_3$) 8.21 (1H, d, *J* 2.0, ArH), 8.00 (1H, dd, *J* 8.3, 1.8, ArH), 7.68 (1H, dd, *J* 3.0, 1.5, ArH), 7.55 (1H, d, *J* 8.3, ArH), 7.48 (1H, dd, *J* 5.1, 3.0, ArH), 7.43 (1H, dd, *J* 5.1, 1.5, ArH), 3.96 (3H, s, OCH_3); δ_C (126 MHz, $CDCl_3$) 170.0 (C), 165.5 (C), 136.1 (C), 133.5 (C), 131.3 (CH), 131.1 (C), 128.9 (CH), 128.3 (CH), 127.7 (CH), 127.2 (C), 126.3 (CH), 125.2 (CH), 52.6 (CH_3); *m/z* (APCI) 244.0423 ($[M + H]^+$, $C_{13}H_{10}NO_2S$ requires 244.0427).

tert-Butyl 3-(2-isocyanophenyl)-1_H_-pyrrole-1-carboxylate (4j)[8]

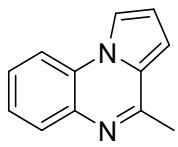


To a solution of tert-butyl 3-(2-formamidophenyl)-1*H*-pyrrole-1-carboxylate (1.03 g, 3.60 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added diisopropylamine (3 mL, 21.6 mmol) followed by dropwise addition of phosphoryl trichloride (0.07 mL, 7.55 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (10 mL) was added and diluted with CH_2Cl_2 (20 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (6:1 Hex:EtOAc) to give the title compound (0.53 g, 55%) as a colourless oil; ν_{max} (neat) 2119 (CN), 1744 (C=O); δ_H (500 MHz, $CDCl_3$) 7.67-7.69 (1H, m, ArH), 7.48 7.51 (1H, m, ArH), 7.42 (1H, d, J 8.0, ArH), 7.36-7.40 (1H, m, ArH), 7.31-7.33 (1H, m, ArH), 7.24-7.28 (1H, m, ArH), 6.62-6.64 (1H, m, ArH), 1.61 (9H, s, 3 × CH_3); δ_C (126 MHz, $CDCl_3$) 167.6 (C), 148.6 (C), 131.6 (C), 129.6 (CH), 129.1 (CH), 128.4 (CH), 127.4 (CH), 123.7 (C), 123.0 (C), 120.6 (CH), 119.1 (CH), 112.0 (CH), 84.4 (C), 28.1 (CH_3); m/z (NSI) 269.1287 ($[M+H]^+$, $C_{16}H_{17}N_2O_2$ requires 269.1285).

General procedure for the preparation mono-methylation products (5)

A mixture of isocyanide (1 eq.), KF (0.5 eq.), DCP (1.1 eq.) and *t*-butanol (0.08 M) was heated at 120 °C in a sealed tube for 18 hr. The mixture was allowed to cool and concentrated under reduced pressure. The residue was purified by column chromatography (99:1 Hex:EtOAc) give mono-methylated products.

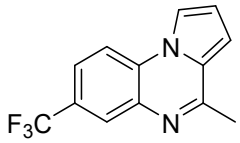
4-Methylpyrrolo[1,2-*a*]quinoxaline (5a)[11]



Isocyanide (0.09 g, 0.54 mmol), KF (0.016 g, 0.27 mmol), DCP (0.16 g, 0.59 mmol) and *tert*-butanol (6.7 mL) were used to afford the *title compound* (81.9 mg, 84%) as a yellow solid; m.p. 132-134 °C; ν_{max} (neat) 3045 (C-H), 2915 (C-H), 1530 (C=N); δ_H (500 MHz, $CDCl_3$) 7.88 - 7.93 (2H, m, 2 × ArH), 7.82 (1H, dd, *J* 8.20, 1.26, ArH), 7.40-7.49 (2H, m,

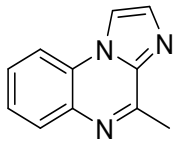
2 × ArH), 6.89 (1H, dd, *J* 3.78, 1.26, ArH), 6.85 (1H, dd, *J* 3.78, 2.84, ArH), 2.74 (3H, s, CH_3), δ_C (126 MHz, $CDCl_3$) 155.2 (C), 135.7 (C), 132.8 (C), 130.1 (C), 129.6 (C), 129.4 (CH), 128.9 (C), 127.7 (CH), 124.1 (CH), 123.9 (CH), 122.6 (CH), 122.5 (CH), 114.5 (CH), 114.5 (CH), 99.9 (CH), 22.2 (CH_3); *m/z* (NSI) 183.0914 ($[M+H]^+$, $C_{12}H_{11}N_2^+$ requires 183.0917).

4-Methyl-7-(trifluoromethyl)pyrrolo[1,2-*a*]quinoxaline (5b)[5]



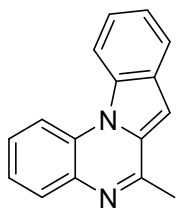
Isocyanide (0.11 g, 0.47 mmol), KF (0.014 g, 0.23 mmol), DCP (0.14 g, 0.51 mmol) and *tert*-butanol (5.8 mL) were used to afford the *title compound* (78.1 mg, 67%) as a yellow solid; m.p. 125-127 °C; ν_{max} (neat) 3126 (C-H), 2923 (C-H), 1535 (C=N); δ_H (500 MHz, $CDCl_3$) 8.20 (1H, s, ArH), 7.95 (1H, dd, *J* 2.5, 1.3, ArH), 7.92 (1H, d, *J* 8.8, ArH), 7.71 (1H, dd, *J* 8.7, 1.7, ArH), 6.97 (1H, dd, *J* 3.9, 1.1, ArH), 6.92 (1H, dd, *J* 3.8, 2.8, ArH), 2.76 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 155.2 (C), 135.6 (C), 129.4 (C), 127.2 (q, *J* 33.6, C), 126.8 (q, *J* 4.0, CH), 126.4 (C), 124.0 (q, *J* 272.5, C), 123.3 (q, *J* 3.5, CH), 114.9 (CH), 114.4 (CH), 114.3 (CH), 107.6 (CH), 22.0 (CH_3); *m/z* (NSI) 251.0790 ($[M+H]^+$, $C_{13}H_{10}F_3N_2$ requires 251.0791).

4-Methylimidazo[1,2-*a*]quinoxaline (5c)[12]



Isocyanide (0.09 g, 0.54 mmol), KF (0.016 g, 0.27 mmol), DCP (0.16 g, 0.59 mmol) and *tert*-butanol (6.7 mL) were used to afford the *title compound* (76.5 mg, 78%) as a colourless solid. m.p. 81-83 °C; ν_{max}/cm^{-1} (neat) 3122 (C-H), 2953 (C-H), 1509 (C=N); δ_H (500 MHz, $CDCl_3$) 8.05 (1H, d, *J* 1.26, ArH), 8.01 (1H, dd, *J* 7.88, 1.58, ArH), 7.79 (1H, dd, *J* 8.04, 1.42, ArH), 7.76 (1H, d, *J* 1.26, ArH), 7.49-7.57 (2H, m, 2 × ArH), 2.93 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 152.7 (C), 138.3 (C), 135.4 (C), 133.3 (CH), 129.5 (CH), 127.9 (CH), 126.7 (C), 126.5 (CH), 114.6 (CH), 112.4 (CH), 20.84 (CH_3); *m/z* (NSI) 184.0868 ($[M+H]^+$, $C_{11}H_{10}N_3$ requires 184.0869).

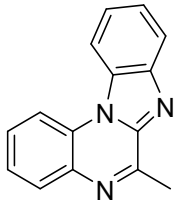
6-Methylindolo[1,2-*a*]quinoxaline (5d)[13]



Isocyanide (0.12 g, 0.55 mmol), KF (0.016 g, 0.28 mmol), DCP (0.16 g, 0.61 mmol) and *tert*-butanol (6.9 mL) were used to afford the *title compound* (111 mg, 87%) as a yellow

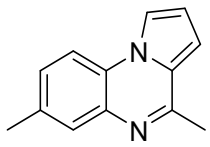
solid; m.p. 103-105 °C; ν_{max}/cm^{-1} (neat) 3045 (C-H), 2915 (C-H), 1532 (C=N); δ_H (500 MHz, $CDCl_3$) 8.36-8.41 (2H, m, 2 × ArH), 7.91-7.95 (2H, m, 2 × ArH), 7.49-7.57 (2H, m, 2 × ArH), 7.39-7.44 (2H, m, 2 × ArH), 7.10 (1H, s, ArH), 2.78 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 155.2 (C), 135.7 (C), 132.8 (C), 130.1 (C), 129.6 (C), 129.4 (CH), 128.9 (C), 127.7 (CH), 124.1 (CH), 123.9 (CH), 122.6 (CH), 122.5 (CH), 114.5 (CH), 114.5 (CH), 99.9 (CH), 22.2 (CH_3); *m/z* (NSI) 233.1072 ([M+H]$^+$, $C_{16}H_{13}N_2$ requires 233.1073).

6-Methylbenzo[4,5]imidazo[1,2-*a*]quinoxaline (5e)[14]



To a solution of *N*-(2-(1*H*-benzo[*d*]imidazol-1-yl)phenyl)formamide (0.09 g, 0.38 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C was added diisopropylamine (0.32 mL, 2.28 mmol) followed by dropwise addition of phosphoryl trichloride (0.08 mL, 0.80 mmol). The resulting solution was stirred for 30 min at 0 °C and at room temperature for 2 hr. The mixture was cooled to 0 °C and a 20% aqueous solution of Na_2CO_3 (5 mL) was added and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and washed with a 20% aqueous solution of Na_2CO_3 (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting mixture was used in the next step without further purification. Isocyanide (0.08 g, 0.38 mmol), KF (0.011 g, 0.19 mmol), DCP (0.11 g, 0.42 mmol) and *tert*-butanol (4.7 mL) were used to afford the *title compound* (78.6 mg, 78%) as a colourless solid. m.p. 155-157 °C; ν_{max}/cm^{-1} (neat) 3098 (C-H), 2933 (C-H), 1535 (C=N); δ_H (500 MHz, $CDCl_3$) 8.39 (1H, dd, *J* 8.35, 1.10, ArH), 8.30-8.35 (1H, m, ArH), 8.09-8.13 (1H, m, ArH), 8.07 (1H, dd, *J* 7.88, 1.58, ArH), 7.67 (1H, td, *J* 7.80, 1.42, ArH), 7.52-7.61 (3H, m, 3 × ArH), 3.05 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 154.4 (C), 143.8 (C), 141.3 (C), 135.2 (C), 130.4 (C), 130.1 (CH), 129.3 (C), 128.6 (CH), 125.5 (CH), 125.4 (CH), 124.6 (CH), 121.9 (CH), 114.5 (CH), 114.2 (CH), 21.7 (CH_3); *m/z* (NSI) 234.1025 ([M+H]$^+$, $C_{15}H_{12}N_3$ requires 234.1026).

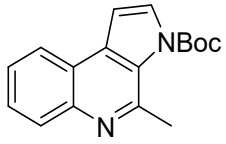
4,7-Dimethylpyrrolo[1,2-*a*]quinoxaline (5f)[5]



Isocyanide (0.12 g, 0.51 mmol), KF (0.015 g, 0.25 mmol), DCP (0.15 g, 0.56 mmol) and *tert*-butanol (6.4 mL) were used to afford the *title compound* (82.7 mg, 83%) as a yellow solid; m.p. 127-128 °C; ν_{max} (neat) 3100 (C-H), 2921 (C-H), 1527 (C=N); δ_H (500 MHz, $CDCl_3$) 7.88 (1H, dd, *J* 2.5, 1.3, ArH), 7.73 (1H, d, *J* 8.2, ArH), 7.71 (1H, s, ArH), 7.30 (1H, dd, *J* 8.4, 1.7, ArH), 6.88 (1H, dd, *J* 3.9, 1.1, ArH), 6.84 (1H, dd, *J* 3.9, 2.7, ArH), 2.73 (3H, s, CH_3), 2.50 (3H, s, C*H*$_3$); δ_C (126 MHz, $CDCl_3$) 153.6 (C), 135.9 (C), 134.9 (C), 129.1 (CH), 128.0

(CH), 126.2 (C), 125.2 (C), 114.0 (CH), 113.4 (CH), 113.2 (CH), 106.2 (CH), 22.0 (CH_3), 21.1 (CH_3); *m/z* (NSI) 197.1070 ($[M+H]^+$, $C_{13}H_{13}N_2$ requires 197.1073).

tert-Butyl 4-methyl-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (5j)

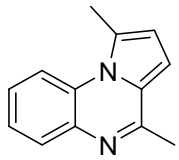


Isocyanide (0.15 g, 0.56 mmol), KF (0.016 g, 0.28 mmol), DCP (0.17 g, 0.61 mmol) and *tert*-butanol (7.0 mL) were used in the reaction. The residue was purified by column chromatography (8:2 Hex:EtOAc) give the *title compound* (0.13 g, 84%) as a colourless solid; m.p. 144-146 °C; ν_{max} (neat) 2997 (CH), 1740 (C=O); δ_H (500 MHz, $CDCl_3$) 8.03 8.06 (2H, m, 2 × ArH), 7.68 (1H, d, *J* 3.8, ArH), 7.57 (1H, ddd, *J* 8.4, 7.0, 1.3, ArH), 7.47 (1H, td, *J* 7.6, 1, ArH), 6.99 (1H, d, *J* 3.8, ArH), 2.98 (3H, s, CH_3), 1.63 (9H, s, 3 × CH_3); δ_C (126 MHz, $CDCl_3$) 170.9 (C), 148.6 (C), 147.9 (C), 143.3 (C), 133.3 (C), 129.9 (CH), 128.3 (CH), 127.2 (CH), 125.5 (CH), 122.7 (CH), 121.5 (C), 104.4 (CH), 84.6 (C), 27.8 (3 × CH_3), 20.8 (CH_3); *m/z* (NSI) 283.1439 ($[M+H]^+$, $C_{17}H_{19}N_2O_2$ requires 283.1441).

General procedure for the preparation of bis-methylation products (6)

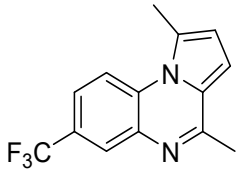
A mixture of isocyanide (1 eq.), $FeCl_3$ (0.2 eq.), 30% w/w H_2O_2 (3 eq.) and DMSO (0.083 M) was stirred at 25 °C under inert atmosphere for 6 hr in a sealed tube. The mixture was extracted with ethyl acetate (3 × 5 mL) and water (3 × 5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (99:1 Hex:EtOAc) give bis methylated products.

1,4-Dimethylpyrrolo[1,2-*a*]quinoxaline (6a)



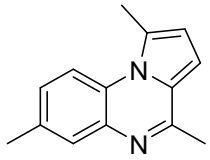
Isocyanide (0.07 g, 0.42 mmol), $FeCl_3$ (0.014 g, 0.08 mmol), 30% w/w H_2O_2 (0.13 mL, 1.25 mmol) and DMSO (5.2 mL) were used to afford the *title compound* (71.9 mg, 88%) as a yellow solid; m.p. 145-147 °C; ν_{max}/cm^{-1} (neat) 3067 (C-H), 2945 (C-H), 1511 (C=N); δ_H (500 MHz, $CDCl_3$) 8.25-8.28 (1H, m, ArH), 7.90-7.93 (1H, m, ArH), 7.40-7.44 (2H, m, 2 × ArH), 6.84 (1H, d, *J* 4.0, ArH), 6.58 (1H, d, *J* 4.0, ArH), 2.97 (3H, s, CH_3), 2.70 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 153.5 (C), 137.2 (C), 129.7 (C), 129.1 (CH), 129.1 (C), 127.1 (C), 126.0 (CH), 124.6 (CH), 115.2 (CH), 114.8 (CH), 105.9 (CH), 21.7 (CH_3), 17.7 (CH_3); *m/z* (NSI) 197.1070 ($[M+H]^+$, $C_{13}H_{13}N_2$ requires 197.1073).

1,4-Dimethyl-7-(trifluoromethyl)pyrrolo[1,2-*a*]quinoxaline (6b)



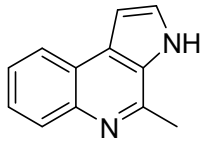
Isocyanide (0.09 g, 0.38 mmol), $FeCl_3$ (0.012 g, 0.08 mmol), 30% w/w H_2O_2 (0.12 mL, 1.14 mmol) and DMSO (4.8 mL) were used to afford the *title compound* (71.5 mg, 71%) as a yellow solid; m.p. 143-144 °C; ν_{max}/cm^{-1} (neat) 3104 (C-H), 2889 (C-H), 1534 (C=N); δ_H (500 MHz, $CDCl_3$) 8.33 (1H, d, *J* 8.8, ArH), 8.19 (1H, d, *J* 1.6, ArH), 7.64 (1H, dd, *J* 8.8, 1.9, ArH), 6.91 (1H, d, *J* 4.1, ArH), 6.64 (1H, d, *J* 3.8, ArH), 2.98 (3H, s, CH_3), 2.72 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 155.0 (C), 137.0 (C), 131.7 (C), 129.7 (C), 127.2 (C), 126.7 (q, *J* 33.6, C), 126.6 (q, *J* 4.5, CH), 124.0 (q, *J* 271.6, C),122.3 (q, *J* 3.6, CH), 115.7 (CH), 115.7 (CH), 106.9 (CH), 21.8 (CH_3) , 17.7 (CH_3); *m/z* (NSI) 265.0948 ($[M+H]^+$, $C_{14}H_{12}F_3N_2$ requires 265.0947).

1,4,7-Trimethylpyrrolo[1,2-*a*]quinoxaline (6f)



Isocyanide (0.08 g, 0.44 mmol), $FeCl_3$ (0.014 g, 0.09 mmol), 30% w/w H_2O_2 (0.13 mL, 1.32 mmol) and DMSO (5.5 mL) were used to afford the *title compound* (77.5 mg, 84%) as a yellow solid; m.p. 139-141 °C; ν_{max}/cm^{-1} (neat) 3064 (C-H), 2944 (C-H), 1531 (C=N); δ_H (500 MHz, $CDCl_3$) 8.14 (1H, d, *J* 8.5, ArH), 7.71 (1H, s, ArH), 7.23 (1H, dd, *J* 8.7, 1.7, ArH), 6.82 (1H, d, *J* 3.8, ArH), 6.55 (1H, d, *J* 3.8, ArH), 2.95 (3H, s, CH_3), 2.69 (3H, s, CH_3), 2.48 (3H, s, CH_3); δ_C (126 MHz, $CDCl_3$) 153.5 (C), 137.2 (C), 134.3 (C), 129.1 (CH), 128.8 (2 × C), 127.5 (C), 127.0 (CH), 115.0 (CH), 114.5 (CH), 105.7 (CH), 21.7 (CH_3), 20.9 (CH_3), 17.7 (CH_3); *m/z* (NSI) 211.1228 ($[M+H]^+$, $C_{14}H_{15}N_2$ requires 211.1230).

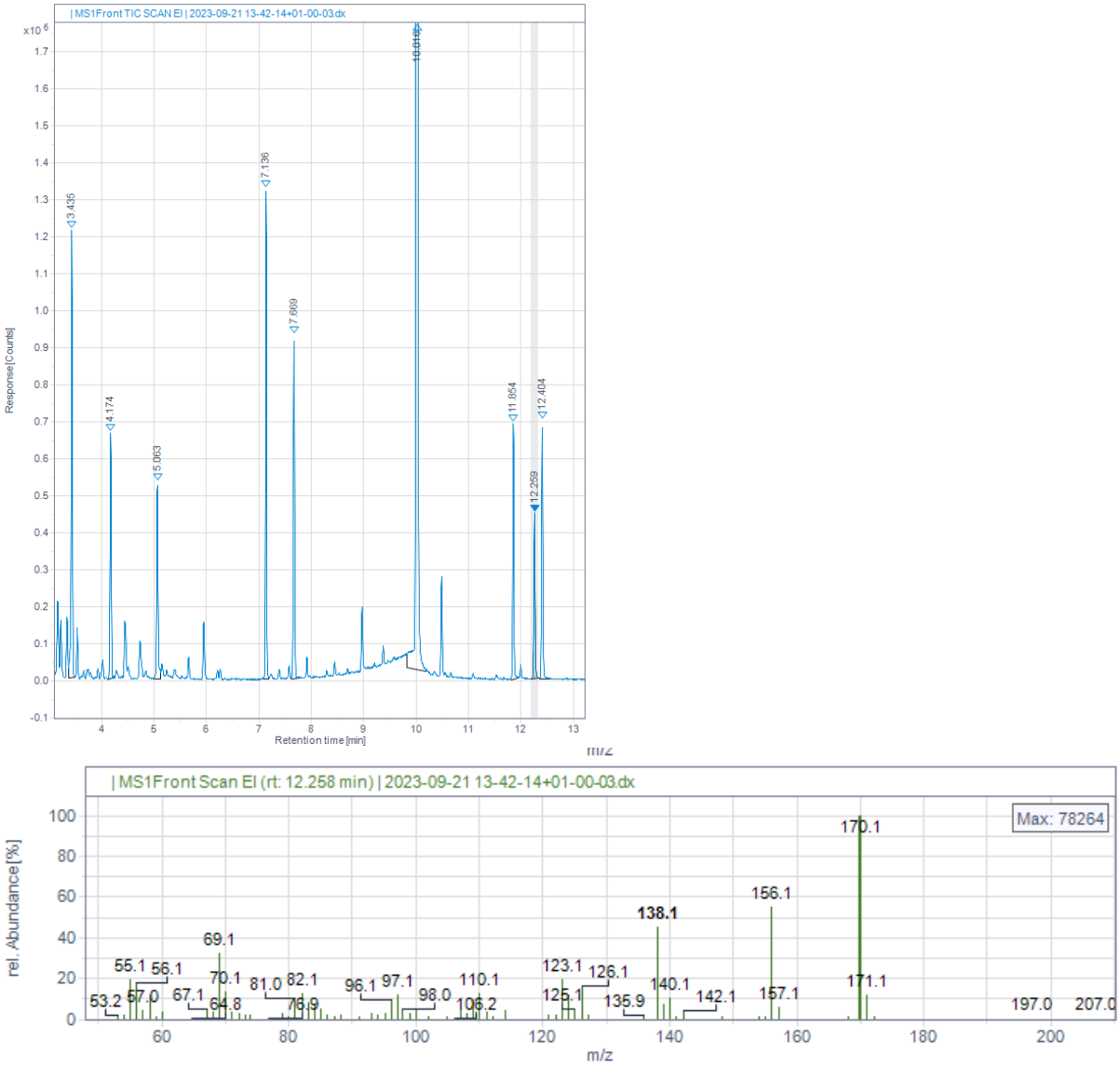
Marinoquinoline A[15]



A solution of *tert*-butyl 4-methyl-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (0.80 g, 0.28 mmol) in CH_2Cl_2 (10 mL) was treated with trifluoroacetic acid (1.10 mL, 14.2 mmol) and stirred overnight at room temperature. The reaction was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and neutralised with a saturated aqueous Na_2CO_3 (pH 7). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 Hex:EtOAc) give the *title compound* (0.45 g, 88%) as a colourless

solid; m.p. 236-238 °C; ν_{max} (neat) 3085 (NH), 2956 (CH); δ_H (500 MHz, acetone-d_6) 11.22 (1H, br. s, NH), 8.20-8.24 (1H, m, ArH), 8.00 (1H, dd, *J* 8.0, 1.7, ArH), 7.58 (1H, d, *J* 2.8, ArH), 7.47-7.54 (2H, m, 2 × ArH), 7.12 (1H, d, *J* 2.8, ArH), 2.83 (3H, s, CH_3); δ_C (126 MHz, acetone-d_6) 147.0 (C), 143.8 (C), 129.9 (CH), 129.8 (C), 128.4 (C),127.2 (CH), 126.1 (CH), 125.7 (CH), 124.2 (CH), 123.8 (CH), 102.0 (CH), 21.3 (CH_3); *m/z* (NSI) 183.0914 ($[M+H]^+$, $C_{12}H_{11}N_2$ requires 183.0917).

GCMS for radical trapping experiment



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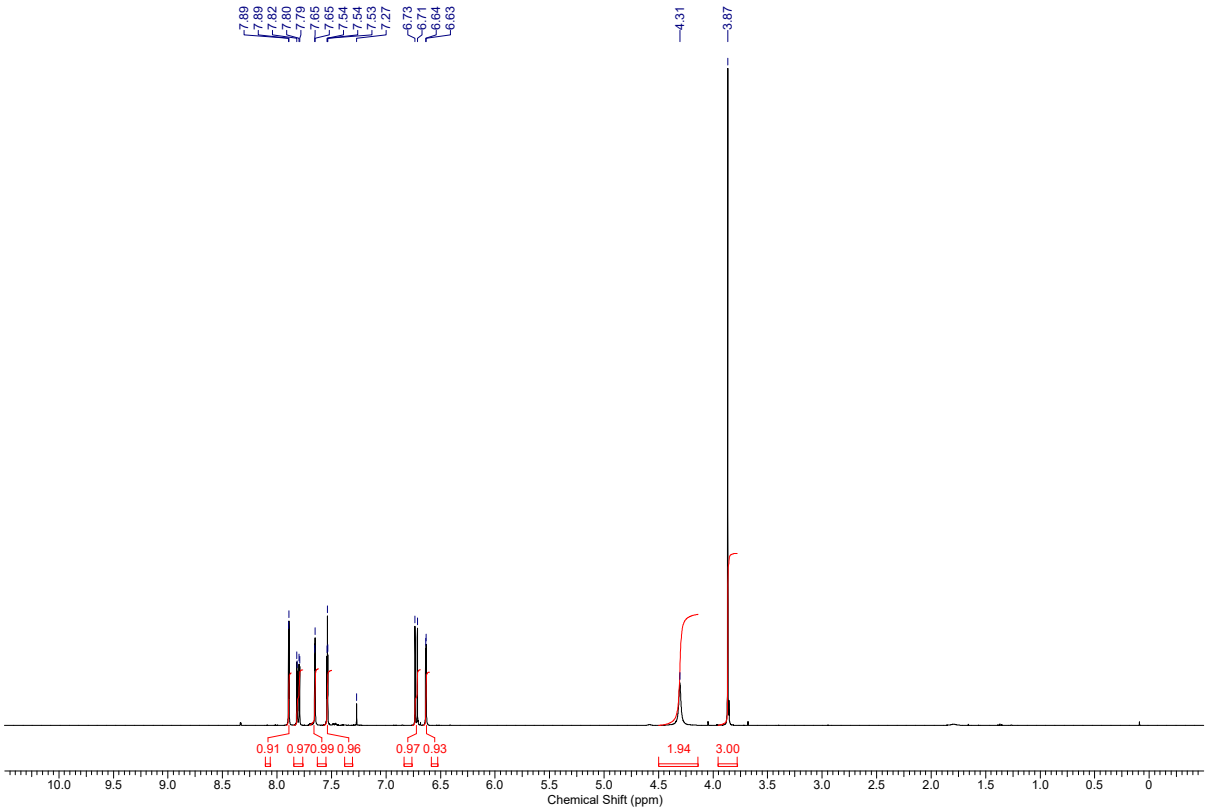
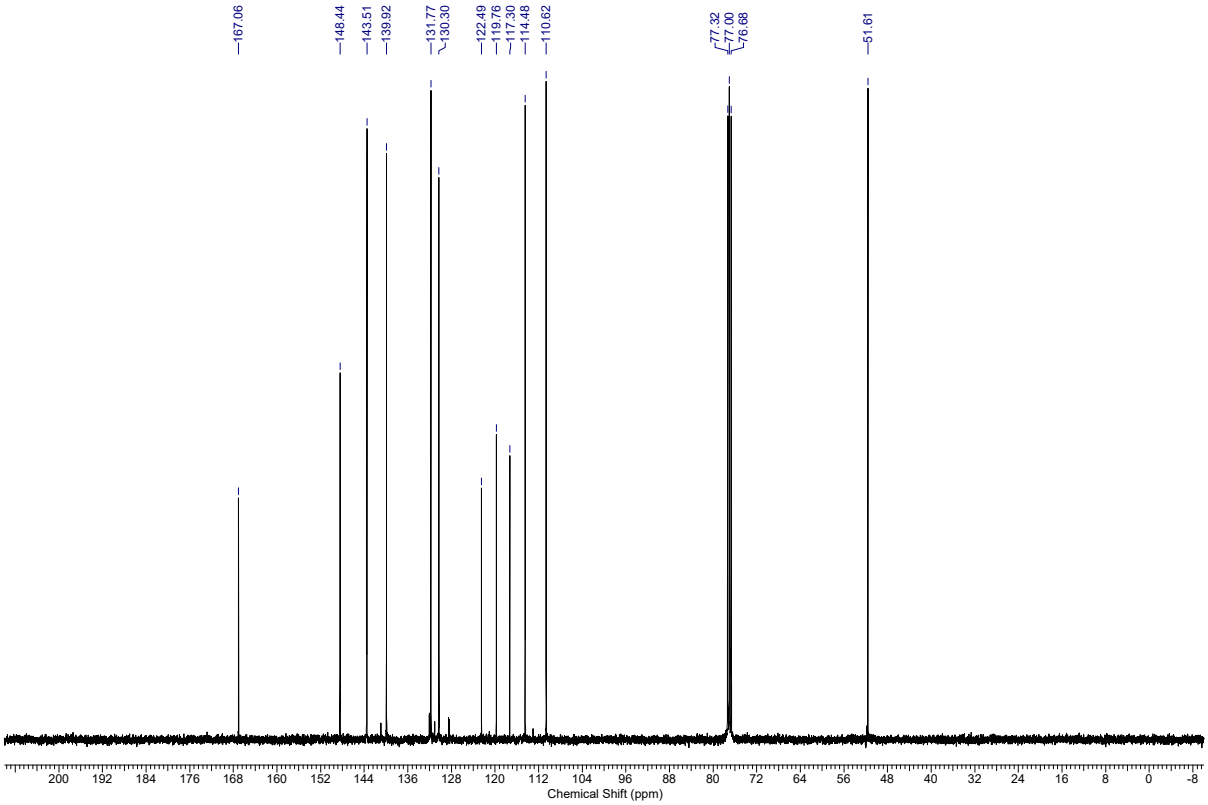
Methyl 4-amino-3-(furan-3-yl)benzoate (2h)





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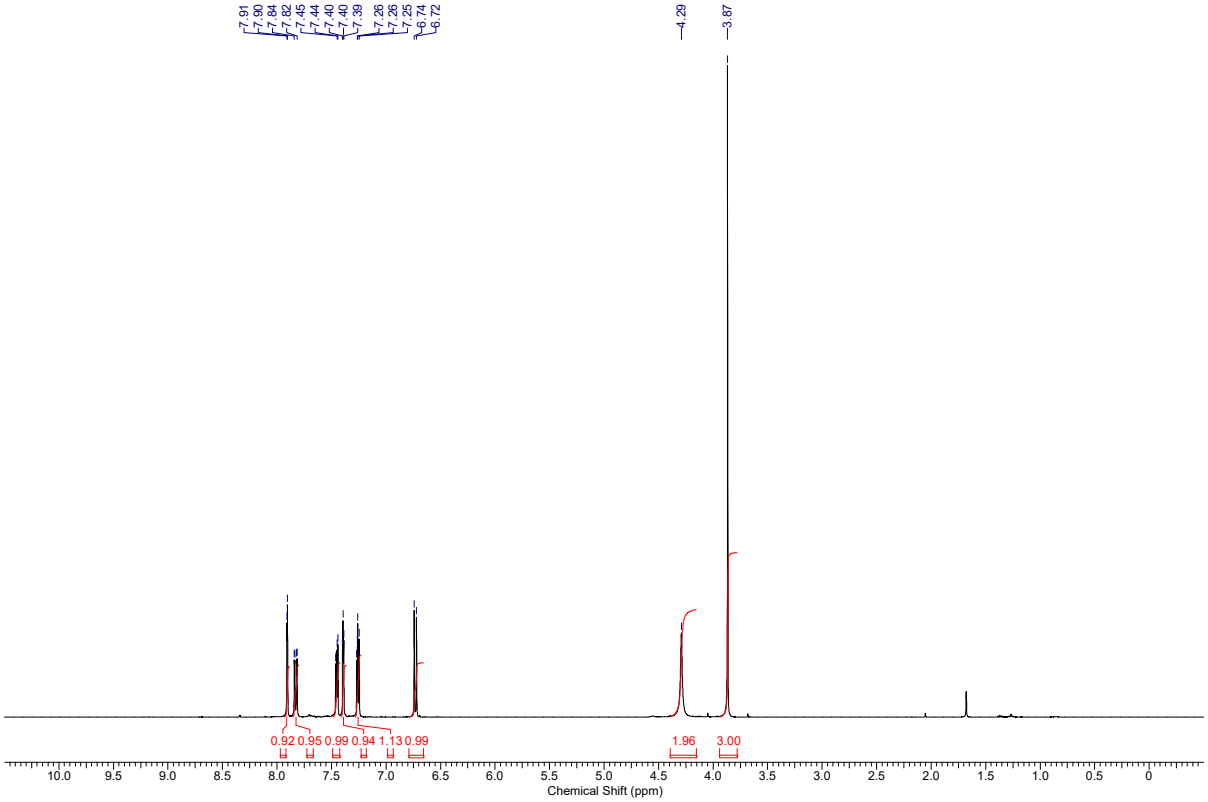

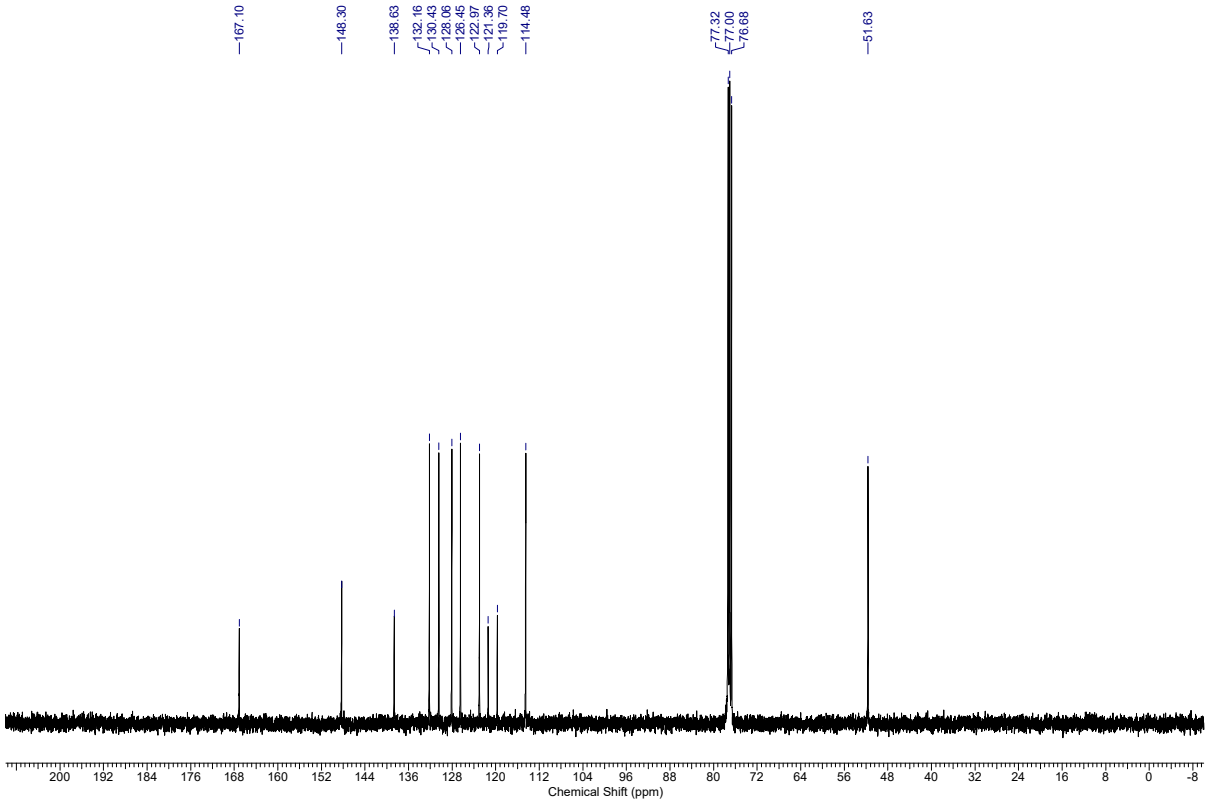

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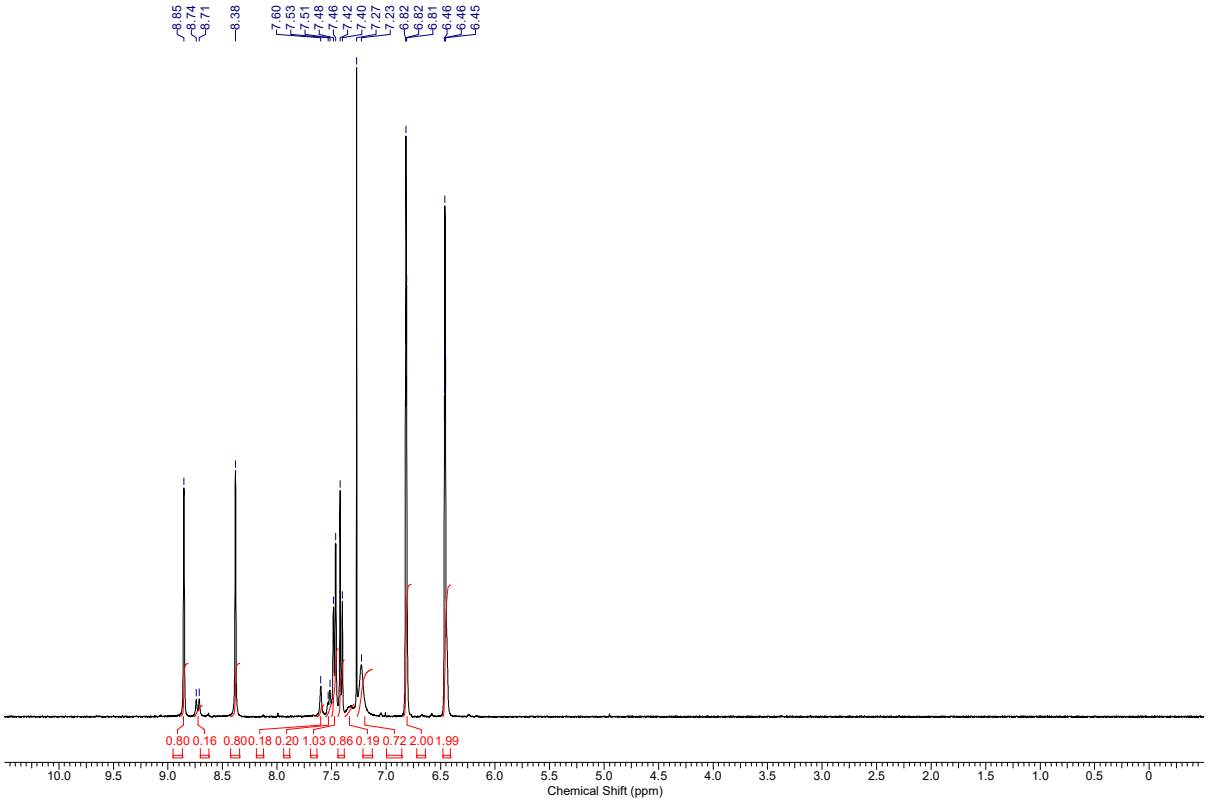

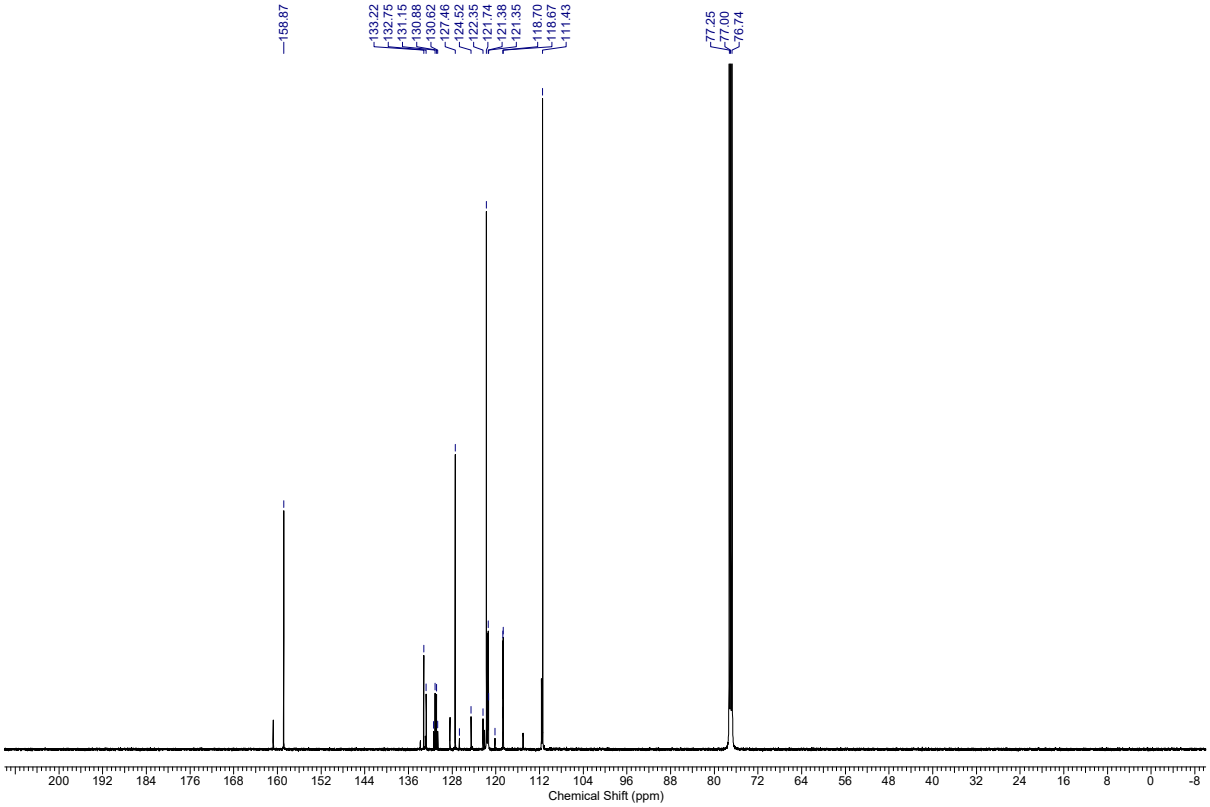

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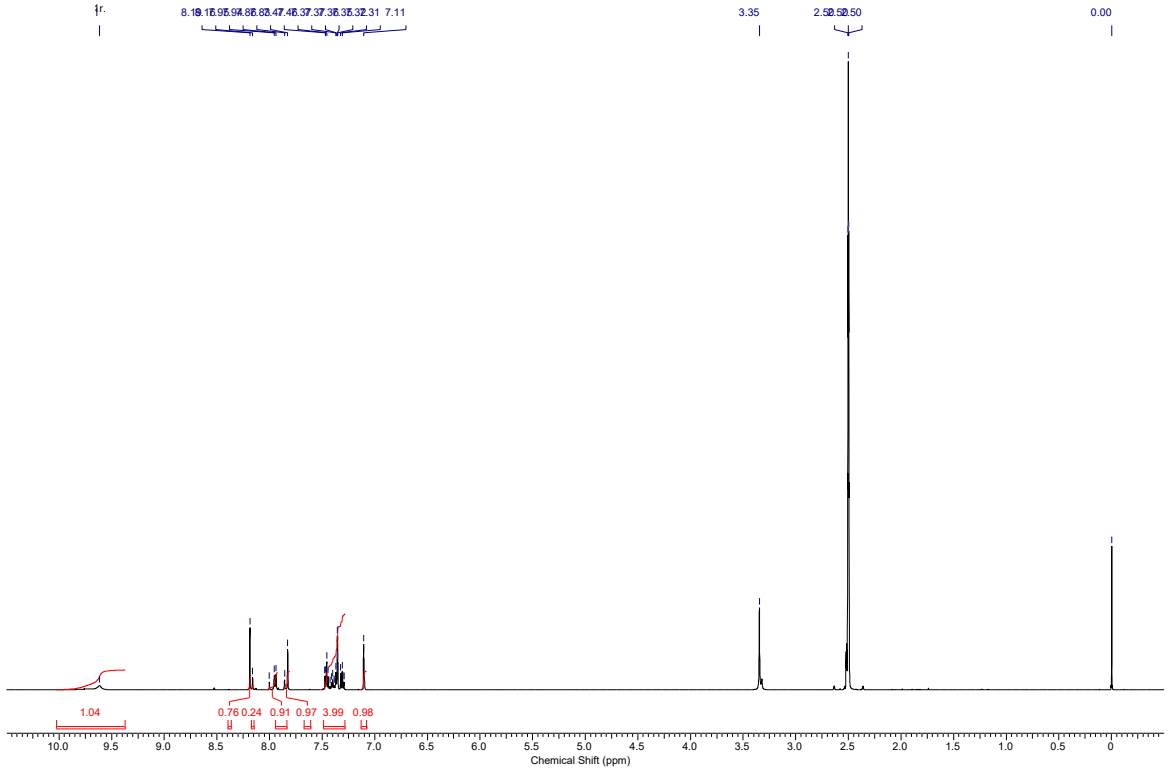

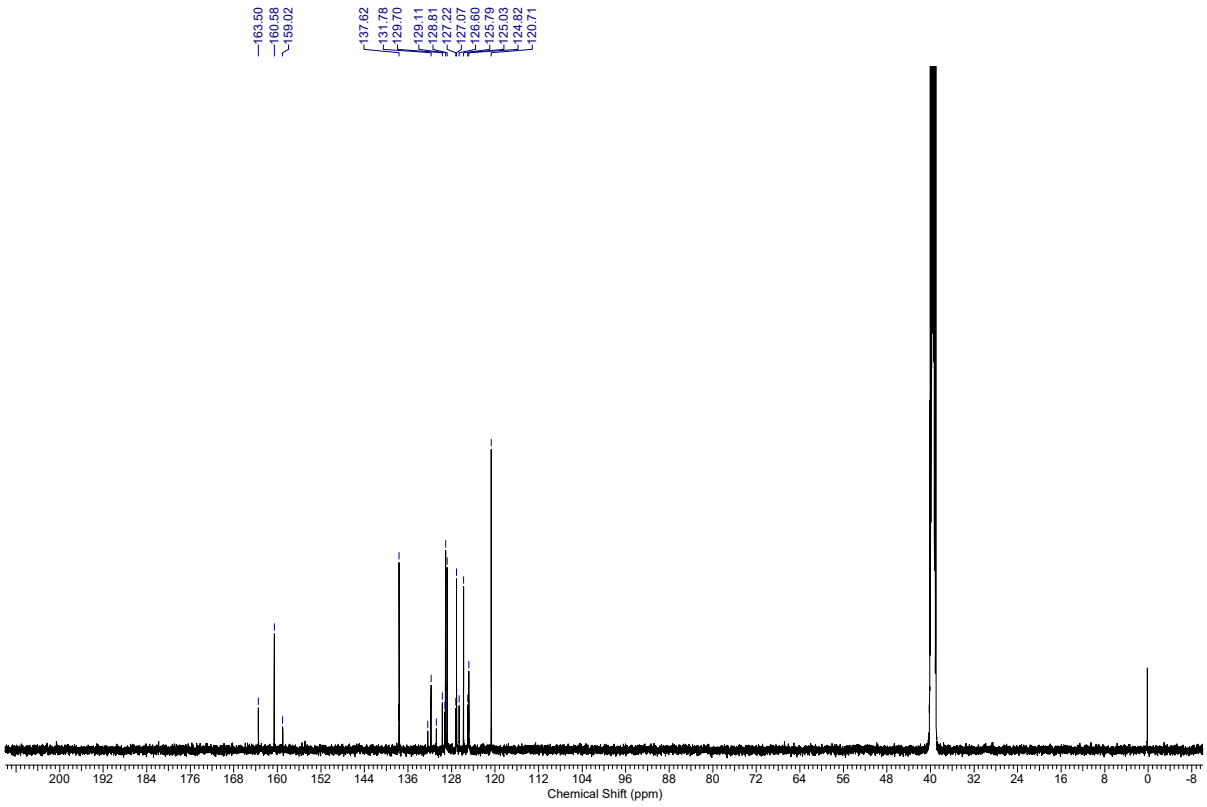

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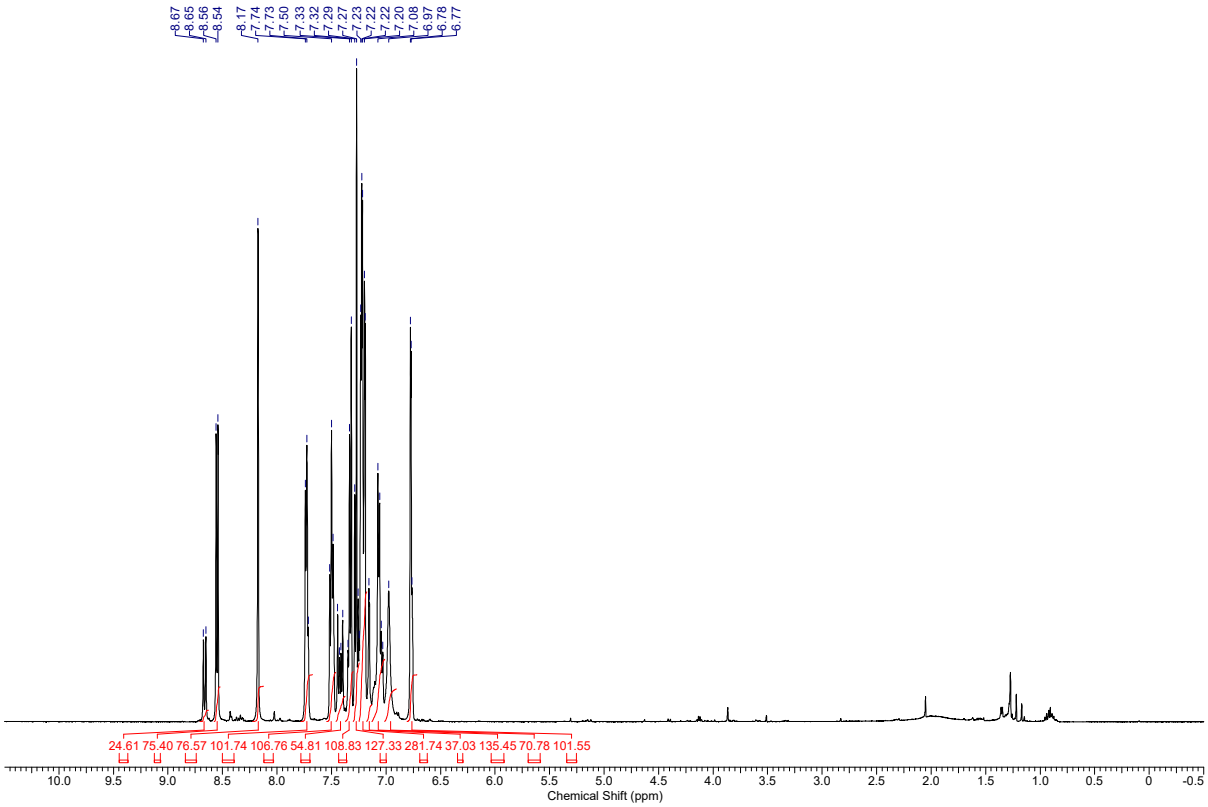

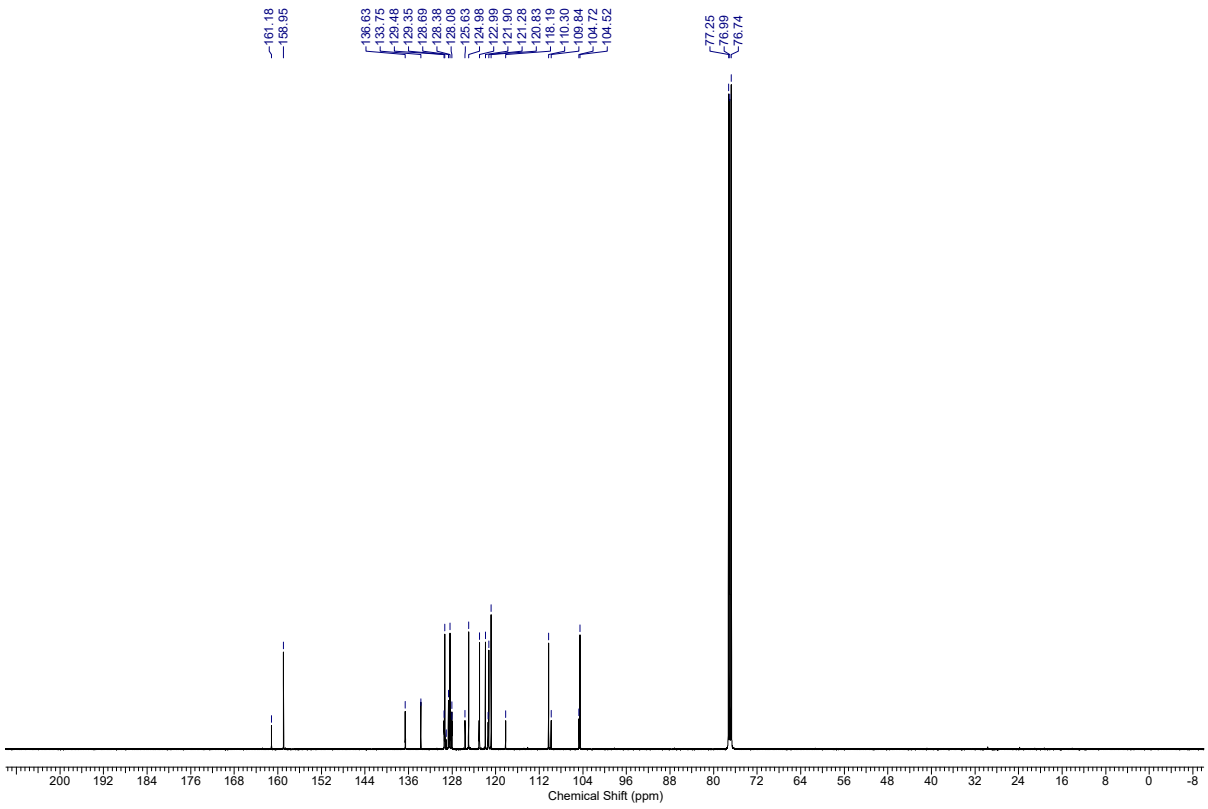

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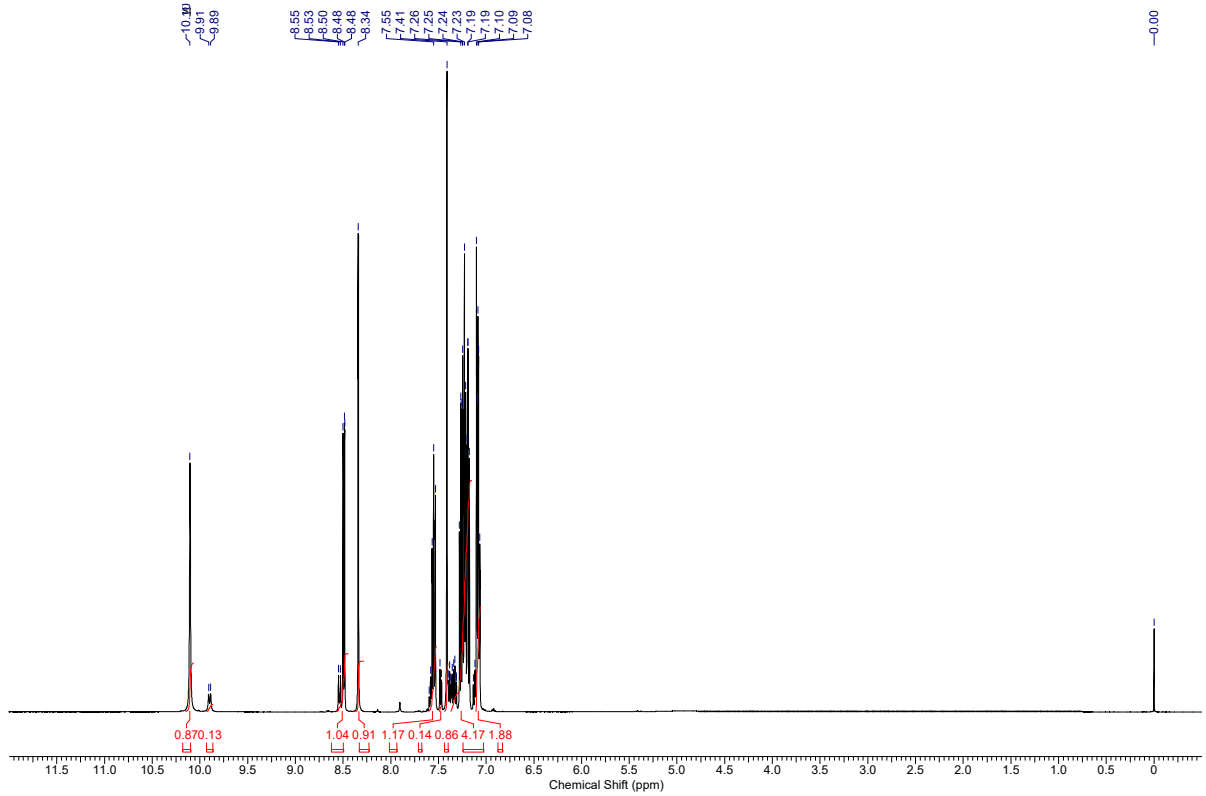
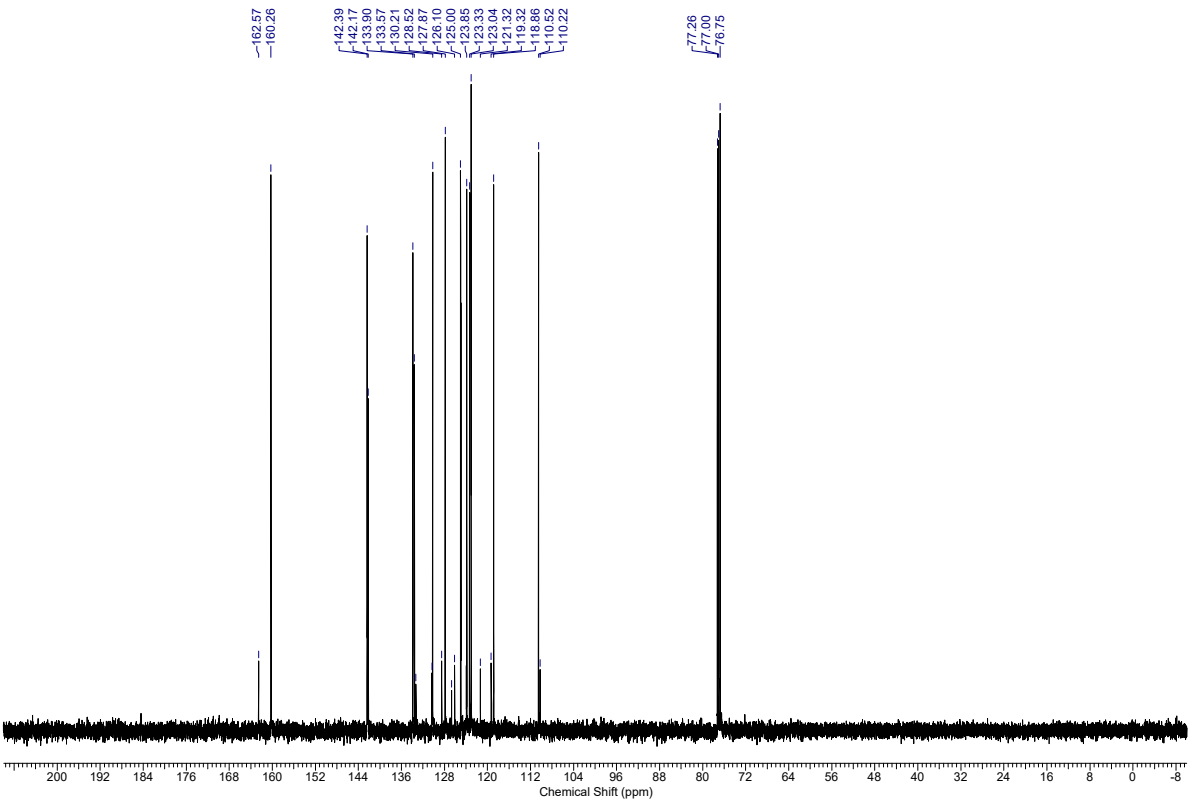
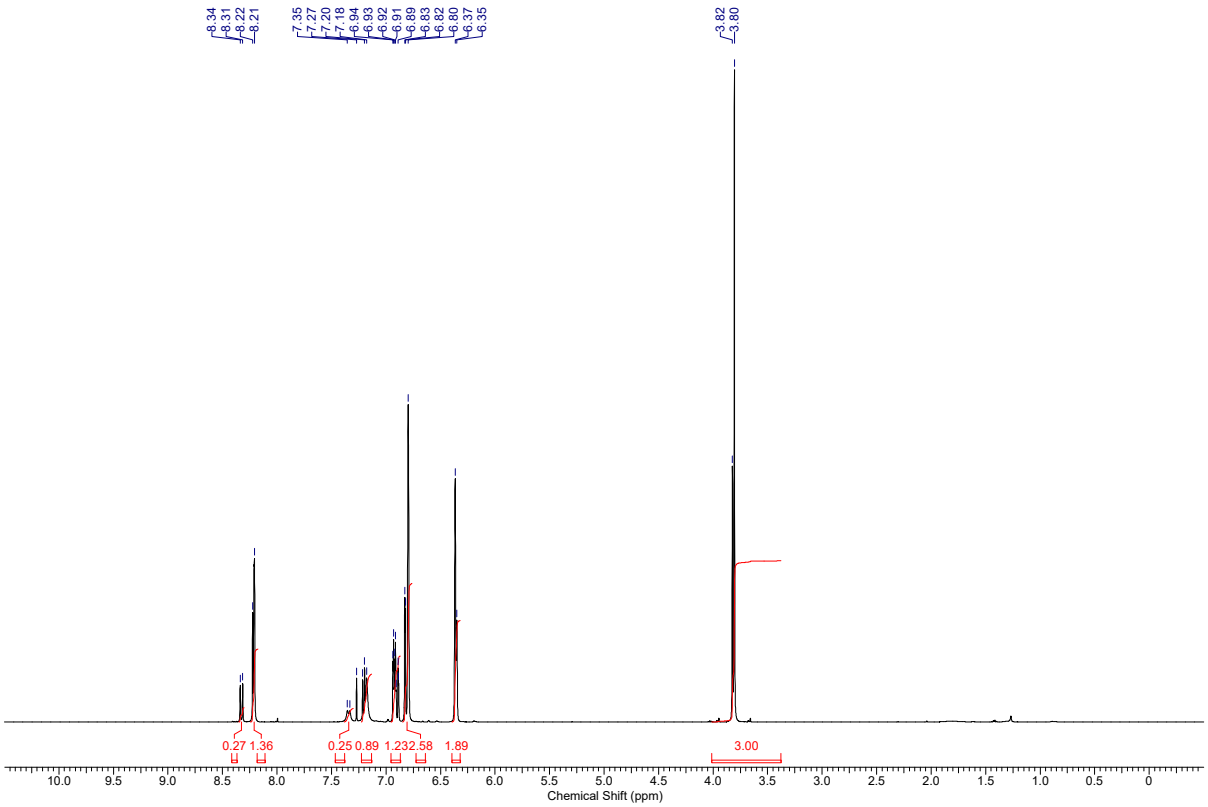
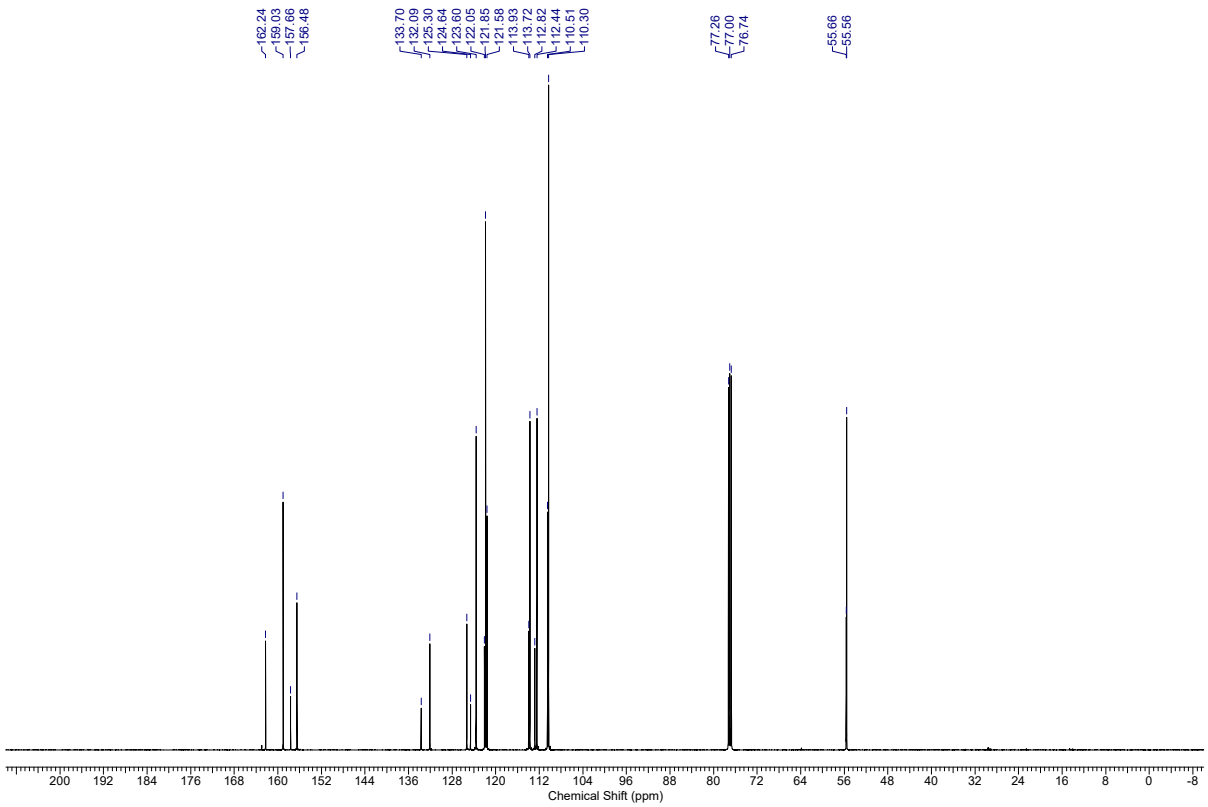


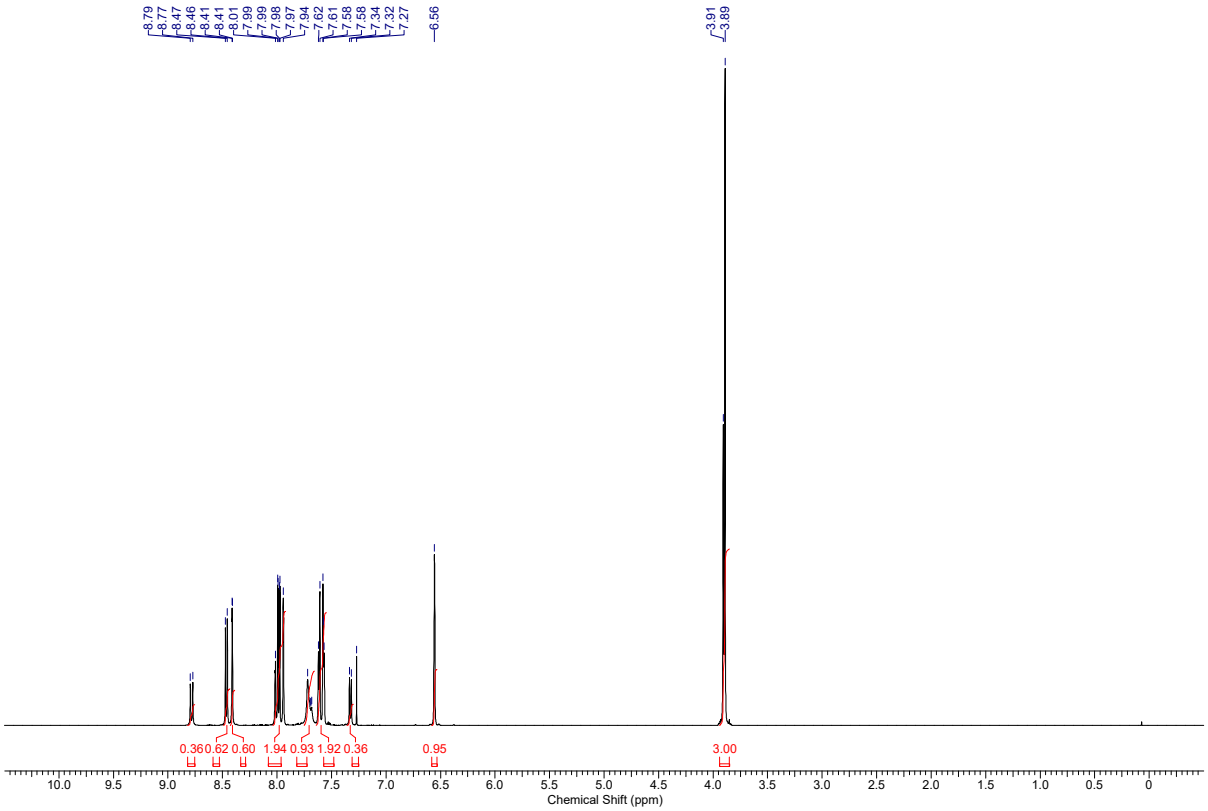


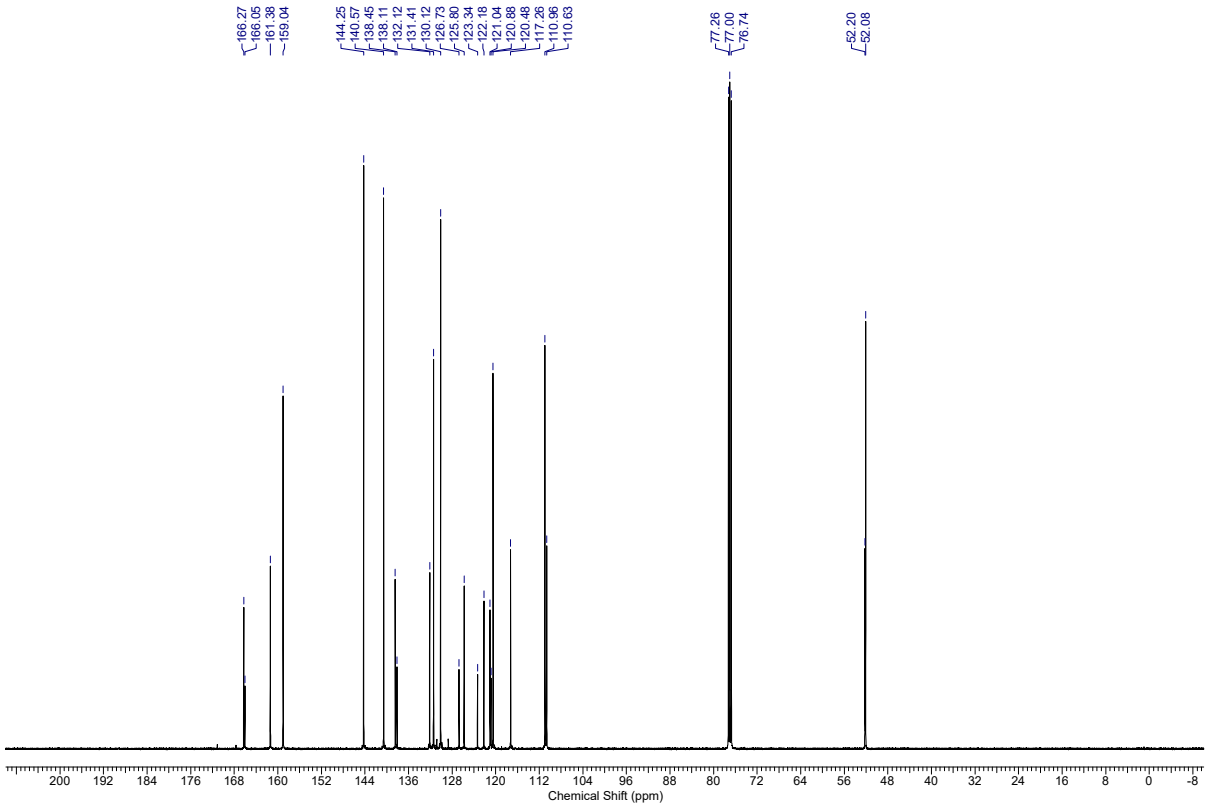
N-(4-Methoxy-2-(1*H*-pyrrol-1-yl)phenyl)formamide (3f)



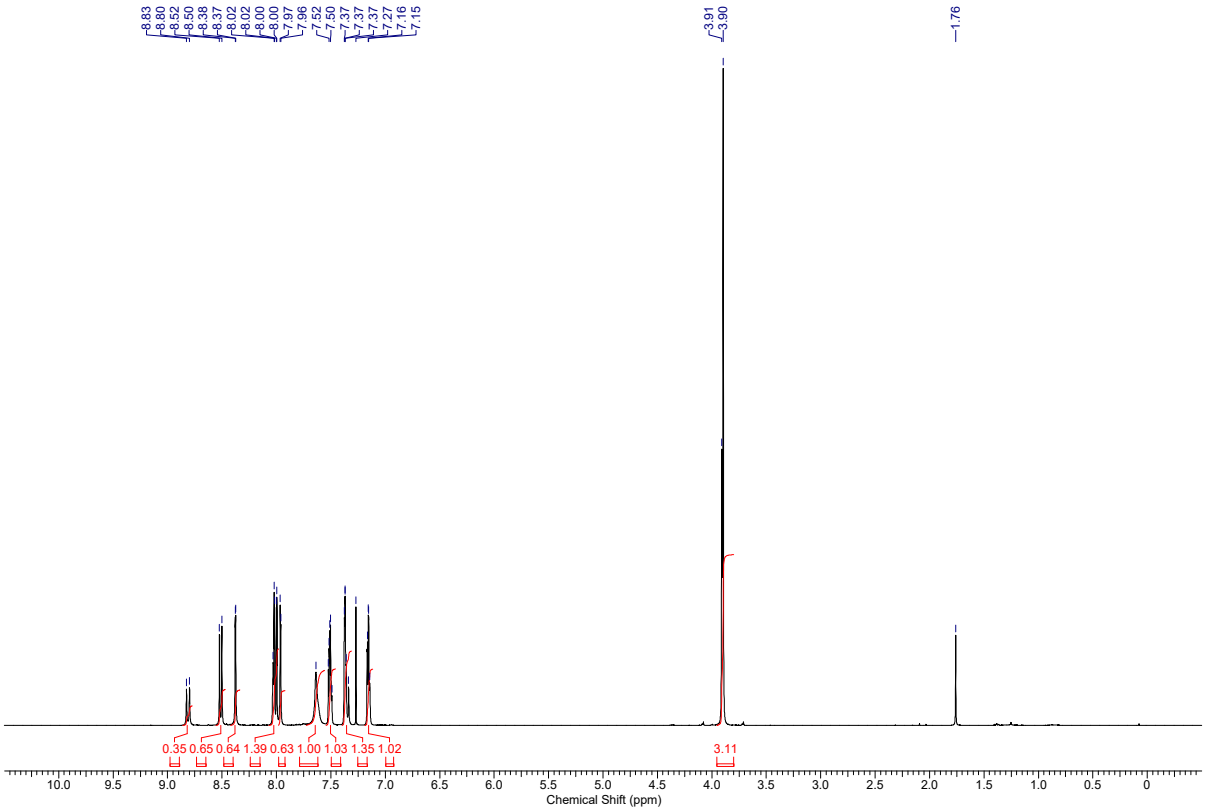


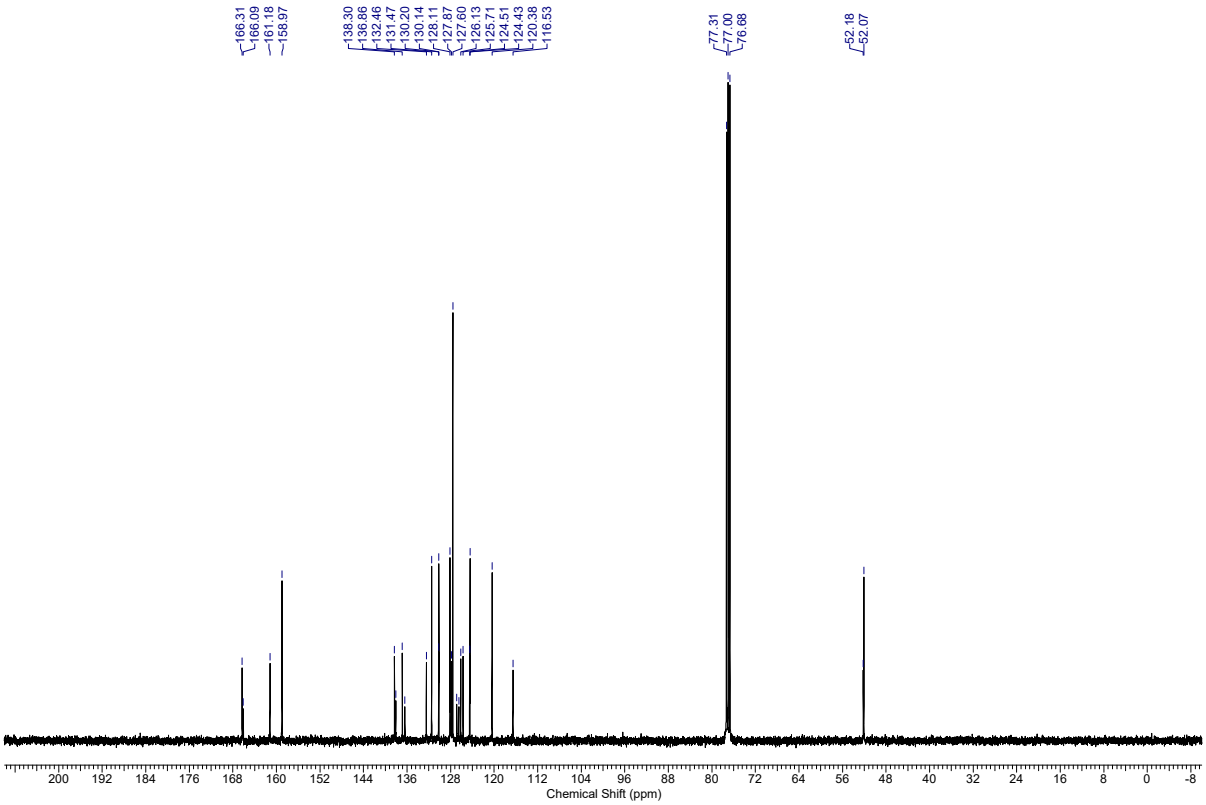
Methyl 4-formamido-3-(furan-3-yl)benzoate (3h)



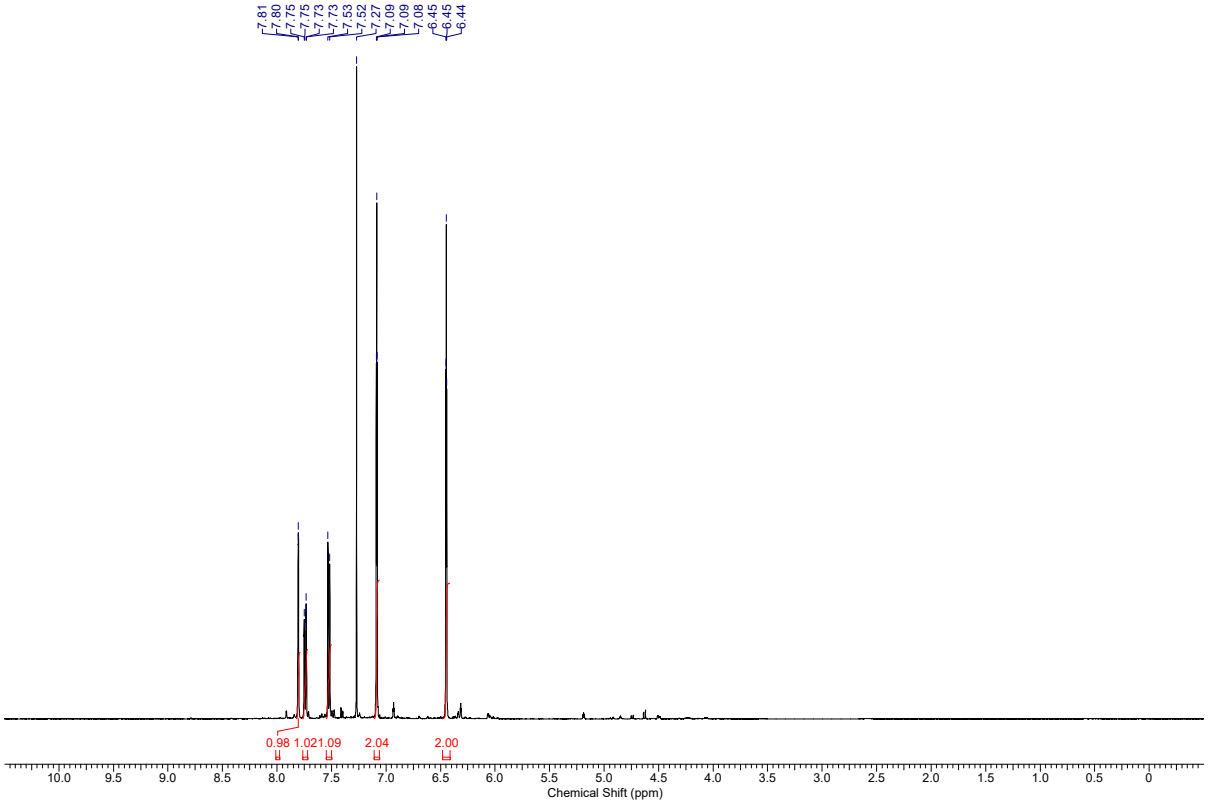


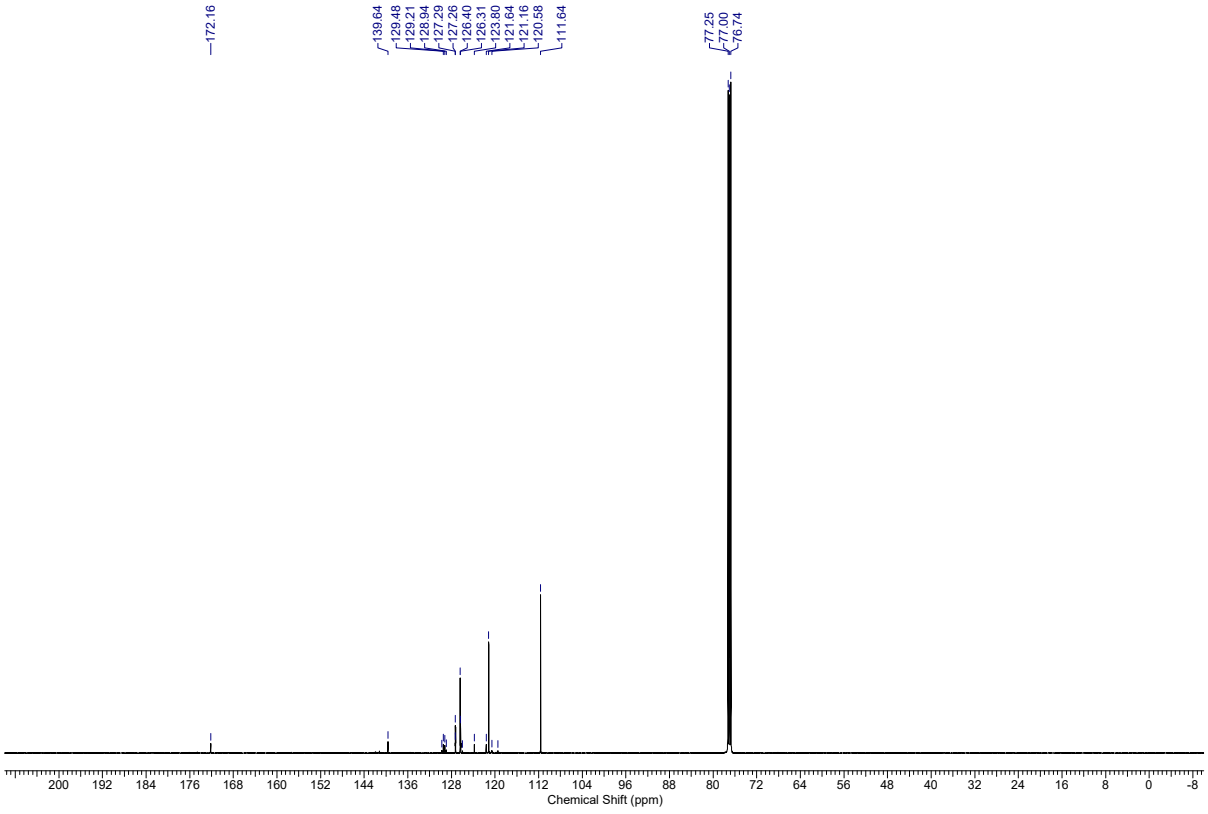
Methyl 4-formamido-3-(thiophen-3-yl)benzoate (3i)



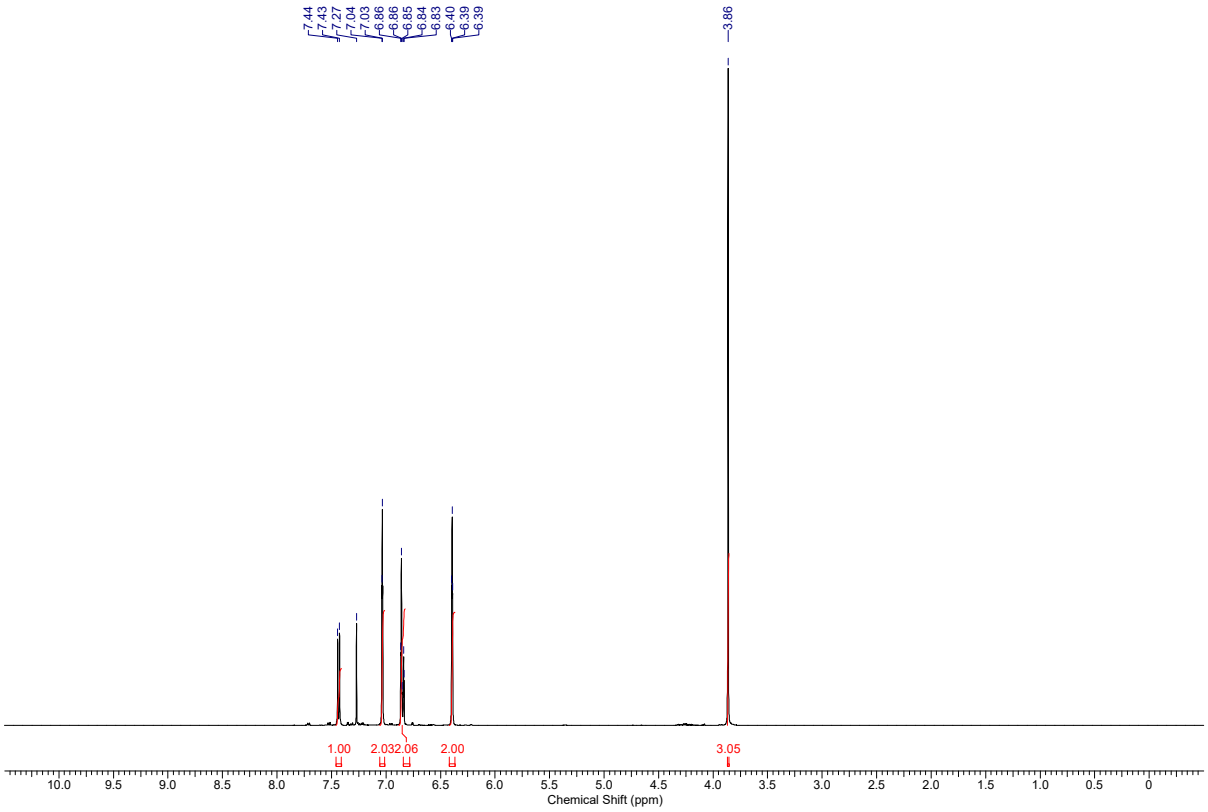


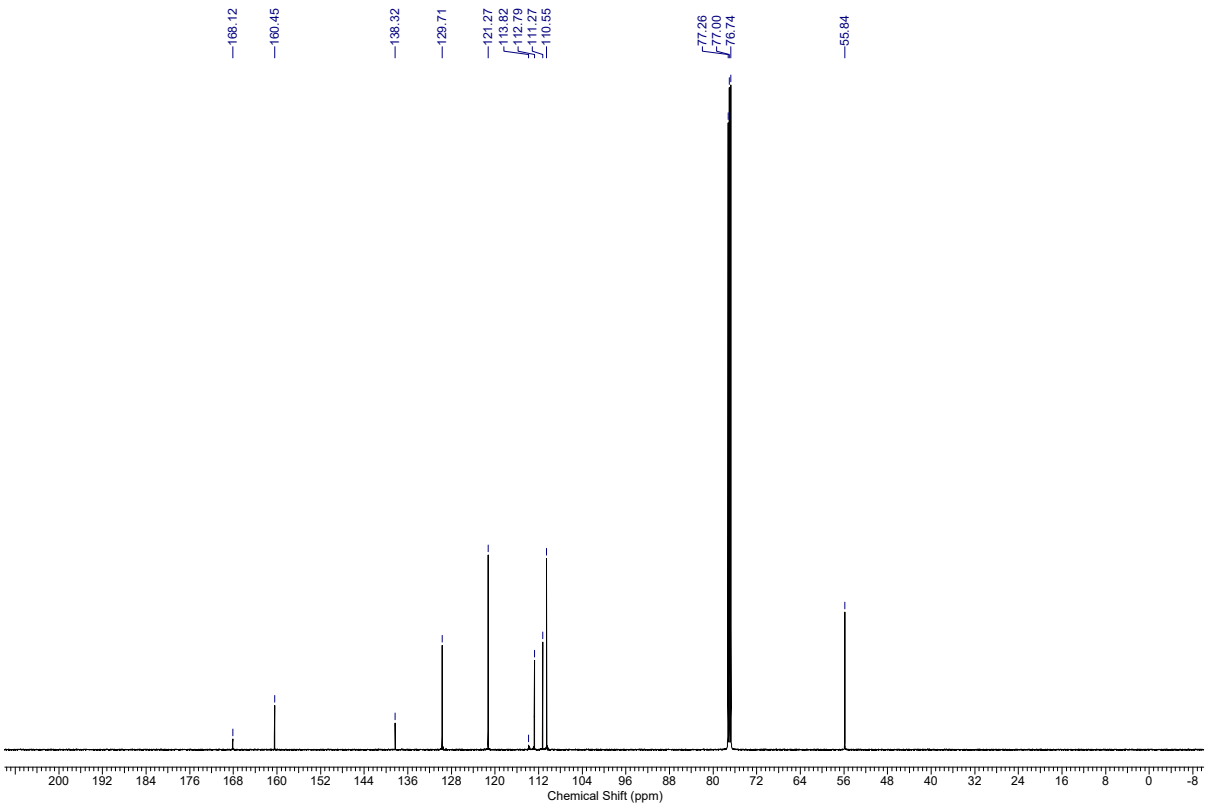
1-(2-Isocyano-4-(trifluoromethyl)phenyl)-1*H*-pyrrole (4b)



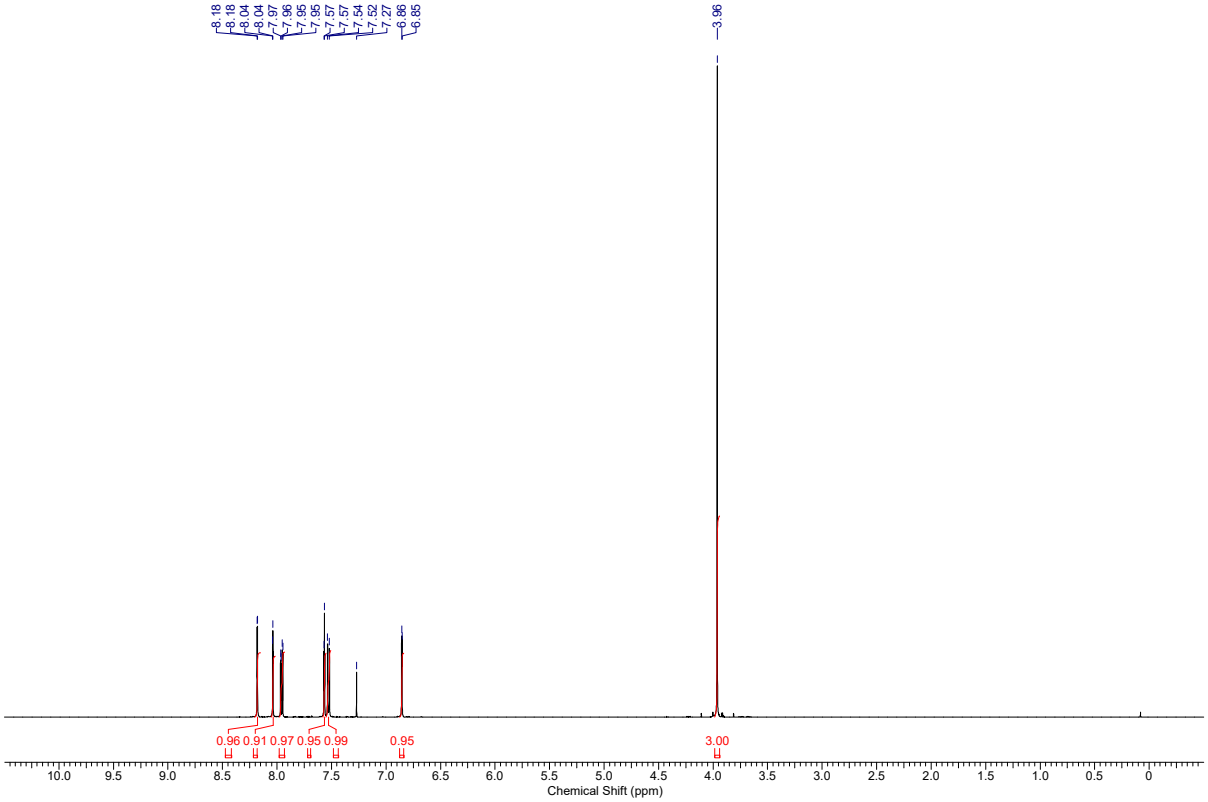


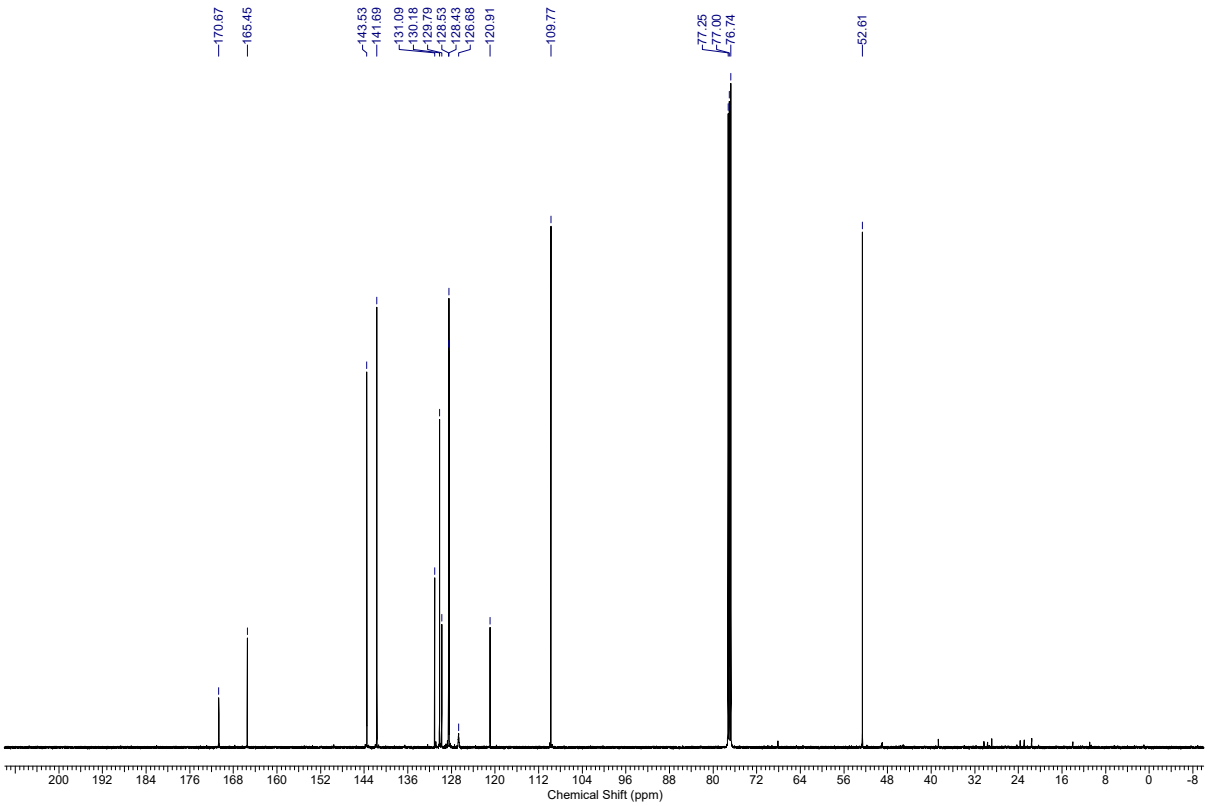
1-(2-Isocyano-5-methoxyphenyl)-1*H*-pyrrole (4g)



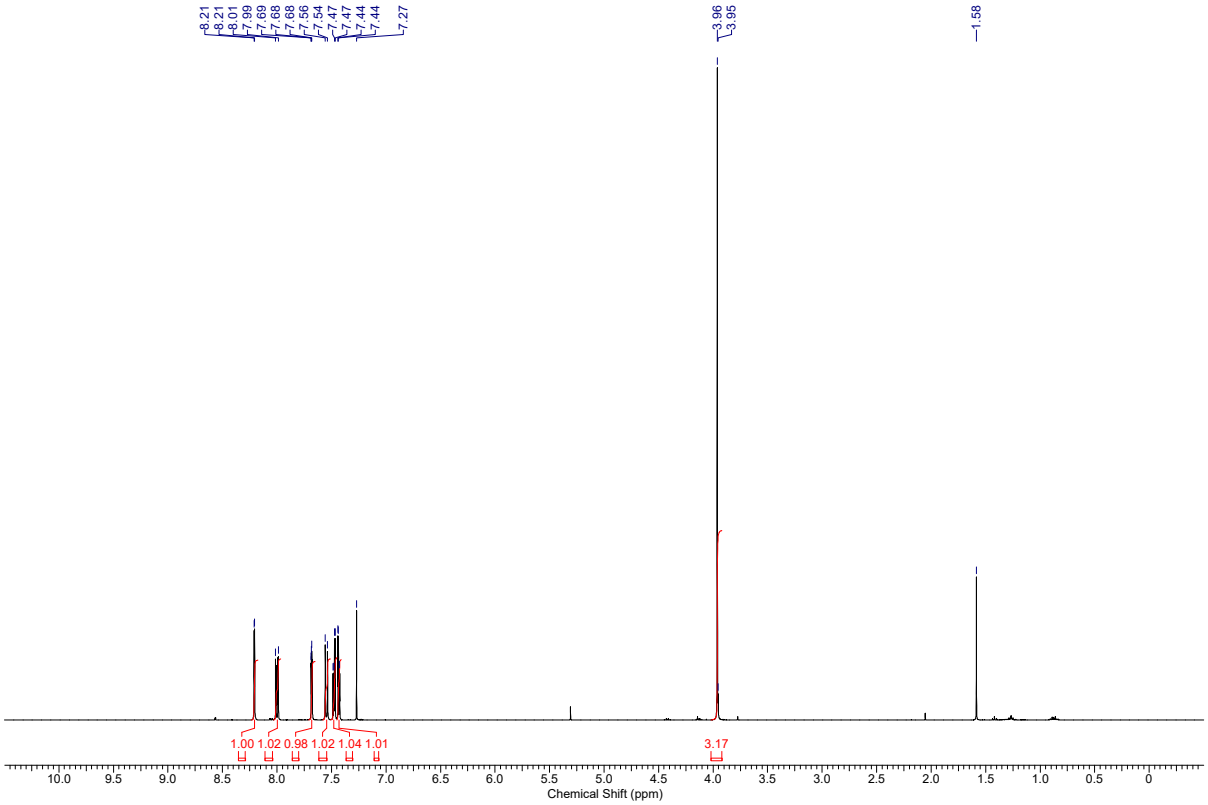


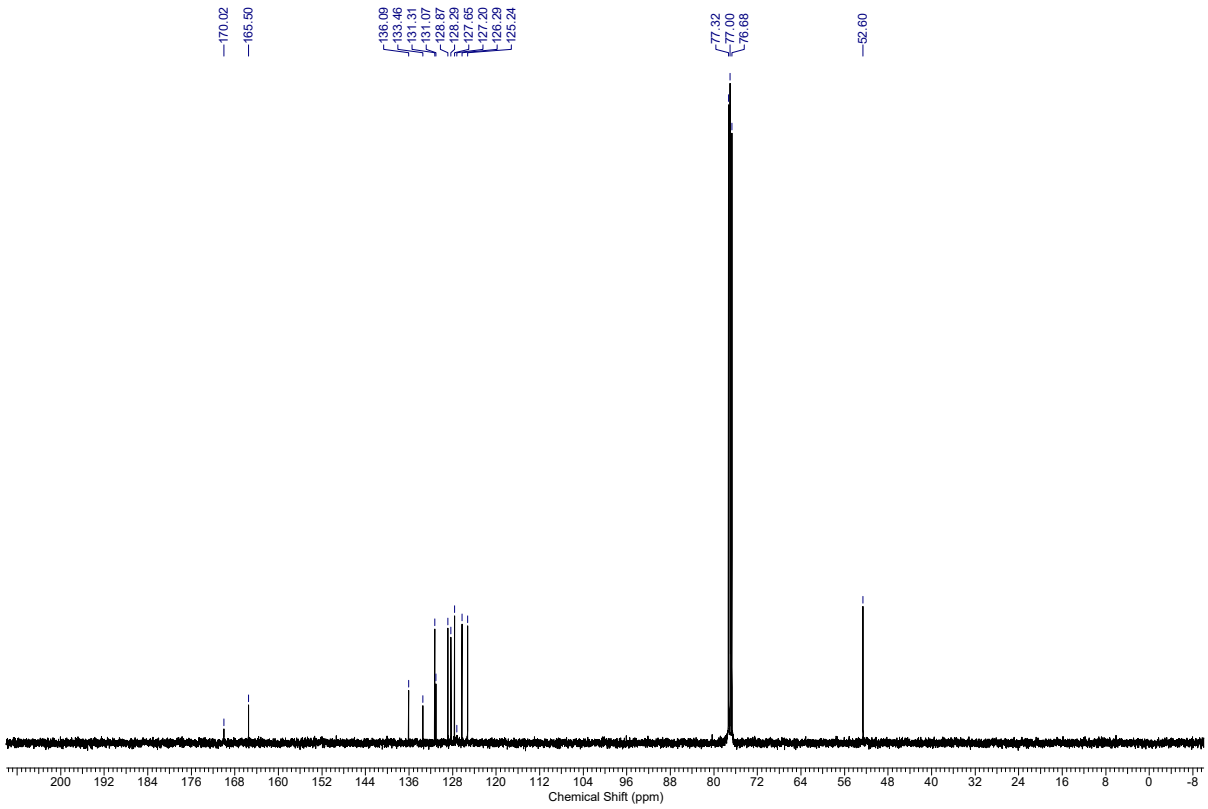
Methyl 3-(furan-3-yl)-4-isocyanobenzoate (4h)



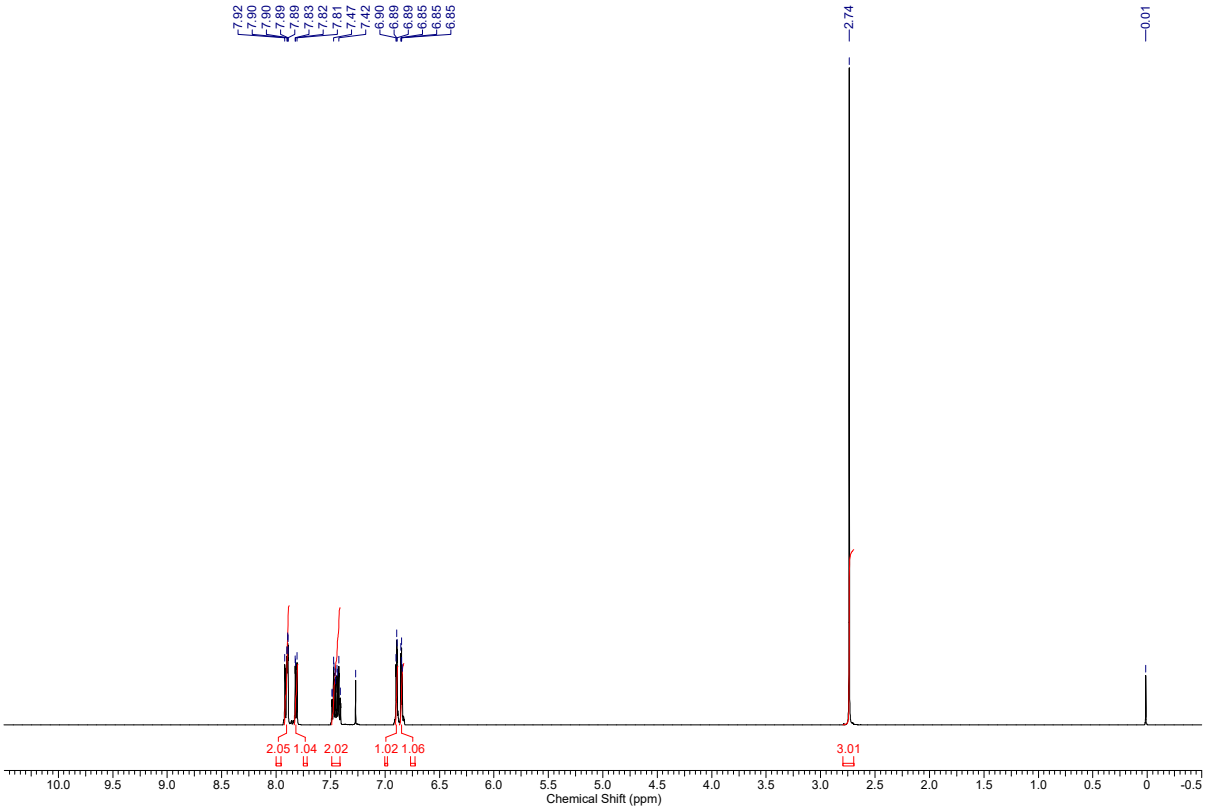


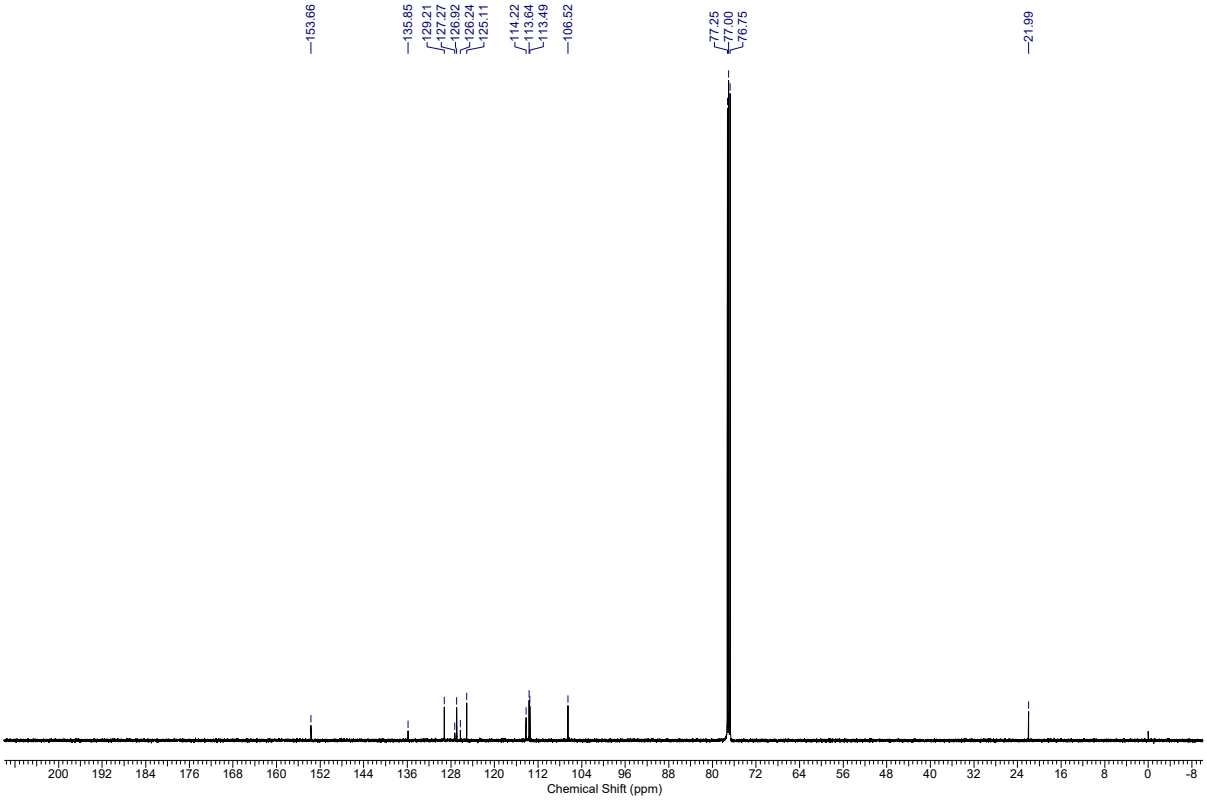
Methyl 4-isocyano-3-(thiophen-3-yl)benzoate (4i)



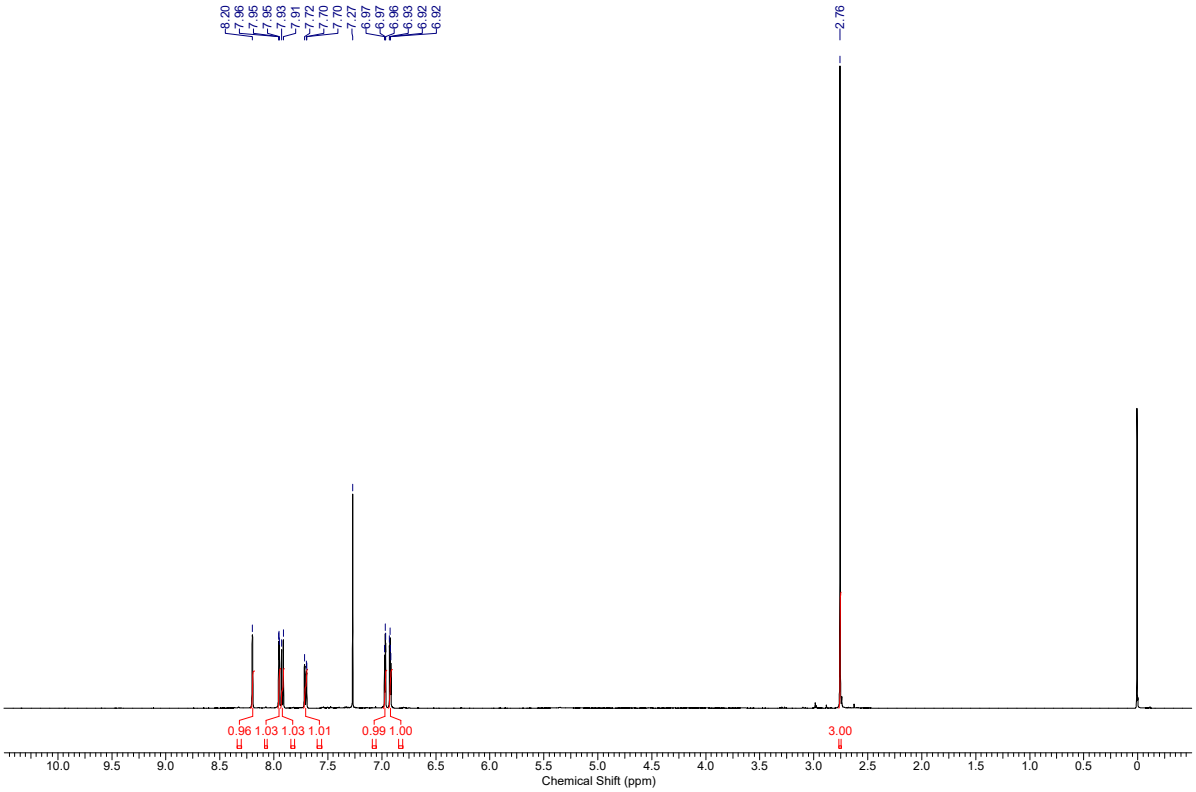


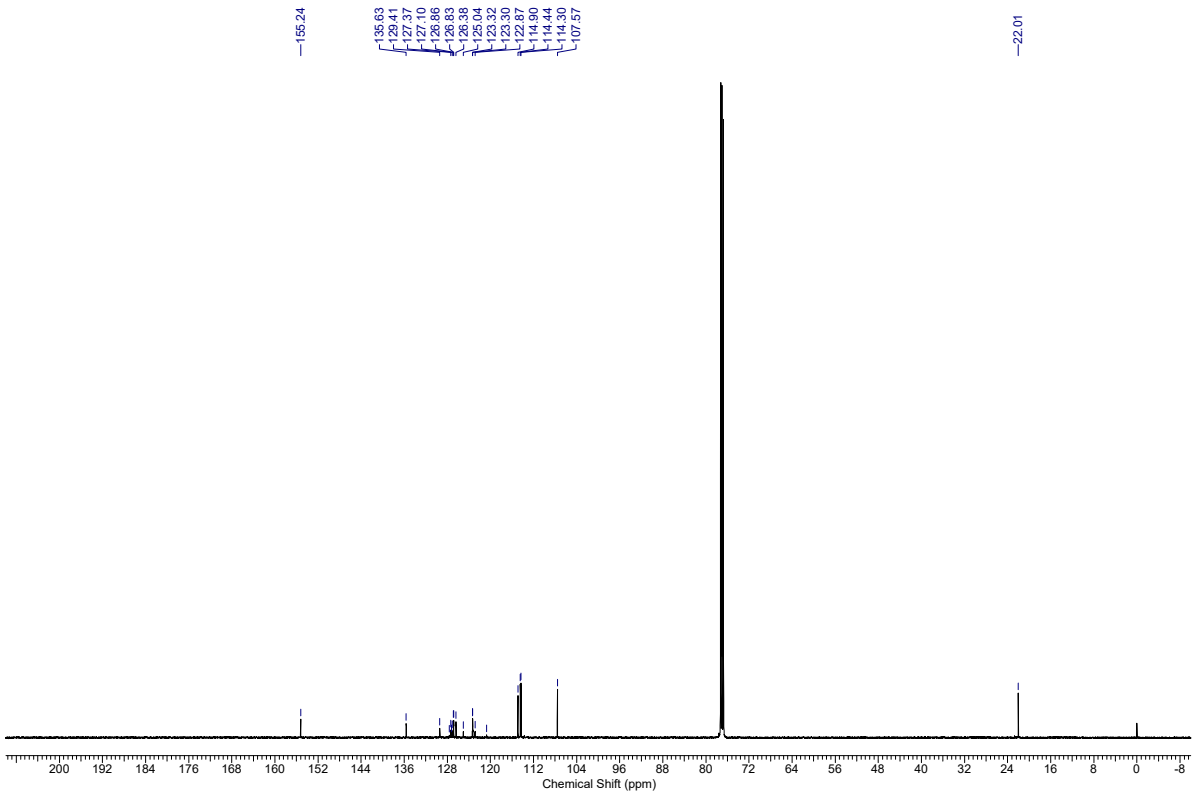
4-Methylpyrrolo[1,2-*a*]quinoxaline (5a)



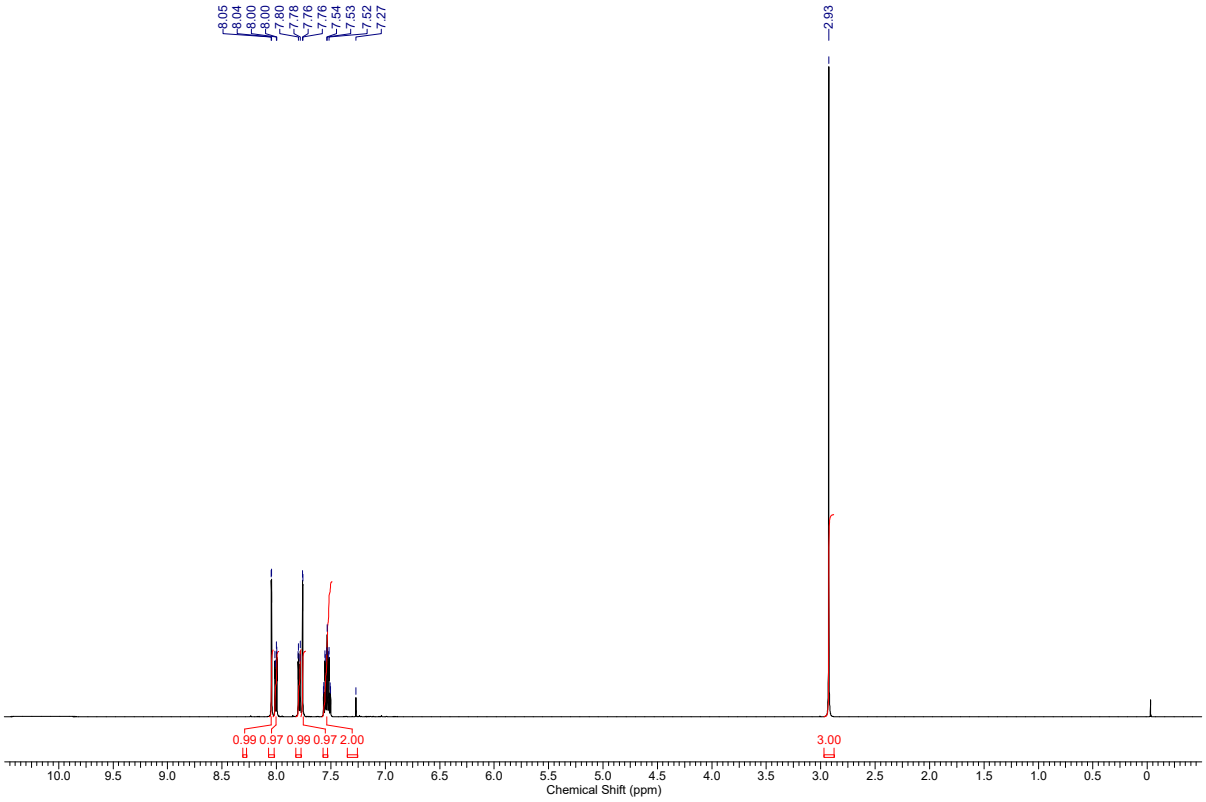


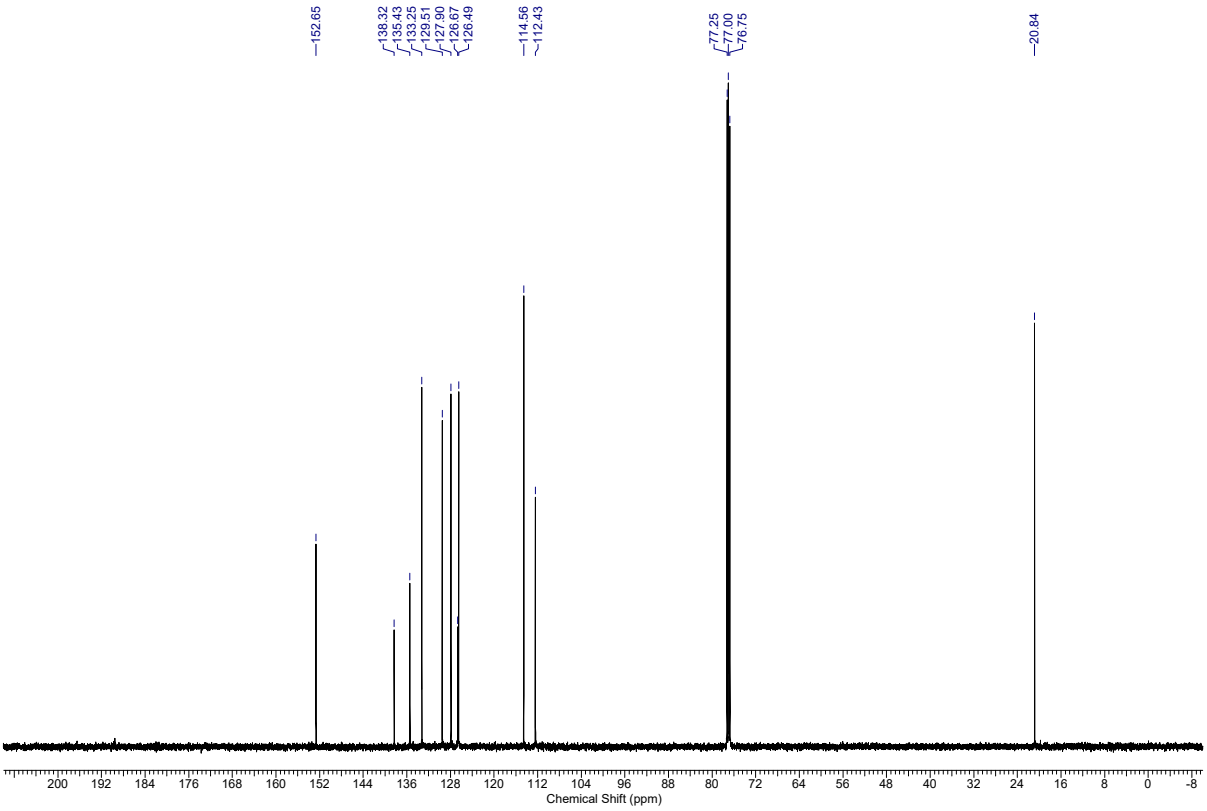
4-Methyl-7-(trifluoromethyl)pyrrolo[1,2-*a*]quinoxaline (5b)



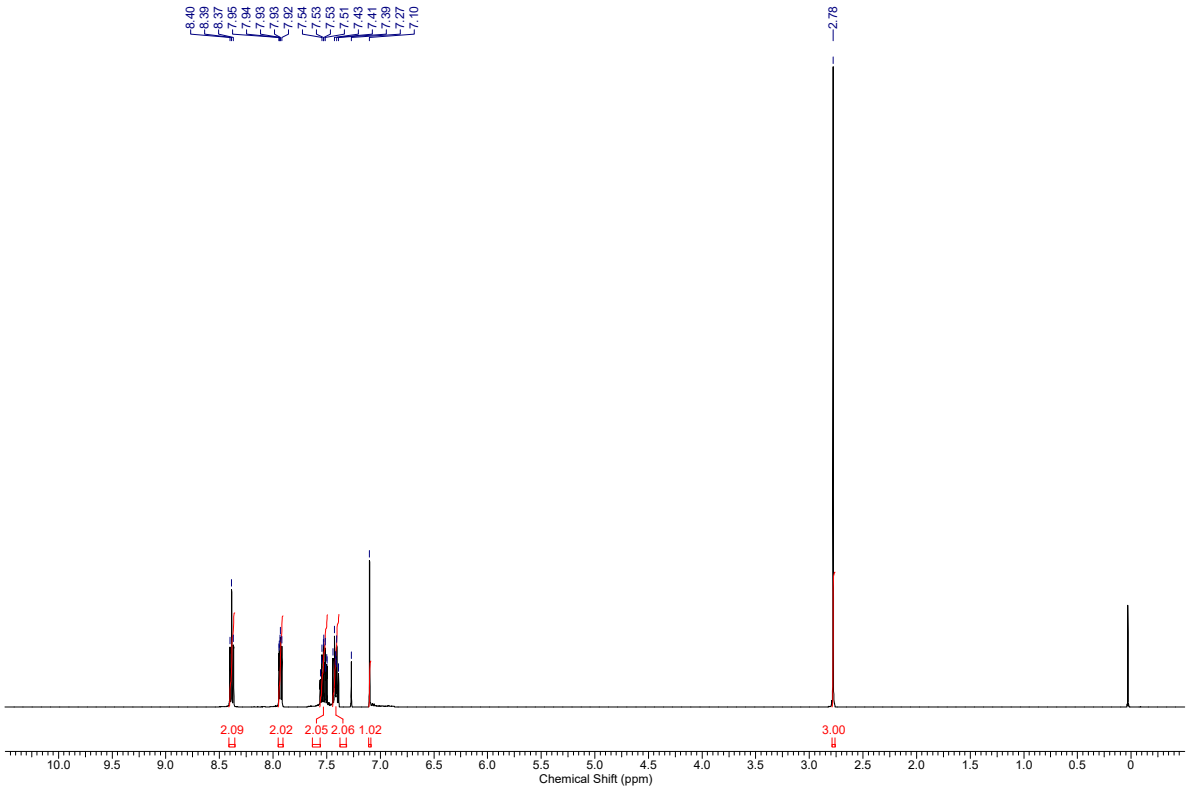


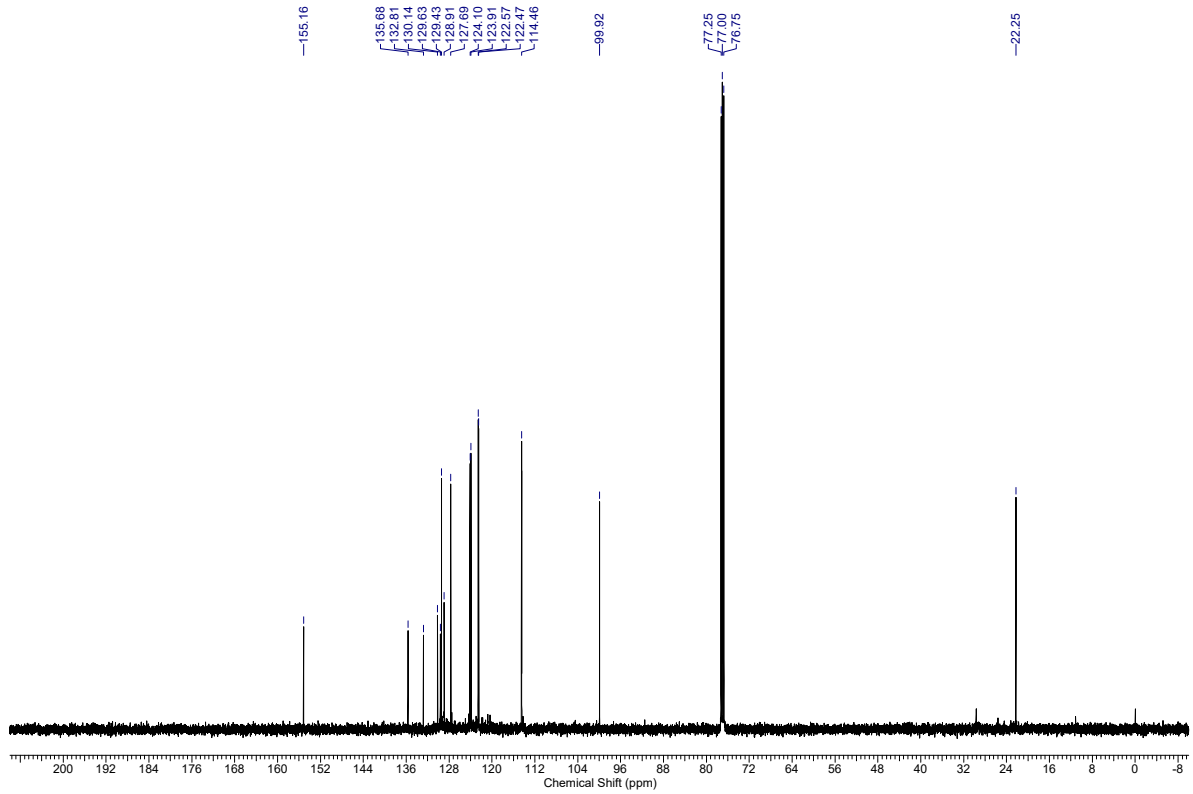
4-Methylimidazo[1,2-*a*]quinoxaline (5c)



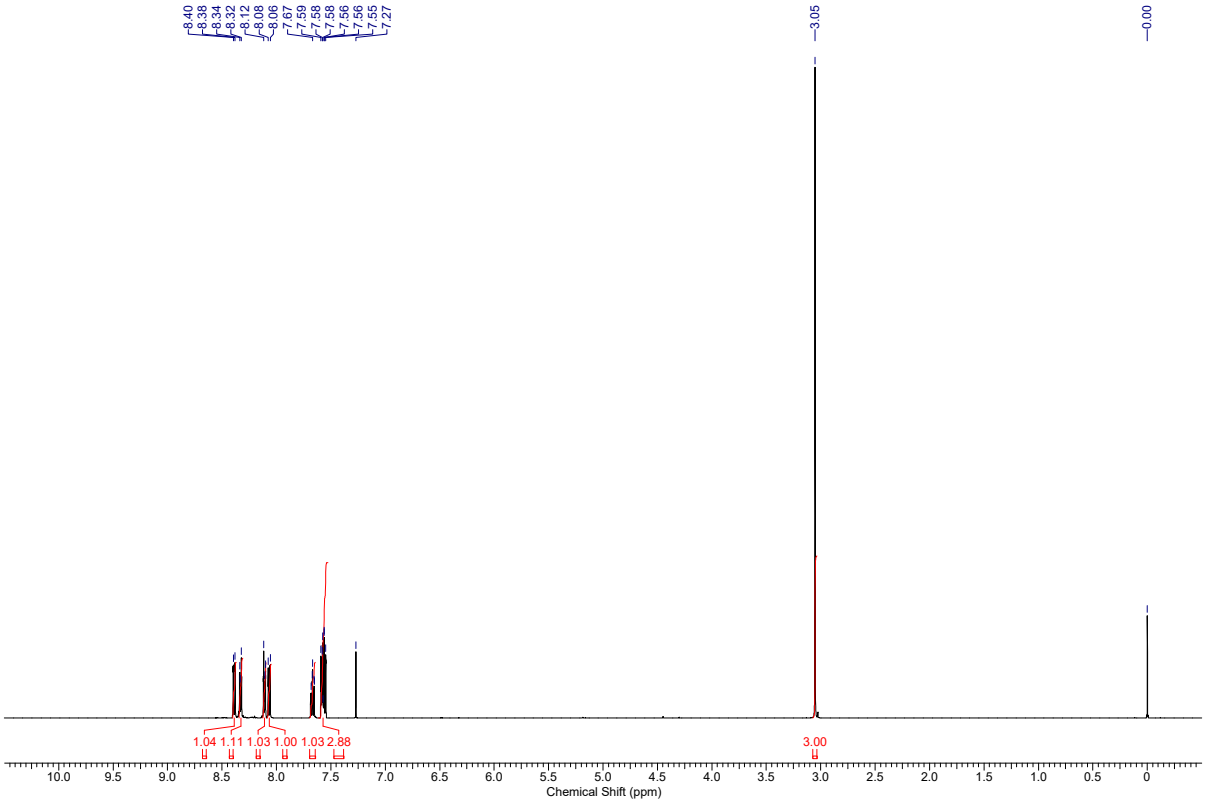


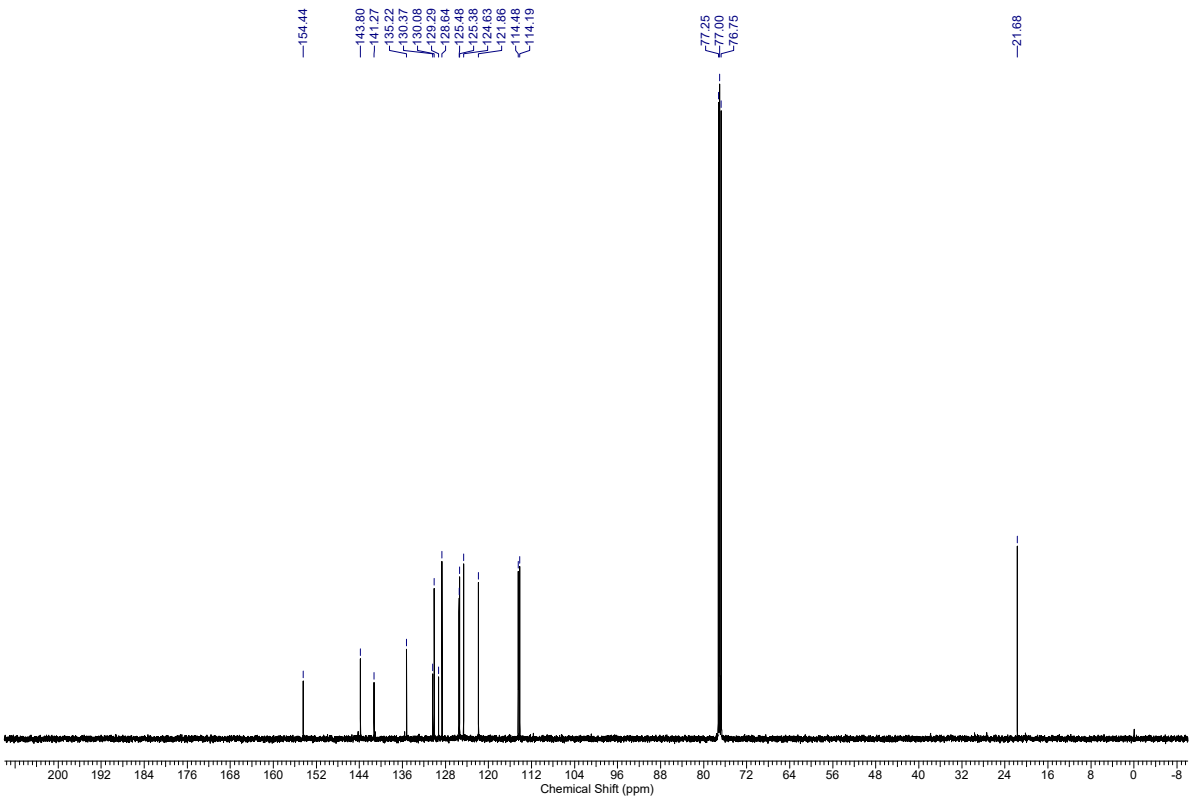
6-Methylindolo[1,2-*a*]quinoxaline (5d)



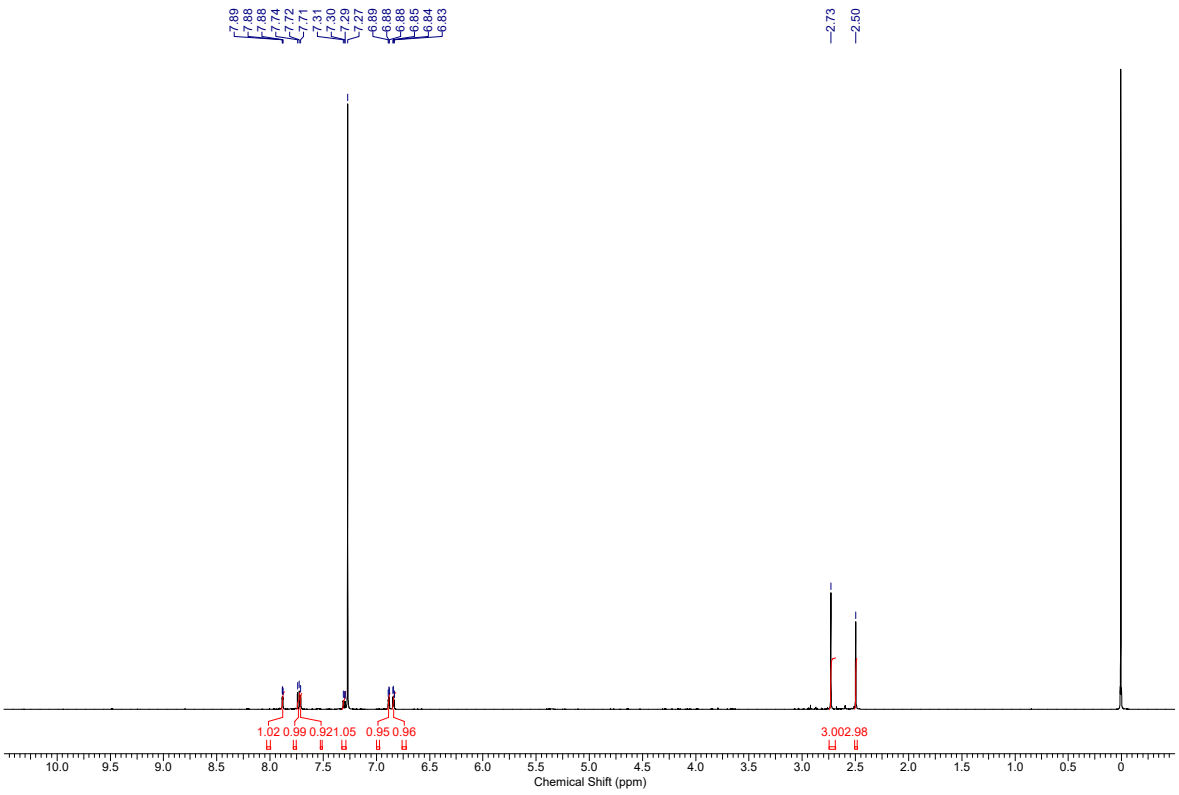


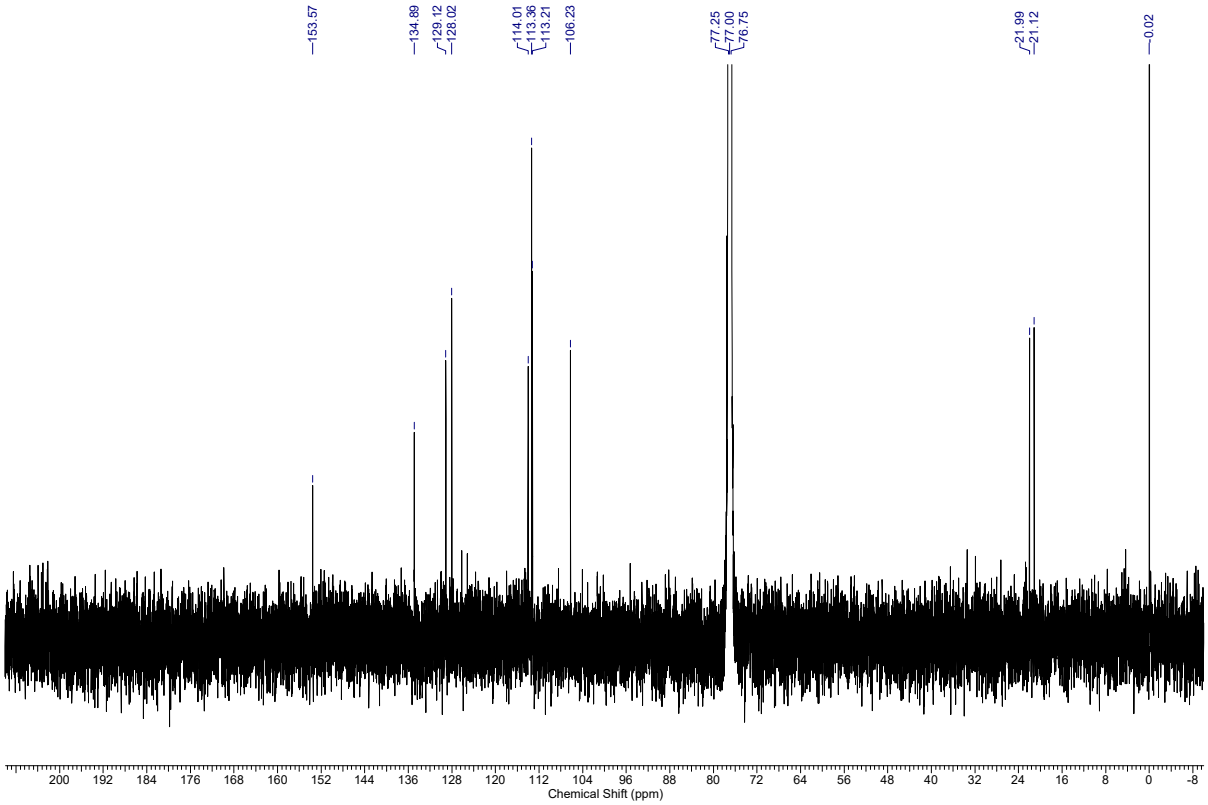
6-Methylbenzo[4,5]imidazo[1,2-*a*]quinoxaline (5e)



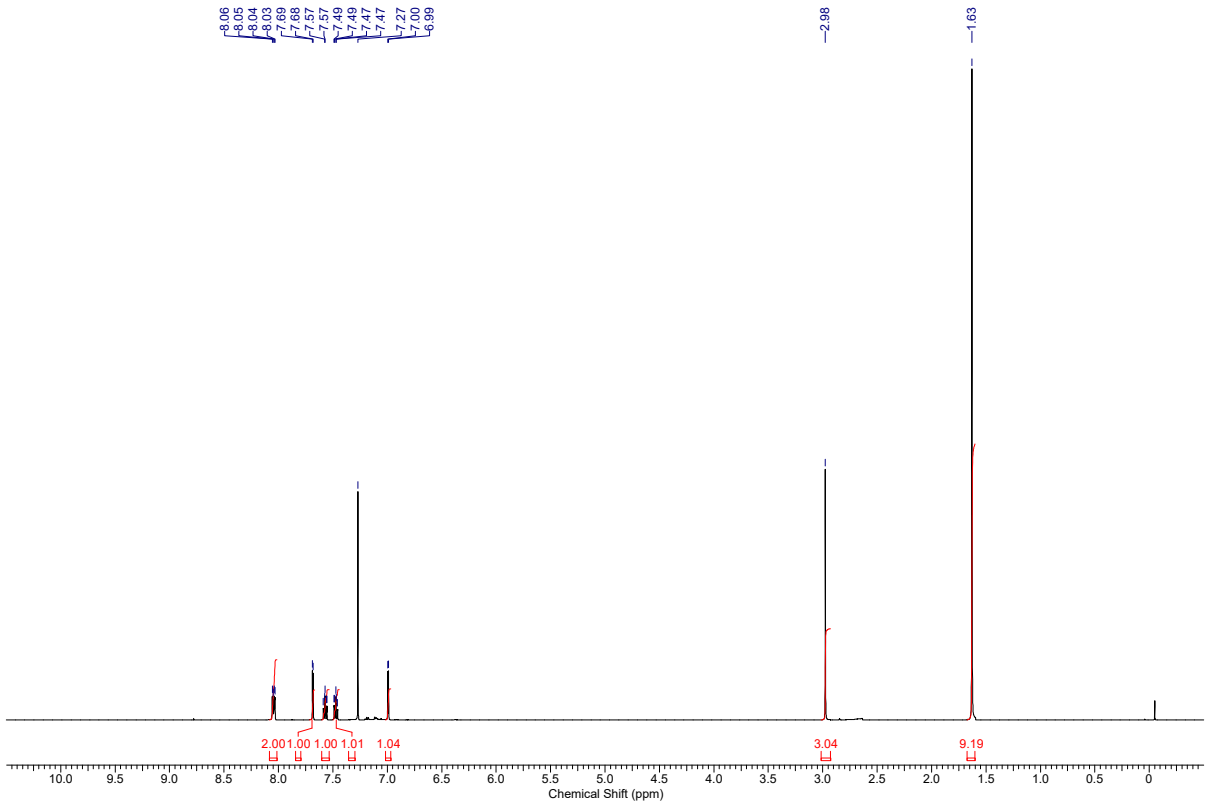


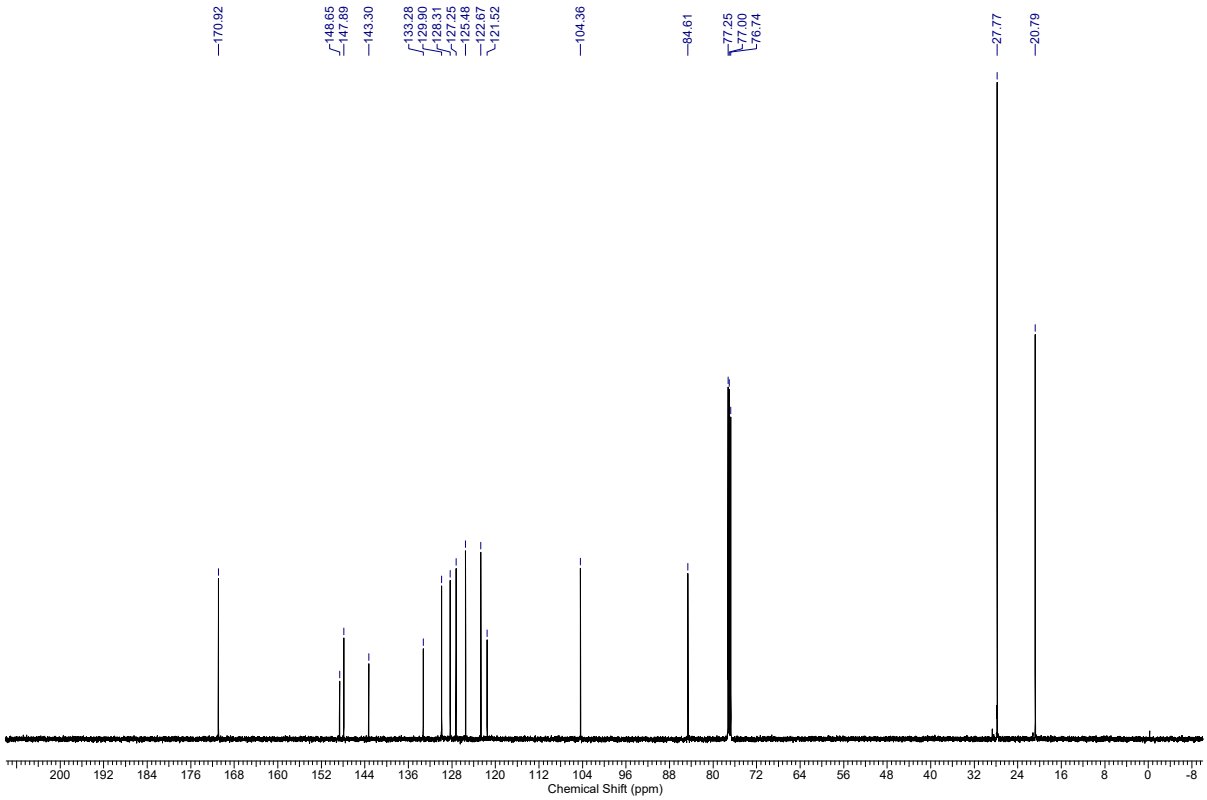
4,7-Dimethylpyrrolo[1,2-*a*]quinoxaline (5f)



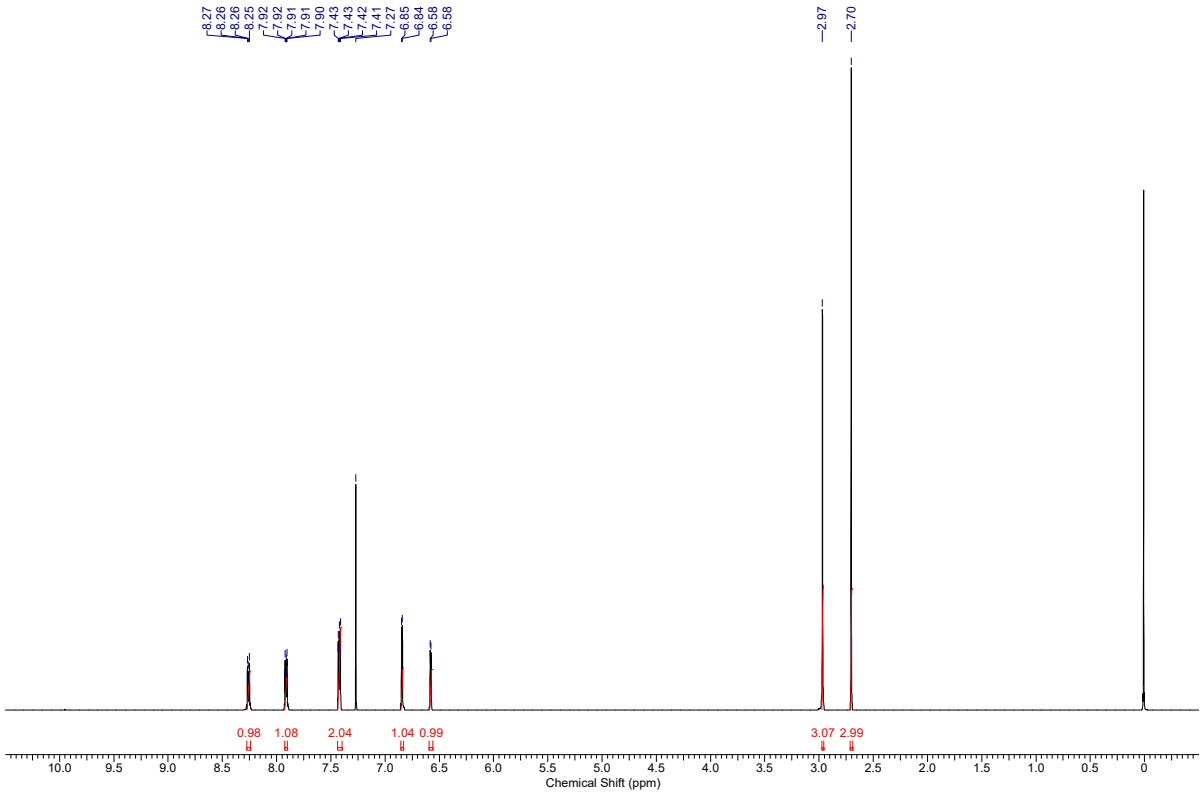


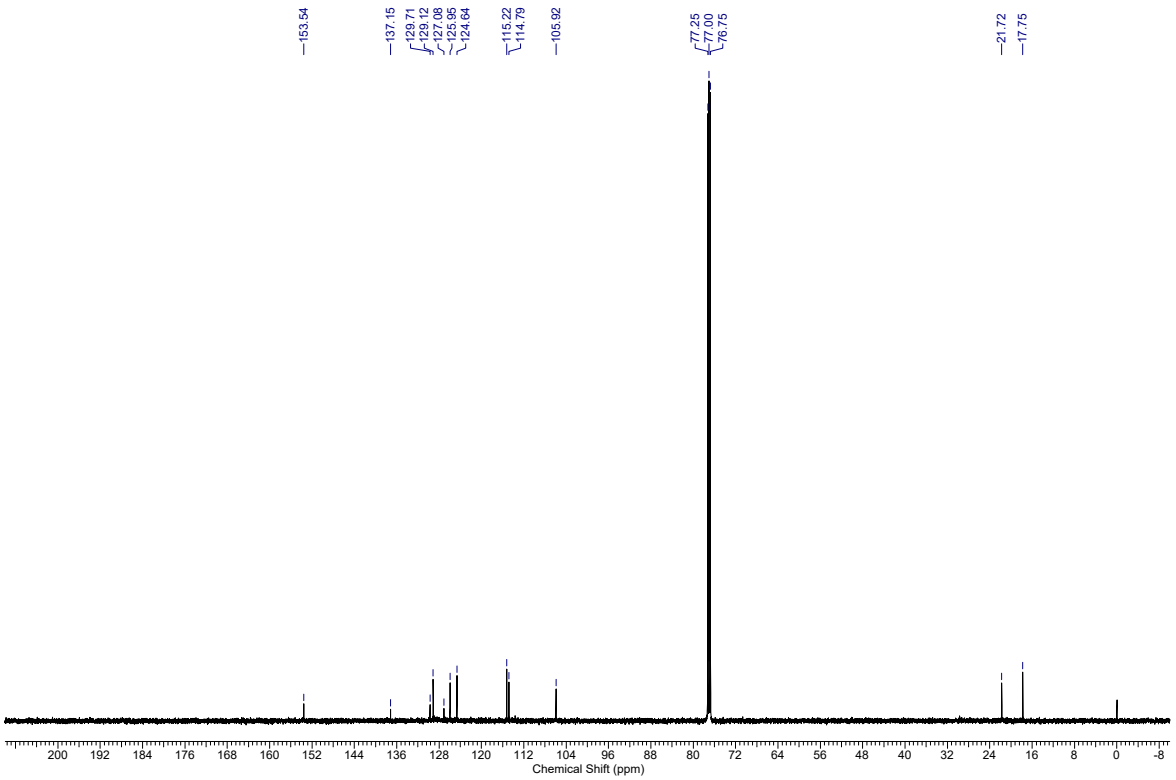
tert-Butyl 4-methyl-3*H*-pyrrolo[2,3-*c*]quinoline-3-carboxylate (5j)



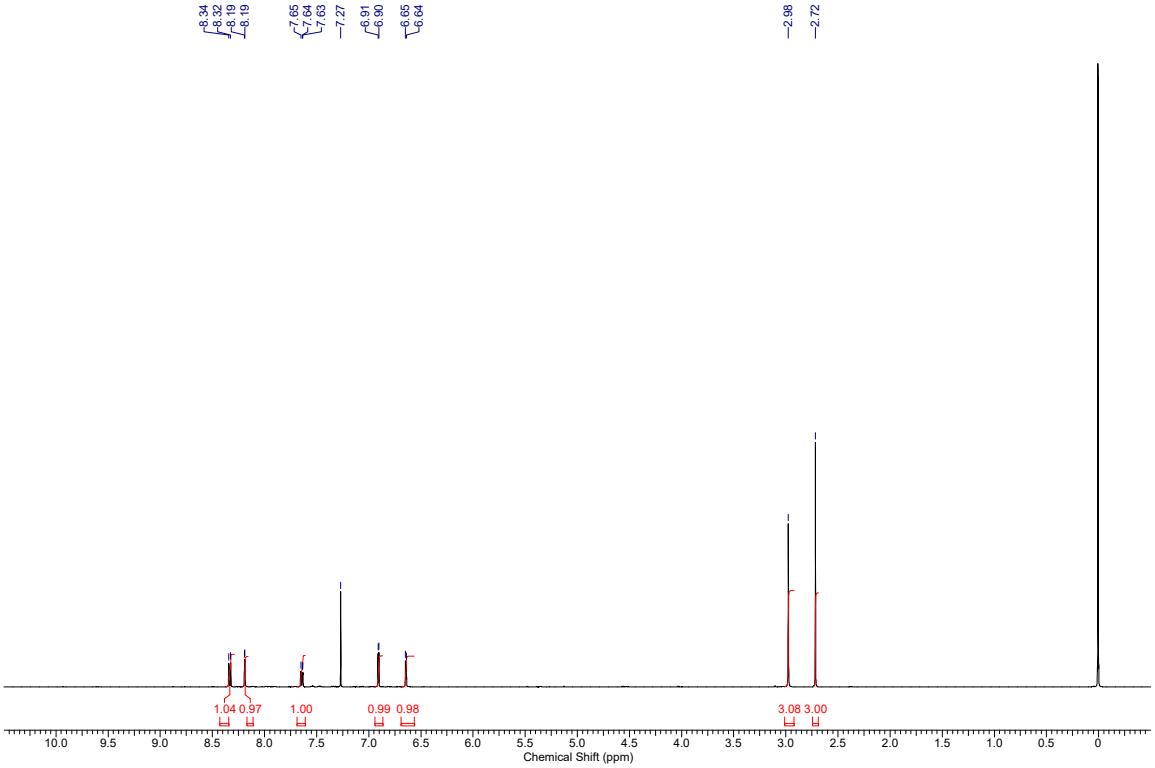


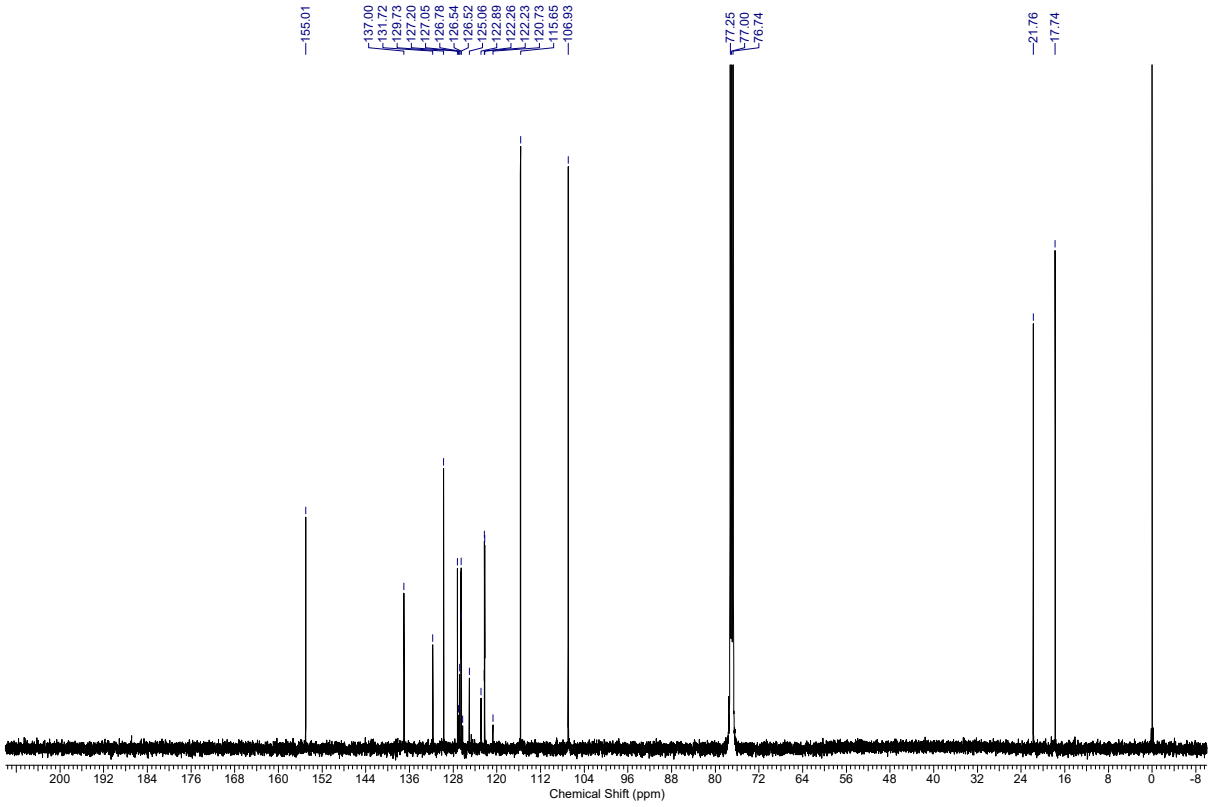
4,7-Dimethylpyrrolo[1,2-*a*]quinoxaline (6a)



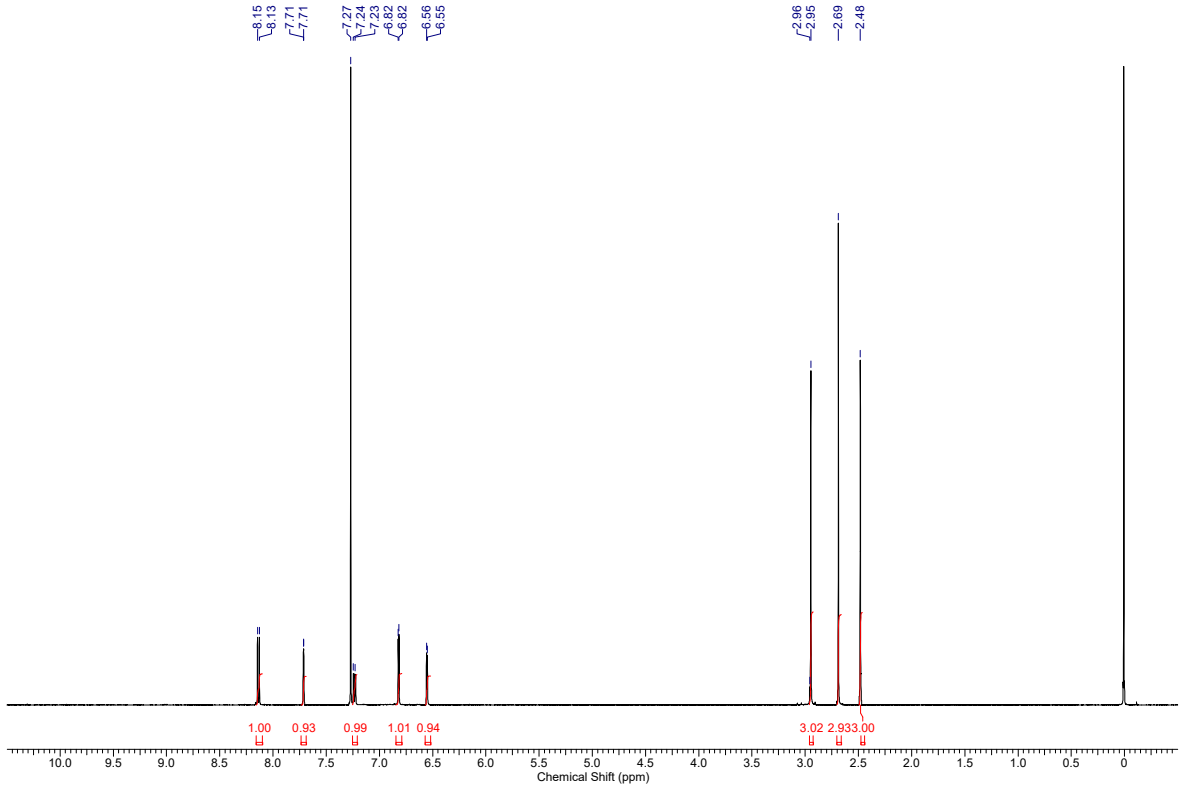


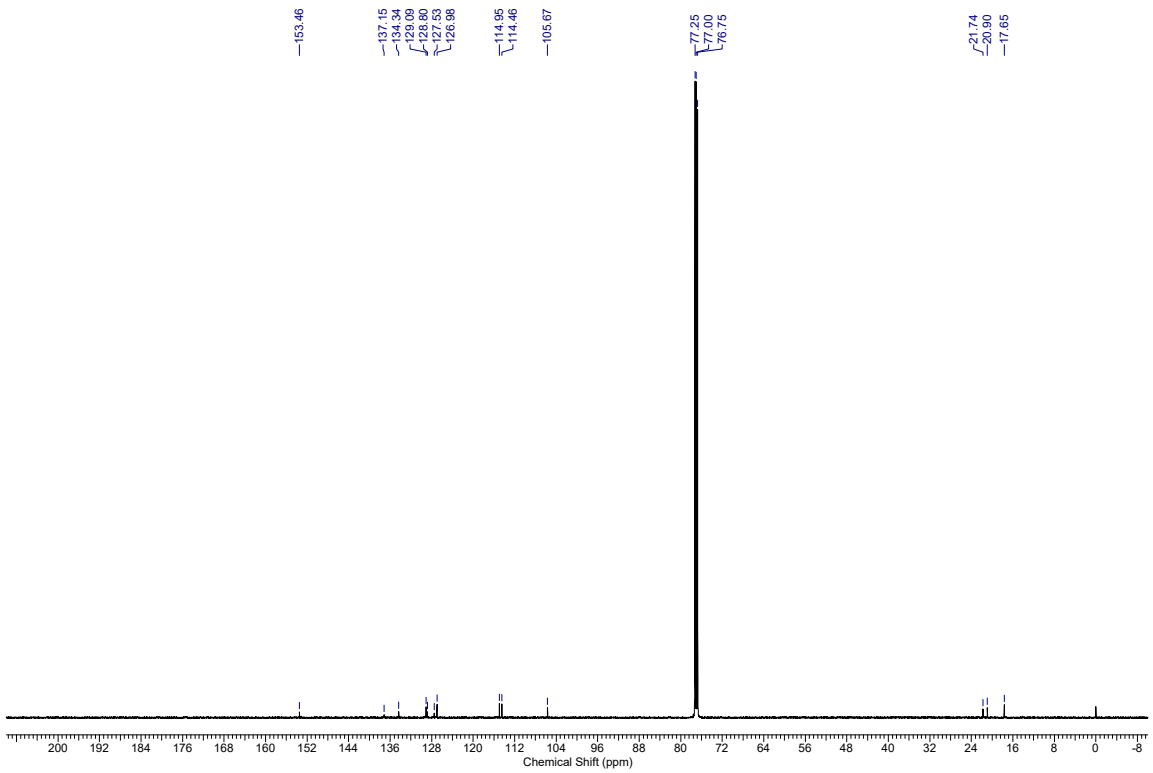
1,4-Dimethyl-7-(trifluoromethyl)pyrrolo[1,2-*a*]quinoxaline (6b)



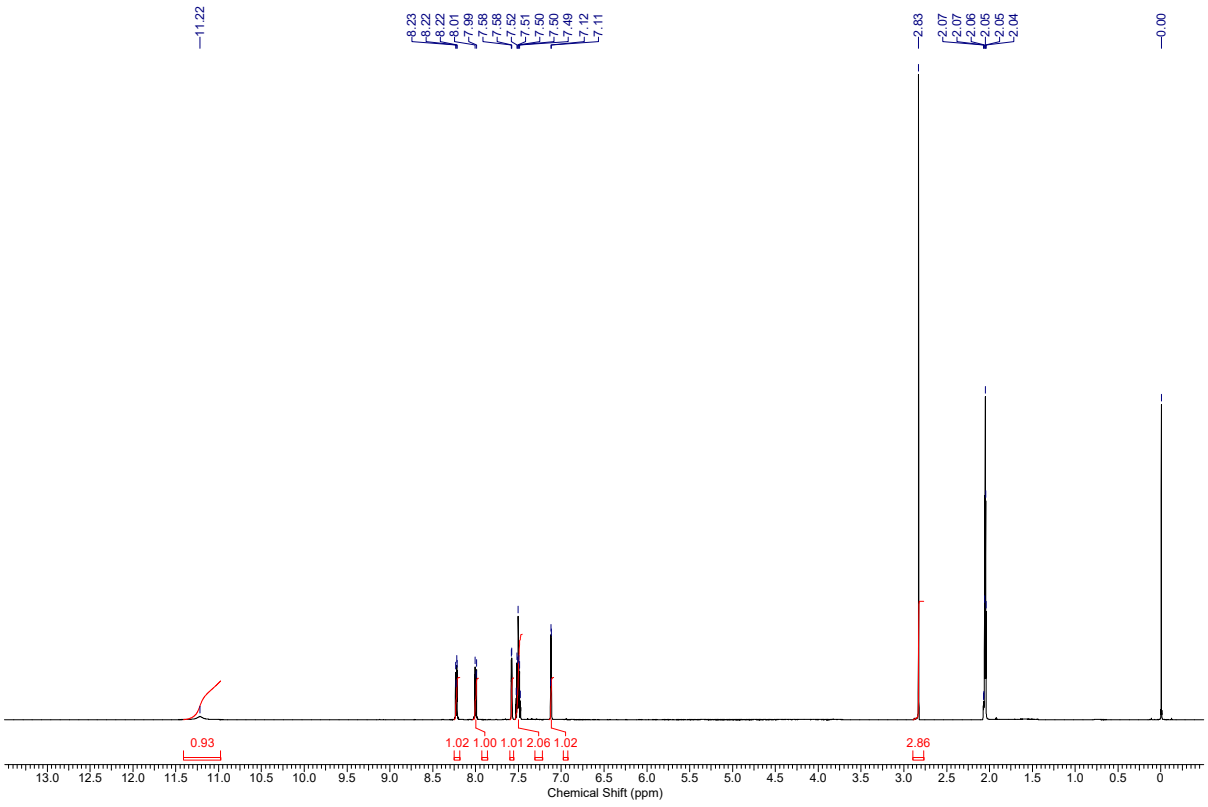


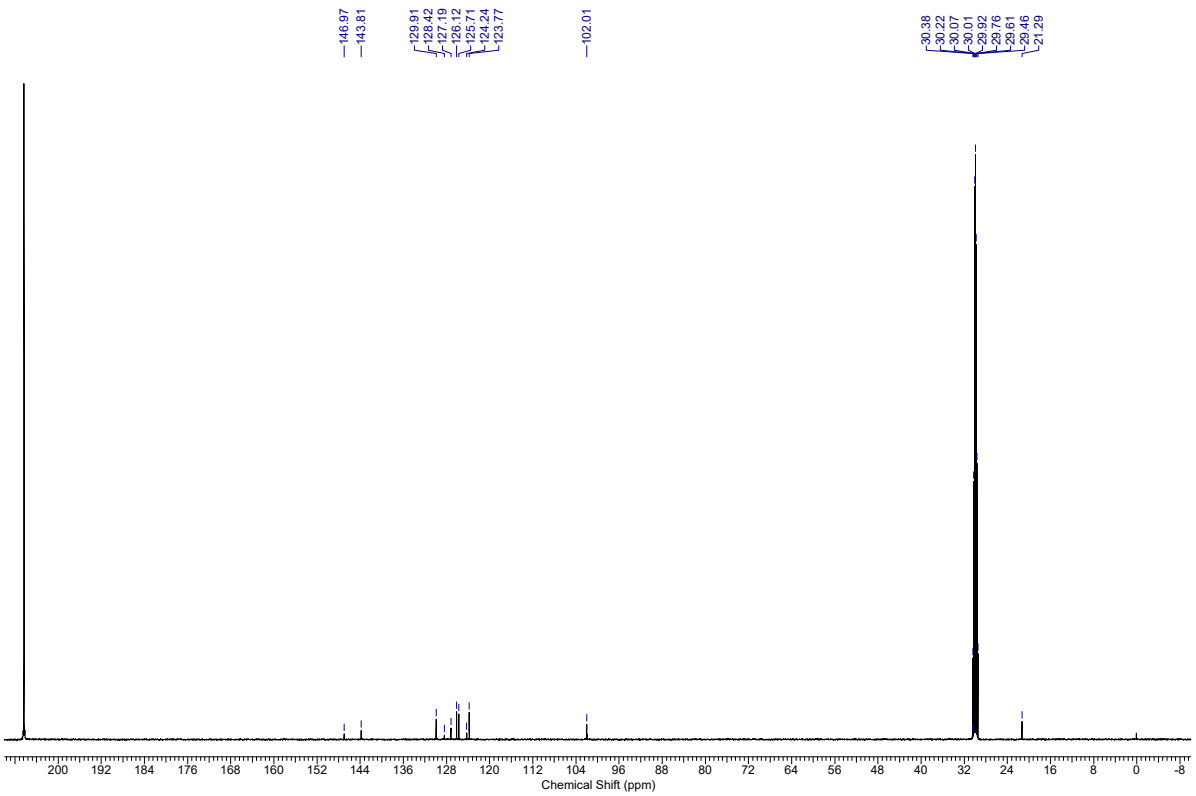
1,4,7-Trimethylpyrrolo[1,2-*a*]quinoxaline (6f)





Marinoquinoline A




146.97
143.81
129.91
128.42
127.19
126.12
125.71
124.24
123.77
102.01
30.38
30.22
30.07
30.01
29.92
29.76
29.61
29.46
21.29
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8
Chemical Shift (ppm)